Leukemia patients remain in remission more than two years after engineered T cell therapy

December 10 2012

Nine of twelve leukemia patients who received infusions of their own T cells after the cells had been genetically engineered to attack the patients' tumors responded to the therapy, which was pioneered by scientists in the Perelman School of Medicine at the University of Pennsylvania. Penn Medicine researchers will present the latest results of the trial today at the American Society of Hematology's Annual Meeting and Exposition.

The clinical trial participants, all of whom had advanced cancers, included 10 adult patients with chronic lymphocytic leukemia treated at the Hospital of the University of Pennsylvania (HUP) and two children with acute lymphoblastic leukemia treated at the Children's Hospital of Philadelphia. Two of the first three patients treated with the protocol at HUP – whose cases were detailed in the New England Journal of Medicine and *Science Translational Medicine* in August 2011 – remain healthy and in full remissions more than two years after their treatment, with the engineered cells still circulating in their bodies. The findings reveal the first successful and sustained demonstration of the use of gene transfer therapy to turn the body's own immune cells into weapons aimed at cancerous tumors.

"Our results show that chimeric antigen receptor modified T cells have great promise to improve the treatment of leukemia and lymphoma," says the trial's leader, Carl June, MD, the Richard W. Vague Professor in

Immunotherapy in the department of Pathology and Laboratory Medicine and director of Translational Research in Penn's Abramson Cancer Center. "It is possible that in the future, this approach may reduce or replace the need for bone marrow transplantation."

The results pave the way for a potential paradigm shift in the treatment of these types of blood cancers, which in advanced stages have the possibility of a cure only with bone marrow transplants. That procedure requires a lengthy hospitalization and carries at least a 20 percent mortality risk—and even then offers only a limited chance of cure for patients whose disease has not responded to other treatments.

Three abstracts about the new research will be presented during the ASH meeting. David Porter, MD, director of Blood and Marrow Transplantation in the Abramson Cancer Center, will give an oral presentation of Abstract #717 on Monday, Dec. 10, at 5 PM in the Thomas Murphy Ballroom 4, Level 5, Building B of the Georgia World Congress Center. Michael Kalos, PhD, director of the Translational and Correlative Studies Laboratory at Penn, will give an oral presentation on Abstract #756 on Monday, Dec. 10, at 5:45 PM in C208-C210, Level 2, Building C. Stephan Grupp, MD, PhD, director of Translational Research in the Center for Childhood Cancer Research at the Children's Hospital of Philadelphia, will present a poster of Abstract #2604 on Sunday, Dec. 9, at 6 PM in Hall B1-B2, Level 1, Building B.

The protocol for the new treatment involves removing patients' cells through an apheresis process similar to blood donation, and modifying them in Penn's cell and vaccine production facility. Scientists there reprogram the patients' T cells to target tumor cells through a gene modification technique using a HIV-derived lentivirus vector. The vector encodes an antibody-like protein, called a chimeric antigen receptor (CAR), which is expressed on the surface of the T cells and designed to bind to a protein called CD19.

The modified cells are then infused back into the patient's body following lymphodepleting chemotherapy. Once the T cells start expressing the CAR, they focus all of their killing activity on cells that express CD19, which includes CLL and ALL tumor cells, and normal B cells. All of the other cells in the patient that do not express CD19 are ignored by the modified T cells, which limits systemic side effects typically experienced during traditional therapies.

In addition to initiating the death of the cancer cells, a signaling molecule built into the CAR also spurs the cell to produce cytokines that trigger other T cells to multiply—building a bigger and bigger army until all the target cells in the tumor are destroyed.

In the patients who experienced complete remissions after treatment, the CAR T cells exhibited vigorous proliferation after infusion, with the most robust expansion activity usually occurring between 10 and 31 days after infusion. Each of these patients developed a cytokine release syndrome—marked by fever, nausea, hypoxia and low blood pressure—which doctors treated when needed with the anti-cytokine agent tocilizumab.

Ultimately, the modified T cell treatment eradicated large amounts of tumor in these patients.

Tests of patients with complete responses also show that normal B cells have been eliminated along with their tumors. Since these cells are important for the body's immune system to fight infection, the patients now are receiving regular gamma globulin treatments as a preventive measure. No unusual infections have been observed.

Provided by University of Pennsylvania School of Medicine