JNCI Journal of the National Cancer Institute Advance Access published April 16, 2013

One Size Does Not Fit All: Personalized Immune Therapies Poised to Take Center Stage

By Anna Azvolinsky

Researchers are taking a patient's own T cells, arming the cells against that patient's cancer, and injecting them back into the patient. The approach is working on metastatic cancer patients who have otherwise run out of treatment options. To date, only a few leukemia patients have been treated with the chimeric antigen receptor (CAR) technique, but researchers believe the CAR technique can benefit many patients—although many more studies are still needed.

"We believe the early responses are every reason to be optimistic," said David Porter, M.D., of the Abramson Cancer Center at the University of Pennsylvania, who along with Carl June, M.D., director of translational research, leads the CAR trials at Penn.

So far, nine of 11 leukemia patients, including two children, have responded to CAR immunotherapy. Two patients have been in remission for more than 2 years.

Adoptive Cell Therapies: Seeking Prime Time

The approval of ipilimumab, an antibody that boosts a patient's immune system to attack cancer, to treat metastatic melanoma, and early results from trials with anti-PD1 and -PDL1 immunotherapy antibodies have recently validated an immunotherapy approach to cancer treatment for most oncologists who treat melanoma, kidney, and lung cancer.

"We believe the early responses are every reason to be optimistic"

CAR and other T-cell treatments using a patient's own T cells, broadly called adoptive cell therapy (ACT), are the next step. Multiple U.S. centers have shown that ACT can result in long-term tumor regression in metastatic cancer patients, including those with difficult-to-treat sarcomas, melanomas, and lymphomas.

"In the last 30 years, we have had virtually no systemic treatments that can eliminate [cancer] and result in long-term survival," said Steven Rosenberg, M.D, Ph.D, chief of surgery at the National Cancer Institute, who pioneered ACT. The technique involves isolating a patient's T cells either from blood or directly from the tumor, growing the T cells that have natural antitumor activity or genetically modifying the cells to target the tumor, and infusing these back into the patient. "What you need is a cell that is capable of recognizing the cancer," Rosenberg explained. "If you can find it naturally, fine, but now we can genetically manipulate cells, creating cells that have not existed before."

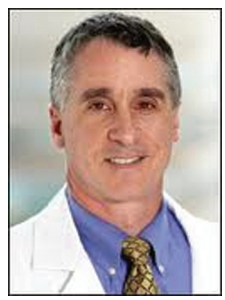
T-Cell Engineering

The CAR approach used in the Penn leukemia trial—first successfully reported by Rosenberg's group at NCI in 2010—involved isolating T-cells from patient blood and engineering the cells to express an antibody against CD19 by using an anti-CD19–encoding HIV lentiviral vector. CD19 is used as the antigen for leukemia patients because it is expressed on cancerous and normal B cells, but any antibody-like protein against a cancer-specific target can be added to the T-cells, researchers say.

All patients who have responded have early-onset, intense symptoms, known as cytokine release syndrome. The good news is the symptoms are a marker of response and are transient. Symptoms include fever, hypoxia, and low blood pressure and are treated with anticytokine therapy in the hospital.

Possible Replacement for Bone Marrow Transplants

Porter, director of blood and marrow transplantation at Penn, says he hopes CAR therapy could someday replace bone marrow transplantation (BMT), the only potentially curative option available for some blood cancer patients. "To cure patients with a safer treatment would be the dream of any transplant physician, and that is what we are striving for."



David Porter, M.D.

Although patients who undergo BMT continue to have long-term risks of graft-versus-host disease and ongoing immunosuppression, side effects observed with CAR therapy appear to resolve with no longer-term risks. The therapy is also an option for older patients for whom transplant is no longer an option.

"ACT is challenging because a certain expertise needs to be reached, but it is not more complicated than BMTs, which are done in many centers," said Patrick Hwu, M.D., who came to the University of Texas M. D. Anderson Cancer Center in Houston almost 10 years ago to set up a T-cell therapy facility after training with Rosenberg at NCI. "In fact, ACT is clinically a lot easier."

At Penn, the next round of advanced leukemia patients will help determine optimal dosing and side-effect management. Trials in patients with pancreatic, ovarian cancer, and mesothelioma begin this year.

Companies Are Getting Onboard

"The pharmaceutical industry is now interested, which is very different than a year ago," said June. Novartis announced an alliance with Penn in August 2012 to commercialize the CAR technology.

In October 2012, Los Angeles–based Kite Pharma announced an exclusive cooperative research agreement with NCI to develop CARs for various tumor types. "The beauty of engineered T cells is the therapy is broadly applicable to many different cancers," said Aya Jakobovits, Ph.D., president and CEO of Kite. Jakobovits is optimistic that although a unique therapy must be created for each patient, the process can be streamlined for cost-effectiveness—in theory, patients treated with ACT will have durable responses and will not need multiple, expensive cycles of therapy. Hwu agrees. He says he believes this approach "is cost effective because the therapies we have now are all very expensive but most provide only an incremental benefit."

UK-based Adaptimmune is developing another T-cell immunotherapy by using affinity-enhanced T-cell receptors (TCRs). The company has several early-stage cancer clinical trials in collaboration with Penn and NCI.

Clinical activity has been demonstrated with both T-cell engineering approaches, but June favors CAR. "My bias is that that TCRs are going to be less potent than CARs." Unlike TCRs, CARs do not exist in nature and are less likely to be suppressed by the tumor microenvironment, according to June. The major hurdle for both methods is antigen selection. Ideal antigens to target are ones found on a tumor, but not on other cells in the body, to prevent T cells from attacking normal tissue.

Giving the Immune System an Advantage

Another type of ACT involves harvesting T cells directly from a surgical tumor sample, called tumor-infiltrating lymphocytes (TILs), without genetic manipulation. The first proof of activity in humans came from Rosenberg's metastatic melanoma patient study in 1988. Melanoma appears unique in having natural T-cell infiltrates that are highly reactive against a patient's tumor. "For other cancer types, it looks like we will have to use genetically engineered cells," said Rosenberg.

Rosenberg led studies of heavily pretreated metastatic melanoma patients; 20%–40% achieved complete regression, an unprecedented number for a cancer still difficult to treat.

Jeffrey Weber, M.D., Ph.D., of the H. Lee Moffitt Cancer Center in Tampa, Fla., has been extensively involved in TIL melanoma trials. "A lot of the patients have survived 5–10 years without recurrence. That is pretty darned impressive."

Los Angeles–based Genesis Biopharma hopes to commercialize the TIL approach. Genesis is in dialogue with the U.S. Food and Drug Administration about the design of a phase III trial in metastatic melanoma and a TIL manufacturing process. "Approximately 18 centers that are experienced in managing immunotherapy side effects in the U.S. could participate in the trial," said Anthony Cataldo, president and CEO of Genesis.

The effectiveness of using TILs to treat melanoma, according to Martin Schroeder, M.S., director of Genesis, is probably due to the highly sensitized, heterogeneous population of TILs with various levels of antigen specificity produced naturally in cancer patients.

Before receiving TILs, patients undergo chemotherapy to get rid of existing T cells. The process is the same for CARs and TCRs. Then, a patient's own TILs are administered along with the cytokine interleukin 2. Toxicity from TIL treatment is mostly due to the administration of interleukin 2.

From Single-Center Trials to Widespread Use

Whether personalized T-cell therapies will work outside the few academic centers where these treatments were developed remains to be seen. Multicenter trials that could demonstrate the broader feasibility of ACT are at least a year away.

Clinicians not directly involved with ACT see many hurdles, including the ability to commercialize the therapy. Michael Atkins, M.D., of the Georgetown Lombardi Comprehensive Cancer Center at Georgetown University, currently sees ACT as a research tool but not as a widespread treatment. "I think the jury is still out on whether this will prove to be practical and whether payers are willing to support this on a larger scale," said Atkins.

Clinicians working on ACT research are more optimistic. "I think you can easily do this, just like BMT," said June.

"There are many mechanisms already in place for commercially developing this therapy. It is already a standard therapy at three cancer institutes in the U.S.," and many data support the TIL approach, said Cataldo.

Rosenberg agrees. "ACT is a treatment that I believe will be ultimately widely available. The only question is when."

 DOI:10.1093/jnci/djt103