The treatments of Carvykti in Multiple myeloma

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Abstract. Multiple myeloma is a severe malignance caused by damaged B cells from bone marrow plasma cells. Multiple treatments have been introduced to release and treat such a disease, but in general, high rate and severity of adverse events and relatively unideal efficacies of those existing treatments necessitate a new therapy achieving a better curative effect. Thus, CARVYKTI, a CAR-T therapy, has been developed for treat patients with multiple myeloma and who have already received several other treatments. By having genetically modified T cells, damaged cancer-causing B cells are targeted and vanished specifically. Recently, the FDA has officially approved CARVYKTI as a treatment for refractory multiple myeloma, and the basic pharmacology and the phase1b-2 clinical trial are summarized in this paper.

Keywords: Clinical, Carvykti, Treatment.

1. Introduction

Multiple myeloma is a type of cancer caused by the aggregation of terminally differentiated plasma cells in human marrow. Overall, around 1.7% of all malignances in the United States are diagnosed as multiple myeloma in 2017 [1]. With its aggressiveness, a high fatality is expected and observed among patients. One common feature of the mutated myeloma cell is secreting a monoclonal immunoglobin protein which is the main biomarker of diagnosing multiple myeloma. Besides helping the diagnosis of multiple myeloma, the monoclonal immunoglobin protein is responsible to many symptoms related to this malignance including anemia and organ damages especially kidney disfunction.

CAR-T immunotherapy has been clinically efficient in curing leukemia, but the efficacy in solid tumors has not been satisfactory, and related problems and solutions have been proposed, from the low infiltration and low killing of tumors by the existing CAR-T itself, to the immune escape of tumor cells, to the inhibition of CAR-T by the tumor microenvironment. In this paper, we explore all the challenges that may affect CAR- T cells for solid tumors and some possible solutions, and we also compare CAR-T with other immunotherapies and point out the maturation and development potential of CAR-T at present.

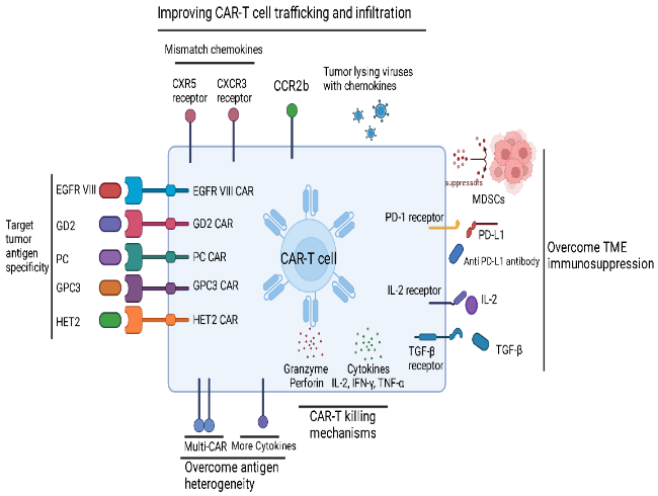

Figure 1. CAR-T cell mechanism and improvement.

2. Etiology

External factor like environments and internal factors like genetic mutations are both considered as contributions in etiology of multiple myeloma. Regarding of environmental impacts, the correlations between ionizing radiation and the disease and between chemicals like pesticides and the disease have been investigated. A week relevance is shown, but more supporting evidence is still needed for having a convincing conclusion. Internal etiological factors like gene are better understood and established. There is a certain level of heredity observed since multiple cases have been recorded in an aggregation of relatives. In addition, genome-wide association studies have revealed that the presence of certain genes could lead to an increased risk of multiple myeloma. To be specific, chromosomal defects including the translocation of immunoglobulin heavy locus are one type of the gene damage causing a greater risk of such a disease. In addition, aneuploidy plays an important role regarding the severity of multiple myeloma. Some data suggests that the worst outcome comes from hypodiploidy, and hyperhaploidy and psudodiploidy bring less harmful outlook. Moreover, studies powered by next-generation sequencing have revealed the correlations of secondary mutations, clonal evolution, and multiple myeloma. Unfortunately, no single mutation is discovered to be the universal one responsible for altering the abnormal differentiation of plasma cells. Instead, the overlapping of subclones is suspected to be a part of the pathophysiology of multiple myeloma. Lastly, epigenetic factors contribute to gene damages and the progression of the disease as well. For instance, DNA methylation including hypermethylation and hypomethylation in a global level is either enhancing the disease development or abundant in the affected plasma cells. With the damaged genetic material, stems cells in the bone marrow further differentiate to B cells with damages. And eventually, damaged B cells differentiate to myeloma cells secreting monoclonal immunoglobin proteins instead of plasma cells with normal functions. Besides genomes, in general, the microenvironment in bone marrow and the level of proteasome also link to the development, aggression, as well as the migration of multiple myeloma.

3. Treatments

Regarding of treating multiple myeloma, several effective treatments including transplantation and pharmacological therapies are well practiced. Haemopoietic stem cell transplantation indeed is an effective treatment for this malignance, however, due to the otherness among patients, not all patients especially the elderly population with multiple myeloma are eligible to receive such a therapy. Thus, drugs have a more universal applicability for most of patients. At one time, chemotherapy like cyclophosphamide and cisplatin was the most chosen one to treat multiple myeloma. This therapy uses chemicals to inhibit and kill cancer cells generally causing a series of adverse events since harsh chemicals are deleterious to healthy cells as well. With more drugs have been newly developed, chemotherapy is less likely used as a primary treatment for most of patients with multiple myeloma [2]. Other pharmacological drugs include corticosteroids, proteasome inhibitors like Bortezomib and Carfilzomib, immunomodulatory drugs like Lenalidomide and Thalidomide, monoclonal antibodies against CD38 like Daratumumab, monoclonal antibodies against SLAMF7 like Elotuzumab, alkylating agents like Melphalan and Bendamustine, and nuclear-export inhibitor like Selinexor. To reach a better performance, a cocktail therapy containing several drugs is preferable as a multiple myeloma treatment than using a drug alone. The combination of Bortezomib, Cyclophosphamide, and Dexamethasone is an example of one of the suggested cocktail treatments. Even though there are tens of therapies for multiple myeloma to choose from, many issues associate with the nature of existing drugs. In general, their effects are short living, their side effects are significant, and the chance of recrudesce is high. Thus, more effective and safer therapies are urgently needed for multiple myeloma to bring a promising vista.

4. Carvykti

With the great demand for a new therapy of treating multiple myeloma, Janssen Biotech, Inc has developed a new treatment, Carvykti, based on CAR-T technology. In general, CAR-T therapy is achieved by genetically modifying patients' T cells with a CAR module. This artificially added module is the product of gene editing on T cells, and it contains five major parts which are the outer most single domain antibody complementary to B-cell maturation antigen (BCMA), a spacer, a hinge region, costimulatory domains, and the inner most CD3ζ chain which is the intracellular signaling domain of the T cell. The CAR-T cell recognizes malignant plasma cells by detecting the complementary integration between Anti-BCMA and BCMA on myeloma cells since the overexpression of BCMA is a biomarker highly specifically for malignant plasma cells and it is essential for the mature of these cells. When a successful detection occurs, the CAR-T cell will be activated and quickly proliferates followed by its secretion of cytokine which kills BCMA-targeted myeloma cells [3].

5. Fda approval

CARVYKTI, the propriety name of ciltacabtagene autoleucel, is a treatment that newly developed by Janssen Biotech, Inc. to treat adults with multiple myeloma and who have been treated with other three or four primary cancer treatments. Its Investigational New Drug Application was submitted to FDA on April 27, 2018, and it was approved as a treatment for such a disease on February 28, 2022, after almost three years of multiple regulatory events. Due to the urgency and high malignancy of relapsed or refractory multiple myeloma, the FDA relatively rapidly approved this drug mainly based on the evidence of safety and efficacy from a phase 1b-2 study named CARTITUDE-1by Berdeja et al.

6. Nonclinical pharmacology

The nonclinical pharmacology of CARVYKTI primarily focused on the cytotoxicity on tumor cell and off-target effects on normal cells. As introduced in the FDA's Summary Basis for Regulatory Action, both vitro and vivo models were studied for the toxicology [4]. By applying this treatment in vitro studies, wanted tumor cell cytotoxicity was found which indicated a potential on treating cancer. In Vivo studies performed on mice and non-human primates, no severe adverse events caused by off-target effects were observed. Besides the toxicity, some other nonclinical findings indicated a promising efficacy. Through those animal models, this drug exhibited an anti-tumor activity which highly depend on the does, and it increased the survival in immune-deficient mice as well.

7. Clinical pharmacology

As mentioned previously, the clinical studies and trials of CARVYKTI were strained in phase 1b and phase 2, and their results and analyzations were presented in CARTITUDE-1. According to this paper, phase 1b in this study was focusing on observing adverse events and deciding the dose used in phase 2, and the main goals of phase 2 were finding the response duration and progression-free survival [5]. Originally, 113 satisfactory patients were recruited for this clinical trial running from July 2018 to Oct 2019. However, 16 patients discontinued and did not receive CARVIKTI treatment due to cancer progression, death, or withdraw. Among the remaining subjects, 29 patients were injected with a single CAR-T cell infusion (target does: 0.75×106 CAR-T cells/kg) after the lymphodepletion in phase 1b. In this 21-day dose evaluation period, safety and pharmadynamics were monitored as priorities [6]. The transgene level as the biomarker for phamardynamic was collected which reached the peak at 12.7 days with a half-life of 25.4 days on average. Regarding the safety, there was no finding of fatal adverse events, and more detailed feedbacks were collected during phase 2.

After progressing into phase 2, 68 patients received the treatment with the same dose as in phase 1b. In this a-year-long trail, efficacy and safety were both well analyzed. Regarding adverse events, 14 patients died during the study period, and 6 deaths were considered as treatment-related [7]. Besides succumbing, other adverse events have shown as well. In general, every subject has suffered from some types of adverse events, but 94% of the adverse events were relatively tolerable and moderate. Among all observed events, hematological diseases were the most common type including neutropenia, anemia, and thrombocytopenia. Another very common adverse event was cytokine release syndrome which 95% patients have encountered with. In 99% cases, the cytokine release syndrome was not life-threatening and remitted within a median of four days by treating with supportive measures [8]. However, there was one patient died because of a severe cytokine release syndrome adverse event at day 99. Other five death related to adverse events were cause by neurotoxicity events. Total of 12 patients suffered from previous neurotoxicity events with variable and unpredictable symptoms which made this type of adverse event to be more severe and fatal than others. Besides the mortality, previous neurotoxicity events had a much longer recovery period whose median was 74.5 days than other events. Thus, the FDA requires the Risk Evaluation and Mitigation Strategy when applying this treatment to ensure patients will benefit more from the effects than be endangered by the risk of cytokine release syndrome and neurotoxicity events. More than half of the patients also had infections like pneumonia and sepsis, gastrointestinal reactions like diarrhea and nausea, and metabolism and nutrition disorders like hypocalcemia. Even though these other adverse events were varied and impacted on many systems and organs, there was no death shown correlations with them. Overall, CARVIKTI's safety is satisfying, and adverse events are acceptable considering its nature of treating severe disease [9].

Regarding efficacy, in general CARVYKTI treatment reached the highest overall response rate comparing to other mainstream drugs, and it's also promising for the patients who are highly refractory. To be specific, in phase 2, the overall response rate of CARVYKTI was 97%, and 67% patients even had stringent complete response with a duration of one month. Even better, those responses were not transient because deepened response had been found commonly in treated patients during phase 2. Besides cellular response of CARVYKTI, patients' survival was also monitored. Within the 12-month trial period, an overall progression-free survival rate has reached 77%, and the overall survival rate was as high as 89% [10]. Thus, based on study-proved treatment effects and acceptable adverse events, FDA approved CARVYKTI to be used as a treatment of "adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody".

8. Post-marketing requirment study

As previous introducing, only phase 1b/2 had been done when CARVYKTI was approved be FDA. Thus, such a small patient population and a short duration would leave many concerns regarding more detailed efficacy, safety, and adverse events. To address those concerns, FDA asks Janssen Biotech Inc. to perform a post-marketing requirement study [11]. In this study, participating patients with multiple myeloma and four prior treatments should more than 1500, and more aspects like secondary and insertional malignancies will be monitored. Overall, this post-marketing study will have a 15-year duration for continuous monitoring, and it is guaranteed to complete on June 30, 2041. With this complementary long-term study, patients could benefit more and take less risk when receive CARVYKTI.

9. Conclusion

Multiple myeloma as a life-threatening disease creates a pressing need of therapies. Even though there are already multiple treatments available, a more efficient and safe treatment has been craving by doctors and patients. Thus, CARVYKTI, a newly developed and FDA-approved treatment brings

new hope for reduce the severeness and enhance patients' survival rate. By genetically modifying and manipulating patients' own T cells, the oncogenic damaged B cells are recognized and killed efficiently and specifically leading to a higher efficacy and less adverse events. After analyzing the results of a phase 1b-2 study of CARVYKTI, an approval has been officially given by FDA in early 2022, and patients with refractory multiple myeloma could have been being benefited from this brand-new treatment. Since only a small population had been studied before the approval, post-marketing long-term study for CARVKTI is still mandatory and significant for monitor its efficacy and adverse events. Overall, CARVYKTI powered by CAR-T cell is a promising treatment for multiple myeloma with a best-in-class curative effect and relatively moderate adverse events.

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