# FDA recommends approval of new leukemia treatment

**Benjamin Mateus**
**23 September 2017**

A panel of the Food and Drug Administration (FDA) recently made a unanimous recommendation to approve the "first-ever treatment that genetically alters a patient's cells to fight cancer, transforming them into what scientists call a living drug that powerfully bolsters the immune system to shut down the disease."

In the summary of their report, the authors explain that in 2014 the FDA granted "breakthrough therapy" designation to CTL019 for being the first time in medical history that personalized cellular therapy has been used to treat patients with a high-risk B-cell leukemia. In their study, they describe how T-cells, which are one of the body's types of white blood cells and a key part of the human immune system, can be engineered to fight malignant cancers.

This area of research gained steam in 2006 after the first human clinical trials using Chimeric Antigen Receptor (CAR) T-cell technology demonstrated that it was possible to redirect T-cells to attack cancer cells. This normally does not happen because T-cells regard cancer cells as native to the body or fail to detect them, and thus do not destroy them. Since then, there have been many investigations in this field that have ultimately led to the current discovery.

The treatment process begins with removing T-cells from a patient's serum and genetically modifying them so they can attack the cancerous B-cells. The researchers used a disabled form of human immunodeficiency virus (HIV) that can carry the new genetic material and incorporate it into the T-cells, thereby reprogramming them. The T-cells can now recognize the protein called CD-19 on the surface of the B-cell and attack it. The reprogrammed T-cells are then infused back into the patient where they multiply and eradicate the cancer.

With such therapy there are also complications involving the Cytokine Release Syndrome (CRS) that can have severe consequences for the patient. This means the inflammatory response to the treatment is brisk and characterized by high fevers, low blood pressures, and low oxygen saturation. The body undergoes an inflammatory-mediated shock similar to a major infection. It becomes imperative to appreciate the delicate but complex systems of interaction that such efforts mediate. Yet, CAR T-cell therapy holds the possibility to eradicate cancer in these patients permanently.

As compared to tumor vaccines that have a low affinity to their target, with responses occurring over several months, T-cell transfer responses are measured in days to weeks. A single reprogrammed T-cell can kill up to 100,000 cancer cells.

There are currently 30 clinical trials open for the treatment of B-cell malignancies involving many major institutions in the United States, Europe, China, and Japan. CAR T-cell therapy is also being investigated for an assortment of hematological as well as solid tumor malignancies such as breast and lung cancer.

CAR T-cell therapy is a seismic shift from current conventions for treatment, yet significant work lies ahead. Unknowns include finding the optimal gene transfer method that is less complicated, safe, and financially feasible, and which ensures a consistent T-cell mediated immune response. The T-cell expansion is currently being carried out at local cancer treatment centers. Suitable methods to scale up production and increase output while adhering to strict quality control is necessary. The appropriate dosing of T-cells needs to be worked out. Protocols need to be standardized from institution to institution.

Because it is a patient-specific treatment, CAR T-cells must be manufactured for each patient on a case-

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by-case basis. Accordingly, it is only feasible now at large academic centers that have extensive expertise and resources. At the same time, however, a single infusion of T-cells is sufficient to induce a tremendous proliferation and rapid response.

The kinetics of T-cell expansion and tumor rejections appear to be dependent on the type of tumor and remain to be further studied. Though CAR T-cells are considered targeted therapy, the mechanisms by which this occurs are unknown and thought to be multifactorial. T-cells are versatile in their ability to target and kill through multiple methods of attack. It is hypothesized that tumors can only escape CAR T-cells through antigen (surface receptor) loss.

If the FDA approves the recommendation for CAR T-cell treatment for B-cell Acute Lymphoblastic Leukemia (ALL), it would be the first gene therapy to reach the market in the United States. Novartis, a Swedish-based global healthcare company, would be the first to offer such treatment while it works to investigate similar approaches to other blood and solid organ malignancies.

B-cell ALL afflicts about 6,000 people in the United States with a peak incidence at 2-5 years of age. These patients undergo a rigorous treatment with multidrug regimen divided into several phases. Most treatment protocols can take two to three years to complete. Many of them will require supportive care with blood products, treatment for infections with broad spectrum antibiotics and correction of metabolic imbalances. Despite the debilitating side effects, most will be cured. However, approximately 15 percent will not respond or relapse.

The results from the clinical trials conducted at the University of Pennsylvania have been dramatic for this subset of patients with a very slim prognosis. One such patient, Emily Whitehead, was treated in 2012 at age 6. Though the side effects of the CAR T-cell treatment were severe and nearly killed her, she emerged cancer free and continues to remain in remission.

The data Novartis presented to the FDA panel included results from 63 patients treated from April 2015 to August 2016. Fifty-two patients (82 percent) went into remission, which is considered astonishing given the severity of the disease. Certainly, the CRS is an issue they are grappling with as well as concerns for possible future medical complications for which there are presently no answers. This means that such patients would likely be treated at specialized centers where expertise with the treatment will be important for patient safety.

Though Novartis has not commented on treatment costs, analysts predict that individualized treatments could cost more than $300,000. It is unlikely insurance companies would approve such an expense. Most likely the only way that working people could obtain such life-saving treatments is to be among the few selected as subjects in clinical trials.

There are certainly ethical issues to this which are not being raised in the mainstream journals. Arguments in support of the high cost follow the irrational logic that these patients will assume high costs of treatment for their cancer in the long run anyway.

Similar arguments have been used by successive administrations to slowly slash federal funding for medical research. Trump’s proposed budget cut for the National Institutes of Health would reduce the organization’s funding by 20 percent, from $31.8 billion to $26 billion. Such cuts will directly and negatively impact any further research into this new way to fight cancer.

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