Engineered immune cells produce complete response in child with an aggressive pediatric leukemia

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By reprogramming a 7-year-old girl's own immune cells to attack an aggressive form of childhood leukemia, a pediatric oncologist has achieved a complete response in his patient, who faced grim prospects when she relapsed after conventional treatment. The innovative experimental therapy used bioengineered T cells, custom-designed to multiply rapidly in the patient, and then destroy leukemia cells. After the treatment, the child's doctors found that she had no evidence of cancer.

Pediatric oncologist Stephan A. Grupp, M.D., Ph.D., of The Children's Hospital of Philadelphia, and colleagues from the University of Pennsylvania presented updated results of the clinical trial involving these engineered cells at the American Society of Hematology (ASH) annual meeting today in Atlanta. Grupp is the director of Translational Research for the Center for Childhood Cancer Research at The Children's Hospital of Philadelphia, and a professor of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania.

Grupp's research builds on his ongoing collaboration with Penn scientists who originally developed the modified T cells as a treatment for B-cell leukemias. The Penn team reported on early results of a trial using this cell therapy in adult chronic lymphocytic leukemia (CLL) patients in August of 2011. Carl H. June, M.D., of the Perelman School of Medicine at the University of Pennsylvania, leads this research group, which along with Grupp's work, is presenting new data at the ASH

meeting showing that nine of 12 patients with advanced leukemias in the clinical trial, including two children, responded to treatment with CTL019 cells.

One of the nine responding patients is the 7-year-old with acute lymphoblastic leukemia (ALL). Grupp and Penn colleagues adapted the treatment to combat ALL, the most common childhood leukemia, and also the most common childhood cancer. Although physicians can cure roughly 85 percent of ALL cases, the remaining 15 percent of such cases stubbornly resist treatment.

The CTL019 therapy, formerly called CART19, represents a new approach in cancer treatment. T cells are the workhorses of the immune system, recognizing and attacking invading disease cells. However, cancer cells fly under the radar of immune surveillance, evading detection by T cells. CAR T cells (chimeric antigen receptor T cells) are engineered to specifically target B cells, which become cancerous in certain leukemias, such as ALL and CLL, as well as types of lymphoma, another cancer of the immune cells.

CD19 is a protein found only on the surface of B cells. By creating an antibody that recognizes CD19, and physically connecting that antibody to T cells, the researchers have created a guided missile that locks in on and kills B cells, thereby attacking B-cell leukemia.

In using the CTL019 treatment in his pediatric patient, Grupp found that the very activity that destroyed leukemia cells also stimulated a highly activated immune response called a cytokine release syndrome. The child became very ill and had to be admitted to the intensive care unit.

Grupp and his team decided to counteract these toxic side effects by using 2 immunomodulating drugs that blunted the overactive immune response and rapidly relieved the child's treatment-related symptoms.

These results were effective enough that this approach is now being successfully incorporated into CTL019 treatments for adults as well.

The immunomodulating drugs did not interfere with the CTL019 therapy's anti-leukemia benefits, which have persisted 6 months after the infusion of cell therapy. This persistence is essential, because the engineered T cells remain in the patient's body to protect against a recurrence of the cancer.

"These engineered T cells have proven to be active in B cell leukemia in adults," said Grupp. "We are excited to see that the CTL019 approach may be effective in untreatable cases of pediatric ALL as well. Our hope is that these results will lead to widely available treatments for high-risk B cell leukemia and lymphoma, and perhaps other cancers in the future."

"This type of pioneering research addresses the importance of timing when considering experimental therapies for relapsed patients," added Susan R. Rheingold, M.D., one of the leaders in the Children's Hospital program for children with relapsed leukemia. "To ensure newly relapsed patients with refractory leukemia meet criteria for options like CTL019, we must begin exploring these innovative approaches earlier than ever before. Having the conversation with families earlier provides them more treatment options to offer the best possible outcome."

Provided by Children's Hospital of Philadelphia