Clinical trial suggests new cell therapy for relapsed leukemia patients

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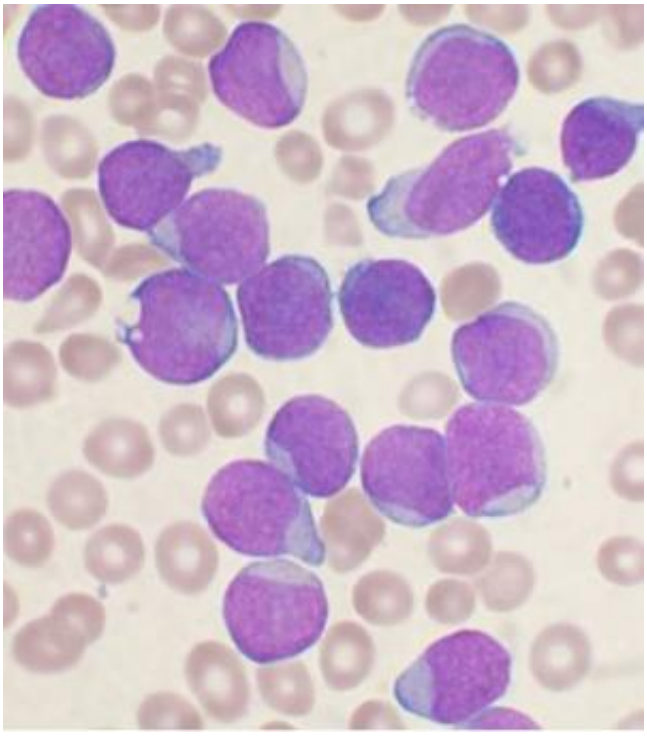

A Wright's stained bone marrow aspirate smear from a patient with precursor B-cell acute lymphoblastic leukemia. Credit: VashiDonsk/Wikipedia

A significant proportion of children and young adults with treatment-resistant B-cell leukemia who participated in a small study achieved remission with the help of a new form of gene therapy, according to researchers at the Stanford University School of Medicine and the National Cancer Institute.

The therapy is similar to but distinct from CD19-targeted chimeric antigen receptor T-cell therapy, or CAR T-cell therapy, in which a patient's T cells are genetically modified to target a molecule called CD19 on the surface of the cancer cells. This therapy was recently approved by the Food and Drug Administration for the treatment of some types of blood cancers.

The new therapy genetically modifies a patient's T cells to target a different molecule called CD22. The new approach is helpful because the cancer cells of some patients who undergo CD19-targeted CAR T-cell therapy stop expressing the CD19 molecule on their cell surfaces.

Fifteen of the 21 patients in the phase-1 study had previously either relapsed or failed to respond to anti-CD19 CAR T-cell treatment, which is currently used only when all other therapies have failed.

'Study gives hope'

"This is the first time that we've seen response rates anything like we achieved when we were first testing the CD19 CAR T therapy," said Crystal Mackall, MD, the associate director of Stanford's Cancer Institute and the director of the Parker Institute for Cancer Immunotherapy at Stanford. "We were all a little worried that we wouldn't find anything comparable. But this study gives hope to the idea that there may be another similar, very potent treatment." Researchers hope that targeting CD19 and CD22 simultaneously may result in a powerful therapy—one that cancer cells are unable to evade.

Mackall, professor of pediatrics and of internal medicine, is the senior author of the study, which will be published online Nov. 20 in *Nature Medicine*. Terry Fry, MD, a pediatric hematologist and oncologist at the National Cancer Institute, is the lead author and led the conduct of the study at the institute.

B-cell acute lymphoblastic leukemia is the most common cancer in children, and it's usually successfully treated with chemotherapy. However, patients who don't respond to initial treatment, or whose cancer recurs after a successful remission, often have a much poorer prognosis.

CAR T-cell therapy relies on a patient's own T cells—a type of immune cell that can be a powerful killing machine. Researchers genetically modify the T cells to recognize specific molecules on the cancer cells' surfaces and kill the cells. Some long-term remissions have followed treatment with the CD19-targeted treatment. But patients whose cancer cells don't express CD19, or which tamp down their expression to evade the treatment, either don't respond or can relapse. Mackall and her colleagues wondered if there was another molecule on the cancer cells that could also be a good target. Her laboratory developed a novel CAR T-cell targeting CD22 to test this idea.

The phase-1, dose-escalation study enrolled patients ages 7 to 30 with B cell acute lymphoblastic leukemia who received varying doses of the anti-CD22 CAR T-cell therapy. Each of the participants had received at least one bone-marrow transplant, and 10 of the 15 patients who had already undergone CD19-targeted treatment no longer expressed any CD19 on the surface of their cancer cells.

Median remission of six months

At the lowest dose level, one in six patients achieved complete remission after treatment with the anti-CD22 CAR T cells. However, when the researchers escalated the dose to the next level in the study, 11 of 15 patients, or 73 percent, entered remission. The therapy was also relatively well-tolerated by the recipients.

The remissions lasted a median of six months; three patients remain in

complete remission at six, nine and 21 months after the therapy. When the researchers investigated further, they learned that cancer cells in those patients who had relapsed had begun expressing lower-than-normal levels of CD22 on their surfaces.

"The take-home message is that we've found another CAR T-cell therapy that displays high-level activity in this phase-1 trial," said Mackall. "But the relapse rate was also high. So this forces the field to get even more sophisticated. How much of a target is needed for successful, long-lasting treatment? What happens if we target both CD19 and CD22 simultaneously?"

Fry and Mackall are already tackling the last question by testing a CAR T cell that recognizes both CD19 and CD22. They've confirmed that this T cell can kill cancer cells in the laboratory dish and in animal models, and they're testing it in a new clinical trial that has opened at Stanford and will open soon at NCI.

More information: CD22-targeted CAR T cells induce remission in CD19- CAR naive or resistant B-ALL, *Nature Medicine* (2017). nature.com/articles/doi:10.1038/nm.4441

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