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."

To mitigate the risk of a common, potentially fatal complication called

tumor lysis syndrome—metabolic abnormalities that can occur when dying cells release their contents into the bloodstream—patients received venetoclax in a stepwise dosing schedule. "The goal was 400 mg, but we were already seeing tumor-cell destruction when we started with 20 mg," Stilgenbauer said. "This highlights venetoclax's dramatic efficacy; there aren't many other therapeutic agents that can achieve a response at only 5% of the target dose."

"These results will change the treatment landscape for a high-risk patient population," said Robert Hromas, MD, chair of medicine at the University of Florida in Gainesville. "It's an enormously exciting time to be working in the blood cancer field. When Rudolf Virchow coined the word 'leukemia' 150 years ago, his principle was 'as the cell goes, so goes the disease, so goes the patient.' Today, it's really 'as the gene goes, so goes the cell, so goes the disease'—we have the ability to define and selectively target molecular defects, and I think that, for the first time, we can begin talking about curing CLL."

Andrew Zelenetz, MD, PhD, of Memorial Sloan Kettering Cancer Center in New York, NY, noted the "completely different, accelerated pace" of drug approvals for CLL, with four therapies in the last 2 years: obinutuzumab (Gazyva; Genentech), ofatumumab (Arzerra; GlaxoSmithKline), ibrutinib (Imbruvica; Pharmacyclics/Janssen), and idelalisib (Zydelig; Gilead Sciences). Venetoclax has been designated a Breakthrough Therapy by the FDA, and Zelenetz thinks it will "almost certainly be approved" in 2016.

"The challenge now will be figuring out how to use these therapies in novel, creative ways that reduce toxicity, shorten treatment durations, and ultimately eliminate this disease," he said. *–Alissa Poh* ■

Tracing Melanoma's Genetic Progression

The process by which some benign skin lesions, or nevi, transform into melanomas remains unclear. A new study illuminates the genetic evolution of melanoma and strengthens the case for a controversial category of intermediate lesions that are midway between nevi and melanomas [N Engl J Med 2015;373:1926–36].

In this study, Boris Bastian, MD, PhD, of the University of California, San Francisco, and colleagues analyzed 37 melanoma samples—each including malignant tissue and its precursor lesion—and identified 150 distinct areas that represented different stages of disease progression. They asked eight pathologists to independently classify these areas as benign, intermediate but likely benign, intermediate but likely malignant, or melanoma. Although the pathologists usually agreed on areas at the benign and melanoma ends of the spectrum, they often disagreed on areas that were in the middle.

To find out if these histologic categories carried different genetic alterations, the researchers sequenced 293 cancer-causing genes in the melanoma samples. They observed that lesions unanimously classified by the pathologists as benign had only one driver mutation, *BRAF* V600E. Mutations in *CDKN2A* and genes that encode members of the SWI/SNF complex, such as *ARID1A*, occurred later, followed by mutations in *TP53* and *PTEN*.

This analysis also shed light on whether intermediate lesions represent a separate category or whether they reflect the limitations of pathologists' ability to discriminate lesion types. Bastian and colleagues found that lesions classified by at least two pathologists as intermediate were genetically distinct. Unlike benign nevi, they carried *TERT* mutations and either *NRAS* mutations or the *BRAF* V600K alteration.

"Our study shows that there is something between benign and malignant," says Bastian, adding that testing for these mutations could provide a better way to distinguish such lesions. "It's a step toward an objective diagnosis of melanoma," he says.

Essentially, lesions can follow several pathways to become melanomas, the researchers propose. Alterations that activate the MAPK pathway—*BRAF* V600E, *BRAF* V600K, or *NRAS* mutations—are the earliest to emerge. *TERT* mutations then switch on telomerase and enable the lesions to escape replicative senescence. By the time lesions have progressed to invasive melanomas, they've accrued *CDKN2A* mutations that disable the G1-S cell-cycle checkpoint.

"I think this is a landmark paper for melanoma," says David Polsky, MD, PhD, of the New York University Langone Medical Center in New York City, who wasn't connected to the study. "Here, they show that there is an intermediate stage in tumor development."

"It adds to our knowledge of the molecular events that are occurring as some melanomas develop from nevi," says Douglas Grossman, MD, PhD, of the University of Utah Health Sciences Center in Salt Lake City.

However, before any of the mutations could be clinically useful, Grossman cautions, researchers need to determine which ones influence outcomes for patients. *–Mitch Leslie* ■

ESR1 Mutations Prevalent in Some Breast Cancers

Mutations in the estrogen receptor 1 (*ESR1*) gene are highly prevalent and associated with worse overall survival in women with advanced, metastatic estrogen receptor (ER)–positive breast cancer, according to data presented at the 2015 San Antonio Breast Cancer Symposium in Texas, held December 8–12. The results shed light on why some tumors resist hormonal therapy and may aid in developing more personalized treatments.

Researchers analyzed cell-free DNA in blood samples from 541 of the 724 women enrolled in the phase III BOLERO-2 trial. All of the participants were postmenopausal women with advanced, metastatic ER-positive breast cancer that had progressed after treatment with an aromatase inhibitor. In that trial, adding the mTOR inhibitor everolimus (Afinitor; Novartis) to the standard hormonal therapy exemestane improved overall survival (OS), leading to FDA approval of everolimus for this use in 2012.

In this new study, almost 30% of the blood samples from BOLERO-2 tested positive for the *ESR1* mutations D538G (15.3%), Y537S (7.8%), or both (5.5%); these mutations have been observed in animal models of the disease and are known to promote resistance to estrogen-deprivation therapy. In these patients, median OS