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Personalized cellular therapy achieves complete remission in 90 percent of acute lymphoblastic leukemia patients studied

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Ninety percent of children and adults with acute lymphoblastic leukemia (ALL) who had relapsed multiple times or failed to respond to standard therapies went into remission after receiving an investigational personalized cellular therapy, CTL019, developed at the Perelman School of Medicine at the University of Pennsylvania. The results are published this week in The *New England Journal of Medicine*.

The new data, which builds on preliminary findings presented at the American Society of Hematology's annual meeting in December 2013, include results from the first 25 children and young adults (ages 5 to 22) treated at the Children's Hospital of Philadelphia and first five adults (ages 26 to 60) treated at the Hospital of the University of Pennsylvania. Twenty-seven of the 30 patients in the studies achieved a complete remission after receiving an infusion of these engineered "hunter" cells, and 78 percent of the patients were alive six months after treatment.

"The patients who participated in these trials had relapsed as many as four times, including 60 percent whose cancers came back even after stem cell transplants. Their cancers were so aggressive they had no treatment options left," said the study's senior author, Stephan Grupp, MD, PhD, a professor of Pediatrics in Penn's Perelman School of Medicine and director of Translational Research in the Center for Childhood Cancer Research at the Children's Hospital of Philadelphia. "The durable responses we have observed with CTL019 therapy are

unprecedented."

Shannon Maude, MD, PhD, an assistant professor of Pediatrics and a pediatric oncologist at CHOP, and Noelle Frey, MD, MSCE, an assistant professor of Medicine and an oncologist at Penn's Abramson's Cancer Center, are co-first authors of the new study. The research team is led by Carl June, MD, the Richard W. Vague Professor in Immunotherapy in the department of Pathology and Laboratory Medicine and director of Translational Research in the Abramson Cancer Center, along with David Porter, MD, the Jodi Fisher Horowitz Professor in Leukemia Care Excellence and director of Blood and Marrow Transplantation in the Abramson Cancer Center.

CTL019 manufacturing begins with a patient's own T cells, which are collected via an apheresis process similar to blood donation, then reprogrammed in Penn's Clinical Cell and Vaccine Production Facility with a gene transfer technique that teaches the T cells to target and kill tumor cells. The engineered cells contain an antibody-like protein known as a chimeric antigen receptor (CAR), which is designed to bind to a protein called CD19 found on the surface of B cells, including the cancerous B cells that characterize several types of leukemia. The modified "hunter" cells are then infused back into the patient's body, where they both multiply and attack the cancer cells. A signaling domain built into the CAR promotes rapid multiplication of the "hunter" cells, building an army of tumor-killing cells that tests reveal can grow to more than 10,000 new cells for each single engineered cell patients receive.

Nineteen patients in the study remain in remission, 15 with this therapy alone, including a 9 year old who was the first ALL patient to receive the therapy more than two years ago. The follow-up periods reported in the study are more than six months for most patients, with a range from 1.4 to 24 months. Five patients went off-study for alternate therapy, three of whom proceeded to allogeneic stem cell transplants while in remission.

Seven patients relapsed, between 6 weeks and 8.5 months after their infusions, including three whose cancers returned as CD19-negative leukemia that would not have been targeted by the modified cells.

All patients who received the CTL019 "hunter" cells experienced a cytokine release syndrome (CRS) within a few days after receiving their infusions – a key indicator that the engineered cells have begun proliferating and killing tumor cells in the body. During this time, 22 of 30 patients experienced mild to moderate CRS, which included varying degrees of flu-like symptoms, with high fevers, nausea, and muscle pain. Eight patients developed severe CRS, which required treatment for low blood pressure and breathing difficulties. Nine patients were treated with tocilizumab, an immunosuppressant drug that blocks the effects of the inflammatory cytokine IL-6, which have been found to spike during the most robust phase of the engineered cells' expansion in the body. Six patients also received short courses of steroids to combat CRS symptoms. All patients on these studies fully recovered from the CRS.

Tests of all patients who experienced complete remissions also showed that their normal, non-cancerous B cells, which also express the CD19 protein, had been eliminated along with their tumors. The researchers note that persistent absence of normal B cells following CTL019 treatment indicates continued activity of the gene-modified T cells, which are thought to provide long-term, vaccine-like activity preventing tumor recurrence. Since B cells play a role in helping fight infection, patients typically receive immunoglobulin replacement to maintain healthy immune function.

"Our results support that CTL019 can produce long-lasting remissions for certain heavily pre-treated ALL patients without further therapy," Frey said. "For our patients who have already relapsed after stem cell transplants, or don't have any options for donors, this option has provided new hope."

In July 2014, the U.S. Food and Drug Administration granted CTL019 its Breakthrough Therapy designation for the treatment of relapsed and refractory adult and pediatric ALL, a step which is intended to expedite the development and review of new medicines that treat serious or life-threatening conditions, if a therapy has demonstrated substantial advantages over available treatments. CTL019 is the first personalized cellular therapy to receive the designation. The first multicenter CTL019 trial has recently opened in the U.S., and additional multisite trials are expected to initiate by the end of the year.