

Leukemia: Genetically Modified T Cells Continue to Produce Responses

BY MARK FUERST



NEW ORLEANS—Three and a half years after demonstrating the first successful use of genetically engineered T cells to fight leukemia, a research team from the University of Pennsylvania and Children's Hospital of Philadelphia have now reported that these modified T cells produce longer-term responses and persist in patients' bodies with vaccine-like activity for more than three years, according to presentations here at the American Society of Hematology Annual Meeting.

"Modified T cells can do the work of normal T cells. They target, trigger, kill, expand, and contract. This is the Holy Grail of adoptive T-cell therapy," Michael Kalos, PhD, Adjunct Associate Professor of Pathology and Laboratory Medicine at the University of Pennsylvania Perelman School of Medicine, said in an interview.

"Infused adoptive T cells are 'serial killers.' Each infused cell or its progeny kills on average more than 1,000 leukemia cells. These cells are poised to replace bone marrow transplantation with a therapy that is less expensive,

more widely available, and less toxic than current allogeneic stem cell transplantation therapy."

The investigational treatment pioneered by the Penn team begins by removing patients' T cells via an apheresis process, then reprogramming them with a gene-transfer technique using a lentivirus vector. The newly built T cells target tumor cells using an antibody-like protein, called a chimeric antigen receptor (CAR), which is expressed on the surface of the T cells and designed to bind to the CD19 protein—which is found on the surface of cancerous B cells associated with both chronic lymphocytic leukemia (CLL) and acute lymphoblastic leukemia (ALL).

The modified cells are then infused back into the patient's body following lympho-depleting chemotherapy. These "hunter" T cells both multiply and attack, Kalos said, and a signaling domain built into the CAR promotes rapid growth of these cells. Cells that do not express CD19 are left untouched by the modified T cells, which limits the prolonged, systemic side effects typically experienced during traditional cancer therapies.



American Society of Hematology/Todd Buchanan

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MAMMOGRAPHY

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from screening), and considering the absolute benefit in terms of the number of women needed to screen (rather than the number needed to invite).

The absolute benefit of mammography screening for the four reviews ranged from 96 women needed to screen to prevent one breast cancer death to 257 after being adjusted—dropping from a 20-fold difference in the findings of the four reviews to a 2.5-fold difference.

"Our conclusion is that deriving an absolute benefit of mammography—which is controversial—from common data sources is contextual," Smith said.

"In short, the absolute benefit once you standardize [the findings]—to a common population, a common screening scenario, and a common duration of follow-up—these differences become not so significant or important at all."

Still the Patient's Choice

Smith's results help explain why some of these major studies had such different results, Osborne noted. "The true benefit of screening will be underestimated if you're counting people who never got screened in the screened group. [Smith] has found a way to analyze the studies on the same playing field. And when you do it that way, they have more similar results. I think

iPad Extra!

Watch on the iPad edition of this issue as **Robert A. Smith, PhD**, explains in a video interview with OT reporter Dan Keller, why four major reviews of the benefits of mammography screening have reached widely varying conclusions.



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Listen on the iPad edition of this issue as **Kent Osborne, MD**, discusses in a podcast with OT Assistant Editor Sarah DiGiulio what makes the findings of mammography screening studies so controversial.



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that was the benefit of his analysis—it makes intuitive sense."

The fact that there is a benefit in most of the studies—albeit small—was a reason to screen, Osborne added. The harms need to be taken into account, but "balanced by the fact that it looks like there is a reduction in mortality—not huge—but there is a mortality reduction in getting a mammogram. You present those two things to the patient and let her have a choice. We need, to the very best of our ability, to educate patients that mammograms have their problems and they probably also help to some extent." ■

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Reports on Three Groups of Patients

At the ASH meeting, the research team reported findings from three different groups of patients:

- Nineteen of 22 children (86%) with ALL had complete responses (*Abstract 67*). Two-thirds of these patients, for whom all other treatments had failed, had ongoing complete responses at more than three months. Five patients had relapsed, including one whose tests revealed new tumor cells that do not express the CD19 protein.

- In that same study, all five adult ALL patients treated so far experienced complete responses, the longest of which continues for six months after treatment. One patient subsequently underwent a bone marrow transplant and remains in remission. One patient relapsed after three months with disease that also tested negative for CD19.

- Fifteen of 32 (47%) adult patients with CLL responded to the therapy, with seven experiencing a complete response (*Abstract 4162*). In a recently completed pilot study of 14 CLL patients, four patients (29%) have achieved a complete response at more than 10 months. And, three of the first 18 CLL patients (17%) in a Phase II, dose-optimization trial have achieved complete responses (*Abstract 873*).

“These new and expanded data provide significant proof that T cells engineered to express cancer-targeting CARs not only work, but work dramatically and in a sustained manner in patients with relapsed, treatment-resistant leukemia, and further demonstrate the potential of this approach to help these patients achieve complete response,” Kalos said.

“Further, our results show that we can potentially measure and track the activity of these engineered cells in the body as a way to monitor treatment—an exciting finding considering that this treatment is often the last hope for these patients.”

How Adoptive T Cells Work

At a news conference at the meeting on “Pioneering Precision Medicine Approaches for Hard-to-Treat Blood Disorders” that featured the studies, Kalos said the essential elements of successful adoptive T-cell therapy are a large number of potent antigen-specific T cells, expansion in vivo in response to antigen encounter, potent anti-tumor activity, contraction and long-term persistence, and the ability to respond to challenge.

Patients with the greatest expansion of T cells (above five percent of the total of all of their T cells) were very likely to achieve complete responses, Kalos said. Those with less robust, but still detectable, cell expansion were partial responders, and those who had no detectable T-cell expansion did not respond to treatment.

For those in complete response, the engineered T cells were usually detectable many months after the infusion and continued to show functional activity.

“We see long-term persistence of the adoptive T cells and ongoing B-cell aplasia in patients who achieve complete response,” Kalos said, noting that in all cases, no further therapeutic treatment intervention is needed after infusion. These patients show massive expansion of T cells, almost all of it within the first month of therapy.

Side Effects

The therapy does induce some side effects. In the trials for both CLL and ALL, all responding patients experienced a cytokine release syndrome (CRS), which marks the process of the engineered cells multiplying and attacking tumor cells.

Patients typically have varying degrees of flu-like symptoms, with high fevers, nausea, muscle pain, and in some cases, low blood pressure and breathing difficulties. About one-quarter of patients require a hospital stay and having breathing difficulties, which are relieved by treatment. The researchers said they have also seen neurological deficits, including delirium, confusion, and aphasia, that disappear in a few days.



STEPHAN A. GRUPP, MD, PHD, called the therapy a “game changer” for controlling the toxicity seen with these engineered T cells, and noted that there has been no graft-vs.-host disease seen.

Kalos said they have learned how to manage the CRS reaction, if necessary, using the immunosuppressant monoclonal antibody tocilizumab, which tamps down elevated levels of the inflammatory cytokine interleukin-6 (IL-6). IL-6 spikes during the most robust phase of the engineered cells’ expansion in the body, he noted. Patients with B-cell aplasia have been managed with replacement therapy.

At his oral presentation later in the meeting, Kalos said that engineered T cells may be the first example of successful “synthetic biology.”

“T cells can be engineered to express antibody fragments that persist and express antibody for at least three years in patients with leukemia,” he summed up. “Complete and durable clinical responses are associated with robust expansion and long-term persistence of the adoptive T cells, and in patients with heavy tumor burden, delayed tumor lysis syndrome and CRS.”

“T cells expand, contract, and persist in responders,” he told *OT*. “We don’t know why some patients respond and others do not. Some robust expansion is part of the efficacy of the treatment.”

He noted that some adoptive T cells transfer to the central nervous system

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iPad Extras!

In video interviews on the iPad edition of this issue with *OT* reporter Dan Keller, **Stephen Grupp, MD, PhD**, elaborates on the clinical implications of his research; and **Laurence Cooper, MD**, gives an overview of how CAR T cells work.



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in ALL patients, and responses are associated with deep molecular remission.

'Extremely Active' Therapy

"The key point is that these adoptive T cells are extremely active," the lead author of the ALL study, Stephan A. Grupp, MD, PhD, Director of Translational Research at the Center for Childhood Cancer Research at Children's Hospital of Philadelphia and Professor of Pediatrics at the University of Pennsylvania, said in an interview.

"Gene transfer technology is used to stably express CARs on T cells, conferring novel antigen specificity. The T cells can be directed against any tumor cell that expresses the CD19 surface antigen. This therapy takes advantage of the cytotoxic potential of T cells, thereby killing tumor cells in an antigen-dependent manner. Persistent adoptive T cells consist of both effector—cytotoxic—and central memory T cells."

At his oral presentation, Grupp said that taking all 27 ALL patients together, 24 patients (89%) have achieved complete remission in a median of 145 days, with six relapses. "The follow-up is short, only 3.4 months. We need more time for long-term results," he said. "We do see persistence out to 18 months in responding patients. In some of these patients, half of the circulating white blood cells are engineered T cells."

He added, "Our results demonstrate the potential of this treatment for patients who truly have no other therapeutic option. In the relatively short time that we've observed these patients, we have reason to believe that this treatment could become a viable therapy for their relapsed, treatment-resistant disease."

He called the therapy a "game changer" for controlling the toxicity seen with these engineered T cells, and noted that there has been no graft-vs.-host disease seen.



LAURENCE COOPER, MD: "If you have refractory leukemia patients, they deserve this therapy now. This could possibly be offered instead of transplant. There is good reason to believe these genetically modified T cells may persist a long time."

Next Steps

Kalos said the Penn team's next big effort is to define why the treatment works in some patients and not others: "Is it the patient, T cells, the disease, or something else that will improve responses?"

"The response rates so far are incredible," he said. "The goal is to move the therapy as early as possible in these diseases."

The Penn researchers have licensed the technologies involved in these trials to Novartis.

The moderator of the news conference, Laurence Cooper, MD, Professor of Pediatrics at the University of Texas

MD Anderson Cancer Center, said in an interview, "T cells extracted from leukemia patients' blood latch onto tumor cells and destroy them. Importantly, this works for a sustained period of time.

"These patients are quite sick, but the CRS is manageable, with expected complications. That the patients do not succumb to their illness is a testament to the skill of these practitioners. These data are encouraging. How the therapy plays out in the marketplace is unknown. It needs time to evolve."

The limitation of the therapy is no longer genetic modification, Cooper

noted. "It's antigen identification. We know it's safe to use these targeted T cells. Can we design trials that capture the adoptive response? Or perhaps we need to sequence therapies, first with CAR T cells and then programmed cell death 1 ligand. Then we can infuse regular T cells. There is the potential ability to turn the cells off with high-dose steroids and blunt the immune response."

At MD Anderson, Cooper said, researchers are thinking about targeting two receptors at the same time—perhaps CD 19 plus either CD 22 or

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Profiles in Oncology Social Media: Howard (Jack) West, MD, @JackWestMD

BY LOLA BUTCHER

Continuing Series

The full archive of Oncology Social Media Profiles can be found in this Collection on the OT website: <http://bit.ly/OT-OncologySocialMediaProfiles>

"If we provide high-quality information, oncologists and other professional cancer care providers can leverage the opportunities to distribute information easily. If we stand on the sidelines, people will still seek information about cancer, but the void will be filled by other sources that are far less constructive."

Excerpt from his bio at #LCSM, the Official Blog of Lung Cancer Social Media (lcsmchat.wordpress.com): "Dr. West currently cares for cancer patients directly at Swedish Cancer Institute in Seattle and also heads multiple national and regional cancer trials. He founded the nonprofit Global Resource for Advancing Cancer Education (GRACE) (cancergrace.org) to provide timely information directly to patients and caregivers. He also moderates #LCSM chat."

When Jack West, MD, Medical Director of the Thoracic Oncology Program at Swedish Cancer Institute, presented at a TEDx conference in 2011, he said something that would make some physicians squirm: "New medical information is being disseminated at such a rapid rate that overwhelmed doctors can't feasibly keep up with all of the progress being made for the range of diseases they are called upon to treat. We are increasingly seeing an individual physician becoming a limiting factor on our ability to capitalize on this new knowledge."

Fortunately, he said, patients can—and will—help overcome this limitation by seeking out new knowledge specific to their medical situation and working with their medical team to make treatment decisions.

"As we evolve to a new era of personalized medicine, patients will need to take a more active role in their own care," he said in that talk. "They will need the right tools, and the medical community has an opportunity—and arguably the responsibility—to provide them so that everyone can benefit from all of the knowledge available, rather



incredibly valuable content there is in the 'asymptotic' tail of the curve—whether that is music that is downloaded from online sources that is not popular enough to ever be in a music store, or Amazon titles that would never be in a book store because too few people in any one geographical area are interested. He makes the point that the Internet makes it remarkably more feasible to deliver digital content that is needed by relatively few individuals over a broad geography.

"I have a significant clinical focus in lung cancer—and within that, I have a long-time interest in never-smokers with lung cancer and a rare type of lung cancer that has historically

than be limited by what any one individual happens to know."

That is why, he says, he founded GRACE, the Global Resource for Advancing Cancer Education, (cancergrace.org) in 2007. Started as his own personal effort to provide blog posts, podcasts, and forums focused primarily on lung cancer, GRACE has since fulfilled his vision by growing to include many contributors covering a wide range of cancer subtypes.

The effort currently serves more than 10,000 cancer patients and their loved ones from more than 120 countries each month.

How did you come to create an online resource for patients who need education about their specific cancer situation?

"I read *The Long Tail* by Chris Anderson, the editor of WIRED magazine, in which he describes how much

been called bronchioloalveolar carcinoma. As the management of lung cancer was becoming increasingly complex several years ago, I had noticed that a lot of these patients were being managed in a way that was less than might have been optimal. This was understandable, because most clinicians had nothing close to a critical mass of experience to guide them.

"The field of lung cancer—and by extension, those of many other cancers—had become so complex that no general oncologist could feasibly keep up with all of the new developments in so many fields.

"So I wanted to upload a distillation of my particular expertise in a condition that I specialize in. If I do a one-time consultation with a patient who comes to me for a second opinion, it can be a very helpful experience for that single person, but the discussion evaporates after that individual consultation. On the other hand, if I spend a comparable amount of time making digital

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CD 20. "Most of these leukemia patients are too advanced for transplantation. But once they are in remission after receiving CAR T cells, they potentially are able to receive a transplant."

At Memorial Sloan-Kettering Cancer Center, he continued, many CAR T-cell-treated patients go on to transplant. "At MD Anderson, we give these patients, mostly those with ALL, some with CLL, CAR T cells and then send them on to transplant."

Cooper has a simple message about adoptive T-cell therapy for practicing oncologists: "If you have refractory leu-

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