Discussion on the Car-t therapy's benefits and side effects by using and analyzing the Therapeutic application of Carvykti in multiple myeloma (MM)

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Abstract. MM, multiple myeloma the cancer of bone is becoming a serious medical problem that more than a hundred thousand people suffer from it nowadays. Recently, it surpassed leukemia and become the top 2 blood system cancer in America. In the US, the lifetime risk of getting multiple myeloma is 1 in 132. And until now, there haven't a proven way to cure this disease completely. In common treatment, corticosteroid drugs and the medicines like Dexamethasone Selinexor and Bortezomib that we use to treat this disease are only proven to control the process of the MM and decrease the pain of the patients. Expect using these drugs or the combination of drugs to interfere with the development of the MM we also have the stem cell transplantation treatment to control the patient's conditions. Of course, there is a common treatment for most cancer is chemotherapy but as we all know this treatment usually has serious side effects. Under such a circumstance, Legend Biotech developed Carvykti, the drug which uses Car-t therapy for treating patients who cannot be cured or even won't going better by using the common therapy. The paper reviews this kind of drug by using its data according to the results of the clinical trials and the FDA reports. Then the paper compares it to the common therapy to overview car-t therapy's possible advantages and disadvantages directly and than try to provide another version to optimize the Car-t therapy in curing MM. This paper also summarizes car-t therapy's development. At last, according to these results to review some possible optimization for car-t therapy.

Keywords: Car-t Therapy, Multiple Myeloma, Carvykti.

1. Introduction

CAR-T therapy is a new biotech therapy, and it is one of the top topics in recent years, and the drug research is gradually deepening. It is a highly complex and innovative new treatment [1]. The principle is that T cells modified by chimeric antigen receptors can specifically recognize tumor-related antigens so that the targeting, killing activity and persistence of effector T cells exceed those of conventionally used immune cells, thereby exerting anti-cancer effects It can effectively resolve the local immunosuppressive microenvironment caused by tumors, thereby breaking the host immune tolerance state. Chimeric antigen receptors are derived from the external antigen recognition domains of cells (usually single-chain antibodies, but also a polypeptide or other protein) and intracellular signaling domains. The outer portion of CAR cells is used to recognize specific tumor antigens. It has the advantage of shorter treatment times, prolonged durability, and fewer side effects. But it also has some possible side effects like CRS and serious nervous system problems. Car-t therapy can be more natural and suitable for patients who got problems with malignant tumors of the blood system, but as a new therapy although it is popular and shows great potential now it still has a risk of side effects, and the paper will show some possible issue by giving the possible side effects of Carvykti. And Car-t therapy still has significant challenges and remains ineffectively targeting solid tumors either. The process of it was shown in figure 1.

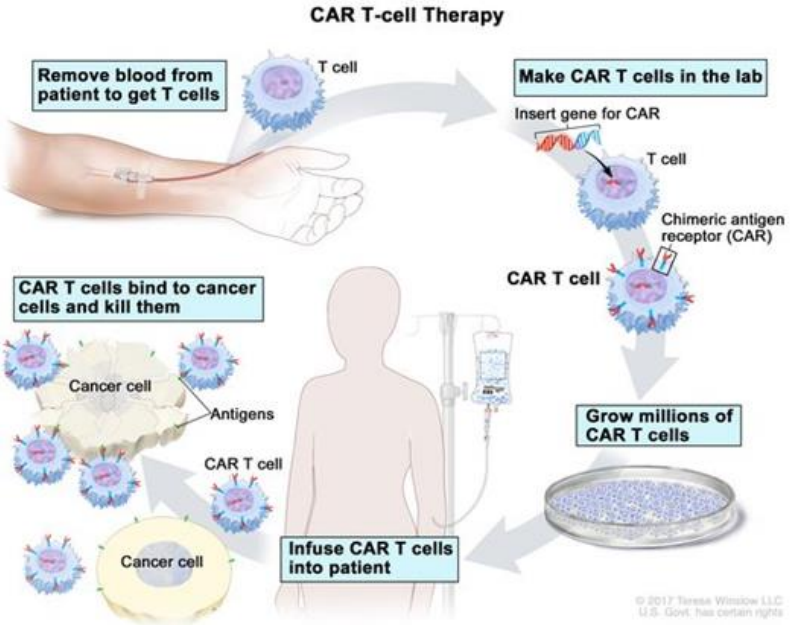

Figure 1. The process of Car-t therapy [2]

Multiple myeloma (MM) is a malignant tumor caused by abnormal proliferation of plasma cells - bone marrow cancer.MM accounts for 1% of oncological diseases and 10% of hematological tumors. It damages the bone, extramedullary infiltration, anemia, infection, renal impairment, hyperglycemia, hyperviscosity syndrome, bleeding tendency, and causes bad pain. In the US, MM has already surpassed leukemia and became the top 2 blood system high incidence tumor second only to lymphoma [3]. Its pathogenesis is a clonal plasma cells' proliferation in bone marrow, causes osteolytic bone damage, in addition to the presence of monoclonal immunoglobulins in serum and inhibition of normal polyclonal immunoglobulin synthesis, as well as the presence of this protein in the urine. Anemia and renal impairment. Its cause is not yet clear, but now Myeloma cells are thought to originate from B memory cells or blast plasma cells. Its potential target -IL-6 is abnormally increased in the bone marrow of patients with progressive myeloma. This phenomenon is generally believed to be that IL-6 is one of the growth factors of myeloma cells, which can promote the proliferation of myeloma cells and inhibit their apoptosis. Its subtypes include Secretory myeloma, nonsecretory myeloma, and smoldering myeloma. And some special, rare subtypes like Solitary myeloma, extramedullary myeloma, and nonsecretory myeloma. And until now, there haven't any proven treatment that can completely cure Multiple Myeloma [4]. But people can control its process by removing malignant cells from the bone marrow and relieving pain, anemia, and kidney damage. And usually use chemotherapy, stem cell transplantation, corticosteroid drugs, Biologic therapy, Targeted therapy, Surgery, and radiation therapy to manage the symptoms.

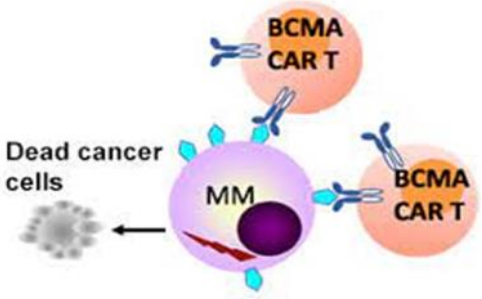

Figure 2. Personalized CAR-T cells kill cancer cells with the help of BCMA [5].

CARVYKTI™ (ciltacabtagene auto excel) is a newly approved drug for the treatment of adult patients with multiple myeloma with Car-t therapy when at least four other treatments are incurable or ineffective. CARVYKTI™ - a drug made from a patient's white blood cells that are genetically

engineered to recognize and attack the patient's multiple myeloma cells. After a single infusion, CARVYKTI™ alters a patient's effector T cells to recognize and attack multiple myeloma cells in addition to recognizing and attacking targets outside of some other healthy cells. So basically, this kind of drug is used to help the patient's immune system against their multiple myeloma cells. Scientists create personalized CAR-T cells by collecting patients' T cells to use Car-t therapy. These cells will recognize and use against bone cancer cells. After these cells are infused into the body, they will multiply in the body, and finally, they will be combined with BCMA, a protein found on the outside of the human body (figure 2 and figure 3).

Figure 3. The process of personalized CAR-T cells [6].

In this review, the paper listed some clinical trials' results of Carvykti like it does and summarized the side effect of Carvykti. Summarize the side effects of Car-t therapy and compare the side effects of Car-t therapy based on the case of Carvykti in MM to the common treatment based on the side effects of dexamethasone. And try to list some possible future development of Car-t therapy like optimization during Pivotal Clinical and using bioprinted to improve.

2. Carvykti clinical trials results compare to the common therapy

In the clinical first-line treatment, patients with multiple myeloma are treated with a chemotherapy group. Because this tumor occurs in bone tissue, and the effect of surgical excision or chemoradiotherapy drugs on this tissue is very limited. After conventional surgery, the removal of bone tissue can also bring great inconvenience to the patient's life, and the open wound increases the chance of infection. Moreover, tumor patients often use immunosuppressants, which undoubtedly creates a better opportunity for pathogenic bacteria. The biggest question is whether surgical removal of the pathogen can completely cure the tumor. The answer to this question is, of course, questionable. Because MM may metastasize in patients with advanced stages. Therefore, the patient may also have to choose a secondary surgical regimen. In addition, in some elderly patients, the burden of surgical trauma is too great. Some patients can barely survive from the operating table. As a result, clinicians need to perform a detailed preoperative evaluation when considering surgical options. Moreover, the anesthesia program during surgery may also affect the prognosis and progress of surgery. Finally, the cost of surgery also needs to be considered. In some cancer patients, whether they can afford long-term hospitalization and surgical costs needs to be considered. As a result, the surgical approach that dominates tumor treatment does not seem to have a good advantage over MM.

In the current clinical chemotherapy regimen, it mainly includes a chemotherapy regimen of a single drug and a chemotherapy regimen of a combination of multiple drugs. The former can use cyclophosphamide, doxorubicin, vincristine and the like. The latter often uses 2-3 drugs that are effective for myeloma monotherapy to form a combination chemotherapy regimen, so as to achieve the therapeutic effect on myeloma. At present, in international guidelines, chemotherapy regimens centered on bortezomib are mostly recommended. At present, there are also some researchers who advocate hematopoietic stem cell transplantation after treatment with high doses of chemotherapy drugs. Mainly after treatment with conventional chemotherapy drugs, the patient's hematopoietic system is significantly suppressed. This leads to many complications, such as anemia and granulocytopenia. This reason can be explained by the fact that the bone marrow is the base of the early hematopoietic system. If this base is destroyed, the obvious hematopoietic function will be destroyed. This programme has also achieved good therapeutic results in recent years.

In advanced patients, complications need to be considered. Because cancer pain is usually the most affecting the quality of life of patients. Clinically, topical treatment can be taken to alleviate this symptom.

Some patients may feel confused, less alert, or disoriented. And what's more some of them may have trouble in speaking or incoherent speech, difficulty in understanding words, reading, and writing, and decline of memory these issues are quite serious in the brain and the whole nervous system. Certain patient populations may also lead to loss of coordination of movement and balance, slow movement, and different handwriting. It can also lead to changes in the patient's personality, including difficulty expressing emotions, taciturnity, low interest in activities, and reduced facial expression. Some muscle issues also may happen as tingling, numbness, pain in the hands and feet, difficulty walking, and leg and/or arm weakness, what's more, difficulty breathing is also a potential side-effect. So, side-effects of Carvykti are also serious problems that need to solve but generally, this drug is relatively feasible and less harmful to the patient. As a living therapy derived from the patient's cells, it still has high reliability and adaptability to the patient. Risks are still acceptable and manageable. It has extremely high application value in dealing with MM cases that are difficult to be treated by conventional therapeutic intervention. But at the same time, we cannot ignore the risk of its potential side effects, and it can still be improved in the future. With the precipitation of time, its curative effect and side effects will become more and more clear.

3. Car-t development

In 1960, the beginning year. Scientists found that immune cells can prevent mice from cancer. But is not completely clearly understood by the scientists. And the T cell's original year is 1961 founded by Jacques Miller. The first success of immunotherapy that was most recognized happened in In 1973, bone marrow transplantation was used to treat cancer. In 1986, tumor-infiltrating lymphocytes began to be used in cancer treatment. While the formal beginning of T cell engineering was in 1992 by Michel Sadelain. But the result was a few years later. Zelig Eshhar, an immunologist at the Weizmann Institute in Israel 1993, Engineered T cells that developed the first chimeric molecule by fusing part of an antibody to part of a T cell receptor, and that's the first-generation CARs developed. The first time Antigen-specific T cells were used in humans happened in 1994. In 1998, co-stimulation was shown to provide scientists with the necessary boost. This lays a good foundation for a new generation of CAR technology. Since entering the 21st century, the rapid progress of biotechnology. 2003 Second-generation CARs were built to target CD19 and in 2009 the recipe for CD19 CARs was published. The Coley Award was awarded to CAR T-cell therapy in 2012. In 2013, the results of CAR T therapy clinical trials in leukemia were announced, and the therapy was named "Breakthrough of the Year". In 2014, the FDA designated CAR as a "breakthrough" therapy, and mesothelin-directed CARs were developed. Armored CARs were developed in 2015. In 2017, another fruitful year, CRISPR CARs were built, and the First CARs crossed the regulatory finish line [8].

4. Car-t possible side effects

CAR T-cell therapy is highly effective for some cancers that are difficult to treat with traditional therapies, but can sometimes lead to some side effects. Because of these possible side effects, they need to be managed in specially trained medical centers and patients need to be closely observed after cell infusion. The following are possible side effects.

When CAR-T cells proliferate, they release a large number of cytokines into the circulatory system and enhance immune system function. Causing symptoms such as high fever and chills. Sometimes patients also feel dizzy, have a rapid heartbeat, are very tired, and have muscle and joint pain. This treatment sometimes affects the nervous system and causes symptoms such as headaches, personality changes, and sometimes side effects such as confusion, difficulty speaking and understanding, and loss of balance.

Other possible side effects of CAR-T cell therapy include anaphylaxis. Some patients have abnormal mineral levels in their blood, such as low levels of potassium, sodium or phosphorus. Resulting in a weakened immune system, severe infections, and lower blood counts.

Table 1. The comparison of the possible side effects of Car-t therapy which is shown in using Carvykti treatment at MM, and the possible side effects of Dexamethasone treatment at MM

Car-t cell therapy	Carvykti	Dexamethasone
Cytokine release syndrome (CRS)	Fever; chills and rapid heart rate	stomach, headache, increased appetite or lethargy, infection, pain, an unstable heart rate, high eye pressure, seizure symptoms. diabetes. Rash, itching, severe dizziness, difficulty breathing.
Nervous system problems	Have trouble inbreathing; low pressure of blood, and dizziness	
Other serious side effects	Confusion, decreased vigilance, or disorientation; may have trouble in speaking or slurring, trouble inreading, writing, or evenin understanding words, and decrease in memory, coordination, unbalance, altered handwriting	

5. Some potential ways for Car-t optimization

5.1. By using the Bioprinted 3D Tumor Mode to improve Car-t therapy

3D tumor modeling is a reproducible approach to optimize CAR-T therapy. "Chimeric antigen receptor (CAR) T cells are often less effective against solid tumors in mouse models and clinical trials than predicted by CAR structure selection in two-dimensional (2D) co-cultures" [9]. Grunewald, L., Lam et al. tested neuroblastoma generation of highly reproducible 3D human tumor models by using 3D bioprinting methods. In the CAR-T cell infiltration model, CAR-T and tumor cells can be isolated into single-cell suspensions in long-term experiments to quantify CAR-T lymphocyte activation and effector function. In the 3D model, the intensity of activation of L1CAM-specific CAR T cells by neuroblastoma cells was higher than in 2D co-culture, but the rate of lysis of neuroblastoma cancer cells was lower. Car-t cell tumor infiltration can be detected and quantified. Represents a superior in vitro assay tool for preclinical CAR-T cell properties and may be better than 2D co-culture to select CAR-T cell performance [9].

5.2. By using Small-Molecule-Based safety switches to optimize CAR-T Cell therapies

Car-t therapy is used to treat leukemia. But there are obstacles. Is hampered by a severe cytokine release syndrome. The safety of this approach could be improved by designing an "off" or "on" safety switch for CAR-T cells. Combining the advantages of genetic engineering and chemical technology, a small molecule safety switch for CAR T cells has been invented. Small molecules FITC, folic acid, rimido, etc., are being studied to design safety switches [10]. This approach appears to provide pharmacological control of activity and toxicity associated with CAR-T cell-based cancer immunotherapy.

6. Limitation

First, the process of CAR-T therapy is time-consuming because it involves extracting cells, engineering them, and then expanding their numbers in the laboratory before injecting them into patients. In addition, not all patients who might benefit from CAR-T-cell therapy can be given cells. Moreover, their cancers may progress so quickly that the window of opportunity closes when the engineered cells are ready. CAR-T therapy has some side effects, which can be divided into three categories. The first is cytokine release syndrome (CRS) . In therapy, the activation and expansion of CAR T cells can lead to the production of large amounts of cytokines, triggering the most severe toxicities. Can be manifested as fever, hypotension and hypoxemia, organ dysfunction and so on. The second is neurotoxicity. Neurotoxicity is associated with CRS, and cytokines are elevated not only in the blood but also in the cerebrospinal fluid, which can lead to extensive white matter and neuronal damage. The third is targeted and non-targeted killing of healthy cells. That is, CAR T cells can target other healthy cells that express the engineered antigen at low levels. If not dealt with in a timely manner may be life-threatening. So CAR-T cells must be closely monitored after infusion

7. Conclusions

Car-t therapy is hot in the biological technology field and shows good potential in recently curing certain blood cancer. As new biotech, it has some benefits that the other treatments don't have. It doesn't need chemotherapy and that avoids a lot of serious side effects. Also, it usually does not require immunosuppression. Multiple myeloma the top two blood cancer in America still doesn't have a treatment to cure it. In this situation, Carvykti, a drug developed by Legend Biotech and used to treat multiple myeloma is approved by FDA this year (2022). This drug is using the new tech-Car-t therapy to treat the blood cancer-MM (multiple myeloma). That seems to show a good direction in curing some certain blood cancer. But Car-t therapy still has some serious side effects which need to solve and improve. Especially the side effects on the nervous system and the circulatory system. That's shown in the case of the Carvykti used in MM. But in general, the side effects and their probability of occurrence are still in control. And this therapy certainly shows a good R & D direction which can be shown in the ORR of Carvykti. In the future, using bio-printed as a preselection tool to detect and quantify and using small-molecule-based safety switches to improve the safety in Car-t therapy seems feasible.

References

[1] NHS England, CAR-T Therapy, https://www.england.nhs.uk

[2] National Cancer Institute, Chimeric antigen receptor T-cell therapy, https://www.cancer.gov

[3] American Cancer Society, Key Statistics About Multiple Myeloma, https://www.cancer.org

[4] National Cancer Institute, CAR T Cells: Engineering Patients' Immune Cells to Treat Their Cancers, https://www.cancer.gov

[5] National Cancer Institute, Carvykti Approval Marks Second CAR T-Cell Therapy for Multiple Myeloma, https://www.cancer.gov

[6] Janssen Biotech and Legend Biotech, CARVYKTI™ (ciltacabtagene autoexcel) Suspension for IV infusion, https://www.carvykti.com

[7] U.S. Food & Drug Administration, HIGHLIGHTS OF PRESCRIBING INFORMATION, these highlights do not include all the information needed to use CARVYKTI safely and effectively. See full prescribing information for CARVYKTI. suspension for intravenous infusion, Initial U.S. Approval: 2022, https://www.fda.gov/media

[8] Memorial Sloan Kettering Cancer Center, CAR T Cells: Timeline of Progress, https://www.mskcc.org

[9] Gruneld, L., Lam, T.,et.al (2021, June 29). A reproducible printed 3D tumor model serves as a preselection tool for car T cell therapy optimization. Frontiers in immunology. Retrieved July 6, 2022, from https://www.ncbi.nlm.nih.gov/pmc/articles

[10] K; Z. Y. N. K. S. C. (n.d.). Optimization of CAR-T cell-based therapies using small-molecule-based safety switches. Journal of medicinal chemistry. Retrieved August 15, 2022, from https://pubmed.ncbi.nlm.nih.gov