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The analysis of future developments and application potentials of CAR-T cells based on their current performance

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Abstract. Currently, CAR-T cell therapy has become one of the most commonly seen ways of immunotherapies to treat cancer, it is specifically targeted, with limited side effects compared with some other treatments like chemotherapy, and it has a high chance of curing the cancer with no reoccurrence. This treatment is preferred by many because of its broad application and adaptability; the T cell is gathered from the patient's own system so they have no risk of rejection reaction and greatly increases the safety of the drug, excluding immune system overreaction and mortalities. This paper is to briefly introduce CAR-T cell therapy as a kind of immunotherapy: its applications for blood cancers, limitations on solid tumors, actions done to solve the treatment problems, and the potential for future applications. If the clinical trials for solid tumors succeed, the potential for safe, effective, and thorough treatment in the appliance of CAR-T cell therapy.

Keywords: CAR-T cell therapy, clinical trials, future developments.

1. Introduction

CAR-T cell therapy is a common and fast-developing process in cancer treatment. The working mechanism of CAR-T cell therapy in cancer is to collect a special kind of white blood cells called T cells from the patient and genetically engineer them to make them target cancer cells in that patient's body. To achieve this, genetic engineering is introduced to enable the T cells with chimeric antigen receptors (CARs) to recognize and attach themselves to the cancer cells' special antigen and successfully launch an attack. This process includes the CAR-T cells releasing large amounts of toxin in the cancer cells, intoxicating the tumor tissues and promoting faster apoptosis.

Currently, CAR-T cell therapy is in practice in many fields of cancer treatment, including B-cell Acute Lymphoblastic Leukemia (B-ALL), Multiple Myeloma (MM), Chronic Lymphocytic Leukemia (CLL), etc. Most of the cancers that are in rather advanced treatment by CAR-T cell therapy are the treatment of blood cancers. However, medical practices on solid tumors still need much development; and there are severe side effects of the treatment currently. Some of the concerns include CRS, limited amounts of toxin entering the tumor cells, antigen escape, and off-target effects; they all lead to side effects like damaging patients' healthy tissue and organs, dizziness and nausea, and pulmonary edema. CAR-T cell therapy is not the only, but main cause of CRS, the mechanism is basically a stimulus and overreaction of the immune system. The CAR-T cells bind to the antigens on the cancer cells and release cytokines, this action might trigger the immune system to release even more cytokines as a part of the response, which might be too much for the patient to overcome; or the large number of tumor cells that were killed once was too much and could release more antigens in the bloodstream, causing the CAR-

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T cells the recognize it and inject toxin and cytokines. The over-release of cytokines could cause the immune system to act as an inflammatory response, and organ damage (especially the kidneys), depression, or overreaction of the immune system. Cytokines such as IFN-γ, IL-6, IL-8, and MCP-1 can contribute to endothelial activation, resulting in hemodynamic instability, capillary leak, and consumptive coagulopathy [1]. Limited amounts of toxin entering the tumor site could lead to inefficient treatment of cancer and not limiting the side effects either. Off-target effects could be led by many different factors, so the risk is very high and the patient will likely get this effect. First, during the formation of the CAR-T cell itself, there could be malfunctions like engineering the wrong CARs, so they might recognize the antigens that are expressed on the non-cancer cells instead. Second, there might be highly similar antigens that are being expressed on the surface of healthy cells, but due to the not-specific-enough CAR, it might be misread. Also, even a rather high dose of CAR-T cells can increase the chance of releasing toxicity into the wrong cells.

This research is to present some of the possible ways to minimize or prevent the side effects mentioned above and show the potential for development in the treatment of blood cancers. Strategies for the elimination of these treatment risks include adding a switch to the CAR-T cells and enabling specific targets. Inserting a switch to the CAR-T cell could enhance ability the ability to control and release of toxins, therefore making it more targeted, and reducing the side effects.

2. Current applications

2.1. B-ALL

B-ALL is a type of leukemia that is commonly seen among children. The number of Acute Lymphoblastic Leukemia occurrences around the world has changed dramatically from the year of 1990 to 2017, it is a relatively large rise for such a short period of time, increasing from 49100 to 64200. However, the age-standardized incidence rate went through a decrease. Research showed that from the year 1990 to 2017, there was a stabilizing trend in some of the countries that were previously rather high in the risk of Acute Lymphoblastic Leukemia, and went through a decrease in age-standard incidence rate, with respect to their previous data [2].

There are many causes of B-ALL, but the general mechanism behind all of the sources is the mutation of normal functioning genes. One of them is the accumulation of immature B lymphocytes inside the bone marrow causing malfunction of the formation of blood cells. The position of chromosomes can also lead to this kind of tumor; when there is some rearrangement of the chromosomes, there is the likelihood of producing a cancer-occurring or developing gene by accidentally fusing genes together.

Currently, extensive collaborative efforts in basic and clinical research have significantly improved patient prognoses. Nevertheless, a subset of patients demonstrate resistance to conventional chemotherapeutic approaches and emerging immunotherapeutic interventions [3]. In the case of B-ALL, the CAR-T cells are designed to target CD19, CD20, and CD22 antigens which are commonly expressed by the tumor cells of B-ALL. Studies have shown a positive trend in the improvement of cancer treatment effects by CAR-T cell therapy, there is success in both pediatric and adult patients (the success rate of complete remissions is 80-90%). However, nearly half of the patients who positively responded to this therapy showed reoccurrence in the time of 1-2 years, for several reasons including the deficiency of the number of T cells and immunology that the tumor has developed against this drug [4]. It is shown that the overall survival rate of the patients in response to CAR-T cell therapy is 60% in 1 year; also, when adding Rituximab with CAR-T, the median survival time is 29.27, which increased about 197.8% of the one without.

2.2. MM

MM is a type of blood cancer that is developed from the proliferation of plasma cells. Plasma cells play crucial roles in a person's immune system, they derive from B lymphocytes and are responsible for producing antibodies; when they become cancer cells, they lead to a series of problems including immunodeficiency, bone tissue destruction, and organ damage.

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Incidence of MM is highly variable among countries but has increased uniformly since 1990, with the largest increase in middle and low-middle SDI countries [5].

In the treatment of patients with MM, in all of the therapies, the median survival time is 10 years, while it is about 5.2 years for the patients undergoing CAR-T cell therapy which is in no need for further or prolonged treatment. In therapy, the CAR-T cells are designed to target two antigens, BCMA and CD19; the effect of the one targeting BCMA is with rather short-term effects and short efficient periods, while the CD19 targeting T cell is of longer capacity and a higher chance of overall cure. There is a relatively low relapse rate in this treatment compared with others: the reoccurrence rate of the patients who respond to the therapy was around 38% of the total number of receivers, while the median number of the cancer-free time of all the responders are about 8 months. Recently, this data also increased dramatically, the reoccurrence rate changed to around 87%, and the time that the patients are cancer-free has risen to 1 year. Also, the severity and response of neurotoxicity are relatively low, about 13% [6].

2.3. CLL

CLL, unlike other types of leukemia, is rather slow in progression, though still depending on specific cases. When the DNA of stem cells mutates, malfunctioning B lymphocytes are generated, and some of these cells possess the characteristics of cancer cells, with long life span and proliferation abilities, causing them to accumulate in the blood, forming cancer. This type of cancer is more commonly seen in adults rather than children. In the case of chronic lymphocytic leukemia, it is in a relatively more severe state than the previously mentioned acute lymphoblastic leukemiaThe case of chronic lymphocytic leukemia (CLL) has increased more than twice between 1990 and 2017. The ASIR of CLL increased by 0.46% per year from 1990 to 2017. More than 85% of all countries saw an increase in ASIR of CLL [7].

The treatment performed by CAR-T cell therapy has shown great significance. Patients respond to it while not doing as well under other immunotherapies and chemotherapies. However, relapse can also occur because of the decrease in antigens like CD19 and forming immune responses to the initial drug of treatment. Efficacy evaluation showed that 73% of patients responded to the infusion, with 12(40%) patients achieving MRD-CR/CRi and 10(33.33%) patients achieving MRD+CR/CRi, for an overall response rate (ORR) of 73.33%. A significant number of patients experience long-term remissions and 76% of patients are in response from 3.5 years to 9.4 years.

3. Commonly safety problems and possible solutions

3.1. Off-target effects

Off-target effects occur when CAR-T cells attack healthy body cells that they are not programmed to target, these are commonly seen side effects of CAR-T cell treatment, because of its many causes, leading to a high probability. These causes include healthy cells expressing the same or similar antigens that were targeted by CAR-T cells, cancer cells repressing the expression of targeted antigens, or the CAR-T cells being programmed with targeting flaws in the first place. For example, CD19 antigen is a protein present on the surface of leukemia and cancerous lymphocytes, however, healthy B cells also express these antigens, so these antigen-targeted CAR-T cells can incorrectly recognize healthy B lymphocytes as the ones that they were supposed to attack, thus causing the off-target effect. Also, another issue is that cancer cells could develop immunity to the CAR-T cell therapy which leads to side effects or resistance like the off-target effect. Some tumor cells down-regulate the targeted antigens to reduce the chance of being recognized and lead to apoptosis, or they upregulate some checkpoint inhibitors like PD-L1 to slow the progress of CAR-T cells.

One of the solutions to problem-solving is adding a switch for the CAR-T cells, this switch allows the CAR-T cells to be activated and inactivated, considering the occurrence of side effects, it promotes the elimination of potential problems with off-target effects and toxicities damaging the healthy somatic cells. This approach includes the suicide gene switch and the novel blue light switch.

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For the suicide gene switch, an inducible caspase-9 system is programmed into the CAR-T cell, when severe side effects happen, a drug like AP1903 will be able to bind to this protein and activate the apoptosis effect of the T cell, acting as a safety mechanism to some off-target effects. This has considerably decreased the significance of damage.

The novel blue light switch uses blue light to control the on and off of the CAR-T cells. When the patients undergo serious side effects like CRS or mass off-targets, blue light radiation can be used on the patient to deactivate some of the toxin-releasing CAR-T cells. However, there are also serious potential problems. People are exposed to blue light for most of the day, for instance, sunlight consists of blue light; these exposures can accidentally cause the CAR-T cells to be turned off and stop functioning, having serious impacts on the length, effectiveness, and afterward follow-ups of the therapy itself.

3.2. CRS

Severe CRSs occur in one-third of cancer patient treatment cases; this is a common source of organ damage and the leading cause of mortalities in the process of treatment using CAR-T cell therapy. The severity of CRS is determined by many factors, including certain molecules that might promote toxin release, the specific type of CAR-T cells used in practice, the immune system of the patient themselves, etc.

Currently, the management of CRS remains on the level of preventing death-causing and irreversible damaging CRS effects without limiting the efficacy of tumor treatment. One possible way of prevention is using tocilizumab; this is an anti-human IL-6 receptor monoclonal antibody that is in use for treating the symptoms caused by CRS like hypotension, fever, and underlying infections [1]. Tocilizumab prevents IL-6 receptors that are produced by the macrophages relatively downstream of the CAR-T activation sight by binding to the receptors, therefore easing the symptoms caused by CRS. This treatment is seen as one of the most effective ways to relieve the impact of CRS at a relatively early intervention stage. However, in some cases, fever and infection still linger, studies use persistent doses of corticosteroids, antibiotics, or other cytokine-targeting therapies to repress these side effects, or they increase the frequency and amount of the dosage.

Another potential treatment plan is to use the JAK/STAT pathway inhibitors like ruxolitinib and itacitinib to inhibit some of the production of the inflammatory cytokines, simultaneously, no signs of compromise of the treatment effect showed [8].

Currently, people are still in the stage of seeking the best possible ways of overcoming CRS as one of the most significant contributors to mortality rates over the range of cancer cures. Although there are still chances that remain of having severe CRS; clinical trials are developing novel combination therapies for problem-solving.

3.3. Neurologic toxicities

Neurotoxicity is the effect of the reaction of the immune system acting on the nervous system due to specific treatments like CAR-T cell therapy or immune checkpoint inhibitors. The severity of neurotoxicity usually correlates positively with the degree of CRS, generally taking place after CRS has subsided; however, in some cases, this has the chance to occur without the presence of CRS or the degree might not be significantly influenced. The symptoms of neurologic toxicities vary widely, it can range from light headaches to deaths caused by drug-led respiratory failure.

Currently, there are ways to treat this side effect. For example, corticosteroids like dexamethasone are used for immunosuppression to lessen the impact of neurologic toxicity. Also, research has discovered that interleukin-6 aggravates immune response and enhances neurotoxicity; so, using anti-IL-6 to block the protein will likely decrease the symptoms of neurotoxicity.

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4. Potentials in the application of solid tumors

4.1. Special targets

Special targets are important to the development in the field of treatment success in CAR-T cells treating solid tumors for various aspects. This is one of the ways of adding additional receptors while editing the extracted T cell the improve the accuracy and persistence of recognition and action. At the same time, it effectively avoids the high risk of off-target effects,

There are potentially many ways to enable specific targets. For example, in programming in apoptosis genes, when there is serious damage to the organs being sensed, the gene will lead directly to the death of CAR-T cells; controlling cytokine release through the use of special proteins will allow people to regulate the intensity of inflammation and other immune reactions led by the immune system, reducing the risk of CRS.

4.2. Experiments

There are currently relatively many clinical trials and experiments done with the target of treating solid tumors; many new drugs are still in early trials. There are many potential solutions presented, for example, combined therapies, entering through immune checkpoint suppression, and cytokine control.
In combined therapies, CAR-T cell therapy is combined with chemotherapy or targeted therapies, these previous therapies help the CAR-T cells to more easily get to the point of a tumor, thus enhancing the efficiency of treatment. Adding antibodies to CAR-T cells that work against the immune checkpoint inhibitors that counteract T cells is crucial for the improvement of CAR-T therapy, this can reduce the frictioncaused by the tumor microenvironment itself. Lastly, controlling the cytokine-releasing mechanism is also important, manipulating the CAR-T cells to release special kinds of cytokine that can be recognized by other immune cells around the tumor's environment can strengthen the force of treatment and recruit the immune system to react to the tumor site.

Recently, experiments have been done aiming to solve the problems with solid tumor treatment, the experiments are mainly based on the process of general cancer treatment using immunotherapies. These include selecting appropriate targets for the CAR-T cells to identify, designing CAR-T cells, developing strategies for dealing with the tumor microenvironment, developing vaccines, and identifying potentials for further application with combined therapies.

4.3. Problems and Solutions

The treatment in solid tumors by CAR-T cells is not as well developed as in blood cancers: it is with less precision, harder to penetrate, and lacks durability. The reason why it is significantly harder to put CAR-T cell therapy into practice with solid tumors is that its tumor microenvironment contains barriers for T cells and immunosuppressive contents, also the blood vessels and tissues on the outer layer make it harder for the T cell to penetrate and perform persistent recognition and reaction to the cancer cells.

However, because manipulating the CAR-T cells to release special kinds of cytokines includes studies to do further modification on this part, so this action has the chance to increase the risk of CRSs and lead back to the problem that it was supposed to solve. Also, if combining other therapies like chemotherapy with CAR-T cell therapy to enhance the efficacy of treatment, it will be likely for the tumor to easily develop an immune effect on the drug, and CAR-T cell therapy will also lose its point; because the development of the immune effect of the tumor will likely change the receptor that the CAR-T cell was designed for.

5. Conclusion

The potential for the application of CAR-T cells in the treatment of solid tumors is very wide, the CAR-T cell treatment therapy itself is one of the most efficient ways to treat cancer. However, it is still limited on the practices with solid tumors, studies have entered through the steps of cancer treatment to resolve this. Experiments show that the success rate of treating solid tumors with CAR-T cells is steadily increasing although it still varies with the specific type of tumor. For example, it has of high success

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rate in treating prostate cancer, gastrointestinal carcinoma, and malignant gliomas; on the other hand, some kinds of solid tumors like pancreatic cancer, ovarian cancer, and some that are easy to spread are in late stages are rather difficult to treat up until recently.

Studies have already found ways to improve the outcome of solid tumor treatment by CAR-T cells, by further editing and enabling more variable and precise functions to the T cells, CAR-T cell therapy will have a better application and expectation in the near future.

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