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Obstacles and side-effects of CAR-T from experiment to clinical

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Abstract. There is a practical and promising therapy that comes out these days called CAR-T therapy. The human immune system detects certain alien cells by matching distinct antigens on their surface. T-cells trigger the immune system to attack the cancer cells by attaching the antigens with its receptors. CAR-T therapy just uses T-cell's ability to carry out the following treatment process. This therapy has already been applied to the treatment of leukemia. However, CAR-T cell treatments for solid tumors have not been well investigated. Because the lacking of samples and clinical trials causes some drawbacks and obstacles to Car-t therapy which can not be ignored. Some strong side effects include cytokine release syndrome (CRS) and neurological toxicity problems and some limitations in particular groups of people. Here, this article mainly focuses on the drawbacks and also talks about obstacles of CAR-T therapy from experiment to clinical which people have not solved yet. This review attempts to highlight some of the remaining issues in CAR T treatment and provide current clinical solutions for certain possible roadblocks.

Keywords: CAR-T therapy, CRS, neurological toxicity, side effects.

1. Introduction

Hematologic malignancies are major health problems all around the world. According to the data which are collected these years. Some chronic forms of leukemia have higher survival rates above 60%. However, some acute leukemia has lower survival rates below 30%. There are now coming up with a novel and promising therapy called CAR-T therapy which not only applies to treat hematologic malignancies but also uses it to cure solid tumor cancer.

The extracellular single-chain variable region of CARs, which are recombinant receptor constructions, was taken from an antibody that was said to be selective for a tumor neoantigen [1]. Immunotherapy known as CAR-T therapy modifies patients' T cells in a lab so they can target cancer cells. Firstly, T-cells are extracted from the patient's body. Then send the patients' cells to the laboratory for adding special receptors on T-cells which can bind with special proteins in cancer cells. Thus, cancer cells can be attacked. It is also called a type of cell-based gene therapy because of the changing of T-cells' genes [2]. These days, hematological malignancies including acute lymphoblastic leukemia (AML), chronic lymphocytic leukemia, and some particular solid tumors are treated predominantly with CAR-T cells. This process takes several weeks to complete. Because cultivating a huge number of CAR-T cells is a process of personal customization. Not only cost time but also incur great expense [3].

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However, with the development of this immunotherapy. Based on the data scientists found that there is still something that hasn't solve yet when CAR-T therapy applies to the clinical, including anti-tumor activity in solid tumor treatment and some strong side effects like CRS, reduction of B lymphocytes, and neurological toxicity. This review is mainly based on current clinical data and new research progress to summarize the obstacle of CAR-T from experiment to clinical and discuss how to re-engineer the T-cells structure to tackle this question [4]. In addition, there is another problem that cannot be ignored is the cost of CAR-T therapy.

2. Application obstacle

According to the clinical trial of CAR-T therapy, CAR-T therapy is the last option for patients who are in the terminal stages of cancer. This therapy is not without any side effects. On the contrary, there are serious side effects to this treatment. Including CRS and neurological toxicity.

2.1. Cytokine release syndrome

Acute systemic inflammation known as CRS is linked to CAR-T therapy, therapeutic antibodies, and haploidentical allogeneic transplantation. CRS was caused by the over-immunity of the immune system to some drugs its should. It is a side effect that is still scarcely foreseeable among individuals [5]. Patients who suffer from CRS may have varied symptoms. Including mild flu to severe life-threatening inflammation like circulatory shock, vascular leakage, disseminated intravascular coagulation, and multi-organ system failure is all possible outcomes. Small, secreted proteins known as inflammatory cytokines are essential for communicating, activating, and attracting more new inflammatory cells by immune cells. These kinds of proteins can be secreted by CAR-T cells themselves. At present, there are three main effective mitigation methods, The main mechanism is to interrupt the generation of IL6. Firstly, use the anti-IL6 drugs, tocilizumab with or without the corticosteroids. Secondly, high doses of corticosteroids. Furthermore, use more doses of other types of drugs like siltuximab or multiple tocilizumab doses [6].

2.2. Neurological toxicity

CRS will cause many symptoms including some severe and fatal consequences, like neurological toxicity [8]. This complication can be found in 50% of patients who receive CAR-T therapy [9]. This complication has a variety of symptoms ranging from a mild headache to severe encephaledema. The typical symptoms include limb weakness, loss of memory, and vision even causing some potentially fatal epilepsy [7].

Currently, the most useful strategy is to rigorously review clinical and nonclinical data for indications of efficacy in neurotoxicity modulation. In fact, by 21 days after receiving CAR-T therapy, neurotoxicity typically disappears in the majority of cases where it develops. However, developing one drug which can ensure the efficacy of drugs without affecting CAR T cells is still necessary for the clinical field. Currently, the most commonly used drug in a clinic is Interleukin-6 (IL-6) antagonist. IL6 is a cytokine that can differentiate B-cells. It is also a substance which relevant to many inflammatory diseases and many cancers and plays an important role in the nervous system10. Although the transcriptional and posttranscriptional mechanisms are controlled, continuous uncontrolled growth of IL6 will harm inflammation and immune system disease. Therefore, tocilizumab a drug that ranges to anti-IL6 was developed [11].

3. Obstacles in solid tumor therapy and solutions

CAR-T therapy is promising in the treatment of hematologic malignancies. CAR-T therapy, to some extent, plays a significant role in the treatment of solid tumors. However, as compared to CAR-T therapy, the efficacy of CAR-T in solid tumors was not considerable, which can be related to various complicated properties of cancer cells. There are certain common therapeutic challenges in solid tumors.

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3.1. Lack of Tumor-Specific Antigens (TSAs)

TSAs are proteins and other compounds present specifically on cancer cells and not on healthy ones. They can be utilized to elicit an immune response against cancer cells and serve as an immunotherapy target. The primary cause for CAR-T therapy's ineffectiveness in clinical practice is a lack of tumor-specific antigens. Tumor-associated antigens are the primary treatment targets for the majority of solid tumors today. (TAAs) [12]. TAA is the protein molecule found in normal cells and tumor cells. Which a lack of specificity, will trigger off-target events to occur. Sometimes the effects are potentially fatal and unpredictable. Currently, scientists customize specific CAR-T cells for this kind of TSA, which help CAR-T cell better target the antigen of the cancer cells. TSA agents are still in short supply. As a result, improving the effectiveness of CAR-T cells in interacting with tumor surface antigens is required [13].

This problem has a single solution. When compared to solo treatments, Combined CAR-T Cell Immunotherapy has improved cancer control. To treat a comparable malignant tumor, it combines two or more therapies with other forms of therapy. This can reduce TAAs and boost CAR-T cells' ability to locate and adhere to tumor cells, improving antigen specificity.

Chemotherapy in combination with CAR-T cells can improve the effectiveness of CAR-T treatment. Chemotherapy in addition to enhancing immunity, reduce tumor burden. The effects of chemotherapy are mainly reflected in the following aspects. It can diminish the activity of immunosuppressive cells, which implies that following chemotherapy, certain cells, such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), will be inactivated. Besides this, Chemotherapy usually be used before other therapeutic techniques which can promote T cell immunogenicity and increase the probability of lymphocyte presence in TME. This can improve not just the endurance and responsiveness of CAR-T cells. Furthermore, proper treatment can improve tumor cell susceptibility to immunotherapy. This may facilitate increased tumor cell penetration by cytotoxic T lymphocytes. Furthermore, Combined CAR-T cell Immunotherapy, still can inhibit the autoimmunity of itself while increasing CAR-T cell persistence. They find a balance to keep a maximum curative effect [14].

CAR-T therapy in conjunction with radiation is a remarkable treatment that is used as an efficient supplementary treatment. It can induce a tumor microenvironment that promotes CAR T-cell invasion and trafficking into tumor sites. There are some research shows that radiotherapy can increase the sensitivity of tumor cells, which respond to tumor-specific cytotoxic lymphocytes. Radiotherapy also stimulates the release of chemicals including pro-inflammatory cytokines, tumour necrosis factor α (TNFα), and IFN-γ and DAMPs. They can trigger the entrance of immune cells which promote the function of the immune system. Radioactive therapy still has something unique in that, it can not only trigger the immune system against tumors by stimulating the specific sides of CTLs but also inhibit the tumor which is far from them. Therefore, the combination with radiotherapy is a sensible way to promote the effect of both therapies [14].

3.2. Tumor Microenvironment (TME) Inhibition

The process of tumor formation is affected by two factors. One of these is the change of genetics in the tumor cells while the other one is the rearrangement of TME. TME refers to the environment which supports the tumor cells' life [15]. TME consists primarily of cancer cells, surrounding immune cells, some hormones, and other types of substances. It can induce both beneficial and opposite consequences [12]. In some cases, TME will inhibit the activity of CAR-T cells in the treatment of solid tumors. Currently, there are several therapeutic methods which in summarize that adapt and modify themselves to each other [16].

Design new CAR-T cells which can maintain their activity in TME and rebuild a new tumor microenvironment to fit the optimum growth of CAR-T cells to target the tumor antigens.

Focusing on the characteristic of TME to find what inhibits the growth of CAR-T, then overcome these by repeating immune cells and activating critical anti-tumor immune cells. experiments. The mechanism of rebuilding TME is that TME suppression is reversed by inhibiting suppressive

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3.3. Economic restriction

The cost of such treatment also needs to be considered and weighed, CAR-T therapy is extremely expensive and only a few types of drugs circulate on the market. Currently, only two types of drugs are widely used. Kymriah and Yescarta are the most common drugs which occur in clinical treatment. However, they still cost a huge amount of money to finish one cycle of treatment, $510,963 and $402,647 respectively [16]. CAR T-cell acquisition expenses range from $373,000 to $475,000 per injection, surprisingly that this does not include the facility cost. Furthermore, CAR-T therapy is only used in an inpatient setting, therefore the cost of hospitalization and follow-up care is still a significant expense, costing additionally $70000 to $80000 [17].

The expensive cost of CAR-T cell immunotherapy severely limits its research and clinical applicability. Thus, the things which take as priorities are reducing the cost and increasing the utilization of drugs in the clinic. There are several reasons for the high cost of CAR-T therapy. First of all, CAR-T treatment has a special mode of action. The methods of gathering and manufacturing significantly increase the overall cost. Secondly is that this therapy has varied side effects. Patients must receive the following treatment against or relieve some symptoms. Additionally, Because of the inaccessible clinical data of CAR-T therapy, it is still an uncertain and unpredictable treatment plan in the medical field. For a lot of patients after treatment, because of some issue or death, the data is not available. Therefore, Long-term effectiveness data for CAR T-cell treatments are lacking, which is an essential factor of cost-effectiveness. For this problem adding more samples and studying with a large group of patients seems like a sensible solution.

There are other ways to reduce costs effectively, like redesigning low-cost CAR-T cells which need fewer manufacturing techniques, but have the same therapeutic effect. Finding a substitute for CAR-T cells seems quite important for reducing the cost. Besides it, establishing and improving the system of processing CAR-T cells also be a trend in the future. Increasing industrial efficiency through automation is one of the major difficulties that must be solved to see cost savings [17].

4. Conclusion

According to recent advances in Car-T therapy, this therapy had already been proven to be a success way in preclinical models. It is undeniable that CAR-T therapy is one of the most effective methods so far for treating hematological malignancies, although there is still some intractable side-effect which is not solved smoothly. This review provides offers several options for treating side effects like CRS and Neurological toxicity, including the use of anti-IL6. However, although CAR-T therapy seems practical and promising in the treatment of hematological malignancies, it still needs to pay attention to the treatment of solid tumors. Lacking TSA and TME inhibition are the obstacles which are needed to be figured out. CAR-T cells in combination with chemotherapy and radiotherapy can be taken as a sensible and effective way to overcome the problems which bring form lacking TSA. Redesigning the CAR-T cells and rebuilding a new tumor microenvironment is the proper way to reduce the effect of TME inhibition. The expense of CAR-T therapy is the main barrier for patients, even though it has shown some promise in the treatment of solid tumors and has a high response rate in patients with hematological malignancies, its cost-effectiveness is debatable because of the high cost and ambiguity of the clinical data. To reduce the cost of CAR-T therapy, collecting the clinical data is the priority things and completing the entire manufacturing chain is also an essential part of decreasing the cost of CAR-T therapy.

This article aims to point out some of the remaining problems in CAR T therapy and give some current clinical solutions for some potential obstacles. This provides ideas for following treatments and gives them some ways and directions for the development of new drugs and new therapy. However, this review still lacks the mechanism and specific details of CAR-T therapy and its side-effect. In the future, more details about the mechanisms need to be researched and discussed, which can make CAR-T therapy more accurate and effective.

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