Application Differences and Mechanism Review of CAR-T cell therapy use in solid tumors and blood tumors

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Abstract. Currently, the review of targets used in cancer immune therapy is not enough, and the mechanism of tumor microenvironment influence is not yet fully understood. The reason for this review's contrast and comparison of solid tumor treatment and blood tumor treatment is that the tumor microenvironment is distinctly different from anatomical features, and therapeutic bottlenecks and failure mechanisms exhibit significant differences. The theme of this review is to highlight the difference in the application of CAR-T cell therapy between solid tumors and hematological malignancies. This review aims to supplement and improve the existing literature, with a focus on tumor therapeutic targets and the regulatory mechanism of the tumor microenvironment. The core mechanism of CAR-T cell therapy is discussed, which can be divided into 4 key steps. This review also analyzes the advantages, disadvantages, and challenges of two types of tumors. Furthermore, the Review clarifies that the process of CAR-T cell therapy in two tumors is similar but has differences in seven dimensions: tumor morphology, growth environment, different levels of choosing targets, CAR-T cells' infiltration and homing, influences of tumor TME, clinical efficacy, and challenges focus. The differences in the treatment of solid tumors and hematological tumors often stem from the fundamental differences between the two types of tumors, such as their existing forms/states.

Keywords: CAR-T cell therapy, solid tumor, blood tumor, treatment.

1. Introduction

Recently, an increasing number of people have paid attention to the phenomenon that many people get cancer and always die. A report shows that global new cancer cases have reached 20 million cases, and 2.7 million of them have been deaths [1]. According to an estimation, about one-fifth of adults will develop cancer in their lifetime, while approximately one-ninth of men and one-twelfth of women will die from cancer [1].

Therefore, the cancer treatment is important, which can be divided into many different types like radiotherapy, chemotherapy, surgical treatment, immunotherapy, and targeted therapy. Each of these treatment types has its own advantages and disadvantages. Immunotherapy has become popular in cancer therapy, especially CAR-T cell therapy, which gives hope to patients who cannot be treated with other therapies. CAR-T cell therapy addresses the suboptimal efficacy of traditional cancer treatments such as surgery, radiotherapy, and chemotherapy in certain scenarios. Apart from that, CAR-T cell therapy pushes cancer from non-specific killing to precision targeting, increasing the safety and efficacy of CAR-T cell therapy. CAR-T cell therapy deepens scientific understanding of tumor-immune interactions and advances cancer treatment toward the goal of functional cure. For most cancers, the aim of traditional therapies is always to extend the life expectancy of patients. Oppositely, CAR-T cell therapy achieves a functional cure (patients do not need medication for a long time, cancer continues easing, and quality of life is close to that of a normal person) for a part of cancer for the first time.

The theme of this review is the difference in the application of CAR-T cell therapy between solid tumors and hematological malignancies. The process of treatment, advantages, disadvantages, and challenges are discussed in this review. To find the relationship and differences between those two tumor types, the tumor morphology and growth environment, different levels of choosing targets, CAR-T cells' infiltration and homing, the influences of tumor TME and clinical efficacy, and challenges are discussed.

2. Mechanism of CAR-T cell therapy

Before starting the entire treatment process, patient need to undergo an assessment to determine their suitability for this therapy [2]. The whole process can be divided into 4 steps.

Step 1 includes using Apheresis to collect T cells from the patient's peripheral blood. This is an advanced way compared to Routine blood draw and takes about 2-4 hours. During this step, patients typically do not need to stay in the hospital. The blood will then be returned to the patient's body, resulting in minimal physiological burden. The main aim is to get T cells for the following treatment.

Step 2 is the introduction of chimeric Antigen Receptor (CAR) [2]. The CAR can give T cells both targeting ability and cytotoxic function, enabling them to identify antigens on the surface of cancer cells. After transformation, normal T cells are transformed into CAR-T cells with targeted anti-cancer capability.

Step 3 is the *in vitro* proliferation of CAR-T cells. Because the number of successfully modified CAR-T cells is too small to combat the great deal of cancer cells in the body, professional incubators and nutrient media are used to proliferate them in a controlled environment. The number of T cells can increase from several million to several billion or even hundreds of billions. This step often takes about 7-14 days.

Step 4 is the transportation of CAR-T cells to the hospital for reinjection into the patient's body through intravenous injection [2]. Before injection, the patient needs to accept 1-2 courses of pretreatment, namely pre-chemotherapy [3]. The purpose of pre-chemotherapy is to decrease interference from other immune cells, create space for CAR-T cells, and improve their survival and operational efficiency. Following monitoring is needed after infusion.

The most core step among the 4 steps is the second step. This modification determines whether the infused T cells can accurately identify cancer cells and effectively launch attacks, which is the critical turning point of CAR-T therapy from common immune therapy upgrade to precision targeted therapy. If gene modification fails, the remaining steps will lose their significance. Failed modification can lead to many different consequences, such as cytokine release syndrome, neurotoxicity, and off-target effects [4].

3. Hematologic Malignancy Treatments

The process of hematologic malignancy treatments is like common CAR-T cell therapy, but there are some considerations in selecting the CAR-T target. In hematologic malignancy treatments, CD19 is commonly selected for B-cell-derived malignancies and BCMA for multiple myeloma. Choosing targets is the key prerequisite for effective treatment.

The benefits of CAR-T cell therapy for hematologic malignancies can be divided into 2 different parts. The first part is its breakthrough in therapeutic efficacy for recurrent or refractory hematological malignancies, partially achieving long-term remission. Traditional treatment like chemotherapy and targeted drugs often fail to cure relapsed or refractory hematologic malignancies (e.g., acute lymphoblastic leukemia ALL, diffuse large B-cell lymphoma DLBCL, multiple myeloma MM). Oppositely, CAR-T cell therapy through gene modification enables T cells to precisely target cancer cells and continuously kill cancer cells. Some patients can achieve no illness for a long time. There is a test for CAR-T cell therapy targeting B-cell maturation antigen (BCMA) used in patients who have relapsed or refractory multiple myeloma (RRMM). The results show that the objective response rate (ORR) is 77%, the patients' completing alleviation rate is 47%, 15 patients have sustained larger than 12 months, and 1 patient has had alleviation time of more than 38 months [5].

The second advantage is its high specificity, reducing damage to normal cells. The main design of CAR-T cell therapy is through CAR to identify an antigen on the surface of cancer cells, attacking only cancer cells that express a specific antigen, thereby causing minimal damage to other tissues [6].

However, CAR-T cell therapy also has limitations. The disadvantages are always safety risks, a limited scope of application, and high treatment costs. More specifically, the reason for safety risks always that the activation and proliferation process of CAR-T cells may trigger excessive immune

response. Some side effects may happen after treatment, and the most common symptom is cytokine release syndrome (CRS), which typically presents as low blood pressure, rapid breathing, fever, and fatigue. CRS can be managed with antipyretic, fluid replacement, and anti-inflammatory drugs [7]. The limited scope of application means that CAR-T cell therapy can only cope with a piece of hematologic malignancy; not all hematologic malignancies can be cured using CAR-T cell therapy, and it is easy to relapse. Because CAR-T cell therapy depends on a high level of target specificity, the conditions for using CAR-T cell therapy are restricted. The reason for cancer relapse is the loss of CAR antigen on the cancer cells' surface [8]. A test showed that the progression-free survival rates at 6 and 12 months were 69% and 53%, respectively [9].

Nowadays, CAR-T cell therapy necessitates to use of T cells from patients to modify. The modification process is complex and requires the support of equipment and technology. Because of that, the cost of the therapy increases. Furthermore, the suitable tumor target antigen is rare [10], further restricting the clinical application of CAR-T cell therapy.

4. Solid Tumors Treatment

The process of solid tumor treatment using CAR-T cell therapy is similar to common CAR-T cell therapy. The difference between common CAR-T cell therapy and CAR-T cell therapy used in solid tumor treatment is the selection of the CAR-T target. The principle of choosing a solid tumor CAR-T target is the high tumor specificity, low expression in normal tissues, and the ability to be effectively recognized. Now, Claudin 18.2 (CLDN18.2) and Mesothelin can be used to treat a wide range of cancers [11,12], which are highly expressed in gastric cancer, pancreatic cancer, and esophageal cancer [11]. Mesothelin is also highly expressed in pleural mesothelioma, pancreatic cancer, and ovarian cancer [12].

There are several advantages of solid tumor treatment; choose CAR-T cell therapy. Firstly, CAR-T cell therapy can attack tumor cells precisely and reduce the damage of normal tissue, which can decrease the incidence of nausea, hair loss, and immunosuppression, increasing the quality. The precise attack on tumor cells avoids the damage of chemotherapy, radiotherapy.

Secondly, CAR-T cell therapy used in solid tumors can break through a part of the dilemma of traditional therapy. For example, CAR-T cell therapy can directly kill tumor cells for patients who are resistant to targeted drugs or insensitive to chemotherapy due to the tumor cells' gene mutation [13].

Third, CAR-T cells have memory of cancer, which can decrease the risk of recurrence. CAR-T cells not only can directly kill the tumor cells, but also CAR-T cells can differentiate into memory T cells and stay in the patient’s body for a long time. Those T cells can monitor whether tumor cells recur in the body. Once T cells discover tumor cells that express the target antigens, they can activate and second attack. Thus, achieving long-term anti-tumor effects and reducing the recurrence rate after solid tumor treatment. This characteristic is hard to achieve for chemotherapy, radiotherapy, and other short-term treatments.

However, CAR-T cells' solid tumor treatment also has some drawbacks. The core bottlenecks of solid tumor treatment that choose CAR-T cells therapy can be divided into 3 parts. First is tumor infiltration is difficult. Solid tumors have a dense matrix barrier, such as collagen, etc. It is hard for CAR-T cells to penetrate and reach inside the tumor to take effect because lots of CAR-T cells are blocked out of the tumors [14].

Second is tumor microenvironment (TME) suppression. Solid TME has many suppressive cells and molecules. Those cells and molecules will numb CAR-T cells and reduce CAR-T activity to kill tumors [15].

Third is the selection of targets is different. The ideal target needs high expression on tumor cells and low expression on normal cells to decrease side effects. However, a lot of solid tumors lack those ideal targets, and most targets are prone to cause CAR-T cells to kill normal tissues (off-target effect) or cause incomplete treatment due to uneven target expression [16].

Nowadays, there are still many challenges in using CAR-T therapy for solid tumor treatment. The first challenge is that it is hard for CAR-T cells to locate solid tumor lesions, even if they have already entered the body successfully. This condition is a low homing rate. A part of the solid tumor's microenvironment stops CAR-T cells' adhesion and migration by downregulation of adhesion molecules on the vascular surface.

The second challenge is that tumor heterogeneity leads to treatment resistance. Tumor heterogeneity means tumor cells that have many genes and different phenotypes. Those cells make CAR-T cell therapy prone to developing treatment resistance and recurrence. Even if a part of tumor cells shows the target at first, in the process of therapy, those tumor cells may down regulation of target expression by gene mutation to avoid being killed by CAR-T cells.

5. The relationship and difference between hematologic malignancy treatment and solid tumor treatment

Although the process of CAR-T cell therapy in hematologic malignancy treatment and solid tumor treatment is similar, there are many differences between hematologic malignancy treatment and solid tumor treatment in 5 different parts (shown in Table 1).

Table 1. The differences between solid tumor treatment and blood tumor treatment

	hematologic malignancies treatment	Solid tumor treatment
tumor morphology and growth environment	Free state suspended in blood and lymphatic fluid. No fix entity structure Easy to connect with CAR-T cells	Solid mess Be packaged by a dense matrix form physical barrier. Living depends on TME.
The different levels of choosing targets	Have ideal targets with high expression and high specificity	Lack of a target with strong tumor specificity
CAR-T cells' infiltration and homing	Through the blood cycle, direct homing and attaching tumor cells No need to cross a physical barrier Infiltration efficiency is high	Hard to cross dense matrix and vascular endothelium outside the tumor Infiltration and homing rate are too low
The influences of tumor TME	Low immunosuppressive effect	Suppressive cells and molecules in the solid TME suppress proliferation and kill the activity of CAR-T cells
Clinical efficacy and challenges focus	remarkable curative effect	Clinical efficacy is limited. Most are still in the clinical trial stage.

6. Discussion

There are many advances in solid tumor treatment and hematologic malignancy treatment in CAR-T cell therapy.

For hematologic malignancy, a new enhanced autologous CAR-T cell therapy huCART19-IL18 is designed and developed by the University of Pennsylvania team, aiming at the relapsed and refractory lymphoma patients that resist CD19 CAR-T cell therapy [17]. This CAR-T cells therapies show an 81% high response rate and controlled safety, and the preparation cycle only has 3 days [17].

In the context of solid tumor treatment, when solid tumors are targeted by CAR-T cells, they secrete increased amounts of small extracellular vesicles (sEVs). These sEVs carry tumor antigens, which in turn trigger fratricide among CAR-T cells [18]. Se9-CAR-T cells can overcome this problem [18]. Se9-CAR-T cells that connect with PD-1 can increase the effect of therapy [18]. CAR-T cell therapy has many potential applications in the future. Firstly, CAR-T cell therapy's adaptability can be expanded. Currently, CAR-T cell therapy is always used in blood tumors like leukemia and lymphoma, and its use in solid tumors is not mature. In the future, CAR-T cell therapy can be expanded to autoimmune diseases. Next, CAR-T cell therapy uniting with other therapy types will

become the future trend. For example, CAR-T cell therapy, connecting with traditional radiotherapy and chemotherapy, may overcome drug resistance effects on tumor cells. CAR-T cells optimization can use the power of AI, as AI can help scientists choose the optimal gene modification case, predict activity, targets, and potential risks of CAR-T cells in different modification ways, and real-time detect patients' bodies when they are in an immune response status of CAR-T cells.

7. Conclusion

This Review through analyzing the process, advantages, and disadvantages of blood tumor treatment and solid tumor treatment to find the relationship and differences in tumor morphology and growth environment, different levels of choosing targets, CAR-T cells' infiltration and homing, influences of tumor TME and clinical efficacy, and challenges between the two cancer types. Finally, this review does not review a certain type of cancer in solid tumors and hematological tumors separately. Future Review could further refine the operationalization of the variables to facilitate an in-depth Review of this issue.

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