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Analysis of the Current Status of CRS Due to Pediatric ALL Treated with CAR-T Therapy

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Abstract:

Chimeric antigen receptor (CAR)-T therapy has been a popular treatment for tumors in recent years, and it has good efficacy for pediatric acute lymphoblastic leukemia (ALL), especially B-lymphoblastic ALL. Generally, CAR-T therapy affects the tumor immune microenvironment and activates the immune response, so it may lead to the occurrence of inflammation and some other adverse effects, most of which are self-limiting symptoms. However, a small number of children will develop severe cytokine release syndrome (CRS), which may be life-threatening in severe cases. Currently, the main means of treating or alleviating CRS is the application of monoclonal antibodies, glucocorticosteroids, boosting drugs, etc. Although these drugs can relieve symptoms, further effects need to be further discussed. The mechanism of CAR-T causing ALL is described in this paper, and the mechanism, advantages and disadvantages of various drugs, and their impact on tumor treatment are compared to analyze the better measures to deal with CRS, so as to provide ideas for further clinical practice.

Keywords: CAR-T cell therapy, pediatric ALL, CRS, immune-related adverse effects, tumor immunotherapy.

1. Introduction

Tumor is a kind of disease produced by the long-term synergistic effect of various internal and external tumor-causing factors, which leads to the disorder of the regulation of local tissue cells, changes in the internal environment, and the abnormal proliferation of cells in the body, in which malignant tumors refer to the uncontrolled proliferation and expansion of tumor cells, thus invading the nearby or even the whole body tissues and organs until it leads to the death of the human body. Malignant tumors are currently the second leading cause of death worldwide, posing a serious threat to people‘s lives. According to the data provided by the official website of the World Health Organization (WHO), about 400,000 adolescents under the age of 19 suffer from cancer every year, and it is often difficult to prevent and identify the disease through ordinary screening, resulting in the discovery of many patients in the late stage of the tumor. stage. ALL is one of the most common and frequent cancers in children, which is caused by the proliferation of leukocytes in the body and blood infiltration, resulting in acute anemia, hemorrhage, fever, etc. The incidence of ALL accounts for 70% to 80% of all leukemias, and 27.3% of all cancers in children [1].

Although tumors still maintain their high morbidity and mortality rates, with people‘s continuous and deep research on tumors, people have gradually mastered some methods to treat tumors, and for children‘s acute lymphoblastic leukemia, it can be treated by traditional radiotherapy, hematopoietic stem cell transplantation and other methods. However, radiotherapy is very harmful to the organism: it kills some healthy cells in the body, by which can reduce autoimmunity and cause damage to the skin mucosa, bone marrow, etc., so it is easy to cause infection in patients. In the cases of death related to radiotherapy treatment measures, the most common causes are infection and bleeding, and the treatment-related mortality rate accounts for 56.3% of the deaths of children with malignant hematological diseases [2]. In contrast, hematopoietic stem cell transplantation has a high relapse rate; in a survey conducted in a hospital in Guangxi, 44 patients with a median age of 21 years who underwent unrelated hematopoietic stem cell transplantation for the treatment of ALL had a cumulative 5-year relapse rate of 36.3%, with 19 surviving [3]. It has been mentioned in many other studies that there is a significant improvement in the current postoperative survival rate after transplantation, but cancer recurrence is the main problem in the current application of hematopoietic stem cell transplantation. In recent years, targeted immunotherapy, which has fewer side effects on the body and good therapeutic effects than radiotherapy and stem cell transplantation, has been moving towards the front line of clinical treatment. Immunotherapy refers

to a biological therapy that uses the body‘s own immune mechanism to enhance the patient‘s immune function through active or passive methods, activate the previously suppressed immune system and use the immune system to kill the tumor. Among them, the application of CAR-T is a promising immune agent that has already entered the clinical treatment stage of pediatric ALL, aiming to activate the patient‘s own T lymphocytes to bind with the tumor antigen receptor and recognize the tumor cells that have previously evaded immune surveillance, so as to achieve the effect of precise treatment of tumors. The aim is to activate the patient‘s own T-lymphocytes to bind to tumor antigen receptors and recognize tumor cells that previously escaped immune surveillance, so as to achieve the effect of precise treatment of tumors.

However, it should not be ignored that CAR-T cell therapy also has certain adverse reactions, most of which are self-limiting, i.e., can be eliminated or alleviated through autoimmunity and regulation, but there are also life-threatening severe toxic reactions, and CRS is one of the most common adverse reactions. CRS is usually characterized by inflammation-induced fever and headache, and in severe cases, life-threatening symptoms such as shock, organ failure, and disseminated intravascular coagulation may occur. Therefore, prevention and mitigation of CRS is a point that should not be taken lightly when applying CAR-T cell therapy. However, at the same time, it should be noted that the treatment of ALL is the most important and fundamental problem for the child, and the efficacy of the tumor should not be compromised when treating or alleviating the adverse effects of CAR-T cell therapy. This paper will review the existing measures for treating and alleviating CRS caused by CAR-T cell therapy, compare and analyze the advantages and disadvantages of these measures, aiming to find a balance between them and tumor therapy, alleviate the pain of side effects when applying immunotherapy in the treatment of pediatric ALL, and combine them with clinical practice to propose measures for preventing immune-related adverse reactions related to CRS.

2. Definition

2.1 Definition of ALL

ALL is a heterogeneous blood disorder caused by an abnormal proliferation of lymphocytes in the body, characterized by the incessant proliferation of immature lymphocytes in the peripheral blood and organs. Most patients present with symptoms of myelosuppression or abnormal hematological indices such as fever, high temperature, bruising, etc. in the early stages of ALL, and many patients may present with symptoms of organ enlargement, especially of the liver and spleen. Factors predisposing to ALL include hereditary factors, including genetic variants, chromosomal aberrations, congenital disorders such as Down syndrome, and environmental factors such as radiation, pesticides, and infections. ALL can be diagnosed by morphological identification, immunophenotypic analysis, chromosomal analysis, etc. Based on the cellular immunophenotype, WHO classifies ALL into lineage B ALL and lineage T ALL, which are associated with B lymphocytes and T lymphocytes, respectively. Lineage B is known as B-ALL, which accounts for 80% to 85% of the incidence of ALL, while lineage T, also known as T-ALL, accounts for 15% to 20% of the incidence of ALL. Factors that contribute to the development of leukemia in children are equally genetic, infectious, and immunodeficient [4]. ALL has a peak age of 0–9 years in children and is a common cancer in children. In recent years, with the improvement of medical technology, the survival rate after treatment of pediatric ALL has increased dramatically, and one study investigated more than 700 children treated with ALL from 1958 to 2018 and found that during the 10-year period from 2008 to 2018, the five-year survival rate of the children increased from 1.2% to 90.7%, and the risk of relapse decreased from 98.8% to 9.9% [5]. The decrease in recurrence rate and the increase in survival rate also mean that the intensity and efficacy of conventional treatment have almost reached their limit, and there is little point in continuing to apply conventional therapies, while the adverse effects of conventional treatments persist. If the survival status of children with ALL and their quality of life are to be further improved, then people must find new treatment methods.

2.2 Definition of CAR-T Therapy

Immune effector cell therapy is an emerging approach with good efficacy, even when the tumor cells escape the immune surveillance of some of the body‘s own immune cells, it can still produce a certain immune response to the targeted tumor cells. The typical immune effector cells are natural killer cells (NK), dendritic cells, plasma cells, and cytotoxic T cells. CAR-T cells, also known as chimeric antigen receptor T cells, are genetically modified T cells that can express synthetic receptors on the cell surface and specifically recognize specific tumor antigens, thus binding to the tumor and killing it. In contrast to the body‘s innate immune T cells, CAR-T cells do not require major histocompatibility complex (MHC) molecules to recognize antigens on the surface of tumor cells. Therefore, CAR-T cells have better specificity than natural T cells and are able to recognize and kill tumor cells more effectively. Currently, CAR-T cell therapy has become a key approach for children with relapsed and refractory B-cell ALL with good efficacy, but sometimes it shows resistance. The main factor is the loss of target antigens (mainly

CD19 target), and the effective expression rate of targets that can replace CD19, such as CD22, is relatively low. The current CAR-T cell therapy in T cell ALL is not effective, so overall immuno-CAR-T therapy needs to continue to be investigated in the long term.

2.3 Definition of CRS

CRS, a common adverse reaction after CAR-T cell therapy treatment, is a cytokine-mediated systemic inflammatory response that may occur while activation and expansion of CAR-T cells in the body occur [6]. When immune cells are activated under CAR-T therapy, they produce a variety of chemo-chemokines and cytokines because of the need to fight against tumors. The mild symptoms of CRS are only fever, malaise, and headache, while the severe cases may have hemodynamic impairment, severe hypoxia requiring ventilator support, cardiac arrhythmia, organ failure, DIC, shock, and other symptoms that may seriously threaten the life of the child. Although the probability of CRS caused by CAR-T therapy is high, from the current point of view, mild CRS can be completely self-healed by the patients, and the incidence of severe CRS symptoms is relatively small, so the benefits of CAR-T therapy far outweigh its adverse effects, including CRS, and after all, the treatment of ALL is the most important problem for the children. However, this paper focuses on children with ALL, in other words, it is not possible to ignore the fact that these children‘s lives have just begun while treating the tumor, and it is necessary to discuss their quality of life from the perspective of long-term development, so it is worthwhile to carry out further research on the side effects of CAR-T, such as alleviation of CRS and reduction of post-CRS reactions, and to pursue the issue of the balance between the alleviation of CRS and treatment of tumors.

3. Mechanisms

3.1 Molecular Mechanism of CAR-T Therapy for Tumor Treatment

The recognition domain of single-chain variable fragment (scFv) connects to an intracellular signaling module consisting of partial fragments of differentiated CD-3ζ chain clusters, which induces T cell activation upon antigen binding. The two are connected via an extracellular hinge structural domain and a transmembrane structural domain to form a first-generation CAR that is capable of binding antigen on the surface of target cells. Signaling is initiated by phosphorylation of the immune tyrosine activation motif (ITAM), mediated by the lymphocyte-specific protein tyrosine kinase within the cytoplasmic domain of CD-3. Second- and third-generation CARs contain signaling endodomains that mimic the co-stimulation of antigen-presenting cells (APCs) during receptor recognition. Fourth and fifth generation CAR-T cells can induce signaling domains expressing cytokine receptors or inflammatory cytokines [7, 8].

3.2 Cellular Mechanism of CAR-T Therapy for Tumor Treatment

The cellular mechanism of CAR-T therapy for tumor treatment is that tumor cells have tumor-associated antigen (TAA), normal T cells need to rely on T cell receptors to bind to them and recognize tumor cells through MHC molecules, while CAR-T cells rely on the CAR structure, which consists of a co-stimulatory structural domain, an information transduction structural domain, and other parts that can be expressed on the surface of T cells and activate T cells. The CAR structure has a co-stimulatory domain, an information transduction domain, and other parts, and it is a structure that can be expressed on the surface of T cells and activate T cells, that is to say, CAR has the specificity of binding to antigens. In other words, CAR has the specificity to bind to antigens. Thus, CAR-T cells formed through genetic engineering have both the specificity of CAR and the cytotoxicity of T cells. After binding specific TAA, CAR-T cells phosphorylate and kill tumor cells by secreting cytotoxins such as granzymes and perforins [8].

3.3 Mechanism of CAR-T Therapy for ALL

In the treatment of B-ALL, CD-19, CD-22, CD-123, CD-38, etc. are the targets that have shown efficacy in the clinic and have been widely accepted, among which CD-19 is the most widely used target in the treatment of B-ALL at present. Its mechanism of action is to maintain the balance of mature B cells in the peripheral blood by helping B cells differentiate into precursor B cells, so that the B cells can better play their role in recognizing tumor cells and killing them through immune response. Other targets, such as CD-22, is one of the most common alternative targets. Its mechanism of action is to maintain B cell tolerance by mediating the inhibitory signaling of B cells. When B cell inhibition is reduced, its immune effect can be exerted. However, it is worth noting that targets such as CD-19 and CD-22 mostly exert good efficacy only in B-cell lines, which play a good role in the treatment of B-ALL and have poor efficacy in the treatment of T-ALL [9].

3.4 Mechanisms of CAR-T therapy Leading to CRS

Studies have shown that cytokines such as interleukin-6 (IL-6), interleukin-10 (IL-10), and interferon gamma (IFN-γ) may be the core cytokines in the generation of CRS from adverse reactions to CAR-T cell therapy [10]. Among them, the high expression of IL-6 produced by

activated T cells has the potential to trigger vascular leakage and activate complement, coagulation cascade, which leads to disseminated intravascular coagulation and myocardial dysfunction [11]. Classical pro-inflammatory molecules or inflammatory mediators, such as interleukin-1 (IL-1), and the application of IL-1 receptor inhibitors rescued mortality from CRS, suggesting that insufficient inhibition of pro-inflammatory factors can trigger CRS [12]. In addition, macrophage expression may also contribute to the inflammatory response. For example, after CAR-T cell therapy is administered, M1 macrophages are the main source of inducible nitric oxide synthase (iNOS), which causes an imbalance of NO in the body, leading to vascular abnormalities as well as the possibility of hypotension and oxygen imbalance, which is a life-threatening clinical symptom of CRS [13]. Many other pro-inflammatory factors may also contribute to CRS.

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4. Comparison of available therapeutic CRS treatments

In general, most of the symptoms of CRS are self-resolving, but there are still severe CRS symptoms present that may lead to death. Based on a survey of the literature [14–19], four of the most commonly used current drugs for the relief or treatment of CRS were compared in terms of their mechanisms, advantages and disadvantages, and whether they would have an impact on CAR-T therapy for the treatment of tumors (Table 1).

Table 1. Comparison of the current status of common drugs for the treatment of CRS

Treatment	Mechanisms of treatment	dominance	inferior	Implications for Tumor Therapy
Tolizumab	Inhibition of IL-6 receptor exerts anti-CRS effects, blocking membrane binding, blocking soluble IL-6 receptor	Reverses most cases of CRS that do not respond to supportive care	Optimal timing of anticytokine therapy not yet determined	Does not affect CAR-T cell expansion, persistence, or response rates
Glucocorticoids (e.g., Methylprednisolone)	Inhibition of the synthesis of inflammatory mediators (e.g. leukotrienes, etc.), development of inflammatory cell activation	Substitute therapy when tolizumab is not effective	Increased risk of hyperglycemia, muscle weakness and infection	Inhibition of CAR-T cell proliferation and activity
Dexamethasone	Corticosteroids, acting like glucocorticoids	Timely and effective improvement of hypotension for use when CRS symptoms are severe	Less effective in prevention	Some studies point to severe inhibition of therapeutic activity, while others suggest no effect
Anabolic Acid	Antagonizes IL-1 receptor	Good results for refractory CRS	May be due to concomitant hemocytopenia	Limited impact on therapeutic activity

Also, drugs targeting anti-cytokines i.e. cytokines such as IL-6 receptor, IL-1 receptor, IFN-γ blocking antibodies such as cetuximab, and drugs directly targeting T-cells such as anti-thymocyte globulin (ATG), and cyclophosphamide are under development and experimentation [14]. Usually, in the presence of fever and headache due to CRS, considering that the patient is undergoing treatment for a tumor and has an inherent inflammatory response in the body, appropriate measures are not given to the patient, and the patient is generally relied upon for relief by his or her own resistance; however, studies have shown that early recognition and early intervention can help improve outcomes, and studies have shown that the earlier anti-cytokine interventions are used, the more severe CRS-related toxicity will be less likely to occur, while early intervention may also reduce the duration of long-term medication use for CRS [14, 20]. In children, the prolonged inflammatory response may lead to a further

decline in immunity and reduced therapeutic success, making it all the more important to prevent CRS in advance and to intervene with tolizumab at the onset of symptoms.

5. Conclusion

A comparison of the available treatments for CRS shows that most non-self-limiting CRS can be treated with tolizumab, while glucocorticoids or related steroids can be used as alternative therapies to tolizumab but inhibit the proliferation and activity of T cells as well as CAR-T cells. This means that there are few therapies that can be used as substitutes when tolizumab does not work well, and numerous therapies are not yet in the clinic or are not supported by more clinical data. As an oncology patient, especially a pediatric ALL patient, the most important task is to treat the tumor, and tolizumab can be used continuously if there is a severe CRS response. If there is hypotension or hypoxia, oxygen or hyperoxia should be given promptly and combined with a blood pressure-raising drug such as dexamethasone. Most importantly, the occurrence of severe CRS should be prevented at the early stage of tumor treatment with CAR-T therapy, and the drug should be given before it is too late. There is currently less clinical data as well as fewer cases to allow for large-scale experimental data comparisons or multidimensional comparisons of a wider variety of drugs and measures to alleviate or treat CRS. At the same time, most of the data come from adults, and there is not enough research on specific treatments for CRS in children, and many rely on the experience of treating adults to treat children. It is hoped that in the future, more inhibitors of cytokines specific to children will be developed to balance the treatment of tumors and inflammatory environments.

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