Researchers report long-term remissions in first personalized cell therapy trial

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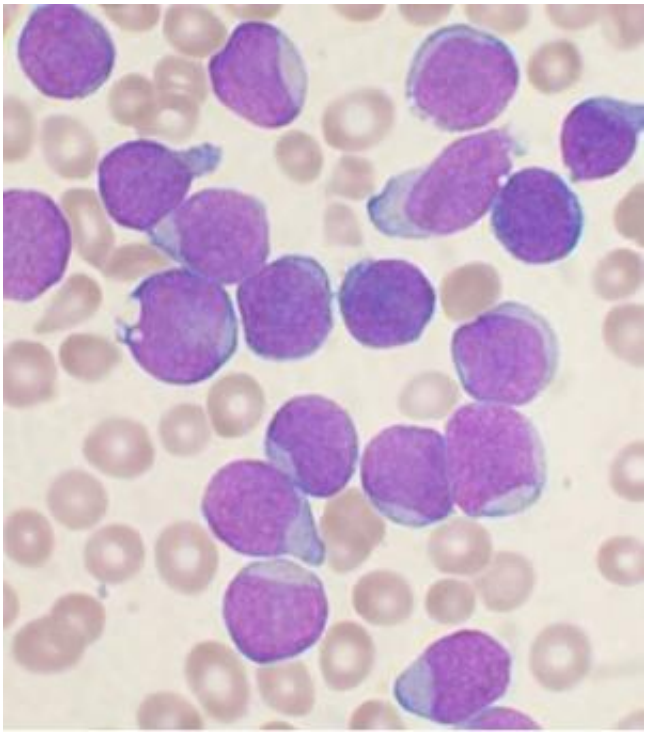

A Wright's stained bone marrow aspirate smear from a patient with precursor B-cell acute lymphoblastic leukemia. Credit: VashiDonsk/Wikipedia

Eight of 14 patients in the first trial of the University of Pennsylvania's personalized cellular therapy for chronic lymphocytic leukemia (CLL) responded to the therapy, with some complete remissions continuing past four and a half years. These results, published today in *Science Translational Medicine*, represent the most mature data from clinical

trials of an approach known as CTL019, developed by a team from Penn's Abramson Cancer Center and the Perelman School of Medicine.

In 2011, the research team published initial findings from the first three patients to enroll in the trial. Two of those patients had complete responses, and their leukemia remains in remission today, more than four and a half years after receiving the therapy. The first patient to receive the therapy recently marked five years cancer-free.

"The durability of the remissions we have observed in this study are remarkable and have given us great hope that personalized cell therapies are going to be important options for patients whose cancers are no longer treatable with standard approaches," said lead author David L. Porter, MD, the Jodi Fisher Horowitz Professor in Leukemia Care Excellence and director of Blood and Marrow Transplantation in Penn's Abramson Cancer Center. "The patients in this study are pioneers, whose participation has given us a foundation of knowledge and experience on which to build this new approach to help more patients."

The new study details the completed, 14-patient pilot trial of CTL019 for CLL, which began in the summer of 2010. The overall response rate was 57 percent. All patients who received the experimental therapy, which is made from their own immune cells, had cancer that had relapsed or continued to progress after receiving multiple conventional Food and Drug Administration-approved therapies, and few were eligible for bone marrow transplants.

Four patients (29 percent) in the study achieved a complete remission. One patient died while in remission at 21 months after the therapy due to infectious complications that occurred after removal of a basal cell carcinoma on his leg. The three other patients remained alive at the time of this analysis with no evidence of leukemia at 28, 52, and 53 months after receiving their infusions, with no further therapy.

An additional four patients (29 percent) achieved partial responses to the therapy, with responses lasting a median of seven months. During the period analyzed, two of these patients had died of disease progression at 10 and 27 months after receiving CTL019, and one died after suffering a pulmonary embolism six months after T cell infusion. One patient's disease progressed at 13 months but remained alive on other therapies at 36 months after receiving the therapy.

Six patients (43 percent) did not respond to the therapy and progressed within one to nine months; tests revealed that the modified T cells did not expand as robustly in these patients as in those who experienced remissions. Two of these subjects later died from their disease or complications of other therapies, and four are receiving other types of treatment.

CTL019 begins with each patient's own T cells, collected through a procedure similar to dialysis. The cells are then reprogramed to hunt and potentially kill cancer cells in the patient's body. After the patient undergoes lymphodepleting chemotherapy, they receive an infusion of their newly engineered cells. The modified T cells contain an antibody-like protein known as a chimeric antigen receptor (CAR), which is designed to target the CD19 protein found on the surface of B cells, including the cancerous B cells that characterize several types of leukemia and lymphoma.

All patients who responded to the investigational T cell therapy developed cytokine release syndrome (CRS) within several weeks after their infusions, typically during the time when the modified cells expanded to their greatest number in the body. This condition included varying degrees of flu-like symptoms, with high fevers, nausea, and muscle pain, and neurologic symptoms including hallucinations and delirium. Four patients experienced more severe symptoms, including low blood pressure and breathing difficulties, which required intensive

care. Prior CAR studies have shown that CRS can be a very serious and life-threatening toxicity. The Penn team has developed a management strategy to treat these side effects, including the antibody drug tocilizumab, which was used in four patients, and two patients received steroids. All recovered from their CRS.

"Importantly, our tests of patients who experienced complete remissions showed that the modified cells remain in patients' bodies for years after their infusions, with no sign of cancerous or normal B cells," said the study's senior author, Carl H. June, MD, the Richard W. Vague Professor in Immunotherapy in Penn's department of Pathology and Laboratory Medicine and director of Translational Research in the Abramson Cancer Center. "This suggests that at least some of the CTL019 cells retain their ability to hunt for cancerous cells for long periods of time."

A laboratory experiment using CAR-modified T cells isolated from one of the first patients to receive the therapy confirmed the potential for long-term function of these cells: At nearly three years after infusion, the patient's CTL019 cells demonstrated immediate and specific reactivity against cells expressing CD19. Typically, patients whose healthy B cells disappear after treatment receive regular immunoglobulin infusions.

This study did not identify demographic or disease-related factors, such as age or types of prior therapies, that could be used to predict response to the therapy, and no association between T-cell dose and response was observed. An ongoing dose-optimization study is exploring this relationship in greater detail. Further future areas of study may include strategies to combine CTL019 with immune checkpoint inhibitor drugs or other therapies to stimulate T cell recognition of tumor cells.

More information: Chimeric antigen receptor T cells persist and induce sustained remissions in relapsed refractory chronic lymphocytic

leukemia, stm.sciencemag.org/lookup/doi/ … scitranslmed.aac5415

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