Cancer-Killing CAR Therapies Gain Speed

CAR T-cell immunotherapies are leading to remissions in hematologic malignancies

Chimeric antigen receptor (CAR) T-cell therapy for hematologic malignancies has created a stir in recent years, as researchers have begun to cross the boundary between preclinical promise and clinical success. Their accomplishments have led to increased industry investment, with dozens of clinical trials now investigating this type of immunotherapy.

CAR T-cell therapy involves removing the patient's T cells and genetically modifying them to express a chimeric protein that couples a targeted antibody-binding domain on the cell surface with stimulatory domains inside the cell that activate its response. The CAR T cells are infused back into the patient, where they multiply and unleash a powerful immune response.

So far, researchers are seeing complete responses from autologous T cells transduced with a CD19-directed CAR in 70% to 90% of children and adults with relapsed or refractory B-cell acute lymphocytic leukemia (ALL)—an otherwise fatal diagnosis for most patients.

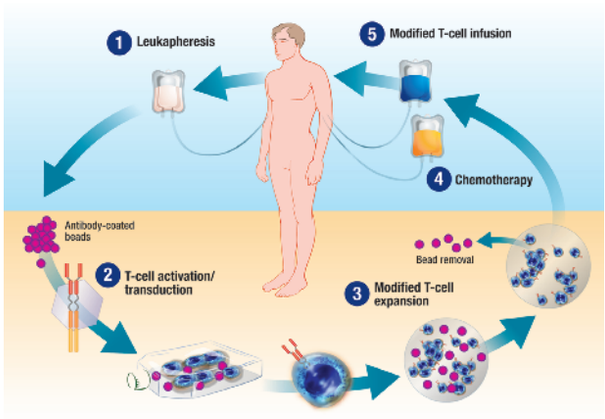
"There has to be caution with anything new, but I've been at this a long time and I've never seen anything… like this," says Stephan Grupp, MD, PhD, of Children's Hospital of Philadelphia and the University of Pennsylvania (Penn).

This "living therapy" is far from the off-the-shelf medicines that have dominated cancer therapy, says Crystal Mackall, MD, chief of pediatric oncology at the NCI. "It requires a new way of thinking about developing therapeutics."

Mackall led the first intention-to-treat trial using CD19-directed CAR T cells in children and young adults with relapsed or refractory ALL. The findings showed that 14 of 20 patients (70%) had a complete response (CR), 10 of whom went on to receive a stem cell transplant and remained cancer-free at a median follow-up of 10 months (Lancet 2014 Oct 12 [Epub ahead of print]).

Grupp's team published a study on another anti-CD19 CAR T cell therapy, named CTL019 (Novartis). CTL019 produced CRs in 27 of 30 (90%) ALL patients 1 month after the infusion (N Engl J Med 2014;371:1507–17). Sixteen patients were still in remission at a median follow-up of 8 months, with only three receiving further therapy, according to updated results reported in December at the American Society of Hematology annual meeting. Some patients have been in remission for 1 to 2 1/2 years, says Grupp.

A key difference between the NCI and Penn therapies is that CTL019 persists longer than the NCI CAR (Kite Pharma), Mackall notes. "That might be a good thing if you're looking to replace transplantation" in patients with B-cell ALL who are medically unable to undergo transplant or who have already had one or several failed transplants, she says. However, she cautions that the data are not yet strong enough to recommend that an eligible patient forego a potentially curative hematopoietic stem–cell transplant. The NCI CAR might work best as a bridge to transplant, Mackall adds.



An overview of CAR T-cell therapy. Cellular reprogramming and *ex vivo* expansion are conducted at a cell-processing facility.

One detail recent trials helped confirm is that researchers have found the right dose range. "Multiple centers are doing this independently, and we've all ended up in the range of 1 to 3 million CAR cells per kilogram," says Mackall.

Current studies have also allowed researchers to anticipate and mitigate the therapy's primary safety problem: cytokine release syndrome (CRS). The deaths of two patients, both with severe CRS, in a trial testing another CD19-directed CAR called JCAR015 (Juno Therapeutics; Seattle, WA) at Memorial Sloan Kettering Cancer Center (MSKCC) in New York, NY, briefly halted the study in March 2014, says Mark Frohlich, MD, the head of R&D at Juno.

MSKCC "tightened up the eligibility criteria on all its CAR studies to make sure patients had good heart-lung function," Frohlich says. They also adjusted the dose based on the degree of tumor burden because the greater the tumor burden, the higher the incidence of severe CRS, he says.

In addition, Grupp's team found that blocking the cytokine interleukin-6 with the immunosuppressant drug tocilizumab (Actemra; Genentech) can effectively treat severe CRS, and he now uses it as a first-line agent in the management of severe CRS.

The next big challenge, experts say, is extending CAR therapy to solid tumors. "The potential targets are less numerous in solid tumors because the healthy tissue that often shares your antigen is one that might not be as tolerable to attack," says Mackall.

However, NCI researchers have found several promising targets. Mackall's group is testing a CAR in pediatric melanomas and certain sarcomas that targets GD2, a tumor antigen overexpressed on the surface of tumors that is expressed at very low levels on normal tissues. Meanwhile, Steven Rosenberg, MD, PhD, and his group at NCI are investigating a CAR for high-grade glioblastoma that targets EGFR variant III, an extracellular domain mutation not expressed in normal tissues but widely expressed in glioblastoma.

Trials of CAR therapies in glioblastoma, mesothelioma, and cancers of the ovary, breast, and pancreas are under way at Penn. "There are early data that show engineered T cells can work against solid tumors," says Grupp. "The question is how well they're going to work." —*Melissa Weber* ■