Bluebird CAR-T Therapy Has High Multiple Myeloma Remission Rate

Most Phase I study participants responded to the experimental immunotherapy.

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All but one patient treated with effective doses of bb2121, a new CAR-T therapy for multiple myeloma, experienced cancer remission, which in some cases lasted more than a year, according to results of a small study presented at the recent American Society of Hematology (ASH) annual meeting in Atlanta.

James Kochenderfer, MD, of the National Cancer Institute presented findings from a study evaluating bb2121, an investigational CAR-T therapy being developed by Bluebird Bio in collaboration with Celgene, for patients with relapsed or refractory (nonresponsive) multiple myeloma.

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 can clump together to form tumors in bones or soft tissue. They also make abnormal antibodies that can build up in the blood and organs.

Chimeric antigen receptor T-cell, or CAR-T, therapy reprograms immune cells to recognize and attack cancer. The process involves collecting a sample of a patient's T cells and sending them to a manufacturing facility, where they are genetically engineered to create a customized "living drug" for each individual. The supercharged T cells are then multiplied and infused back into the patient.

Bluebird's bb2121 uses an inactivated virus to modify T cells, inserting a receptor that targets the B-cell maturation antigen (BCMA) on B cells, which is commonly expressed on malignant plasma cells. The two currently approved CAR-T therapies, Kymriah (tisagenlecleucel) from Novartis and Yescarta (axicabtagene ciloleucel) from Kite Pharma, a Gilead company, target the CD19 protein on B cells that grow out of control in leukemia and lymphoma.

This Phase 1 clinical trial (known as CRB-401) included 21 highly treatment-experienced patients with relapsed or refractory multiple myeloma at nine sites in the United States. About 60 percent were men, the median age was 58 and they had had multiple myeloma for a median of five years.

Study participants had previously tried at least three other types of treatment (median of seven previous therapies) and had undergone autologous stem cell transplantation. Genetic testing showed that they had more than 50 percent BCMA expression on cancer cells.

All participants received a single infusion of patient-specific engineered T cells at escalating doses. Modified cells were successfully manufactured for all patients. Before the bb2121 infusion they received strong conditioning chemotherapy to kill off existing immune cells and make room for the new ones. There was no placebo or comparison regimen.

Researchers previously reported that while the lowest dose of 50 million modified T cells was ineffective, higher doses over 150 million cells performed better. These promising results led the Food and Drug Administration to grant bb2121 a breakthrough therapy designation in late 2017, meaning it addresses a serious unmet medical need.

Longer-term results presented at the ASH meeting showed that after a median of 40 weeks of follow-up, the overall response rate was 86 percent, rising to 94 percent for patients who received higher doses of bb2121. That is, 17 of the 18 study participants who received the effective doses experienced partial or complete remission. The complete response rate was 56 percent.

In comparison, only about a quarter of multiple myeloma patients respond to other new therapies after several treatment failures. The three people in this study who received the lowest—now known to be inactive—dose of bb2121 died of multiple myeloma progression within a year, according to an ASH press release.

Patients took about a month to respond to treatment and around four months to achieve a complete response. The median duration of response was not reached, as most people were still responding, some for nearly a year and a half.

At six months, the progression-free survival (PFS) rate, meaning patients were still alive with no worsening of disease, was 81 percent; at nine months, this rate fell to 71 percent. The median PFS duration could not be determined because a majority of participants are still alive and doing well.

CAR-T therapy can cause potentially life-threatening side effects, as unleashing modified T cells not only kills cancer cells but can also trigger an excessive immune response that harms healthy tissue. CAR-Ts that target malignant B cells can also kill off normal antibody-producing B cells, resulting in increased susceptibility to infections.

A majority of study participants experienced cytokine release syndrome, which can cause symptoms ranging from fever to organ failure. Around 20 percent developed neurological problems. In most cases, however, these side effects were mild to moderate and could be managed, in some cases using the immune-suppressing drug Actemra (tocilizumab). One person had serious neurotoxicity and brain swelling, but this was successfully managed. Most patients developed severe neutropenia (low white blood cell counts) attributable to the conditioning regimen.

“We are excited about the early results in a patient population with very advanced myeloma for whom previous therapies have failed,” Kochenderfer said in the ASH press release. “We have patients who have a sustained response and have been able to go for over a year with no additional myeloma therapy and tolerable adverse effects.”

A larger Phase II trial of bb2121, known as KarMMa, is now recruiting participants. Additional trials are planned for multiple myeloma patients with less extensive prior treatment experience. Bluebird has also started testing a next-generation BCMA CAR-T called bb21217.

Click here to read the bb2121 ASH abstract.

Click here to read an ASH press release about CAR-T studies at ASH.

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