ADVANCES IN LLM

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Advances in CAR T-Cell Therapy for the Treatment of Multiple Myeloma

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H&O What is the rationale for the use of chimeric antigen receptor (CAR) T-cell therapy in multiple myeloma?

NS Multiple myeloma cells express B-cell maturation antigen (BCMA), a protein that is not expressed on many other types of cells. By targeting BCMA with an active T cell, it is possible to achieve a specific cytotoxic effect.

H&O Are there other potential target antigens in multiple myeloma?

NS There are fewer target antigens in multiple myeloma than might be expected. Two known antigens are CD38 and SLAMF7. CD38 is mainly used for antibody-based therapy. This antigen is a target for daratumumab (Darzalex, Janssen) and isatuximab-irfc (Sarclisa, Sanofi Genzyme). CD38 is present on several other types of cells, so it may not be the best target for CAR T-cell therapy. SLAMF7 is targeted by the antibody elotuzumab (Empliciti, Bristol-Myers Squibb).

H&O What did early data show about CAR T-cell therapy in multiple myeloma?

NS The early data were promising. Among heavily pretreated patients, the response rates ranged from 80% to 90%. For example, the initial report of the bb2121 product (idecabtagene vicleucel) demonstrated an 85% response rate at the active dose levels. It was the first time this high response rate was achieved in patients with such heavily pretreated multiple myeloma.

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H&O What are the CAR T-cell therapies currently in development for multiple myeloma?

NS There are several CAR T-cell products in development for multiple myeloma. Each is somewhat different from the others. The bb2121 product will likely be the first CAR T-cell therapy to gain approval from the US Food and Drug Administration (FDA) in multiple myeloma. This agent uses a lentiviral vector with a 4-1BB costimulatory molecule. JNJ-68284528, which is being studied in the CARTITUDE-1 trial (A Study of JNJ-68284528, a Chimeric Antigen Receptor T Cell [CAR-T] Therapy Directed Against B-Cell Maturation Antigen [BCMA] in Participants With Relapsed or Refractory Multiple Myeloma), also uses a lentiviral construct with a 4-1BB costimulatory molecule. However, the external surface of JNJ-68284528 has a region that attaches to 2 areas of

BCMA, rather than just 1. The product JCARH125 has a different vector from the other CAR T-cell therapies. It is cultured to control the proportion of CD4 to CD8 cells. The product bb21217 is similar to bb2121, but it is cultured in the setting of a phosphoinositide 3-kinase. Theoretically, this type of culture should increase the proportion of stem-like memory cells for the T-cell product, thereby improving persistence, a known challenge.

There are CAR T-cell products in development that do not use lentiviral vectors. For example, P-BCMA-101 uses a transposon system known as piggyBac. The external motif on the T cells, the extracellular domain, is small. The design of the cell allows insertion of more genes as compared with a lentiviral vector. A suicide gene was added to minimize toxicities from cytokine-release syndrome. Thus far, the clinical data show very little cytokine-release syndrome, so this feature has not yet been widely implemented.

H&O What are the results from clinical trials of CAR T-cell therapy in multiple myeloma?

NS Most of the clinical trials have reported only on overall response. A few have reported on duration of response. In a study of bb2121, the overall response rate was 85%, and 45% of patients had a complete response or stringent complete response. The study of bb2121 originally reported a median progression-free survival (PFS) of 11.8 months. The more recent phase 2 data showed that PFS was approximately 11.3 months with the highest dose.

The LEGEND-2 trial (LCAR-B38M-02 Cells in Treating Relapsed/Refractory [R/R] Multiple Myeloma) from China evaluated LCAR-B38M in patients with relapsed/refractory multiple myeloma. The median PFS was 20 months. The median overall survival was 36 months, and was not reached among patients with a complete response. PFS was longer than that seen with bb2121, but the patient population in the 2 trials was different, as patients in the LEGEND trial had received fewer lines of therapy than those in the study of bb2121. A similar phase 2 study of the same product, known as JNJ-68284528 in the United States, is ongoing in this country. Preliminary results of this trial, CARTITUDE-1, were presented in 2019. All patients responded, and the complete response rate was 69%. All patients evaluable for minimal residual disease were negative.

H&O What are the toxicities associated with CAR T-cell therapy in multiple myeloma?

NS The adverse events in multiple myeloma are similar to those seen in other cancers. They include cytokine-release syndrome, neurotoxicity, and cytopenias.

H&O Is it known why some patients with multiple myeloma do not respond to treatment with CAR T-cell therapy?

NS The factors that determine whether a patient will respond are not known. Some factors possibly associated with a deep response include in vivo T-cell expansion and T-cell persistence. However, it is not known how to improve expansion and persistence. Response may relate to the original condition of the patient's T cells, since the T-cell product is autologous. Another factor might be the condition of the patient as a host to receive the T cells.

> Some patients can receive CAR T-cell therapy and then remain off treatment for months, if not a year.

H&O Are there ways to improve the efficacy of CAR T-cell therapy in multiple myeloma?

NS Many groups are evaluating ways to encourage T cells to persist longer. It may be possible to administer these therapies earlier in the disease course, so that the cells can be generated when a patient's immune system is less exhausted before multiple lines of treatment. Another strategy might be to target 2 antigens at once. Research groups are evaluating combination strategies, as well as trying to identify novel antigens that have not yet been studied in clinical trials.

H&O What are some needed areas of future research?

NS CAR T-cell therapy is poised to become a valuable tool for patients with relapsed/refractory multiple myeloma. Some patients can receive CAR T-cell therapy and then remain off treatment for months, if not a year. This time off treatment is very valuable to patients. CAR T-cell therapy may not work for all patients, and it will not provide the same duration of response for everyone. Hopefully, better research will provide insight into correlative data that can be used to predict which patients will respond to therapy.

Disclosure

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Suggested Readings

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