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Phase 2 CAR-T study reports significant remission rates at 15-month follow up

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A study involving the recently approved CD19-targeting chimeric antigen receptor (CAR) T cell therapy shows that 42 percent of patients with aggressive large B-cell lymphoma remained in remission at 15 months following treatment with axi-cel (marketed as Yescarta).

The study, named ZUMA-1, also reported measurable responses in 82 percent of patients and complete responses in 54 percent. Fifty-six percent were alive at 15 months following therapy, with some remaining cancer free two years post-treatment.

The findings, reported in the Dec. 10 online issue of The New England Journal of Medicine, and to be presented Dec. 11 at the annual meeting of the American Society of Hematology (ASH) in Atlanta, resulted from a 22-institution study led by Sattva Neelapu, M.D., professor of Lymphoma & Myeloma at The University of Texas MD Anderson Cancer Center and Frederick Locke, M.D., vice chair and associate member of the Department of Blood and Marrow Transplant and Cellular Immunotherapy at Moffitt Cancer Center.

"With the FDA's recent approval of this therapy, we believe this is a major advance in the treatment of patients with relapsed or refractory large B-cell lymphoma and is likely to save or prolong lives of many patients," said Neelapu. "This study demonstrated that axi-cel provides remarkable improvement in outcomes over existing therapies for these patients who have no curative options."

The study, which began in April 2015, administered axi-cel to 108 patients who had failed prior chemotherapy and autologous stem cell transplantation. In some cases, the patients who had received chemotherapy were too far progressed to undergo stem cell transplantation and were placed on the trial following chemotherapy. The patients' T-cells were extracted through a process called leukapheresis and genetically reengineered with CAR molecules that help T-cells attack cancer cells. The reengineered T cells are infused back into the patient.

"This is the first FDA-approved gene therapy to treat adult lymphoma. Axi-cel consists of the patients' own T cells that have been reprogrammed, and then reinfused to detect and destroy lymphoma. Many patients' lymphoma tumors melted away within a month. The long term follow-up results of the ZUMA-1 trial show that axi-cel remissions can last years, and these are patients that did not respond to chemotherapy," said Locke.

Most complete responses in patients with diffuse large B-cell lymphoma (the most common aggressive non-Hodgkin lymphoma), primary mediastinal B-cell lymphoma and transformed follicular lymphoma, occurred by the first month of treatment, although some were reported as late as one year out from therapy. Ongoing durable remissions have been observed in patients two years out from treatment. While investigations are ongoing, one mechanism of resistance to the therapy appears to be due to loss of the CD19 target on the tumor cells. Understanding these mechanisms of resistance are expected to lead to development of novel approaches to further enhance the efficacy of this therapy.

About the study patients

The drug was manufactured for 99 percent of the 108 study participants

and given to 91 percent of enrolled patients. On average, it took 17 days from the time T-cells were harvested from the patient to when the drug was administered, a relatively quick turnaround time for patients with a rapidly growing disease such as large B-cell lymphoma.

Among patients treated with axi-cel, the median age was 58 ranging from 23 to 76 years of age. Eight-five percent of the patients had stage III or IV disease. The study also reported that prior to receiving axi-cel, 77 percent of patients continued to have aggressive disease progression following second-line or later therapies, and 21 percent had disease relapse after stem cell transplantation. At least 69 percent of patients received a minimum of three prior therapies, and 26 percent had a history of primary refractory disease.

All 108 patients experienced some adverse effects, although not all were linked to axi-cel with 95 percent having Grade 3 events including fever, lower white blood cell and blood platelet counts, and anemia. Cytokine release syndrome, a form of inflammatory response, occurred in 93 percent of patients but most were low-grade. Approximately 64 percent of patients experienced neurological events, including encephalopathy, general confusion and difficulty speaking, which normally occurred about five days into treatment, resolving within two weeks.

The study reported three patient deaths related to adverse effects. Two of the patients had cytokine release syndrome due to axi-cel, and one experienced a pulmonary embolism deemed unrelated to axi-cel. These deaths occurred early in the course of the study and in response, additional safety guidelines were adopted across all 22 study sites to ensure consistent monitoring and prompt management of adverse effects. The study observed that CAR-T levels peaked in the patients' blood systems within 14 days and were detectable in most patients 180 days after infusion. Three patients who remain in complete remission at two years out from treatment continue to have detectable CAR-T levels.

Only treatment centers certified to provide stem cell transplantation are eligible to be considered as axi-cel treatment sites. The drug's manufacturer, Kite Pharma, a Gilead company, ultimately anticipates certifying up to 90 centers across the U.S. Physicians must undergo special training and follow stringent guidelines and procedures before administering the new therapy.

Provided by University of Texas M. D. Anderson Cancer Center