CAR-T Therapies for Multiple Myeloma Show High Response Rates

90% to 100% of study participants achieved complete or partial responses to treatment.

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Two new dual-target CAR-T therapies produced high overall response rates in people with relapsed or nonresponsive multiple myeloma in ongoing clinical trials, researchers reported at the American Society of Hematology (ASH) Annual Meeting taking place this week in Orlando.

“To see some patients in this heavily pretreated population surviving for a year or more with a one-time treatment and a manageable safety profile is remarkable,” said Deepu Madduri, MD, of the Tisch Cancer Institute at Mount Sinai in New York, who presented one of the studies. “These patients feel that they have their quality of life back. They no longer have to come into the clinic for weekly treatments and some are well enough to travel.”

Multiple myeloma involves uncontrolled growth of plasma cells, a type of B cell that produces antibodies. These malignant cells multiply in the bone marrow and make defective antibody fragments called M proteins. Abnormal plasma cells can crowd out normal blood-producing cells and can form tumors in bones or soft tissue, leading to increased risk of infection, bone fractures and damage to the kidneys and other organs.

A wide variety of chemotherapy medications, immunomodulators and targeted therapies are used to treat multiple myeloma—typically in combination—but these treatments often stop working and relapse is common.

“We can get the disease into remission, but most patients unfortunately relapse, and outcomes are very poor for patients who have relapsed multiple times,” Madduri said.

Chimeric antigen receptor T-cell therapy—better known as CAR-T—involves removing a sample of a patient’s white blood cells, reprogramming the T cells to attack their cancer, manufacturing a large number of the altered cells in a laboratory and infusing them back into the body.

The two approved CAR-T therapies, Kymriah (tisagenlecleucel) and Yescarta (axicabtagene ciloleucel), target the CD19 protein on B cells that grow out of control in people with leukemia and lymphoma. The new therapies presented at the ASH meeting target the B-cell maturation antigen (BCMA), which is often found on malignant plasma cells in people with multiple myeloma.

Madduri presented findings from CARTITUDE-1, a Phase Ib/II study of JNJ-4528, which uses two molecules to target different pieces (epitopes) of BCMA. Chinese researchers previously evaluated the same dual-target CAR-T (then called LCAR-B38M) in the LEGEND-2 trial (ClinicalTrials.gov NCT03090659). Janssen licensed the product from the Chinese biotech company Legend. JNJ-4528 has received a breakthrough therapy designation from the Food and Drug Administration, intended to speed up development of treatments for unmet medical needs.

This analysis included the first 29 enrolled participants with progressive multiple myeloma. They had extensive prior treatment using different types of therapies including proteasome inhibitors, immunomodulators and anti-CD38 targeted therapies.

The participants underwent T cell collection, received strong conditioning chemotherapy to kill off some existing immune cells to make room for the new ones and received a single infusion of the genetically engineered cells.

The patients' blood, bone marrow and urine were examined after a month, six months and a year. Measuring response to multiple myeloma treatment is complex and continues to evolve as new tests make it possible to detect an ever smaller number of cancerous cells.

People treated with JNJ-4528 had an overall response rate of 100%, meaning all 29 patients saw a reduction in their cancer. Of these, 66% had what is known as a stringent complete response and 3% had a complete response (no detectable myeloma cells in their blood or bone marrow), while 17% had a very good partial response and 14% had a partial response. All patients evaluated for minimum residual disease tested MRD negative, meaning less than one myeloma cell per 100,000 bone marrow cells. All but two were free of disease progression at the six-month mark.

Yu Hu, MD, PhD, of Huazhong University of Science and Technology in Wuhan, China, presented findings from a Phase I trial of a different dual CAR-T therapy, dubbed BM38, that targets both BCMA and the CD38 receptor—the same molecule targeted by the monoclonal antibody Darzalex (daratumumab).

"Our thinking was that targeting both of these proteins would improve treatment efficacy without increasing toxicity, and induce deeper, more durable remissions," Hu said.

This study enrolled 22 participants with relapsed or nonresponsive multiple myeloma after trying at least three prior therapies. Nine people had extramedullary tumors in their organs or soft tissue, which are associated with poor prognosis.

Again, patients' T cells were harvested and genetically modified to target their cancer. The participants underwent conditioning chemotherapy to make room for the new cells and they received a single infusion of the CAR-T product.

The overall response rate was 90%, including 55% with a stringent complete response and 32%

with a good partial response. Bone marrow assessment showed that 82% were MRD negative. Eight of the nine people with extramedullary disease experienced complete or partial tumor shrinkage. The median progression-free survival was not reached, meaning most participants are still alive without worsening disease.

Both treatments were generally safe but most participants experienced side effects. Most had low blood cell counts, likely due to the chemotherapy they received to prepare for CAR-T administration.

Introducing genetically engineered T cells can trigger a strong immune reaction known as cytokine release syndrome (CRS). CAR-T side effects may include low blood pressure, brain inflammation and organ failure. Although almost all patients in the JNJ-4528 study experienced CRS, only two had severe (Grade 3 or higher) symptoms and one had severe neurotoxicity; however, one person died from treatment-related complications. In the BM38 study, four developed moderate (Grade 2) CRS, five had severe CRS and no serious neurotoxicity was observed.

Madduri noted that CRS often occurred about a week after administration of JNJ-4528, indicating that these modified T cells appear to multiply more slowly than other CAR-T therapies. Findings from these studies suggest that dual-target CAR-T may be less likely to lead to severe CRS than single-target products.

A Phase III trial called CARTITUDE-4 is now underway to compare JNJ-4528 versus standard combination therapies (ClinicalTrials.gov number NCT04181827). Phase II studies of BM38 are planned in both the United States and China.

Click here to read the JNJ4528 study abstract.

Click here to read the BM38 study abstract.

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