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Research on the Effect of CAR-T Cell Therapy on Cancer

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Abstract: As an important branch of cellular immunotherapy, the rapid development and widespread application of CAR-T cell therapy has revolutionized immunotherapy. The essence of this therapy is to genetically modify the patient's own T cells and then give them new abilities in the laboratory, which allow them to identify and bind to antigens on cancer cells through specific receptors. T cells are first extracted from the patient as part of this therapeutic procedure. These cells undergo genetic modification in the lab to produce CARs that can identify and bind to tumor antigens. After the modification is completed, these T cells will be expanded to greatly increase their number, so that when they are injected into the patient's body, they can effectively recognize and attack cancer cells. These carefully designed T cells can accurately track and eliminate cancer cells with particular antigens after they are re-introduced into the patient's body. This article aims to use a series of research data to deeply explore the efficacy of CAR-T cell therapy in the treatment of diffuse large B-cell lymphoma (DLBCL). This article will assess this therapy's effectiveness in clinical practice and examine how it has changed the DLBCL therapeutic landscape. In addition, this article will discuss in detail the possible adverse effects of CAR-T cell therapy, including but not limited to cytokine release syndrome, neurotoxicity, and other possible immune system impacts, to fully understand the benefits and risks of this emerging treatment modality.

Keywords: diffuse large B-cell lymphoma(DLBCL), CAR-T cell therapy, side effect of CAR-T cell therapy

1. Introduction

The synthetic receptor combines an antigen binding domain with a T cell activation domain, so when the they are reinfused into the patient, T cells can recognize specific cancer antigens and effectively kill cancer cells. Using the above techniques, the researchers conducted experiments on B-cell malignancies. Ultimately, they successfully used these techniques to treat patients with blood malignancies. Therefore, scientists were inspired by this great progress and began to explore CAR-T cell therapy for other types of cancer. By 2023, the US FDA had approved 6 CAR-T cell therapy drugs. However, for current CAR-T, it is still difficult to apply them to various types of cancer [2].

Recently, CAR-T cell therapy has become a new treatment for the difficult-to-treat disease (R/R) DLBCL. This article examines some data, focusing on the treatment effects of 3 different CAR-T cell therapy drugs (Liso-cel, Axi-cel, and Tisa-cel) on DLBCL patients. The study shows the analysis of clinical studies of the three drugs on DLBCL patients, and the results show that the three

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drugs have a positive effect on R/R DLBCL. Then, this article will also use data to discuss the side effects of these three drugs.

2. The introduction of CAR-T cell therapy

We will introduce the basic mechanisms of CAR-T and its treatment range. We will also use data online to illustrate the effectiveness of CAT-T cell therapy for R/R DLBCL.

2.1. The mechanisms of CAR-T cell therapy

The main component of CAR-T is CAR, which researchers created as a synthetic receptor that redirects lymphocytes (usually T cells). Compared to native T cell surface receptors, it allows T cells to identify a greater variety of target antigens including tumor antigens without the need for HLA. CAR is mainly divided into three generations. The first generation of CAR uses the tyrosine activation group on the CD3ζ chain or FcεRIY to activate T cells. The CD3ζ chain produces signal I that activates T cells and releases IL-2. However, because the first generation of CAR only targets CD 19 and CD 20, the modified T cells still have limitations in anti-tumor effects. Therefore, researchers began to study the second and third generation CARs. The intracellular domain of the second generation CAR adds additional cost stimulation signals, and these additional "signal II" signals increase the proliferation of T cells and improve the secretion of anti-apoptotic proteins. More researchers are looking into the third generation of CAR, which incorporates more signals than only signals I and II, in an effort to enhance its functionality. Nevertheless, the trials' findings indicate that because of the greater CAR-T cell activation, the third generation of CAR is associated with a larger risk of immune-related adverse effects. But until now, there are still no clear conclusions for which generation is better when comparing the second generation and the third generation, more studies should be conducted in clinical trials. Recently, the fifth generation of CAR has been developing by adding one more intracellular binding domain and adding drug-dependent switches(both open or off) to regulate the CAR depletion or activation. However, for each CAR, there are 4 major components of CAR: an intracellular signaling domain, a hinge region, a transmembrane domain, and an antigen-binding domain We will discuss each part of CAR in detail [1,3,4,5,6].

The extracellular target antigen binding domain, which is composed of the monoclonal antibody’s variable heavy and variable light components, has target antigen specificity. For both VL and VH, these components are joined by glutamine-lysine short linker peptides to create scfv (single chain variable fragment). Affinity is a special and significant characteristic in the antigen-binding domain. For CARs to recognize certain antigens, trigger signaling, and stimulate T cells, the affinity parameter needs to be high. Conversely, toxicity and T cell death will result from an insufficient affinity [3,4].

The hinge region, sometimes referred to as the spacer region, is the region that extends the binding units from the transmembrane domain. To enable the extracellular target antigen-binding domain to reach the specific cell surface epitope, the hinge aims to lengthen and increase the flexibility of CARs. The research's findings demonstrate that changes in the length and constituent parts of the hinge area can impact CARs in a variety of ways, including signaling, epitote recognition, and CAR expression. In a real clinical trial, the hinge's length is not predetermined; rather, it must be customized for a particular antigen-binding domain [4].

Transmembrane domain :This is one of the CAR components with the fewest properties in the transmembrane domain. The primary job of transmembrane domain is to adhere CAR to the membrane of T cells. Although some research indicates that the transmembrane domain may

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actually influence the stability of CAR expression, it is unclear how the transmembrane domain affects CAR because it is constantly altered by the need for intracellular signaling domains.[4].

Anchor the CAR to the T cell's membrane is the main function of intracellular signaling domains, which are important for the effector function of CAR-T cell. CAR will cluster together and give the signal to intracellular binding domain when an antigens binds to it. The intracellular binding domain will transmit the activated signals into the cells [4].

2.2. The treatment range of CAR-T cell therapy

In recent years, chimeric antigen receptor T cell therapy (CAR-T cell therapy) has made breakthrough progress in hematological malignancies. Especially for diseases such as large B-cell lymphoma, multiple myeloma, non-Hodgkin lymphoma, and B-cell leukemia. CAR-T cell therapy has demonstrated significant clinical efficacy. When it comes to treating solid tumors, CAR-T cell therapy still confronts numerous obstacles.

First, the location of solid tumors in the body hinders the effectiveness of CAR-T cell therapy to work. Unlike hematological malignancies, the growth environment and biological features of solid tumors are more complicated. CAR-T cells need to cross the blood vessel wall and enter the tumor tissue to be effective. However, the microenvironment of solid tumors often inhibits CAR-T cells, which makes it challenging for them to reach the core area of the tumor.

Secondly, another obstacle for CAR-T cell therapy is the harsh tumor microenvironment.. There are many factors that inhibit immune cells in the solid tumor microenvironment, such as tumor-associated macrophages, regulatory T cells, etc. These factors will make it more difficult to eliminate tumor cells by weakening the killing power of CAR-T cells. In addition, the tumor microenvironment's hypoxia, acidity and other conditions also adversely affect the survival and functionality of CAR-T cells.

Furthermore, intratumoral or extratumoral toxicity is another problem with using CAR-T cell therapy to treat solid tumors . the inability of CAR-T cells to accurately identify tumor cells due to the heterogeneity of solid tumors may result in accidental damage to normal tissues. In addition, excessive activation of CAR-T cells in the body may trigger severe immune reactions, such as immune effector cell-associated neurotoxicity syndrome (ICANS) and cytokine release syndrome (CRS), posing life-threatening consequences to patients.

Despite this, researchers have not given up exploring CAR-T cell therapy to treat solid tumors. Currently, clinical trials for solid tumors are ongoing. Researchers are trying to overcome the above challenges through the following approaches: improving the design of CAR-T cells and improving their ability to recognize and kill solid tumor cells; adjusting the tumor microenvironment to reduce their Inhibitory effect on CAR-T cells; develop new CAR-T cells to reduce toxic reactions and improve treatment safety.

2.3. The investigation of the effect of CAR-T cell therapy

2.3.1. Clinical studies for Axi-cel

The Axi-cel therapy was evaluated across various clinical scenarios for patients with LBCL in the ZUMA-7 and ZUMA1 studies. Within the ZUMA-7 Phase III trial, individuals who had early relapses or were refractory to treatment for DLBCL were randomized to receive either standard therapy (involving 179 patients) or Axi-cel treatment (180 patients). salvage chemotherapy, high-dose chemotherapy and autologous stem cell transplant (ASCT) as second-line treatment are standard treatment options . The results of the most recent 47.2 months of follow-up are as follows: 82 deaths occurred in the Axi-cel cohort, compared with 95 deaths in the standard therapy cohort. Compared to the conventional therapy cohort, which had a median progression-free survival (MPFS)

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of 3.7 months, the Axi-cel cohort had a median MPFS of 14.7 months. The median overall survival (mOS) of the Axi-cel cohort did not reach the 31.1 months of the standard therapy cohort. This ZUMA-7 investigation was limited to patients 65 years of age and older. In addition, the results showed that the overall response rate (ORR) and complete response rate (CRR) were higher in the Axi-cel group compared with the standard therapy group (ORR rate was 88% vs. 52%, and CRR rate was 75% vs. 33%, respectively). Notably, patients in the Axi-cel cohort, who were more vulnerable and at an elevated risk for complications, did not encounter grade five cytokine release syndrome or severe neurological adverse events [6].

A recent study also showed the efficiency of Axi- cel to first-line therapy, not only confined to second-line therapy. There are 40 patients enrolled in this study: 22DLBCL patients, 16 with double- or triple-hit lymphomas, and 2 HGBL. After Axi-cel treatment, the results showed that 78%CRR and 89% ORR, and only 8% of patients had grade 3 cytokine release syndrome [6].

2.3.2. Clinical studies for Tisa-cel

Tisa-cel's effectiveness in treating adult patients with R/R DLBCL has also been studied. The phase II multicenter JULIET study's findings indicate that it has 12% PR, 40% CR, and 52% ORR. Neurologic problems occur in 12% of patients, while cytokine release syndrome is seen in 22% of individuals. The JULIET trial's long-term findings, which included 115 patients, revealed a 39% CRR and a 53% ORR; the mOS was 11.1 months and the mPFS was 2.9 months. CAR-T treatment is superior to chemotherapy, according to a comparison of the JULIET and CORAL research data (the median overall survival (mOS) with CAR-T base treatment is 12.48 months, which is more than the 4.40 months of chemotherapy). [6].

Tisagenlecleucel isn't always better than chemotherapy, though. 322 patients with aggressive B-cell lymphomas were randomly assigned to receive either Tisa-cel or conventional care (salvage chemotherapy or HSCT) in the BELINDA trial. This time, the ORRs of the two therapies were comparable. In this particular clinical trial, Tisa-cel did not outperform the group receiving standard treatment [6].

The safety analysis of DLBCL patients treated with Tisa-cel revealed that the negative effect of Tisa-cel LT did, in fact, occur against the backdrop of the JULIET trials. Of the patients that responded, 14% had LT cytopenias that lasted for 90 days. CAR-T treatment helped some individuals with hypogammaglobulinemia by making their condition worse. Few individuals experienced LT infections[6].

2.3.3. Clinical trials for Liso-cel

The effectiveness of Liso-cel for R/R LBCL patients was demonstrated by TRANSCEND trials. In addition to receiving at least two lines of treatment, those patients were given three distinct dose levels of CAR-T cells: -50×106, 100×106, and 150×106. The trial's findings revealed few neurological events and high ORR and CRR (73% and 53%, respectively) [6].

In the TRANSFORM study, 184 patients with R/R LBCL received Liso-Cel (100×106 CAR-T cells) or standard therapy. The EFS was 10.1 months in the Liso-Cel group and 2.3 months in the usual therapy group, with a median follow-up of 6.2 months. After 17.5 month, the results showed that 74% CRr for Liso-cel and 43% for standard-care group; Liso-cel did not reach mOS but standard-care group reached. Grade 3 cytokine release syndrome and neurological events were present in only 1% and 4% of patients, respectively [6].

Indeed, in the fight against some tumors, CAR-T cell therapy has become a potent treatment with demonstrable advantages. Nonetheless, the accompanying side effects of this therapy are substantial and cannot be dismissed lightly. The multitude of negativereactions connected with CAR-T cell

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therapy is so vast that providing a comprehensive analysis of each one would be impractical in this context. Among the array of side effects, tumor lysis syndrome (TLS) stands out as a particularly significant concern. TLS occurs as a result of the quick killing of cancer cells by the CAR-T cells, which can lead to potentially fatal side effects such as severe arrhythmias and renal failure. In light of this, it is imperative to implement prophylactic measures for individuals receiving CAR-T cell therapy, particularly those with a high tumor burden. These preventive strategies typically include aggressive hydration to maintain kidney function and the prophylactic administration of medications that lower uric acid levels, thereby reducing the risk of TLS. Despite these efforts, the technology and methodologies for effectively mitigating the adverse effects of CAR-T cell therapy are still being developed and are not yet considered fully mature [6].

3. Conclusion

Recent findings suggest that three different CAR-T cell therapies showed considerable efficacy in treating diffuse large B-cell lymphoma (DLBCL), a non-Hodgkin lymphoma. These innovative therapies are highly effective in treating diffuse large B-cell lymphoma, even in patients who have failed to respond to traditional first-line therapies such as chemotherapy. CAR-T cell treatment has shown remarkable efficacy, providing a new, potentially life-saving option for patients with this aggressive cancer.

However, despite promising results, it must be acknowledged that CAR-T cell treatment has drawbacks. One of the biggest concerns is the range of possible side effects of the treatment. Cytokine release syndrome, neurotoxicity, and other immune-related adverse events are examples of these mild to severe side effects. Technologies and methods aimed at mitigating these side effects are still in the development stage and have not yet fully matured. This means that, while CAR-T cell therapy can be highly effective, it also requires careful monitoring and management to address potential risks associated with its use.

Additionally, there are inherent limitations to the experimental nature of these therapies. Current studies have not provided clear and definitive data on which specific CAR-T cell therapy drugs are most effective in curing DLBCL. The lack of such data presents a challenge for clinicians who must make informed decisions about the best treatment options for their patients. This also highlights the necessity of more thorough clinical trials and studies to fully comprehend the comparative effectiveness of each CAR-T cell therapy drug.

In addition to concerns about side effects and efficacy, there are several practical limitations to the usage of CAR-T cell therapies. These limitations include the complexity and cost of treatment, the need for a personalized manufacturing process for each patient, and the limited availability of these therapies in certain regions. As the field of CAR-T cell therapy develops, addressing these limitations and improving treatments to increase their safety and effectiveness remain top priorities for researchers and healthcare professionals.

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