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T-Cell Therapy Has Lasting Effects

A T cell–based immunotherapy produces durable remissions in acute lymphocytic leukemia (ALL) and some B-cell lymphomas, according to data presented at the American Society of Hematology 57th Annual Meeting, held in Orlando, FL, December 5–8.

In the chimeric antigen receptor–modified T cell–based (CAR T) therapy, T cells isolated from patients are genetically engineered to recognize the B-cell marker CD19. These cells are then infused back into the patient, where they multiply and attack CD19-bearing tumor cells.

Stephan Grupp, MD, PhD, of The Children's Hospital of Philadelphia, PA, presented data from an ongoing pediatric trial of Novartis's CAR T therapy, CTL019. Among 59 children with relapsed or refractory ALL who received the therapy, 55 achieved complete remission (CR) within 1 month of therapy, a 93% response rate. With a median follow-up of 1 year, 34 (55%) were still in remission, with 18 patients maintaining a CR for a year or more. One patient has been in remission for 3.5 years.

The short-term activity of the treatment continues to be "phenomenal," says Grupp. As the long-term data accumulate, Grupp says, "the numbers are a lot higher than you would expect and have not been seen before with non-cell therapies in this population."

The 1-year survival rate in the trial was 79%, compared with 20% among similar patients who receive standard care.

In another study of CTL019, about half of a group of adults with relapsed or refractory B-cell non-Hodgkin lymphomas experienced CR, according to data presented by Stephen J. Schuster, MD, of the University of Pennsylvania School of Medicine in Philadelphia. The trial had a median follow-up of 14 months. All of the subjects had already exhausted available therapies; all had a poor prognosis.

Schuster reported that seven of 15 patients (47%) with refractory diffuse large B-cell lymphoma achieved a response after one infusion of CTL019. Eight of 11 patients with follicular lymphoma (73%) experienced a response, while one of two with mantle cell lymphoma showed a CR. Of the 15 responders with diffuse large B-cell or follicular lymphoma, 10 are still in remission after a year. The median duration of response has not been reached.

"This shows for the first time the durability of the response, and the fact that a single treatment can lead to a long-lasting response," says Schuster. "That these people are alive beyond a year without disease is amazing, given the prognosis."

The results "suggest this may be more than just a bridge to transplant or an alternative therapy, it may be an end in itself for therapy for some patients," Schuster adds.

A common side effect of CTL019 was cytokine release syndrome (CRS), in which the attacking T cells overproduce cytokines, causing adverse events ranging from mild flu-like symptoms to life-threatening respiratory distress. CRS occurred in 88% of patients in the ALL study, with 28% of patients experiencing serious CRS requiring management with tocilizumab, an FDA-approved anti-IL6 drug. In the non-Hodgkin lymphoma trial, serious CRS was reported in only four patients.

Some relapses in the ALL trial resulted from acquired resistance to the CAR T cells. Of the 20 children who relapsed, 13 developed CD19-negative tumors. In the non-Hodgkin lymphoma trial, CD19-negative relapses were generally not seen—patients either responded durably or usually relapsed with CD19-positive tumors.

Novartis is testing CTL019 in two phase II international, multisite trials for pediatric ALL and adult B-cell lymphomas, and aims to apply for FDA approval by the end of 2016. Three other companies are also testing CD19-targeted CAR T-cell treatments. *–Pat McCaffrey* ■

Venetoclax Yields Strong Responses in CLL

Results from an international phase II trial show that the investigational drug venetoclax (ABT-199/GDC-0199; AbbVie/Genentech) is effective in patients with chronic lymphocytic leukemia (CLL) who lack part of chromosome 17 (17p deletion), which contains *TP53*, and are refractory to standard treatment.

American Society of Hematology

Stephen Stilgenbauer presents the findings of a phase II trial of venetoclax for the treatment of chronic lymphocytic leukemia in patients with a 17p deletion. These patients have a particularly poor prognosis.

The data were presented by Stephan Stilgenbauer, MD, of the University of Ulm in Germany, at the annual meeting of the American Society of Hematology in Orlando, FL, held December 5–8.

Up to 10% of patients newly diagnosed with CLL have the 17p aberration, which also occurs in 30% to 50% of patients with relapsed, refractory disease. Their prognosis is "most dismal," Stilgenbauer said, because they respond poorly to standard chemo-immunotherapy, with a median progression-free survival (PFS) of less than 12 months. Venetoclax targets the antiapoptotic protein BCL2, which is overexpressed in CLL cells. By binding to and inhibiting BCL2, "this agent can drive cells toward death despite the lack of *TP53*," Stilgenbauer explained.

The study enrolled 107 patients with treatment-resistant CLL, all harboring the 17p deletion. The overall response rate was 79.4%, with eight patients experiencing complete remissions, and 84.7% maintaining their response at 12 months. Minimal residual disease—small numbers of leukemic cells that remain in patients even during remission, a major cause of relapse—was undetectable in over 20% of responders. The median PFS and overall survival have not been reached.

Venetoclax's toxicity profile was acceptable, Stilgenbauer said, and its main side effects, neutropenia and upper respiratory tract infections, "were lower than seen with front-line chemo-immunotherapy."

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