

CAR-T Therapy: A Promising Cancer Treatment

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Abstract. CAR-T therapy is a new clinical treatment option. It is the focus of an increasing number of researches, all of which suggested that it has a beneficial therapeutic effect on a variety of diseases, especially blood cancer. In this paper, clinic applications of CAR-T therapy for many diseases are listed, including B-cell acute lymphoblastic leukemia, Hepatitis B, and Human Immunodeficiency Virus. The differences between CAR-T therapy and other cancer treatments like tumor-infiltrating lymphocyte and T cell receptor therapy were discussed, standard biological medicines, and antibody-mediated anti-cancer drugs. The study also looks at the limitations and side-effects of CAR-T therapy, such as toxicity, and missing the target. The disadvantages, constraints, and options for improvement were also discussed in the paper. To summarize, CAR-T therapy has a good therapeutic function on some illnesses, although it is still in the experimental stage and is not commonly used in the clinic. In the near future, CAR-T therapy is likely to be used in a rising range of therapeutic therapies. In general, this paper can help get a better knowledge of CAR-T treatment, as well as a more exact comprehension of its future evolution.

Keywords: Cancer, CAR-T, Blood Cancer, Clinical Application.

1. Introduction

Chimeric antigen receptor T cell therapy, CAR-T therapy, is a breathing new weapon into the fight against cancer, primarily based on the fact that some specific tumor cells tend to overexpress certain antigens and CAR-T therapy makes it available to exploit these engines and use them to attack cancer.

CAR is a cell surface receptor that can recognize specific proteins (antigens), which are composed of parts of other receptors (chimeras). CAR receptor is made up of three primary components: the extracellular region, the transmembrane region, and the intracellular region. They are made up of antibodies with single-chain fragment variable (scFv) chains that are incorporated with T cell surface receptors on the T cell. The extracellular part of the scFv detects and binds the target antigen; the transmembrane region is the hinge or spacer area that secures the scFv to the cell membrane; the intracellular signaling domain includes co-stimulatory factors and the CD3 signaling domain. A stimulatory signal is created to the intracellular signaling domain when the antigen is identified and bound, and the T cell is activated and performs its effector function [1-3].

When it comes to CAR-T therapy, T cells from a patient's own immune system are extracted, grown, and engineered in vitro to equip them with molecules that allow them to recognize and attack specific cancer cells [4,5]. The engineered T cells are then injected back into the patient's body, where they respond to the cancer cells to destroy it [5]. And therefore, instead of only killing tumor cells with high expression of cell surface antigen, like antibody-mediated anti-tumor drugs, CAR-T cells effectively kill tumor cells with low expression of cell surface antigen at a deeper level. In addition, CAR-T is an alive drug, which will be greatly expanded in the body during the treatment of patients. Compared with traditional biological drugs, CAR-T therapy has the advantages of rapid response, high response rate, and long response time [2,4-6].

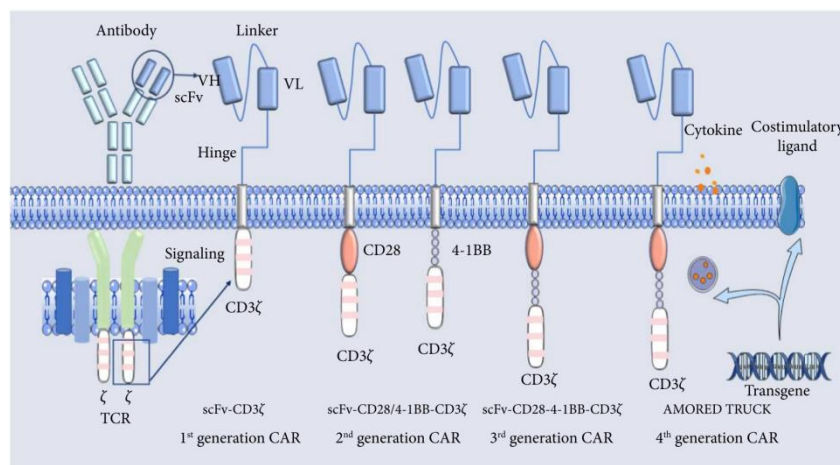


Figure 1. The first four generations of CAR-T are already in use or undergoing clinical trials [7].

With the development of technology, CAR-T therapy has developed to the fourth generation, as figure 1 can show, and it is expected to progress to the fifth generation, which is supposed to break through individual limitations and be used across individuals for large-scale production and treatment [5]. However, there is also something that needs to be improved. The first thing is its limitations. So far, it has only been used to treat blood cancers [2,7], and trials have shown little influence on solid cancers [1,7]. Besides, side effects can come on suddenly and strongly. And when the side effects happen, failure to recognize the signs or react appropriately could prove fatal.

In this paper, we list the clinical application of CAR-T therapy in the treatment of blood cancer diseases, summarize the advantages of CAR-T therapy compared to other cancer treatments, and expound on the limitations and side effects of CAR-T therapy. Given these constraints, we eagerly await the advancement of CAR-T therapy approaches and provide our recommendations for improvement.

2. Clinical application of CAR-T therapy

Although CAR-T therapy is not extensively utilized in clinical practice at the moment, studies have demonstrated that it is beneficial in treating specific malignancies. Actually, it can treat particular cancers. Acute lymphocyte leukemia, B cell non-Hodgkin lymphoma, and multiple myeloma tumors are among the hematological malignancies to which it is now addressed. Treatment for AIDS and HBV has a therapeutic impact as well.

2.1. B-cell acute lymphoblastic leukemia (B-ALL)

It was around a decade ago when the safety and efficacy of CAR-T therapy for B cell malignancies (primarily B cell lymphoma, leukemia, and B-ALL) was first documented [8]. Shortly after, a number of reports were published claiming that CAR-T constructs directed by Cluster of Differentiation (CD) 19 had achieved significant and unprecedented results in the treatment of relapsed or refractory B-ALL, including patients who had relapsed after hepatic stellate cell transplantation (HSCT). In these studies, full remission was reported in 70-97 percent of individuals expected to have a disappointing outcome [9]. CAR-T cell treatment is a bridge to HSCT for many people [10].

Another remarkable clinical outcome was reported around the same time in patients undergoing CD19-directed CAR-T therapy, which is the most common treatment for non-Hodgkin lymphoma and diffuse large B cell lymphoma in the context of recurrent and refractory illnesses. Patients had relapsed following a previous autotransplant included in the study. These patients would be inadequately treated if they didn't have access to a typical salvage chemotherapy regimen. According to subsequent reports, 33-57 percent of patients were in total remission, with the majority of them having maintained complete remission and long-term follow-up [11]. As previously stated, prior to lymphoid loss, CD19-directed CAR-T-cell treatment generates an environment permissive to T cell

multiplication. Even in people who have never taken these drugs previously, lymphoblastic chemotherapy is expected to contribute little to tumor control in this scenario [10].

The Food and Drug Administration (FDA) authorized the first CAR-T treatment, tisagenlecleucel T, for pediatric and young people (up until age 25) with B-ALL in August 2017 based on early findings from a phase 2 multicenter study. In 75 children and young adults, this crucial investigation revealed a 60 percent complete remission rate and an 81 percent overall response rate (ORR). Furthermore, responses were long-lasting, with a relapse-free survival (RFS) rate of 80 percent after six months. Longer identification of CAR-T cells in peripheral blood mononuclear cells (median of 168 days) and extended B-cell aplasia were linked to sustained remissions.

The first CAR-T cell treatment for lymphoma (axicabtagene ciloleucel) was approved in October 2017 based on the results of the scoping multicenter ZUMA-1 trial. After an average follow-up of 27.1 months, 101 individuals with refractory aggressive lymphomas had an 83 percent ORR and a 58 percent complete response (CR), with 39 percent having continued responses.

2.2. Hepatitis B (HBV)

CAR-T therapy appears to be safe in individuals with HBV when combined with targeted antiviral therapy such as entecavir, according to available data. HBV reactivations, including fulminant hepatitis and death, have all been documented in patients who stopped taking entecavir.

There were no significant differences in toxicity or responsiveness to CAR-T therapy between HBV and non-HBV populations. Three patients with concurrent B-ALL and HBV were discovered in a retrospective cohort study conducted in China. All of the patients had chronic HBV and were taking antiviral medication to treat it. During the follow-up period, no patient suffered HBV reactivation. They examined the impact of HBV positivity on the anti-tumor performance of generated CAR-T cells using ex-vivo and in-vitro models, finding that both were effectively successful in eradicating tumors [12]. During treatment, the two HBV patients were given antiviral prophylaxis. During CAR-T therapy, no patient had fulminant hepatitis, and all three had viral control and normal liver function tests. However, one patient had viral reactivation 13 months after stopping his prophylaxis, indicating the relevance of CAR-T therapy in immunological compromise [13].

2.3. Human Immunodeficiency Virus (HIV)

CAR-T therapy can also treat HIV patients. It was utilized to treat two individuals with AIDS-related B-cell lymphoma at Massachusetts General Hospital [14]. At the time of the final follow-up, the first participant had received CAR-T therapy and was in full remission from lymphoma. He was on antiretroviral therapy (ART) with an undetected viral load and was in complete remission of his lymphoma. The second patient had HIV under control on ART at the time of his cancer diagnosis, and he had CAR-T therapy successfully with no serious adverse events. Intriguingly, retroviruses (including lentiviruses) are employed in the manufacture of CAR-T cells for gene transfer, leading to retrovirus components remaining in the injected CAR-T cell output. As a result, false-positive HIV nucleic acid testing has been reported on people who have received such goods. Although the retrovirus is replication-incompetent and hence unable to produce new retrovirus, the consequences of a false positive test can result in delays in cancer treatment and unnecessary stress for families. These case reports demonstrate that CAR-T products can be generated despite active viral infection, that they can be given safely with antiviral medication, and that they can elicit a long-lasting remission without dramatically increasing toxicity in patients with blood-borne viruses [13].

In addition to cancer, CAR-T therapy can be utilized to cure a range of disorders. However, according to recent studies, CAR-T therapy in the therapy of some diseases is sometimes poor and even fails to produce satisfying outcomes. The specifics are covered in a later section of this article.

3. Advantages

CAR-T treatment is accomplished by three basic stages, as seen shown in Figure 2. One of the processes in the extraction of T cells for in vitro growth makes it considerably specific [5,15,16].

In detail, the process of creating automotive T cells begins with the isolation of T cells from the patient. T cells are filtered and isolated from the patient's blood. These T cells from the patient are taken directly to the lab where they are placed in culture and grown with the chimeric antigen receptors they have been trained to recognize. Once the vehicle has genetically modified the budding T cells, they are reinfused into the patient, a process much like a typical blood transfusion. As they re-enter the patient's bloodstream, new and improved automated T cells leap into action. These genetically modified T cells can now search for and destroy the engines they are trying to exploit. The hope is that auto-t therapy makes it impossible for cancer cells to evade detection. And these patients will experience complete remission, long-term remission [2,5,15,16].

In this process, equipping T cells with molecules that recognize specific cancer cells, similar to special detectors, is one of the secrets of CAR-T treatment. These altered T cells, known as CAR-T cells, travel through the body, and when the detector detects a certain signal on the surface of another cell, it activates the CAR-T cells and assaults it, destroying it as an enemy. Engineered CAR-T cells cannot determine if an opponent is malignant or not. They can instead tell whether there is a signal to kill it and if there is no signal to not attack. If a normal cell has the same chemical, T cells will assault indiscriminately until the cell is killed with hazardous side effects. As a result, the specificity of this signaling molecule is critical. This will be the case with the following system, allowing the patient's own T cells to more efficiently search out and destroy cancer cells.

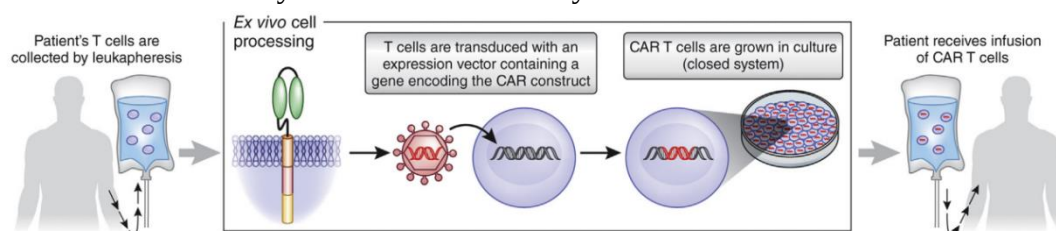


Figure 2. CAR-T treatment process [17]

And therefore, CAR-T cells have a unique specificity for eradicating cancer cells that have the matching TAAs as compared to regular adaptive immune cells [5,15]. This technique will help to prevent the unwanted destruction of healthy tissues to some extent. Furthermore, CAR-T cells can detect cell surface molecules even when HLA expression is absent. It has an advantage over the prior method in that malignancies frequently avoid T cell immune surveillance by concealing HLA or other antigen processing and presentation components. Moreover, the flexibility of CAR's intracellular signaling domain can counteract cancer cells' direct or indirect downregulation of co-stimulatory molecules. CAR-T cells, for example, can identify practically all types of possible antigens, including carbohydrate, lipid, and protein antigens that may be bound precisely by antibodies [2,4,5,18].

Yet, other benefits will be shown by comparing other therapies.

3.1. Compared with traditional treatment

Currently, there are three main traditional treatment modalities used in clinical practice, chemotherapy, radiotherapy, and surgery. Since the difference between cancer cells and normal cells is whether cell division is controllable, before understanding these three treatment modalities, understanding the lifecycle of cells in detail is important. If cancer cells are not directly moved out of the body through surgery, they have to be killed, which must require operation in the life cycle of the cells [19].

3.1.1 Chemotherapy

Chemotherapy refers to the treatment of cancer by chemical drugs. They destroy cancer cells by acting on them only at one specified moment. For instance, some medications are more effective

against S-stage cancer cells than others, so after chemotherapy, there are still some G0 phase (resting phase) cancer cells in the body, which will re-enter the G1 phase and start a new cycle after being stimulated by external signals, leaving the root of cancer recurrence. Moreover, chemotherapy is not ideal for slow-growing tumors: most of these tumor cells are in the resting stage and are not sensitive to chemotherapy drugs. In addition to this, the resistance of cancer cells - especially multidrug resistance - limits the use of chemotherapeutic drugs. Multidrug resistance means that cancer cells, after being exposed to one anticancer drug, will develop resistance to multiple other anticancer drugs with different structures and different mechanisms of action, which is the main reason for the failure of chemotherapy [2,19].

CAR-T cells target cancer cells not only because they are cancer cells, but also because CAR-T cell treatment is a targeted therapy. Furthermore, CAR-T cells may selectively identify cancer cells for a precise attack, based on their specificity: whether they acknowledge the signal or not, considerably boosting the potential to destroy cancer cells. As a result, CAR-T therapy is regarded as a highly effective anti-tumor treatment. CAR-T cells have emerged as one of the most important new cancer research targets in recent years. Many traditional chemotherapy treatments were also transformed as a result of this breakthrough [5-7,19].

3.1.2 Radiation therapy

Radiation therapy is a type of cancer treatment that uses high-energy radiation to destroy cancer cells. However, for slow-growing tumors, in which there may be a large number of cells in the resting phase, the dose of radiation is required, but too high may cause more damage to normal cells, and too low a dose may allow cancer cells to remain and tumors to recur [19].

Based on the selectivity of CAR-T, the risk of mistakenly killing normal cells owing to misinterpreting the erroneous signal is still low when compared to radiation. Besides, radiation exposure is one of the causes of mutations in several cancer-causing genes. When radiation goes through your body, it endangers the organism's normal cells. CAR-T therapy reduces this risk by gathering T cells from the patient's blood and growing them for infusing back into the patient, lowering the risk of other normal cells developing cancerous. [18].

3.1.3 Surgical treatment

Direct removal of tumors using surgery is also a common modality in cancer treatment. But the surgical treatment does not apply to all cancer patients. Undergoing surgery can cause some trauma to the body and lower one's immunity. Whether the patient's physical condition can withstand the surgery is a factor that must be considered. In addition, there is a great risk of performing surgery on tumors in sensitive areas (e.g., brain tumors). Moreover, surgery is a local treatment method and has little effect on leukemia patients or patients whose cancer cells have spread [19].

However, in the case of CAR-T treatment, CAR-T cells can migrate throughout the body via the blood, which is efficient for spreading cancer-like disorders [2,10,23-24]. Besides, CAR-T cells can live in the human body for more than ten years, reducing the likelihood of cancer recurrence. Furthermore, because CAR-T treatment is based on the patient's own T cells, the trained T cells are returned to the patient with little immunological rejection, which not only decreases the chance of reducing the patient's resistance but also eliminates the stress caused by surgery [2,4,21-22].

3.2. Tumor-infiltrating lymphocyte (TIL) and T cell receptor (TCR)

In malignant melanoma and renal cell carcinoma, TIL is a commonly used adoptive cell transfer (ACT) treatment [21]. TIL is lymphocytes infiltrated in the tumor, isolated and amplified in vitro by IL-2 and other factors, and finally reinfused into the patient [22,23]. However, in most cases that we mentioned below, TIL cannot be applied [21-23]:

Some patients lack tumor specimens or have few TIL in tumors and metastases.

It is difficult to obtain fresh tumor tissues and isolate and expand TIL; the returned TIL cells are functionally impaired and often cannot effectively recognize tumor cells in vivo.

The strong immunosuppressive microenvironment in tumors reduces the killing ability of the returned cells.

These issues restrict the general use of TIL, which is successful in just a few malignancies, including malignant melanoma and renal cell carcinoma, and ineffective in the majority of tumors.

In such cases, ACT requires the use of peripheral blood lymphocytes. Current ACTs using peripheral blood lymphocytes include lymphokine-activated killer cells (LAK), cytokine-induced killers (CIK), dendritic cells-cytokine-induced killers (DC-CIK), anti-CD3 antibody-induced activated killer cells (CD3-AK cells), etc [20,22].

However, CIK and other non-specific activated lymphocytes lack tumor-specific response-ability. In this situation, scientists have started to introduce T cell receptor (TCR) or CAR genes that recognize tumor antigens into lymphocytes through genetic modification to make them TCR gene-modified T lymphocytes (TCR-T) or CAR-T cells with tumor antigen targeting recognition ability [22,24,25].

Overall, the current CAR-T has advantages over TIL and TCR in terms of principle, structure, and production process [26].

(1) CAR-T cell treatment takes less time to administer. CAR-T takes the least amount of time to develop T cells since it requires fewer cells to get the same therapeutic effect. The in vitro culture cycle is cut in half to two weeks, saving time.

(2) CAR-T cells are not constrained by MHC, which is the particular recognition of antigen and antibody, and may thus destroy tumor cells with antigen specificity more efficiently. TIL and TCR, on the other hand, can only identify MHC-presented antigens, which may avoid immune surveillance owing to tumor cells down-regulating or changing their MHC molecules, and have specific clinical limitations.

(3) CAR may identify not only peptide antigens but also glycans and glycolipid antigens, therefore broadening the range of tumor antigen targets. CAR-T cell treatment is not limited by tumor cell protein antigens since it is not constrained by MHC. CAR-T may recognize antigens in various dimensions and can use the glycolipid non-protein antigens of tumor cells.

(4) CAR-T cells have an immunological memory function and can live in the body for an extended period of time. This is therapeutically significant for preventing tumor recurrence.

(5) TIL and TCR-T employ doses that are 2--3 orders of magnitude lower than CAR-T cell treatment. Because CAR-T cells recognize tumor surface antigens with great specificity and overcome MHC limitations, the number of cells infused in a single session of CAR-T cell treatment (10 - 100 million) is significantly smaller than TCR-T (1 - 10 billion) and TIL (10 - 150 billion) with the same therapeutic efficacy.

(6) CAR-T has certain broad-spectrum replicability. Since certain loci are expressed in a variety of tumor cells, such as EGFR, CAR genes targeting such antigens can be widely utilized once they are constructed.

4. Limitations of CAR-T therapy

It is believed that CAR-T therapy has broad development prospects as one of the most promising tumor treatments, but this therapeutic method still has some limitations and side effects in the clinic.

4.1. Cytokine-release syndrome

Cytokine release syndrome (CRS) refers to a cellular chain reaction caused by the release of abundant cytokines during the interaction between immune cells and tumor cells. It can cause inflammation and high fever. In severe cases, it can lead to hemodynamic instability, capillary leakage, and multiple organ failure [27]. Most cancer immunotherapies are accompanied by cytokine release syndrome, as to one

of the cellular immunotherapies, CAR-T therapy will lead to fever, discomfort, and vomiting. Cytokine release syndrome is often accompanied by high levels of IL-6 secretion and leads to

macrophage activation syndrome. The study of Alexandre v. Hirayama [28] showed that IL-1 would release before IL-6 to trigger CRS in some cases.

4.2. CAR-T cell-associated encephalopathy syndrome

Side effects of CAR-T cell immunotherapy include neurotoxicity, which can cause neurological problems. In case of confusion or mental disorder, the patient is always difficult to understand what others said. The study of GUST [29] found that in patients with severe neurotoxicity, there were phenomena such as disseminated vascular coagulation, capillary leakage, and increased permeability of the blood-brain barrier. In addition, compared with normal cases, the protein level in cerebrospinal fluid of patients with CAR-T therapy associated encephalopathy syndrome (CRES) is usually increased, which proves that there was the destruction of the blood-brain barrier (BBB) [29].

4.3. Off-target toxicity

When CAR-T therapy attacked tumor cells, it may attack other normal cells uncontrollably, which was what we called the "off-target effect". The off-target effect of CAR-T therapy is that the target antigen targeted by CAR is not unique to tumor cells and is expressed in normal cells. Therefore, CAR-T cells with a strong affinity for the target antigen will attack normal tissues and cause tissue damage while clearing tumors. In a clinical trial of CAR-T cell products targeting carbonic anhydrase IX (CAIX), several patients with renal cell carcinoma had abnormal liver enzymes. These adverse reactions were caused by the infiltration of CAR-T cells into the bile duct epithelium expressing CAIX, and then the patients were prevented by using an anti-CAIX monoclonal antibody, which provided strong evidence of off-target toxicity [30].

4.4. Other limitations

At present, there are many obstacles to extending the application of CAR-T therapy to other cancers except blood cancer. The development of effective CAR-T therapy for the treatment of solid tumors is facing a series of unique challenges. Inherent tumor heterogeneity is a key issue. This trait hinders the identification of effective targets, and the related antigen loss is the key factor hindering remission. In addition, some clinical data showed that many patients had a short remission period or face the risk of recurrence due to poor persistence of CAR-T cells and/or strong CAR-T resistance caused by antigen loss or regulation. This poses a certain threat to the long-term stable role of CAR-T therapy and the complete eradication of cancer.

5. Improving CAR-T therapy effect

Although CAR-T therapy still has many limitations and deficiencies, as a new cell therapy for cancer, it is considered by many researchers as one of the most promising tumor treatment methods. In recent years, except for leukemia and Hodgkin's lymphoma, CAR-T therapy was also expected to be used in the treatment of solid tumors, autoimmune diseases, and so on. Scientists are also committed to developing new improvement measures for CAR-T therapy.

5.1. Universal CAR-T cells

In order to achieve CAR-T treatment, patients need to meet the standards of receiving CAR-T treatment. For example, CAR-T cell products can be successfully produced and re-fused into patients and CAR-T cells can effectively mediate cytotoxic reactions in vivo. Obtaining T cells from healthy donors to produce allogeneic CAR-T cells is a potential method to solve the quality problem of CAR-T cells. Several companies began to develop this kind of "Generic CAR-T cells" therapy and began to avoid the delay and cost of autologous CAR-T cell collection and manufacture as well as the use of T-cells [31] derived from potentially malfunctioning patients. However, such products may require additional genetic modifications to limit CAR-T cell rejection and/or graft-versus-host disease.

5.2. Further optimize the design of CAR-T cells

With the development of molecular biology, gene-editing technology- the CRISPR / Cas9 system became a promising tool to solve some CAR-T treatment obstacles. By modifying CAR expression and other cellular pathways using CRISPR/Cas9 technologies, antitumor function and persistence of CAR-T cells can be improved in the immunosuppressive tumor microenvironment. With the application of CRISPR / Cas9 gene-editing technology, the antitumor activities of CAR-T and TCR-T cells have been greatly improved. Compared with traditional commercial products of CAR-T cell by transcription activator-like effector nucleases (TALENs) and zinc-finger nucleases (ZFNs), those created by CRISPR / Cas9 are more natural, and efficient, and have fewer side effects [32].

5.3. "Logic gating" conditional expression system

A synthetic biology model is used to increase the specificity of CAR-T cells to tumor cells detected by various antigens to overcome the absence of tumor-specific antigens. The synthesis system includes the use of a synthetic Notch receptor (synaptic receptor) to recognize TAA. Its activation can encode a specific target of the second TAA and induce the expression of the vehicle including the T cell activation domain. The simultaneous presence of two cell surface antigens is required for CAR-T cell activation. Expression of vehicle targeting specific TAA depends on activation of other transgenic TAA receptors (e.g., scintillator receptors), and multiple TAA must be coupled to complete CAR-T cell activation is also induced by factors associated with the tumor microenvironment (TME) such as hypoxia (hypoxia-inducible factor, HIF). This method prevents cart - T cells from attacking normal cells in vivo and increasing recognition specificity.

5.4. Dual target CAR-T

The traditional and most widely used CAR-T therapy is for single antigens, such as CD19-CAR-T therapy. Resistance to CD19-directed CAR-T therapy is a common occurrence as a result of CD19 surface antigen loss (as a result of various molecular changes in the CD19 gene). To solve this problem, an alternative CAR with scFv identifying CD20, CD22, kappa light chain, and ror1 has been developed and is at various stages of clinical and clinical development. Simultaneously, dual-specific CAR-T cells targeting two surface antigens now have the ability to inhibit drug resistance through antigen avoidance. Clinical research on these treatments is being carried out actively. At the 2020 European Society of medical oncology virtual conference (ESMO 2020), the clinical research data of a bispecific CAR-T product AUTO3 was published for recurrent/refractory diffuse large B-cell lymphoma (DLBCL). AUTO3 is a new dual-target CAR-T cell product. Compared with traditional CD19-CAR-T cell products, AUTO3 also has a CD22 target. AUTO3 has positive safety and effectiveness, and can effectively reduce the tumor recurrence rate of patients.

In order to solve the problem of antigen escape in acute lymphoblastic leukemia (ALL), researchers at Los Angeles children's Hospital designed a CAR that can simultaneously target CD19 / CD20 / CD22 proteins on leukemia cells. This study found that CD19 / 20 / 22 CAR-T cells took longer to find and kill the first target cell than CD19-CAR-T cells. However, after that, the time to identify and kill the second and third target cells was significantly shortened, because CD19 / 20 / 22 CAR-T cells could more effectively induce the apoptosis of cancer cells [33].

In addition, other dual target CAR-T cell products targeting CD116 / CD131 [34] or CD33 / CD3 [35] are also considered to have good therapeutic prospects.

5.5. Combination therapy

Many clinical studies are evaluating combinations of CAR-T cell therapies tried with many potential additives or synergistic agents. These drugs increase the antitumor activity of CAR-T cells and reduce T cell depletion or decrease toxicity. The most important is the use of CAR-T in combination with checkpoint inhibitors, immunomodulators, and Bruton tyrosine kinase (Btk) inhibitors. Disruption of PD-1 / PD-L1 immune checkpoint by PD-1 and PD-L1 inhibitors demonstrated activity in many types of malignant tumors, including Hodgkin's lymphoma. The use

of a checkpoint inhibitor by CAR-T therapy reduces CAR-T cell depletion and promotes a stronger antitumor response. In addition to the immunological checkpoint blocker, they can also be used in combination with cytokine antibodies such as IL-6 or IL-1 monoclonal antibodies. Studies [36] showed that these antibodies can effectively reduce the risk of CRS and CRES.

6. Conclusion

CAR-T therapy is a new type of targeted therapy, which is very promising in cancer treatment. At present, CAR-T therapy is mainly used in hematological malignancies in clinical practice, such as acute lymphoblastic leukemia, B-cell non-Hodgkin's lymphoma, and multiple myeloma; It is also reported to be effective in the treatment of AIDS and hepatitis B (HBV).

As a new type of cellular immunotherapy, CAR CAR-T treatment has many advantages over traditional cancer treatment, such as stronger specificity, higher efficiency, faster onset time, and so on. Compared with chemotherapy and radiotherapy, CAR-T therapy takes less time, and T cells have immune memory function so they can survive for a long time in vivo, which reduces the risk of recurrence to a certain extent.

Although CAR-T therapy is not widely used in clinical treatment and has some side effects of cytokine release syndrome, neurotoxicity, etc. etc. at At present, as an effective cellular immunotherapy for cancer, CAR-T treatment shows broad prospects and is wide concern by scientists. They did research and make improvements to the limitations of CAR-T therapy. This kind of treatment will be safer and more efficient in the field of multi-target CAR-T therapy, combined precision therapy, and universal CAR-T cells in the next 5-10 years. With the continuous improvement of CAR-T therapy and the practice of combination therapy with other cancer treatments, CAR-T therapy will play a greater role in the treatment of hematoma, and it will occupy a more important position in the treatment of solid tumors in the future.

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