2014 Top Stories in Oncology: Leukemia

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The engineered attack on ALL

The leukemia story chosen as the most noteworthy of 2014 is the expanded experience with chimeric antigen receptor–modified T cells for treatment of acute lymphoblastic leukemia in relapse. The largest published group[1] included 30 patients and built on University of Pennsylvania's study of other lymphoid malignancies. There will be dozens of papers devoted to this form of therapy from other centers, including the NCI and Memorial Sloan-Kettering, and educational and scientific sessions at December's American Society of Hematology meeting.

This is an experimental, labor-intensive, and very toxic approach that involves genetically engineering a patient's cytotoxic T lymphocytes, obtained by leukapheresis, to target the CD19 antigen on his lymphoblastic leukemia cells. [1,2] At Penn, these engineered attack cells, formerly known as CART19, are now called CTL019. The keys to success in obtaining and maintaining complete remission with this type of therapy, which have eluded investigators for 2 decades, are the expansion of CTL019 cells in the patient and their persistence over months. The group of 30 high-risk patients in the *NEJM* paper included 25 younger than 22, 18 of whom had disease relapse after allotransplant, and 4 adults aged 26 to 60, 3 with primary refractory ALL. Responses were seen in 27 patients, whose median percentage of CTL019 cells was 39.8%; amounts varied up to 69%. The probability of persistent CTL019 at 6 months was 68%; the patient with the longest response continued to show the presence of CTL019 cells at 2 years. Morphologic remission was obtained in 90% 1 month after infusion; at least 81% of these were MRD-negative at 3 months. Most received no further therapy. Seven patients relapsed between 1.5 and 8.5 months. Two-thirds were still event-free at 6 months.

These promising results were obtained at significant physical cost to the patients. All experienced cytokine-release syndrome, requiring hospitalization and intensive care for the 27% most severely affected. High levels of IL-6 correlated with syndrome severity, as did leukemia burden prior to beginning the study and high levels of CTL019-positive T cells. Tocilizumab, an IL-6 receptor blocking antibody, was effective in treating the syndrome, and all recovered. Other important toxicities are encephalopathy and B-cell aplasia. CNS effects were transient and patients with B-cell aplasia were maintained on immunoglobulin.

There are no treatments for relapsed ALL that offer good chance for cure, other than stem cell transplant for those who are eligible, which has its own significant toxicity and relapse rate. The door is thus wide open for the potential of engineering patients' cells to eradicate their leukemias. There is enormous potential that improvements in this type of approach will increase benefit while decreasing toxicity. However, this will not be the treatment for everyone. The optimal care of acute leukemia remains careful assessment of each case and its potential to be cured with the best protocol chemotherapy, with close monitoring for evidence of disease resistance and early relapse. Should relapse occur, a patient has the best chance for success with salvage therapies, including transplant or engineered T cells, if delay is avoided and decisions are made in consultation with centers that have experience in these treatments.