CAR-T Therapy in Treating Solid Tumor: Application and Limitations

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Abstract. CAR-T therapy has emerged as a revolutionary approach in the battle against cancer. By leveraging the body's own immune system, this technique harnesses the power of T cells, which are genetically engineered to recognize specific antigens found on cancer cells. The procedure involves isolating lymphocytes from patients, followed by laboratory-based genetic modifications to infuse them with distinct CAR genes. Once these enhanced CAR-T cells are reintroduced into the patient, they actively target and neutralize cancer cells. However, the journey of CAR-T therapy is not without challenges. The selection of the right antigen is paramount, as an incorrect choice can lead to unintended consequences. Moreover, the application of this therapy in solid tumors presents its own set of complexities. This review aims to shed light on the clinical potential of CAR-T therapy, the obstacles faced in the realm of solid tumor treatment, and the ongoing research endeavors to refine and improve this promising therapeutic strategy.

Keywords: CAR-T therapy, lung cancer, colon cancer, ovarian cancer, solid tumor.

1. Introduction

The treatment for acute leukemia and non-Hodgkin lymphomas is currently known as CAR-T therapy. It creates a chimeric protein in vitro by joining the CD3-chain or the intracellular portion of FcRI with the antigen-binding site of an antibody that identifies a tumor antigen. By means of gene transfer, chimeric antigen receptors (CARs) are expressed on patient T cells. Numerous tumor-specific CAR-T cells are produced once the patient's T cells are "reencoded". The fundamental idea is the same as other immunotherapies: employ the patient's own immune cells to eradicate cancer cells. The distinction is that this is a cell therapy rather than a medicine.

Although the therapy has undergone modifications and has been utilized in clinical practice recently, it has been the subject of extensive research for many years and is already clinically mature for the treatment of lymphatic carcinoma and hematologic malignancies. The FDA has authorized six businesses' medicines for use in clinical settings: The first CAR-T therapy to receive FDA approval is Novartis' Kymriah, a CD19-directed CAR-T cell immunotherapy. The FDA authorized Gilead's CD19-targeting CAR-T treatment in October 2017. Just before the FDA approved Yescarta, a huge pharmaceutical corporation acquired CAR-T researcher Kite Pharma. Gilead's CD19-targeting cell treatment, Tecartus, was given another FDA nod in October 2021. The FDA approved the fourth CD19-targeting CAR-T treatment in February 2021. BECM is the first BCMA-targeted CAR-T therapy, Carvykti, was created by the Chinese company Nanjing Chuanqi Biological and was authorized by the FDA in February 2022. It has been the first cell therapy product approved by FDA in China and the second CAR-T cell immunotherapy approved for BCMA globally as a result of its strong anticancer efficacy and clinical benefit [1-5].

However, success in solid tumors has been more limited due to unique challenges posed by the solid tumor microenvironment. Therefore, scientists have found some ways to solve the problems.

This review focuses on efforts to apply CAR-T therapy to three prevalent solid cancers – lung, colon, and ovarian carcinomas. It will examine obstacles faced in designing effective CAR-T therapies for these diseases, including choosing appropriate antigens, engineering T cells to infiltrate and persist in solid tumors, and combining with other treatments to overcome immunosuppression.

2. Application

Finding the tumor cell and suppressing or killing the tumor cell are the two phases that solid tumors present as unique obstacles to CAR-T treatment.

The first step, finding, is supported by the reaction between the antigen and the protein label on the cell membrane. The protein label is the “target” in the process of the therapy. The biggest challenge of the therapy is to find a label that is specific on the tumor cell, and doesn’t appear on the normal cells. This can most effectively protect the normal cells from the is attack of the edited car T cells. It has been a challenge for researchers to find tumor-specific proteins that can be used in CAR-T therapy without harming healthy organs.

Three different types of mechanisms are typically used to perform the second phase, killing. The first is that granzyme and perforin are secreted by CAR-T cells [6] Granzyme is carried into the interior of tumor cells after perforin "punches a hole" in their surface, killing tumor cells instantly or inducing apoptosis through physical effects. The second method involves a high production of TNF ligands, which can cause tumor cells to undergo apoptosis [7]. Finally, CAR-T cells can release particular cytokines. These cells can thereby alter the tumor microenvironment, increase the activity of CAR-T [8].

However, the first problem in identifying cancer cells is to find the specific protein label expressed on the plasma membranes of cancer cells.

Since he centers around proteins that are just communicated in malignancies, Mitchell Ho, Ph.D., is the trailblazer in tracking down an answer for this issue. In 2014, Ho and postdoctoral partner Nan Li, Ph.D., began chipping away at the GPC2 protein, which is one of these. Practically the tissues were all found to be GPC2-negative, making GPC2 a phenomenal possibility for Vehicle Lymphocyte treatment with the possibility to fix neuroblastoma. Then, at that point, they made a clever assortment of Vehicle Immune system microorganism that can explicitly target GPC2. The group found a counter acting agent known as CT3, which can tie to GPC2 however not to different targets. The resistant cells may then more actually target, tie to, and kill disease cells that produce GPC2 because of the specialists' alteration of Lymphocytes to communicate CT3 [9, 10].

2.1.Lung Cancer

The traditional treatment of lung cancer includes surgery, radiotherapy, chemotherapy, targeted drug therapy, and traditional Chinese medicine therapy. The latest treatment technology has gradually entered the field of cell therapy, the most representative of which is PD-1 monoclonal antibody therapy and CAR-T therapy, and other cell therapy such as ATCL, CAR-NK, TIL, etc.

According to reports, DLL3 is expressed positively in tumor tissues in roughly 80% of individuals with small cell lung cancer (SCLC), but barely at all in healthy tissues. SCLC targeted treatment with AMG 119 is being researched. The T cells "modified" with AMG 119 target delta-like protein 3 (DLL3), in contrast to previous CAR-T treatments. 41 SCLC patients with disease progression or recurrence following at least one previous platinum-based chemotherapy treatment are currently anticipated to join in the AMG 119 study. Additionally, there are other medications being investigated for this target, such as rovalpituzumab tesirine (Rova-T). Additionally, AMG 757 is undergoing a phase I study in SCLC that similarly targets DLL3. The OR2H1 protein has been shown to be a tumor-specific marker.

2.2.Colon Cancer

CAR-T therapy has been tested in clinical trials for colorectal cancer, but most of which are autologous cells, and the most rapidly progressing cells are in phase 1/2. At present, the potential targets of CAR-T therapy for colorectal cancer clinically found include carcinoembryonic antigen (CEA), GUCY2C, EpCAM, NKG2D, HER-2, EGFR, CD133, etc. Among them, CYAD-101 and CAdVEC+HER2 CAR-T are special.

Of note with respect to CYAD-101, Celyad Oncology's CYAD-101 is the first allogeneic CAR-T candidate in the pipeline for a solid tumor indication.

In addition, Celyad voluntarily stopped the CYAD-101-002 (KEYNOTE-B79) phase 1b trial (NCT04991948) on February 28 because "there was not enough information to assess the risks of the program." The FDA formally suspended the trial. The trial, which is currently under recruitment, was lifted by the FDA on August 2 after Celyad Oncology changed the eligibility criteria for the trial.

About CAdVEC+HER2 CAR -T, participants in this phase I study (NCT03740256) were patients with HER2-positive cancers, including bladder cancer, head and neck squamous cell cancer, salivary gland cancer, colorectal cancer, and pancreatic cancer. Two CGT agents will be used to treat the trial, including HER2 CAR-T and CAdVEC. Oncolytic adenovirus Ad and helper dependent Ad (HDAd), which may splice in 34 kb of foreign genes, make up the binary construct known as CAdVEC. Combining HER2-specific CAR-T cells with IL-12 and PD-L1 (CAdVECIL12_PDL1) inhibits tumor development and lengthens survival. The two medicines were combined in the trial because the researchers think they would work together more effectively than they would alone [11].

2.3.Ovarian Cancer

Ovarian cancer is often asymptomatic in its early stages, and about 75% of patients are diagnosed with advanced cancer. This is because the ovaries are hidden deep in the pelvic cavity, and early ovarian cancer is harder to detect due to its deep hiding position. Even if there is a tumor in the ovary, a woman's hormone secretion and menstruation may not be abnormal. The 5-year relative survival rate for advanced ovarian cancer is 29%, while the 5-year survival rate for those diagnosed early can reach 92%.

Mesothelin (MSLN) is exceptionally communicated in different growth tissues, like pancreatic disease, ovarian disease, bosom disease, endometrial malignant growth, prostate malignant growth, and bile channel malignant growth. MSLN is a glycoprotein secured to the layer surface. It is profoundly communicated in various growths and is firmly connected with cancer multiplication, attack and unfortunate anticipation. Like HER2, MSLN is a well-known research focus for immunotherapy. In a stage I clinical preliminary of Vehicle White blood cells focusing on MSLN, six patients with pancreatic malignant growth showed variable enemy of cancer ability [12].

A potential and promising objective for immunotherapy is MSLN. Clinical preliminaries have been endorsed for various cancer types, and empowering discoveries have been delivered in the exploratory period of mesothelin-based Vehicle Lymphocyte examinations. Moreover, mesothelioma, ovarian malignant growth, and cellular breakdown in the lungs preclinical examinations have been completed utilizing subcutaneous or in situ mice models with mesothelioma, mesothelioma, and cellular breakdown in the lungs. MaxCyte revealed in July 2018 that the FDA had approved the organization's Vehicle cell treatment for strong cancers created utilizing mRNA non-viral innovation to start clinical preliminaries. MCY-M11, which targets mesenchymal (MSLN), was the principal Vehicle project totally possessed by MaxCyte [13]. intraperitoneal infusion treatment for patients with peritoneal mesothelioma and intermittent/recalcitrant ovarian malignant growth.

MUC16 is often expressed in the reproductive, pulmonary, and corneal epithelium, largely to guard against invasion by extracellular pathogens. When MUC16 expression is unusually elevated, it may make it easier for cancer cells to evade the body's immune surveillance in the tissues that are impacted. Ovarian, pancreatic, cervical, and lung malignancies are invariably found to overexpress MUC16. MUC16 and CA-125 can both be employed as significant markers for the early detection of ovarian cancer since relevant studies show that they are overexpressed in more than 80% of ovarian cancer patients. A research on the in vivo anti-tumor effectiveness of MUC-CD-targeted T lymphocytes in SCID-Beige mice with peritoneal human MUC-CD+ tumor cell lines was reported in Clin Cancer Res. 4H11-28z+T cells after systemic intravenous infusion

On August 5, 2019, Precigen announced that a Phase I clinical study (clinical trial identifier: NCT03907527) evaluating a novel UltraCAR-T therapy, PRGN-3005, in advanced solid tumors has completed the first administration in a patient with advanced ovarian cancer. Using the UltraCAR-T

therapeutic platform from Precigen, PRGN-3005 is a novel treatment. Using non-viral gene delivery technology, PRGN-3005 is being tested for the treatment of advanced recurrent platinum-resistant ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. Conventional CAR-T cells have a limited capacity to endure owing to exhaustion, which is connected to their low ability to block the development of aggressive solid tumor cells (indicated by green fluorescent protein) in long-term in vitro culture. UltraCAR-T cells, in contrast, showed prolonged tumor cell death and restrained tumor development, demonstrating the potential for long-lasting anti-tumor responses.

3. Limitation

Compared with liquid tumors, CAR-T faces three key challenges in the treatment of solid tumors:

(1) Due to the high heterogeneity of solid tumors, it is difficult to achieve specific recognition of all tumor cells by targeting a single antigen;

(2) Solid tumors are usually surrounded by physical barriers that limit the invasion of T cells;

(3) T cells infiltrated into solid tumors face a highly immunosuppressive tumor microenvironment, resulting in the reduction or even loss of their antitumor activity.

How to solve these challenges is the key to the realization of CAR-T solid tumor therapy.

3.1. Target Antigen Selection

The choice of target antigen is a major determinant of the safety and efficacy of CAR-T therapy. In principle, the ideal target should be highly and uniformly expressed on tumor cells and not present on normal tissue cells. This can most effectively protect the normal cells from the attack of the edited CAR-T cells. To deploy CAR-T therapy to treat solid tumors without damaging vital organs, researchers have struggled to find tumor-specific proteins. The majority of tumor antigens, however, are now expressed in healthy cell subpopulations as well. Therefore, it is quite likely that targeted non-tumor cell toxicity will occur if only tumor-associated antigens, rather than tumor-specific antigens, are recognized.

To address this, several strategies to improve CAR-T targeting specificity have been developed over the past decade. One strategy is to fine-tune the affinity of CAR-targeted antigens so that only tumor cells that overexpress the target antigens will be killed, while low-expressing tissue cells will be isolated. However, this strategy is only suitable when there is a large difference in antigen expression levels between tissues and tumor cells, and often limits the efficacy.

3.2. Invasion of CAR-T Cells in Solid Tumor

As compared with hematomas, the microenvironment of solid tumors is highly susceptible to recruitment of immunosuppressive cells and stromal cells (e.g., cancer-associated fibroblasts, resulting in a dense fibrotic environment) and vascular dysregulation (reduced expression of adhesion factors required for T-cell infiltration), thereby creating a physical barrier against T-cell infiltration.

3.3. Immunosuppressive Microenvironment of Solid Tumors

In solid tumors, CAR-T therapy also faces an immunosuppressive microenvironment caused by tumor metabolism. Studies have shown that the exhausted CAR-T cells in solid tumors generally have problems such as glycolysis, mitochondrial metabolism and mitochondrial function impairment, and tumor cells will also compete with CAR-T for essential nutrients, such as glucose and tryptophan, leading to CAR-T exhaustion. Metabolites secreted by tumor cells, such as lactate and kynurenine, can affect the proliferation and activity of effector T cells, thereby affecting the efficacy of CAR-T therapy [14].

3.4. Toxicity and Safety

Although the efficacy of CAR-T in solid tumors needs to be further verified, its safety still needs to be fully considered. In addition to targeted nontumor cellular toxicity as discussed previously,

patients receiving CAR-T therapy can experience other fatal side effects, such as cytokine syndrome (CRS) and neurotoxicity.

At present, a variety of strategies to improve the safety and controllability of CAR-T cells have been applied in the treatment of hematological malignancies. For example, the bioinert small molecule AP1903 induces iCasp9 dimerization, which activates Caspase 9-mediated apoptosis to turn off CAR-T cells at the onset of CRS. However, these CAR-T suicide switches usually result in permanent depletion of CAR-T cells, forcing treatment termination [15].

4. Conclusion

At present, there are still many obstacles in the treatment of CAR-T in solid tumors, including the difficulty of target selection, the poor infiltration of T cells, the immunosuppressive microenvironment, and the toxicity. In order to make progress in this field, CAR-T therapy needs to define the therapeutic targets more scientifically, develop strategies to overcome the tumor microenvironment, and find targets that are specific in solid tumors. It is believed that in the near future, with the gradual deepening of the understanding of tumor targets, microenvironment and related signaling pathways, the therapeutic effect of CAR-T in solid tumors will also undergo leap-forward development.

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