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Advances in Car-T Cell Immunotherapy for Malignant Hematologic Diseases

Xinyu Tan

School of Pharmacy, Nanjing University of Chinese Medicine, Nanjing, Jiangsu 210033, China.

Abstract

In recent years, Chimeric antigen receptor T-Cell Immunotherapy (Car-T) has shown strong therapeutic effects in turns of the treatment of hematological malignancies, and has brought hope to patients with advanced and rare malignant tumors. CAR-T cell immunotherapy is mostly aimed at the treatment of various types of leukemia, while in the treatment of MM is still in the exploratory stage, and there are certain differences in the efficacy of different diseases. The CAR-T cell immunotherapy will be more widely used in clinical practice, because CAR-T therapy will continue to optimize the selection of target molecules. In addition, CAR-T therapy will also design safer vectors and apply more gene editing technologies to the treatment of hematologic malignancies. The common adverse reactions include cytokine release syndrome (CRS), targeted/off-target toxicity, and neurotoxicity. The research and development of CAR-T cell immunotherapy has a lot of room for development in the future.

Keywords

CAR-T cell immunotherapy; Hematologic malignancies; Lymphoma; Leukemia; Multiple myeloma.

1. INTRODUCTION

At present, the human body's hematopoietic function is on account of stem cell models, in which a small number of multifunctional hematopoietic stem cells (HSC) enter the blood's different cell lineages through self-renewal and differentiation [1]. This process needs to be strictly controlled to ensure the number of mature stem cells with characteristic functions and avoid depleting the original stem cells [2]. When the body's hematopoietic dysfunction may further lead to the development of hematological malignancies, immature accumulation of blood forms tumor cells in tissues. Recent, the morbidity of hematological malignancies has been increasing, which has severely affected the living and survival quality of patients. In 2019, the American Cancer Society released data showing that there were 176,200 new cases of hematological malignancies and 56,770 deaths [3]. These diseases mainly include malignant lymphoma, various leukemias, and multiple myeloma, and etc. The conventional treatment modes are traditional radiotherapy, chemotherapy and bone marrow (BM) transplantation. However, the traditional treatment model has many problems, such as treatment of pain, adverse reactions, etc. Many treatments can only achieve temporary relief, and the risk of recurrence is still high. These factors are the main reasons for the failure in turns of the therapy that used to cure hematological malignancies [4]. Immunotherapy is used as a means to treat hematological malignancies like chimeric antigen receptor T (CAR-T) cell therapy. Because it can improve the body’s immune ability and attack cancer cell, which has caused people's attention. Nowadays, many effective treatments for hematological malignancies have be founded, the Car-T cell immunotherapy is currently being part of them. The CAR gene is embedded in T lymphocytes through genetic engineering to stimulate autoimmune cells to kill

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cancerous cells . They are considered one of the most promising new tumor therapies, bringing new hope to many cancer patients, especially those with hematological malignancies. In 2017, the CAR-T product targeting CD19 was authorized by the FDA for the rescue therapy of refractory/relapsed acute B lymphocytic leukemia and B-line lymphoma patients under the age of 25. The CAR-T cell immunotherapy is thus Entered a brand new era.

2. OVERVIEW OF THE PRINCIPLES OF CAR-T CELL IMMUNOTHERAPY

CAR-T cell technology, tumor-specific antigens identified by scFv fragments, and molecules involved in T cell activation transmembrane segment consisting of fused [5]. And then this gene fragment is transfected into T cells extracted from the patient's peripheral blood by means of lentiviral or retroviral gene transduction to become CAR-T cells expressing chimeric antigen receptors, and then proliferate to CAR-T cells at a therapeutic concentration return to the patient's body to achieve the anti-cancer effect [6]. The CAR-T cell immunotherapy process mainly includes 4 steps: (1) T cell separation: Collect the peripheral blood of the patient and separate and extract T cells from it. (2) Modification: CAR composed of three parts: extracellular region, transmembrane region and intracellular signal transduction region. It uses CD3ζ and costimulatory molecules for signal transmission and induces activation of T cells, and then uses lentivirus and retroviral systems And so on as a medium to transduce into activated T cells to form CAR-T. (3) Expansion: The modified T cells are expanded in vitro to reach the number of cells required for clinical use. (4) Reinfusion: After quality control, the CAR-T cells that meet the requirements are returned to the patient to inhibit and kill tumor cells [7]. Compared with the traditional T cell immune process, CAR-T cells are unique in that: (1) Recognizing tumor antigens does not require major histocompatibility complex (MHC) restrictions, and can recognize MHC-independent targets [8], which allows CAR-modified T cells to recognize a wider range of targets compared with natural T cells. (2) CAR-T can enhance the lethality of T cell immunity through costimulatory molecular signals, and overcome immune escape that caused by tumor cells down-regulating MHC expression or inhibiting the secretion of costimulatory molecules.

In recent years, CAR-T has undergone changes from the first generation to the fourth generation through the transformation of the intracellular signal area design. The first generation contains only one intracellular signal region. The signal is mainly transmitted through the immunorecepter tyrosine-based activation motif (ITAM) on CD3ζ, and lacks the second signal to promote T cell proliferation. The anti-tumor effect is weak [9]. In the second generation, costimulatory molecules (such as the active domains of CD27, CD28, 4-1BB and OX40 molecules) are connected in series with CD3ζ and integrated into CARR to improve the effect of T cells while achieving self-expansion. The third generation contains 2 costimulatory molecules in the intracellular signal region, which is stronger than the second generation CARR in vivo amplification and cytokine production. The fourth generation is to add selectable marker modification functions on the cell surface, such as encoding IL-12, IL-18, and other anti-tumor cytokine genes. The fourth generation CAR-T has obvious advantage in the termination of T cell expansion.

3. METHOD

The data were collected from many databases, such as Pubmed, Medline, etc. The search keywords are specifically "CAR-T" + "hematologic malignancies", "CAR-T" + "Lymphoma", "CAR-T" + "Leukemia" and "CAR-T" + "Multiple myeloma". We summarized the collected documents and analyzed them further.

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4. RESULTS

4.1. Research on CAR-T Cell Immunotherapy in Lymphoma

Human lymphoma has been divided into NHL and HL. NHL includes a large number of lymphoid malignant tumor B cell, T cell or natural killer cell that expand at different stages of differentiation. The malignant Reed-Sternberg (RS) cell of HL can detect the hematopoietic markers corresponding to the abnormal expression. The difference between HL and NHL is that malignant RS cells are less in the microenvironment and are relatively prominent non-malignant infiltrating cells, which play a crucial part in the treatment of HL[10]. Both HL and NHL occur in lymphoid tissues, so antibodies and cell-based immunotherapy are easily available. T cells targeting B cell lymphomas express tumor-associated antigens that may be co-stimulated. They need to get through the immune checkpoints because B cells have great antigen-presenting function.

In 1989, the concept of CAR was proposed by Gross [11]. They fused the antigen binding region of the antibody scFv with the intracellular part of CD3- ζ chain or Fc ε RI γ to form a chimeric antigen receptor. The CAR of lymphoma is based on scFv, The CAR of lymphoma is based on scFv, and CAR's innate affinity along with the characteristics of the recognized epitope determine its effectiveness to a certain extent [12]. Leukemia has a greater effect than CAR-T cells that recognize distal epitopes and have higher activity [13]. After antigen recognition, T cells receive the transmission signal after the activation of the CAR inner domain. T cell activation depends on the presence of motifs (ITAM) in the cytoplasmic CD3-ζ domain of the phosphorylated TCR complex based on the activation of immunoreceptor tyrosine [14]. For the sake of build up the function and durability of CAR-T cells, co-stimulatory domains (for instance, CD28, OX40 or 4-1BB)were integrated into the second (or even the third generation) CAR, which can ensure that the transgenic T cells are in contact with them. The target is fully activated after specific binding [15-17].

Although it is possible to transiently express CARDNA plasmid or mRNA in T cells by transfecting CAR with naked cells (for example, to safely test its toxicity, because any unfavorable elimination of the transgene, the effect should be reversed). Generally, the goal of the test is for the achievement of the sustained expression thus ensure the durability of the response. Because of the retrovirus production is time-consuming and expensive, especially when it is done under good fabricating practices. Therefore, certain researchers have used non-viral methods for eternal transduction, especially transposon-based transduction systems, which can achieve transgenes, although it may not be effective. In ideal condition, CAR molecules should be transplanted into the collection area which can be transported to the tumor in T cells, subjected to advisable stimulation, and persist in the body.

CAR-T cell is suitable for targeting highly uniformly expressed lineage-specific antigens to eliminate malignant B cells, such as CD19, CD20, etc. But these antigens also have the normal expression of corresponding antigens, and B cell ablation has also become a common side effect. But in general, most of the targets are restricted to lineage-related antigens, such as BCMA [18].

CD19 is expressed in all B cell variation phase apart from both hematopoietic stem cells and plasma cells. Moreover, tumor transformation has occurred in most of them [19]. There are treatment results that show the feasibility of this method for B cell malignant tumors, but there are also certain objective factors, and its anti-tumor effect also has certain problems. The first generation of CAR with a single signal functional site was used in these experiments [20]. The first generation of CAR-T cells which are used in these experiments did not achieve the expected purpose. The results of many experiments showed that stimulating a single area did not fully activate the chimeric T cells. By way of addition, we can find that when host lymphocytes are reduced, it can promote the expansion of subsequent transfer T cells.

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The decrease of lymphocytes creates a certain space for adoptive transfer of cells, which enhances the overall balance of the body. In addition, it also exhausts the usual secretion of inhibitory cytokines that inhibits the expansion of T cells, such as TGF β, IL-10, and etc. [21]. A study have found that after patient with advanced follicular lymphoma received CAR treatment, the patient's tumor is well suppressed, and the transgene can still be detected in the peripheral blood 7 months after the infusion [22].

Many studies have conducted studies on the first-generation CAR-CD20. Among them, patients who had mantle cell lymphoma went to the injection of CD20-specific CAR-modified T cell infusion are least toxicity. The polyclonal activation of T cells, plasmid electroporation, and modified T cells that can last up to 9 weeks in vivo[23]. By exploiting the clonal restriction of mature B-cell malignancies and expressing kappa or lambda light Ig chains, targeting B-cell malignancies may be feasible and more selective. For example, CARs targeting κ light chains should selectively target κ+ lymphoma cells and excess normal B cells to express non-targeted λ light chains to reduce damage to humoral immunity. Studies have shown that NHL/CLL patients have received κ-directed CAR treatment, the infusion is well tolerated, and there are no side effects [24]. The analysis showed that the molecular signal reached a peak 1-2 weeks after infusion and could be detected within 9 months.

4.2. CAR-T Cell Immunotherapy in Leukemia

Leukemias mainly include B-ALL, AML, T cell leukemia, and etc. AML cells express multiple antigens on the cell membrane like CD33, CD34, and etc. According to the clinical observation results of the clinical CART-19 information, it can be inferred that the myeloid should be ablated with powerful CAR T cells targeting CD33. If the anti-CD123 CAR is used, pan-marrow ablation using T cells may occur. Some experimental data proved this prediction [25].

A study found that mice with severe immunodeficiency in non-obese type diabetes are implanted with primary human AML cells. After treatment with CAR-T , AML was eradicated and its hematopoietic function is affected. The main problem was the lack of real AML-specific surface antigen [26]. The use of electroporable "biodegradable" T cell anti-CD123 CAR mRNA to reduce CAR persistence, thus eliminating the risk of bone marrow ablation or endothelial toxicity [27]. The overall verdict of a small number of AML patients receiving CAR-T cell therapy in the world is that anti-AML CAR-T cells have demonstrated narrow activity. Hence, the strategy to trim back CAR T cell activity to potentially improve safety is not clear.

Malignant tumors of normal stem progenitor cells (HSPC) cannot be recognized by CAR T cells because they have the same characteristic antigen. This also directly reduces the incidence of concomitant bone marrow toxicity. But if they are of the same species, the donor hematopoietic stem cells can be redacted so that they lack shared antigens with no significantly impairing their functions, and the "normal" hematopoietic function can be eliminated and restored. Therefore, continuously circulating anti-myeloid CAR-T cells can protect patients from relapse and will not cause bone marrow failure.

The researcher took TKI-resistant, recurrent, and pH-positive ALL patients as the research object, and infused anti-CD19 CAR-T. They found that the number of bone marrow cells in one patient was significantly reduced, and the other patient had MRD [28]. The CLL patients received Cy + Flu chemotherapy first, followed by CD19 CAR-T infusion. As a result, 4 weeks after the infusion, the total remission rate was 71% [29]. According to relevant clinical studies, CD123 CAR-T has significant anti-tumor activity in the treatment of AML [30]. A researcher used B-ML/ALL as the research object and used CD19 to target the third-generation CAR-T therapy for phase I/II clinical trials, and the result was a CR of 86% [31].

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4.3. CAR-T cell Immunotherapy in Multiple Myeloma

MM is a malignant disease that occurs in middle-aged and elderly people and occupies about 10% of hematological malignancies. It is mainly manifested by abnormal clonal plasma cell proliferation. Although the survival rate has been improved with the development of several new drugs recently, there are still many problems in the treatment of MM [32]. The effect of proteasome inhibitor treatment on patients is poor, the overall therapeutic effect of immunomodulatory drugs and anti-CD38 monoclonal antibodies is not very good, and there are fewer treatment options. In recent years, the rapid evolution of CAR T cell therapy makes it promising to turn into an effective method for the treatment of relapse and relapse therapy/refractory MM.

CAR-T cell immunotherapy has not yet approved CAR-T cell therapy for MM. CAR therapies such as BCMA, CD38 and CD138 are being studied in clinical trials. In majority, BCMA is specifically expressed in MM cells, but not in hematopoietic stem and original cells and non-hematopoietic vital organs. It has recently been proved that BCMA is the most promising antigen in CAR-T cells against MM [33]. The current results indicate that BCMA's CAR-T cell therapy is expected to be used for RRMM. However, its long-term efficacy is still unsatisfactory, and most patients will eventually relapse. The main mechanism of recurrence after BCMA CAR-T cell therapy is that low expression of BCMA and insufficient duration of BCMA CAR-T cells in soma. Therefore, researchers are also looking for other target antigen targets.

CD19-directed CAR T cell therapy can be used for acute lymphoblastic leukemia and large cell lymphoma, which has been approved by the US Food and Drug Administration. CD19 does not show high expression in malignant plasma cells, for example, the expression level of CD19 in a small number of myeloma cells may be reduced. It is speculated that such cells can only be targeted for treatments like high-dose chemotherapy after non-CD19 expressing myeloma cells have been reduced, but only moderate clinical activity has been observed [34]. CAR T cell technology based on k light chains has been developed and tested, and some researchers have done some clinical trials [35].

After conventional treatment, due to the existence of residual disease, most MM patients eventually progress to the relapse and refractory stage or even die. As CAR-T technology continuous develop in the field of R/R ALL treatment, its application in MM and solid tumors has also attracted more and more attention from researchers. The CAR-T target antigen must be expressed on tumor cells, but not expressed on normal cells or expressed at a low level. There are many potential antigens of CAR-T screened for the therapy of MM, mainly including B cell maturation antigen (BCMA), CD19, compound CAR-T, and etc. The current clinical trials mostly use BCMA as an immune target, and on the basis of some studies, dual-target CAR-T cells are more tumor-killing than single-target CAR-T cells [36].

4.4. Toxic Side Effects and Technical Shortcomings

Cytokine Releases Syndrome, (CRS) is part of side effects of CAR-T cell technology in clinical application . The main reason is that CAR-T cell technology eliminates many cancer cells in a short time and produces a large number of cells. Factor, which causes an immune response. At the same time, the release of cytokines caused by the massive proliferation of T cells causes the body to develop symptoms such as fever, myalgia, hypotension, and respiratory failure, which can be life-threatening in severe cases. Studies have observed that CRS is related to disease progression or tumor burden, and patients with high disease burden often have higher cytokine release. In general, the second and third generation CARs are more likely to touch autoantigens and cause lethal CRS. In addition, the use of IL-6 receptor antagonist drug tocilizumab (tocilizumab) and hormone prevention can alleviate the symptoms [37]. It should be noted that hormone shocks will reduce the efficacy of CAR-T.

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Most of the toxic factors of CAR-T treatment are the "off-target" phenomenon of tumor-associated antigen-specific T cells, which leads to the recognition of self-antigens lowly expressed in normal tissues of the body, and then causes toxic side effects, such as hypogammaglobulinemia caused by CD19 molecules in the treatment of B cell hematological diseases. This is also an indirect evidence of the adoptive follow-up response of CAR-T cells. In addition, 5%-10% of patients still lack CD19 antigen in treatment, thus evading the recognition and killing of CD19-CAR-T cells, leading to missed targets. In addition, CAR-T cell therapy targeting Her-2 can cause attacks on other tissues or organs other than the tumor site, such as possible cardiopulmonary system poisonousness.

Use CAR-T to treat leukemia may result in neurological symptoms. These symptoms are diverse, for example, movement disorder, hepatic encephalopathy, delirium, speech disorder, etc. Some symptoms can subside spontaneously. CAR-T can also cause the body's risk of autoimmune diseases. In children with CAR-T treatment, some studies have observed macrophage activation syndrome [38]. CAR-T requires individualized treatment for each patient, so there are problems such as high treatment prices, uncertain efficacy and instability. The results of various centers of CAR-T clinical trials are inconsistent, and standardized treatment needs to be further established. Recurrence after CAR-T treatment also needs attention, and its long-term efficacy and safety need to be further studied.

5. DISCUSSION

CAR-T cell technology may be the fastest technology from laboratory to clinical application, greatly promoting the development of translational medicine. Compared with chemotherapeutic drugs and targeted drugs, CAR-T is more targeted and can be modified to achieve multiple targets. The multiple advantages of immune targeted therapy help treat some rare tumors with very poor prognosis. We have reason to believe that with the maturity of future technology, the further improvement of CAR components and the gradual decline of treatment costs, CAR-T cell technology is likely to become a routine treatment method in hospitals and outpatient clinics. Moreover, CAR research is not limited to tumors. In the current bottleneck in the therapy of refractory diseases, CAR-T cell technology may be an effective weapon for us to overcome refractory diseases, such as anti-HIV and other virus treatment research.

The upgrading of CAR-T cell technology has been in continuous research and development, and the advancement of each component may bring more clinical benefits. The rapid development of biotechnology in recent years is also the driving force for the maturity of CAR-T cell technology. As the future of tumor treatment is bound to be built on the idea of immunotherapy-based combination therapy, it is believed that more biotechnology will be invested in the research and development of tumor immunotherapy. The research and development of CAR-T may solve the problem of large-scale clinical application. Knocking out the endogenous TCR gene of T cells derived from normal third-party cells, exclude pathogens caused by allogeneic TCR, and improve the tumor-killing efficiency of CAR-T. CAR-T (ENG-CAR-T) cells that produce bispecific adaptor molecules have stronger and longer lasting anti-tumor effects. The multi-target CAR-T cell technology has shown stronger anti-tumor effects in preclinical experiments.

Since most pre-clinical models use immunodeficient animals and cannot fully verify the interaction between immune cells, the toxicity that appears in clinical trials is sometimes safe in actual treatment. There is still much work to be done in terms of potentially life-threatening cytokine release syndrome and neurotoxicity, and high treatment costs. In clinical treatment, CAR-T treatment is highly personalized and highly professional. It requires nursing staff to be familiar with the indications, toxicity, and limitations of these treatment options, and when to

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consider patient referral. In addition, combination strategies, bispecific and multispecific CAR-T cell therapy and tunable CAR are under development to improve the effectiveness and safety of the therapy. If the prospects of CAR-T cell technology are recognized, it may change the treatment and prognosis of relapsed/refractory aggressive lymphoma in the future.

6. CONCLUSION

So far, car-T technology has been developed into the fourth generation technology for more than 30 years, during which time it has experienced a lot of affirmation and also experienced a lot of doubts. As an epoch-making immunotherapy, with the continuous development and maturity of technology and continuous breakthroughs in medical treatment, CAR-T technology will eventually bring more patients good news.

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