FDA Committee Recommends New Gene Therapy for Leukemia in Children

CAR-T therapy CTL019 trains immune system to recognize and fight cancer cells.

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A Food and Drug Administration (FDA) advisory committee has unanimously recommended approval of a groundbreaking new kind of cancer immunotherapy that has shown remarkable effectiveness in children and young adults with advanced leukemia.

CTL019, or tisagenlecleucel, is the first chimeric antigen receptor T cell (CAR-T) therapy to go before the FDA. Treatment involves removing a patient's white blood cells, genetically "reprogramming" them to attack cancer cells and putting them back into the body.

The FDA's Oncologic Drugs Advisory Committee (ODAC) held a hearing on July 12 to discuss the efficacy, safety and manufacturing process for CTL019. Drugmaker Novartis has requested approval for the treatment for use among children and young adults (ages 3 to 25 years) with relapsed or refractory (not responding to treatment) B-cell acute lymphoblastic leukemia (ALL).

The ODAC expert advisory panel heard researchers and Novartis representatives describe CTL019's efficacy and address key safety concerns. Parents of children in these studies testified in favor of approval, including the father of Emily Whitehead, the then-6-year-old girl who was the first child to be treated with CAR-T therapy and who remains in remission five years later.

B-cell acute lymphoblastic leukemia, a type of blood cancer, is the most common childhood cancer in the United States, according to a Novartis press release. Existing treatments are not very effective for children who relapse or develop advanced disease.

CAR-T uses gene therapy to modify a patient's killer T cells, the main soldiers of the immune system, making them better able to find and kill cancer cells. T cells are first extracted from the blood using a process known as leukapheresis. The cells can then be frozen and shipped to the manufacturing facility.

Inactivated HIV is used to insert a receptor into the T cells that target the CD19 antigen on the surface of B cells. Modified T cells that express the new receptor are grown in the laboratory and infused back into the patient. The process usually takes around 22 days, according to Novartis.

CAR-T therapy was initially developed by Carl June, MD, now director of the Center for Immunotherapies at the University of Pennsylvania Perelman School of Medicine, and colleagues—as an attempt to cure HIV—and tested at the Children's Hospital of Philadelphia. June calls CTL019 "a true living drug."

"It is encouraging to see the FDA panel's recommendation and continued momentum behind this innovative therapy, which has potential to help young patients with relapsed/refractory B-cell ALL," June said in a Novartis press release.

The Phase II ELIANA trial enrolled 88 children with advanced B-cell ALL who had received multiple prior therapies and in many cases had undergone stem cell transplants. Among the 63 patients treated with CTL019, 83 percent achieved remission within three months, and three quarters remained cancer-free after six months. Among those with longer follow-up, the 12-month survival rate was 79 percent—at least twice the rate seen with other available treatments.

Safety issues are a primary concern with any new type of treatment, and CAR-T has come under more scrutiny after several adult patients in clinical trials of other companies' CAR-T therapies died from cerebral edema, or brain swelling.

Unleashing genetically modified T-cells not only kills cancer cells but also can lead to an excessive immune response that harms healthy tissues. This is known as cytokine release syndrome, or a "cytokine storm." CRS can cause symptoms ranging from fever and flu-like symptoms to organ failure.

Nearly half of the children in the ELIANA study experienced CRS, in many cases severe. However, CRS was managed successfully and led to no deaths. More than 40 percent experienced symptoms of neurological toxicity, but no cases of brain swelling were reported.

The expert panel also expressed concern that the gene therapy could potentially trigger new cancers or that the inactivated retrovirus used in the process could become reactivated, or replication competent. Novartis will follow study participants for 15 years to look for long-term problems.

Finally, the panelists heard about manufacturing issues. CAR-T therapy is labor- and technology-intensive—and will no doubt be expensive—because treatment is customized for each patient. Novartis said its facility in Morris Plains, New Jersey, has produced CTL019 for hundreds of patients in clinical trials worldwide. The company expects that the treatment will be available at 30 to 35 centers in the United States.

The ODAC voted 10 to 0 that the benefits of CTL019 outweigh potential drawbacks and recommended its approval. The FDA is not required to follow its committees' recommendations, but it usually does so. A final decision is expected by early October.

Novartis plans to also request approval of CTL019 for adults with relapsed or refractory large B-cell lymphoma.

Other companies—including Bluebird Bio, Juno Therapeutics and Kite Pharma—are also developing CAR-T therapies.

Kite has requested FDA approval of its KTE-C19 for adults with aggressive non–Hodgkin lymphoma. KTE-C19 showed good results in the ZUMA-1 trial, but one participant died of brain swelling. Kite has also seen good results in a study of KTE-C19 for adults with relapsed or refractory ALL. Juno recently reported promising data for its JCAR017 in adults with non–Hodgkin lymphoma. Juno stopped development of an earlier CAR-T candidate (JCAR015) after five patients died of brain swelling.

Although CTL019 may be used only by a small number of children with leukemia who don't respond to standard therapy, it represents a new approach that may one day be used to treat other kinds of cancer.

To read a Novartis press release about the CTL019 recommendation, click here.

To see the FDA briefing document on CTL019, click here.

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