Chimeric Antigen Receptor T-Cell Immunotherapy Tackles Blood Cancers

By Vicki Brower

In a pilot study of 39 children with highly aggressive acute lymphoblastic leukemia (ALL), treatment with a chimeric antigen receptor (CAR) T-cell immunotherapy resulted in a complete response in 36, or 92%, at 1 month, and an event-free survival of 70% at six months. Of those patients, 76% remained in complete remission at 6 months after treatment with CTL019. Although 10 of these patients relapsed, and five died, the first patient to receive the treatment remains cancer free since being treated in April 2012. These children, who had no other treatments available, received autologous...

The University of Pennsylvania, with its partner Novartis, has treated more than 125 patients with CTL019. Penn is one of a half-dozen research groups that presented dramatic results in December 2014 at the ASH annual meeting of using CAR T-cell immunotherapies directed at the CD19 antigen, which is found on B cells. To produce this treatment, scientists remove patients’ T cells and genetically modify them to express a CAR and then reinfuse them into patients. There the cells recognize and attack cells carrying the CD19 antigen. The CAR T cells are generally given only once, and they continue to kill cancer cells for months—sometimes years.

Penn is testing the same CTL019 treatment in multiple myeloma and non-Hodgkin lymphoma (NHL), as well as in chronic lymphocytic leukemia (CLL), said primary investigator David L. Porter, M.D., director of blood and marrow transplantation at the University of Pennsylvania.

“This therapy not only treats the disease, but detects and kills residual malignant cells,” he said. Two patients with CLL, treated 4.5 years ago, remain in remission.

CD19 is the first antigen to be selected for CAR T-cell therapy by several research groups, and it is the first such treatment to reach the clinic. Researchers are testing it in B-cell cancers, which include NHL, ALL, and CLL.

One confirmation of CD19 as a viable target for B-cell immunotherapy came last fall, when Amgen’s bispecific CD19 antibody, blinatumomab, was approved in the U.S. in December for ALL 5 months ahead of schedule. This drug will compete with all CD19 CAR T-cell therapies being tested.

“Nobody knows at this point which will be more successful,” Porter said. “This drug will probably have a different role than CAR T cells, as the response rate is impressive but temporary,” he said.

Also in development are CAR T-cell therapies for solid tumors, with different antigen targets, including mesothelin for mesothelioma, ovarian, and pancreatic cancers; epidermal growth factor receptor for glioblastoma; and CD30 for acute myelogenous leukemia.

“Although no one knows for sure, we think that the treatment is so successful in ALL for our and other groups’ researchers is because the ALL cells are in the blood and bone marrow and are therefore accessible to the treatment. This is the same reason why allogeneic bone marrow stem cell transplants in this population are not successful.”

Treating Leukemias

Many groups began testing their CD19 CAR T cells in CLL, the most common CD19 leukemia, with modest but good results, Sadelain said.

“But results in ALL, a devastating disease in adults, were a critical turning point for the field,” he said.

In December 2014 Sadelain’s group reported an 89% complete remission rate in 27 evaluable adult patients with relapsed or refractory ALL (ASH abstract 382; https://ash.confex.com/ash/2014/webprogram/Paper76573.html). At 6 months’ median follow-up, 12 remained disease free, including seven with follow-up of 1 year or more, and seven who did not receive a stem cell transplant. Sadelain’s group sees CAR T-cell therapy as a bridge to transplant, the standard of care.

“But as more patients are treated and may not be able to go on to transplant, we can follow patients who may remain in remission without transplant. And in the future, transplants may no longer be needed,” he said. In November 2014, FDA granted this treatment, JCAR015, orphan drug designation.

Results from a phase I study of a National Institutes of Health–Kite Pharma study in 20 pediatric refractory ALL patients discussed at ASH showed a complete response rate of 70%, with 60% achieving minimal residual disease-negative response (ASH abstract 381; https://ash.confex.com/ash/2014/webprogram/Paper75723.html). Ten had subsequent
stem cell transplants, and the two who did not relapsed. The expansion of CAR T cells in patients statistically correlated with response, and disease burden statistically correlated with severity of side effects.

“Although no one knows for sure, we think that the treatment is so successful in ALL for our and other groups’ researchers is because the ALL cells are in the blood and bone marrow and are therefore accessible to the treatment,” said James N. Kochenderfer, M.D., investigator in the experimental transplantation and immunology branch at the National Cancer Institute’s Center for Cancer Research. “This is the same reason why allogeneic bone marrow stem cell transplants in this population are not successful,” he said.

The NIH group sees these results as confirmation that this therapy serves as a good bridge to autologous stem cell transplant.

“There is no doubt the CAR T-cell therapy targeting CD19 induces remissions in children with ALL,” Sadelain said. That children are easier to treat is well-known but not well-understood, he said.

In CLL, in which the microenvironment is more immunosuppressive, the Penn group gave an update at ASH on a phase II dose optimization study with 24 patients. Kochenderfer said that 10, or 42%, responded. Five, or 21%, had complete responses, and five had partial responses (ASH abstract 1982; https://ash.confex.com/ash/2014/webprogram/Paper68877.html). Overall survival was 68% at a median follow-up of 9 months.

Lymphoma Trials

NIH is making a big effort in lymphomas, Kochenderfer said. It treated its first patient in 2010, who remains in remission 4.5 years later.

“To date, we have seen durable complete and partial responses in patients with refractory indolent and aggressive large B-cell lymphomas,” Steven A. Rosenberg, M.D., Ph.D., chief of the surgery branch and head of the tumor immunology section at NCI’s Center for Cancer Research.

NIH and Kite Pharma are tackling a type of B-cell malignancy, diffuse large B-cell lymphoma (DLBCL), which according to Kochenderfer is tougher to treat than ALL. In a trial of 15 patients (nine with refractory DLBCL, two with indolent lymphomas, and four with CLL), Kochenderfer’s group treated patients with low doses of chemotherapy to reduce side effects, followed by CAR T cells (J. Clin. Oncol., online Aug. 25, 2014; doi:10.1200/JCO.2014.56.2025). Four DLBCL patients achieved remissions, with three of these four ongoing, with durations from 9 to 22 months. Acute side effects were fever, hypotension, delirium, and other neurologic side effects. One patient died suddenly 16 days after treatment.

In an update at ASH, Kochenderfer said that of 30 patients now treated, 22 of 27 evaluable patients had gone into either complete or partial remission (ASH abstract 550; https://ash.confex.com/ash/2014/webprogram/Paper72899.html). Ten remain in complete remission of 1–37 months. Eight of nine new patients in the study had refractory DLBCL. Of these, one achieved a complete remission, and four partial remissions occurred.

The Penn group’s lymphoma results are comparable. Five patients with follicular lymphoma (FL) and 11 with DLBCL received one infusion of CTL019 and were examined 3 months afterward. All five with FL, and five of 11 with DLBCL, responded to therapy, with four complete remissions in both groups. The longest complete responses are ongoing, at 7.4 months for FL and 8.8 months for DLBCL, with other responses continuing.

Allogeneic CAR T-cells, Nonviral Gene Transfer

Several institutions are also testing allogeneic CAR T-cell therapies, including Baylor College of Medicine in Houston; the University of Texas M. D. Anderson Cancer Center (MDACC), also in Houston; and NCI. Allogeneic cells apparently do not cause adverse immune reactions in patients, possibly owing to being cultured ex vivo, according to Laurence Cooper, M.D., Ph.D., associate professor of pediatrics at MDACC. Using allogeneic cells would enable patients who cannot provide T cells themselves to receive CAR T-cell immunotherapy. It would also allow allogeneic cells to be prepared and infused as an off-the-shelf product, which is likely to be less expensive than autologous CAR T cells, Cooper said.

MDACC is currently alone in using a nonviral approach to gene transfer to produce the engineered cells. The system Cooper and colleagues is using is called “Sleeping Beauty,” because it “awakened” an existing transposon derived from fish. The DNA in the guise of the Sleeping Beauty system can readily insert itself into a T cell’s genome, Cooper said. It does so by using an enzyme, transposase, that binds to flanking sequences in the DNA molecule, or plasmid, and then excises the transposon from the plasmid and pastes the cargo load into the genome.

“This system, which uses electroporation to introduce elements of the Sleeping Beauty system into T cells, is typically simpler and cheaper to use than viral-based vectors,” Cooper said.

Partow Kebriaei, M.D., associate professor in the department of stem cell transplantation and cellular therapy at the M.D. Anderson Cancer Center reported results at ASH of using the Sleeping Beauty platform to genetically reprogram both allogeneic and autologous CD19 CAR T cells in patients with ALL, NHL, and CLL, in the adjuvant setting after hematopoietic stem cell transplantation, or for active disease. Three of 10 patients with ALL are in remission 5 months after infusion, and four of five patients with NHL remain in remission at a median of 12 months after treatment. In the group of 13 treated patients who had relapsed, three are alive and in remission at a median of 3 months after infusion. No CRS occurred in any patients, which Cooper attributes to a patient population with reduced disease burden.

Kochenderfer is primary investigator in a trial with allogeneic donor-derived anti-CD19 CAR T cells in 10 patients with B-cell malignancies that persisted after allogeneic stem cell transplant (Blood 2013;122:4129–39; doi:10.1182/blood-2013-08-519413).

“Since that paper was published, we have been getting much better results—probably because we have increased the cell dose, but all of these newer results are unpublished,” he said.

CD19 CAR T-cell therapies employ several gene transfer methods, gene constructs, and costimulatory molecules. Which will be most safe and effective, and which patients will respond, is unknown. Cost, ease of manufacturing, and regulation of these cells are also unanswered questions. Many researchers believe that in the future, CAR T-cell therapy will be best used in earlier-stage disease and with other immunotherapies, such as checkpoint inhibitors, and may eliminate the need for chemotherapy.

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