

CAR-T cell therapy in part of the B cell hematological malignancies

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Abstract. Chimeric antigen receptor T-cell immunotherapy, more often known as CAR-T cell treatment, has emerged as one of the most promising immunotherapies in nowadays. This treatment uses the patient's own immune cells in an effort to eradicate cancerous cells. Since it was discovered, people have begun to create as many possibilities as they can for CAR-T cells from various perspectives, such as the treatment of specific diseases or a wide range of targets. The first CAR-T cell treatment, CD19-targeting, is still the most widely utilized kind of CAR-T cell therapy that is commercially available, and it continues to play an essential role. Since multi-targeting CAR-T cells are able to focus on a variety of targets at the same time, they are able to effectively block immunological escape by tumor cells. However, this also raises the likelihood that a cytokine storm may occur. The effectiveness of treating non-lymphoma, Hodgkin's and multiple myeloma with BCMA targeting CAR-T cells has been proven by massive clinical trials. The goal of this review is to summarize and analyze the research that has already been done on the typical CAR-T cell treatment and some of the B cell hematological malignancies that they are effective against in most cases.

Keywords: CAR-T Cell, Immunotherapy, B Cell Hematological Malignancies.

1. Introduction

Cancer is one of the most mysterious diseases that affects people the most. From the International Agency for Research on Cancer's 2020 global cancer dataset, there are about 10 million people died of cancer [1]. Despite the surgery and chemotherapy that aim to directly eliminate cancer cells, immunotherapy has become one of the most reliable treatments for patients. Immunotherapy focuses on strengthening the immune system while also reminding it to correct errors, such as letting go of malignant cells. By strengthening the immune system with the help of medicines and techniques, the body can kill the cancer cells itself. There are basically five types of immunotherapy: checkpoint inhibitors, cytokines, vaccines, monoclonal antibodies (MABs) that were made of artificial hybridoma, and CAR-T treatment.

The discovery of CAR-T treatment gave people that suffer with relapsed and refractory malignant tumors a greater possibility of living. The precursor is a T cell, a member of the adaptive immune system. It starts growing in the hemopoietic stems, then the ancestral cells of T cells move to the thymus and finish their growth there. T-cells often first build connections with the target cells, then start dividing and releasing proteins that point at dissolving or breaking down the target cells, and finally finish their work and leave. The procedure of CAR-T treatment is quite straightforward. The doctor will have to estimate whether the patient qualifies for it first. The next step is to activate the T cells after they have been isolated from the patient's blood. Later on, through the process of gene editing, particular antigen receptors can be added to the original T cells, transforming them into CAR-T cells. After that, culture the CAR-T cells in the lab. The dose of cells is often decided by the weight of the patient and the length of time of the therapy, generally 10 million to 1 billion units. Before sending CAR-T cells back to the body, the patient needs to experience a tiny chemotherapy aimed at eliminating the lymphoma cells, which leaves space for the CAR-T cells to divide inside their body and reduce the tumor burden. While meeting the specific target antigen, CAR-T cells would first combine with it and then kill it. With different targets, the CAR-T cell therapy can be targeted toward a variety of cancers.

This review seeks to summarize and evaluate the existing research on the several typical targets of CAR-T treatment for B cell hematological malignancies for which they are effective in the majority of cases.

2. The structure of the new thretment

All of the CAR-T cells started to have similar structures. With the help of single chain variable fragment (scFv), T cells can recognize and combine with the antigen, so CAR-T cells could work without MHC (major histocompatibility complex) and avoid the possibility that tumor cells escape through adjusting the MHC molecules [2]. Massive research shows, the activity level of CAR-T cells is directly proportional to the length of the hinge domain. Regulating the length of the hinge could let the distance reach the optimum point. The transmembrane part connects the extracellular part and the intracellular receptor signaling domain together and anchors the receptor on the membrane. The transmembrane part can promote the expression of CAR on the exterior of the cell and are put into use in many clinical tests [2]. The cytoplasmic domain is composed of a costimulatory domain and a signaling domain. The former can turn on both costimulatory molecules and intracellular signaling at the same time, which keeps T cells dividing and releasing cytokines that make T cells better at fighting tumors. The signaling domain can transduce the T cell signal. In ten years, CAR-T has gone through four generations, each of which is more accurate, efficient, and permanent than the previous one. The structure of the first generation CAR was designed relatively easily, but it lacks the necessary item of the CAR-T cell — costimulatory signal. This means that the cell cannot be fully activated later, and didn't amplify as well as expected. With the knowledge gained from the first generation, the CD28 costimulatory domain was introduced to the second edition of CAR, which alleviated the previous problem and extended the time it could work. This version of CAR-T cell has the largest amount of clinical data, making it the major choice among all CAR-T cell products. Two costimulatory domains comprise the third generation. One of them is CD28 or 4-1BB, and the other is OX40, CD28 or 41BB. Although the edition 3 CAR appears to be stronger and lasts longer in clinical testing data, it may cause cytokine over-release. The newest version is the fourth generation, which is also called TRUCK-T cells, which include a nuclear factor to lets CAR-T cell to release specific cytokines which get other immune cells to start working.

3. CD19 targeting CAR-T cell

CD19 located on the exterior of B cells and is widely used as a symbol for B cells. It can be discovered on B cell cancers like B-ALL, B-CLL also B-NHL. In spite of the truth that CD19 is located on normal B cells. It is expressed during the vast majority of the maturation phase of B cells, with mature B cells expressing three times more than naive B cells [3].

3.1. B cell acute lymphoblastic leukemia

B-CLL take for around 80% of ALL cases worldwide. This kind of ALL can affect individuals of any age. According to the statistical report of SEER (a huge database compiled by the NCI, specifically National Cancer Institute of the United States) for the years 2015-2019, the median age of getting related diagnosis is roughly 17 years old, at the same time, more than fifty percent of diagnosed people are under the age of twenty. Acute lymphoblastic leukemia is particularly prevalent in younger generations, including children and adolescents. 30–40% of patients diagnosed with leukemia will ultimately be diagnosed with ALL. The complete response (CR) rate of ALL in adult patients varies from 60% to 90%, and the five-year overall survival (OS) rate is greater than 90%; nevertheless, more than half of patients may experience a recurrence, which is linked with a worse prognosis [4-5]. An estimated 30 to 60% of patients will have disease-free survival (DFS) within three to five years [6].

When looking at the long term, both children and the elderly can benefit from CAR-T cells targeting CD19. And it is successful also relatively safe during the treatment for B-ALL, and often used to patients with refractory and relapsed B-ALL. The efficacy and safety of it have been shown by voluminous clinical studies. With the aid of it, the OR rate is between 60% and 90%, and the median OS duration is greater than one year [4-5]. Despite the fact that the patients have not been re-diagnosed with the disease, it have been more than 10 years following their treatment in a number of investigations [5].

However, the recurrence of B-ALL after the treatment remains an intractable challenge. Davila ML et al. [7] suggested that the percentage of patients who recover after undergoing allo-HSCT treatment for relapsed ALL ranges from 25% to 65%. Both of these studies were published in The patients must be in complete remission before allogeneic stem cell transplantation may be considered; hence, salvage therapy must be maintained. In light of the aforementioned facts, only 5–30% of patients with refractory ALL are able to meet this requirement, substantially limiting the application and efficacy of allo-HSCT. In addition, there is a 50% probability that the disease may return in one of the three patients who consent to undergo allo-HSCT treatment [8--9]. Six months is the average amount of time a patient can anticipate to live after receiving this treatment. CAR-T may in fact be useful even at present. A CAR-T cell that has been created from the diagnosed people's original T cells is autologous. It is quite inexpensive and has been investigated in a variety of clinical research studies, albeit with conflicting findings [10], despite its low cost. To eliminate the patient's original immune cells and prevent a rejection reaction, chemotherapy must be administered before the first application of it. This would not only cause the allogeneic T cells to be less permanent and divide less, but it also leads to reduced division and growth of T cells and a lower number of effector T cells when they are used a second time, thereby reducing their efficacy [3].

3.2. B cell non-hodgkins lymphoma (NHL)

NHL is the most prevalent form of malignant malignancy. According to SEER statistics, roughly 80,500 people were impacted in 2022, and patient age was positively correlated with the likelihood of being diagnosed. The body loses control of normal lymphocyte division as a result of the antigen keel's long-term stimulation. By its original cells like T cells or B cells and their characteristics, NHL is subdivided into a number of hypotypes and is associated with numerous disorders. NHL could cause immunologic insufficiency, making it the second most prevalent malignancy among HIV patients. Patients with non-lymphoma Hodgkin's may experience side effects such as gastrointestinal lesions and frequent infections, which can negatively impact the chemotherapy procedure.

The majority of NHL clinical cases, approximately 70% to 85%, are B-NHL. For instance, between 50 and 85 percent of individuals with DLBCL can be healed with first-line therapy. However, the prognosis for a resurgence of the disease after a brief remission or an incurable disease is sometimes very bad. The median overall survival (OR) of these individuals was 6 months, and only 20% of them struggled for more than two years after the reappearance. Since the introduction of CD19-targeting CAR-T treatment, the median OR has doubled to one year, and the two-year PFS rate has reached 45% [11]. James N. Kochenderfer et al. [12] conducted a research with 15 patients; nine of them had DLBCL, two had indolent lymphoma, and the remaining patients had CLL. The fact that eight patients attained complete remission and four patients experienced partial remission suggests the feasibility of the treatment. The FDA has authorized four distinct CD19-positive tumor cell-targeting CAR-T cell products for the hope treatment of B-NHL patients, two of which are now in use: tisagenlecleucel and axicabatogene.

4. BCMA targeting CAR-T cell

BCMA (TNFRSF17) is a tumor necrosis factor (TNF) cell. For most of the time, they are expressed on the exterior side of B-lymphocyte cell and plasma cell as a signal protein of a mature B-lymphocyte cell [13], also highly expressed in malignant proliferating B-lymphocyte like leukemia cells. APRIL,

which is a ligand that induces proliferation, and BAFF that stands for B cell activating factor are the two ligands for BCMA. Both APRIL and BAFF is a type of TNF receptor, named TNFSF-13A and TNFSF-13B. APRIL could enhance the survival rate of bone marrow blood cells and plasmablast after the combination with BCMA. By uniting with BCMA, BAFF could activate the NF- κ B pathway, finally increase the B cell division speed and survival rate. By reading these ligands, the body knows that it is time to turn B-cells into plasma cells, which keeps the bone marrow plasma concentrate (BMPC, a key point of a stable and abiding neutralizing antibody) stable. The BCMA CAR T-cell therapy focuses more on MM, which is multiple myeloma. When the body produces an excess of bone marrow plasma cells, it also produces an excess of immunoglobulin. The over-production of these two cells could lead to the damage of the related end organs and eventually cause death. Multiple myeloma can not be cured with the existing technologies, and the people haven't got a conclusion for the incentive. It can cause neopathy like pathological fracture, paraplegia also renal failure, which renal failure is one of the major reasons for MM patients' death.

B cell maturation antigens are present in mature B leukomonocytes and are significantly expressed in B leukomonocytes. These antigens can be found in mature B leukomonocytes and plays a vital character in cell transport, division and medicine fast, these characteristic make BCMA a target for treating MM patients. There is often too much BMPC in the BCMA of MM patients, which not only stimulates the malignant plasma cell to divide, but also keeps it alive and finally leads to the growth of the disease. Correspondingly, by blocking the BMPC signal path thereby suppress or stop the condition from getting worse. The BCMA targeting CAR-T therapy can focus on and only kill the malignant plasma cells. Abecma is one of the products that were permitted by the FDA [14].

According to the data from SEER, around 60 percent of all MM patients could live for more than 5 years. The clinical treatments are PI (proteasome inhibitors), immunosuppressive drugs, and antibodies like anti-CD38. The result of the clinical trail II about idecabtagene vicleucel, which is a type of BCMA CAR-T cell that is known as bb2121, suggesting that among 128 patient that received ide-cel, 84% are triple-class exposed. Patients were divided into groups by the dosage of CAR-T, and the efficiency was shown positively related with the dosage, the group with the largest dosage's median progression free survival time is approximately a year [16]. Around 73% of the tested patients had a respond after the treatment, and 33% off all had at least a complete response, yet most patients had toxic effects on the third grade and forth grade [18]. Berdeja JG et al. [17] shows the utilization of ciltacabtagene autoleucel, it contains two BCMA targeting single domain antibodies, which bring combination with relatively high affinity with patients. There are 97 patients with triple-class exposed and 65 of them completely responded, the PFS rate for living 1 year is 77% [17]. Having BCMA targeting CAR-T cell as the corresponding therapy for MM patients could bring toxic side effects, mostly cytokine release syndrome. Since CAR-T cells amplify massively, eliminate tons of tumor cells and release series of mediators of inflammation within a short period, the patient will have to cope will several side effects like fever, epilepsy and so on.

5. Multi-targeting CAR-T cell

Among all of the relapsed and refractory patients, CD19 CAR-T therapy's ORR is 80%. The rest of them are not able to be advantaged by this treatment. This is because some cancer cells do not have CD19 antigen, meaning that CD19 CAR-T can not work as usual and could increase the possibility of inducing cancer to reappear. Thus, combination therapy with other medicines like Tandem CD19/20 targeting CAR-T treatment or TanCAR7-T could replace the original therapy. Wei Donghan et al. [18] are the first group that developed CD19/20 TanCAR7-T and tested it in the recent refractory and relapsed NHL clinical program. They suggest that their tandem CD19/20 CAR-T cell therapy could enhance the CR, also lengthen the relief duration and bring stronger anti-tumor function, with 54% CR and median PFS for almost 6 months. The research shows that with 28 patients that attended the TanCAR7-T cell therapy, the ORR (79%) was found, and the CR rate was 71%. The PFS rate after 6 months since the therapy is 79%, and the PFS rate after a year is 64%. At the ASCO

2020 conference, Han and his team also provided another clinical research study, there are totally 74 patients that are estimable. The median survival time is 13.5 months and 62 patients get an partial response, while 55 patients get a complete response. Although many patients in this research have a relatively poor body condition, they still get a pleasant OSR and CRR. This research takes the lead in tandem targeting CAR-T cell therapy and has inspired more relative therapies.

6. Conclusion

The incidence of cancer in the world is increasing, and it has gradually become the number one fatal disease of human beings. Traditional methods have many disadvantages for its treatment. The birth of immunotherapy may have opened up a new era of tumor treatment, bringing hope to countless cancer patients. Especially relapsed and refractory tumors with high mortality. CAR-T cell treatment has historically been a pretty efficient immunotherapy with a high success rate. Clinical trials have proved the efficacy and security of this medication for patients with B cell NHL, B-ALL and multiple myeloma in a variety of contexts. On the other hand, there are still a large deal of unresolved, unexplored, and unknown concerns connected to it. The potentially lethal consequences of toxic side effects such as CRS and off-target on-target tumors are explored. How to raise the specificity of CAR-T cell treatment targets while simultaneously reducing the possibility of erroneous harm is one of the most pressing issues for the future of research and development.

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