Infusion of stem cells and specially generated T-cells from same donor improves leukemia survival

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In a significant advance for harnessing the immune system to treat leukemias, researchers at Fred Hutchinson Cancer Research Center for the first time have successfully infused large numbers of donor T-cells specific for a key anti-leukemic antigen to prolong survival in high-risk and relapsed leukemia patients after stem cell transplantation. Both the stem cells for transplant and the T-cells came from the same matched donors.

Reporting results of a pilot clinical trial in the Feb. 27 issue of the journal *Science Translational Medicine*, researchers describe the use of T-cells that were taken from a donor, programmed in the lab to recognize the Wilm's Tumor Antigen 1 (WT1) and kill leukemia cells, grown in large numbers, and then infused into patients to promote anti-leukemic activity. The WT1 protein is overexpressed in leukemias and is in part responsible for why the cells have become leukemic.

The best results were achieved when some of the patients received T-cell clones that were exposed to interleukin 21 (IL-21) during the programming and growth process, based on the hypothesis that such exposure would create cells that could survive longer and produce greater anti-leukemic activity after transfer. IL-21 promotes T-cell expansion while helping those cells acquire characteristics of central memory T-cells.

"This is the first time patients have received an infusion of WT1 specific T-cells, and thus also the first demonstration that such cells can provide a therapeutic anti-leukemic effect, as has been suggested from earlier vaccine trials that induce less potent responses," said Philip Greenberg, M.D., corresponding author and head of the Immunology Program at Fred Hutch.

"Ours is also the first report to show that greatly improved T-cell in-vivo persistence can be achieved after transfer by modifying the way cells are generated in tissue culture for therapy with inclusion of the cytokine IL-21," said Aude Chapuis, M.D., lead author on the study and a research associate in the Fred Hutch Immunology Program.

The findings support expanding efforts to target WT1 and provide insights into what is necessary to establish potent and persistent T-cell responses in patients, and such second generation studies have recently been initiated at Fred Hutch.

All of the patients, who were treated post-transplant at Seattle Cancer Care Alliance, Fred Hutch's site for patient care, received adoptively transferred infusions of billions of enhanced CD8 cytotoxic T-cell clones. They were considered at high risk of death because they had already relapsed and/or had a poor prognosis due to unfavorable characteristics of their leukemia.

Four of the 11 patients in the trial received infusions of T-cells that targeted WT1 and were generated in the presence of IL-21. One had detectable relapsed disease and entered complete remission shortly after the T-cells were infused. All four survived after T-cell therapy without relapse for more than 30 months without suffering graft-vs.-host-disease and required no additional anti-leukemic treatment, according to the study. GVHD is a major complication of stem cell transplantation.

Among the seven patients who received infused T-cells generated without the presence of IL-21, two showed direct evidence of anti-leukemic activity, including one patient with advanced progressive disease who had a temporary response.

Researchers undertook the clinical trial because relapse remains a leading cause of death after allogeneic hematopoietic cell transplantation for patients with high-risk leukemias. An obstacle to survival is that the beneficial graft-vs.-tumor effect of a transplant can be offset by concurrent GVHD. Interestingly, patients who develop GVHD have reduced relapse rates. This suggests that lymphocytes present in engrafted donor stem cells can cause a concurrent therapeutic graft-vs.-tumor effect. However, because donor stem cells are not selected for specificity for leukemia antigens and commonly recognized proteins expressed by many other host tissues, substantial morbidity and mortality from GVHD can occur.

The scientists theorized that infusions of T-cells that target WT1 could potentially promote additional anti-leukemic activity without inducing GVHD. WT1 is expressed 10 to 1,000 times higher in leukemic cells compared to normal CD34 blood stem cells, and the magnitude of expression correlates with the aggressiveness of acute myeloid leukemia, acute lymphoid leukemia and myelodysplastic syndromes.

More information: "Transferred WT1-reactive CD8 T cells can mediate antileukemic activity and persist in post-transplant patients," *Science Translational Medicine*, 2013.

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