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Idecabtagene Vicleucel: The Ultimate CAR T-Cell Therapy for Multiple Myeloma?

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Dear Editor,

On March 26, 2021, the United States Food and Drug Administration (FDA) approved idecabtagene vicleucel for medical use in certain adult patients with relapsed or refractory (R/R) multiple myeloma (MM) (1). Adult MM patients can be eligible for this therapy class following four or more unsuccessful prior treatments. Idecabtagene vicleucel is the first FDA-approved chimeric antigen receptor (CAR) T-cell therapy for MM (1).

Idecabtagene vicleucel is a CAR T-cell product made of autologous T lymphocytes genetically engineered to express CAR molecules redirected against B-cell maturation antigen (BCMA) (2). This means that each course of this therapy uses the patient's own T-cells modified to express the mentioned CAR molecules on their surface. In detail, first, the peripheral blood mononuclear cells are collected from the patient, and then T lymphocytes are separated. Further on, the collected T lymphocytes are genetically modified and expanded to a therapeutic level in ex vivo conditions. Finally, the engineered T cells are reinfused into the patient.

The BCMA, also known as tumor necrosis factor receptor superfamily member 17 or TNFRSF17, is a transmembrane receptor belonging to the tumor necrosis factor receptor superfamily (3). The BCMA is expressed in mature B cells and has a critical role in B cell development and autoimmune responses (3). The aberrant expression of BCMA is observed in various types of neoplasms, including various leukemia, lymphomas, and MM (3). Moreover, BCMA has limited levels of expression in vital human organs, making this tumor-associated marker an ideal target for cancer immunotherapy (3).

The MM is the malignancy of abnormal plasma cells capable of metastasis to the bone marrow and many bones of the body (4). Plasma cells are a type of B cell mainly responsible for the production of antibodies. Therefore, MM is alternatively known as plasma cell myeloma (4). The MM impairs the ability of bone marrow to make sufficient numbers of normal healthy blood cells (4). As a result, MM patients often demonstrate low blood counts in diagnostic tests. The precise cause for MM occurrence has not been fully elucidated to this day (4).

According to global statistics, in 2015, near half a million individuals were diagnosed with MM, 20% of whom died as a result of the disease's progress. The MM usually emerges after the age of 40 and is more common among men than women. With a 10-year survival rate of about 3% after commonly available treatment methods (including chemotherapy and radiation therapy), MM is still known as one of the most challenging hematologic cancers to treat (4). In this regard, more novel treatment modalities, such as cancer immunotherapy (including monoclonal antibody-based therapy or CAR T-cell therapy), can be of valuable advantage for MM patients.

The safety and efficacy of idecabtagene vicleucel were evaluated in a multicenter study on 127 patients with R/R MM who had undergone at least three unsuccessful prior MM treatments (5). Of note, about 88% of the enrolled patients in the aforementioned clinical trial had undergone four or more prior lines of MM therapy (5). The efficacy of this product was evaluated in 100 patients who had received idecabtagene vicleucel (with a CAR T-cell dose range of 300 - 460 $\times$ 10^6) (5). The efficacy of the product was evaluated based on overall response rate (ORR), complete response ([CR], described as "disappearance of all signs of

disease") rate, and duration of response of the patients (5). In detail, a CR rate of 28% and an ORR of 72% were reported for the studied patients (5). It is important to mention that 65% of the patients who had demonstrated CR stayed in CR for at least a year (5). Such clinical efficacy is tremendously valuable for the treatment of patients with nonresponsive progressive MM.

With all the good news surrounding this new MM treatment approach, there are also some downsides. Treatment with idecabtagene vicleucel can lead to critical adverse events (which can occur from one week after the treatment or later). Among the aforementioned adverse events, the cytokine release syndrome (CRS), hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS), various levels of neurologic toxicities, and prolonged cytopenia can be experienced by the recipient (5). It is worth mentioning that all of the aforementioned adverse side effects can manifest themselves in variable levels (from mild to fatal or life-threatening) (5). The CRS and HLH/MAS, which can mediate high fever flu-like symptoms, are both the results of rapid activation and in vivo expansion of the infused CAR T-cells and the hyperactivation of the recipients' immune system (5). Cytopenia is known as a decline in the number of a particular type of blood cells for a long-term period (5). More common side effects of this type of therapy might include infections (e.g., bacterial, viral, or fungal that might be due to the onset of cytopenia or generally the impaired immune system of the recipients), hypogammaglobulinemia, exhaustion, and muscle pain (5).

As the first FDA-approved cell-based gene therapy for MM, idecabtagene vicleucel has proven effective in the treatment of R/R MM patients with multiple unsuccessful prior lines of therapy. However, considering that there is no effective treatment modality for R/R MM, durable clinical responses after treatment with idecabtagene vicleucel are also variable based on various conditions of the patient (including gender, age, and disease stage at the time of diagnosis). Moreover, due to the severity of the side effects and their life-threatening nature, MM patients might have to consider careful consultation with their healthcare professionals before stepping toward this type of therapy. Currently, FDA requires all healthcare facilities to use highly trained and professional staff for the prescription, dispense, or administration of all FDA-approved CAR T-cell products. Such professionals are highly trained to identify, diagnose, and control CRS, neurologic toxicities, and other side effects of CAR T-cell therapies. In a nutshell, the FDA approval of idecabtagene vicleucel can be considered good news for patients with this kind of hard-to-manage neoplasm.

Footnotes

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