Does CAR-T Therapy Cause Secondary Cancers? [UPDATE]

The FDA is investigating the risk of new T-cell malignancies among patients receiving the engineered T cells, but so far, cases are rare.

January 27, 2024 By Liz Highleyman

[Update: On January 19, 2024, the Food and Drug Administration (FDA) issued letters to all CAR-T therapy manufacturers saying their package inserts must include a boxed warning about the risk of secondary cancers. Abecma and Breyanzi from Bristol-Myers Squibb, Carvykti from J&J, Kymriah from Novartis and Yescarta from Gilead/Kite will carry a warning stating that people taking these therapies have developed new T-cell malignancies. Tecartus, also from Gilead/Kite, will get a revised warning stating that new cancers may occur.

As described in the January 24 issue of The New England Journal of Medicine, the FDA is aware of 22 cases of new T-cell malignancies among CAR-T recipients. In three cases with available sequencing data, the engineered receptor inserted into the modified CAR-T cells was present in the secondary cancer cells. However, FDA officials emphasized that the benefits of CAR-T therapy—typically used by people with advanced blood cancers who have run out of other options—outweigh the risks. More than 27,000 patients have used CAR-T therapy since the first one was approved in 2017.]

[Update: On December 9, 2023, researchers described the first case of T-cell lymphoma linked to CAR-T therapy at the American Society of Hematology annual meeting. It was also published in the journal Blood.]

This report was originally published on November 30, 2023.

The Food and Drug Administration has launched an investigation after receiving reports that people who received CAR-T immunotherapy have developed secondary malignancies, including T-cell lymphoma. There have been about two dozen reports of suspicious T-cell cancers in CAR-T recipients during the six years these therapies have been on the market, and for many patients, the benefits exceed the risks.

“Although the overall benefits of these products continue to outweigh their potential risks for their

approved uses, FDA is investigating the identified risk of T-cell malignancy with serious outcomes, including hospitalization and death, and is evaluating the need for regulatory action," the agency said in a statement.

Chimeric antigen receptor T-cell therapy, often described as a "living drug," reprograms a patient's own T cells by using a modified retrovirus to insert a synthetic receptor that recognizes their cancer. The treatment 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.

The first CAR-T therapy, Novartis's Kymriah (tisagenlecleucel), was approved in August 2017, followed by Gilead Sciences/Kite's Yescarta (axicabtagene ciloleucel) that October. There are now four additional approved CAR-T therapies: Abecma (idecabtagene vicleucel), Breyanzi (lisocabtagene maraleucel), Carvykti (ciltacabtagene autoleucel) and Tecartus (brexucabtagene autoleucel).

CAR-T therapy has led to remarkable outcomes for some patients with advanced blood cancer that does not respond to other types of treatment. The first two adults who received the therapy are still alive more than a decade later. The first child treated with Kymriah, Emily Whitehead, is now a freshman at the University of Pennsylvania, where the therapy was developed. But CAR-T therapy does not cure all treated patients, and while it is effective for blood cancers like leukemia and lymphoma, it does not work well for solid tumors.

The latest concern relates to the development of new T-cell cancers, including lymphoma, in CAR-T recipients. In some cases, the malignant T cells carried the synthetic receptors inserted during the manufacturing process. The FDA has determined that the risk is applicable to all currently approved CAR-T therapies that target B-cell maturation antigen (BCMA) or CD19, two proteins expressed on malignant B cells. It is possible that the modified retrovirus vector used to introduce the receptors could cause genetic mutations that trigger the development of cancer.

This concern is not new, and the potential risk of secondary cancers is included as a warning in the prescribing information for all approved CAR-T therapies. The FDA requires 15 years of follow-up for CAR-T clinical trials.

The risk of new malignancies in patients receiving CAR-T therapy appears to be very low. Among the more than 20,000 people treated with the engineered T cells to date, only 19 cases have been reported to the FDA. Novartis, Gilead and Bristol Myers Squibb, which makes Abecma and Breyanzi, told various news sources that they have not identified a link between their products and new malignancies. What's more, other types of cancer treatment can also trigger secondary cancers.

"I don't think it changes the risk-benefit calculation for any particular patient considering CAR-T right now," Marcela Maus, MD, PhD, of Mass General Cancer Center, told STAT. "As an oncologist,

we treat patients with things like chemotherapy and radiation which also have a risk of future malignancy, and it's not well defined. I would be very disappointed if this field was singled out as riskier than others if it has a very low frequency of events."

At this time, the FDA is not advising patients with advanced blood cancers to avoid using CAR-T therapy, but it does call for long-term surveillance.

"Patients and clinical trial participants receiving treatment with these products should be monitored life-long for new malignancies," the agency stated.

Click here for more news about CAR-T therapy.

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