Armored CAR-T Therapy Shows Promise for Liver Cancer

In its first human trial, C-CAR031 shrank liver tumors in six out of the eight patients who received the highest dose.

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A next-generation armored CAR-T therapy called C-CAR031 led to regression of liver tumors in more than half of patients with advanced hepatocellular carcinoma, rising to 75% for those who received the highest dose, according to study results presented Tuesday at the American Society of Clinical Oncology Annual Meeting (ASCO 2024).

"C-CAR031 showed a good safety profile and promising efficacy in late-stage hepatocellular carcinoma patients, who typically have a limited number of treatment options available," principal investigator Tingbo Liang, MD, PhD, of the First Affiliated Hospital of Zhejiang University in Hangzhou, China, said in a news release. The observed tumor shrinkage in the vast majority of patients "suggests that C-CAR031 has the potential to bring clinical value and offer hope to these patients."

Over years or decades, chronic hepatitis B or hepatitis C, fatty liver disease, heavy alcohol consumption and other causes can lead to liver fibrosis, cirrhosis and hepatocellular carcinoma (HCC), the most common type of liver cancer. HCC is often detected late and is difficult to treat, as it generally does not respond well to chemotherapy. Standard treatment for advanced HCC may include targeted therapy and checkpoint inhibitor immunotherapy.

Chimeric antigen receptor T-cell therapy—better known as CAR-T—reprograms a patient's own T cells by inserting a synthetic receptor that recognizes their cancer. The process involves removing a sample of an individual's white blood cells, genetically altering T cells to attack their cancer, manufacturing a large quantity of the engineered cells and infusing them back into the body. Several CAR-T therapies are approved for blood cancers, like leukemia and lymphoma, but so far this approach has not worked well for solid tumors.

C-CAR031, designed by AstraZeneca and manufactured by AbelZeta in China, targets GPC3, a surface antigen heavily expressed in liver tumors but usually absent in healthy tissue. It is a so-called "armored CAR" designed to fend off an immunosuppressive cytokine (TGF-beta) that can turn off T-cell activity.

Qi Zhang, MD, also of Zhejiang University School of Medicine, presented results from the first human clinical trial of C-CAR031 (NCT05155189). This Phase I open-label dose-escalation study enrolled 24 patients with advanced HCC who experienced disease progression despite receiving at least one and up to six prior systemic therapies. Almost all had tried tyrosine kinase inhibitor targeted therapies and checkpoint inhibitors. More than 80% had cancer metastasis beyond the liver.

C-CAR031 was custom-made using T cells from each patient. After undergoing strong chemotherapy to kill off their existing immune cells and make room for the new ones, each participant received a single IV infusion of the CAR-T therapy at one of four dose levels.

After a median nine months of follow-up, 91% of the 23 evaluable patients saw some reduction in tumor size, both in the liver and in metastatic lesions. The objective response rate, meaning tumors shrank by a specified amount, was 57% overall across all dose levels, increasing to 75% for those in the highest dose group. The disease control rate, meaning tumors either shrank or remained stable with no further progression, was 91%. Based on this early data, the estimated median overall survival time is about 11 months.

Side effects were common but generally manageable. Many adverse effects were attributable to the preparatory chemotherapy, including reduced lymphocyte counts, neutropenia and low platelets. Introducing engineered T cells can trigger a strong immune reaction, known as cytokine release syndrome (CRS), and neurologic toxicity. Zhang reported that no dose-limiting toxicities or neurologic toxicity were observed. Most patients developed CRS, but only one case was considered severe (Grade 3 lung inflammation). All adverse events were ultimately reversible.

“The study showed a manageable safety profile and encouraging antitumor activity of C-CAR031 in heavily treated advanced HCC patients,” the researchers concluded.

According to AbelZeta chairman and CEO Tony (Bizuo) Liu, “The early data presented today provide compelling proof-of-concept to potentially redefine therapeutic paradigms in HCC and other GPC3-expressing solid tumors.”

Based on these findings, AstraZeneca and AbelZeta will advance C-CAR031 into an international Phase II trial that will include sites in the United States. If future results hold up, this could be one of the first next-generation CAR-therapies that works well against solid tumors.

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