High-tech gene-therapy advances offer hope for patients with hard-to-treat blood disorders

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A series of advancements in genetically engineered cell therapies demonstrate early efficacy and safety in patients with blood disorders for whom standard treatments have been unsuccessful, according to data showcased today during the 55th American Society of Hematology (ASH) Annual Meeting and Exposition in New Orleans.

Today, many patients with newly diagnosed blood disorders – ranging from cancer to rare genetic conditions – respond well to modern treatment regimens. However, for more than half of newly treated patients, therapies fail to work or patients experience a relapse that may negatively affect their prognosis. Thankfully, an emerging field, dubbed "precision medicine," aims to improve success rates by attacking the specific targets that are responsible for a patient's disease. Using a patient's own re-engineered cells to attack their disease is an example of this approach. Building on the existing concept of turning the immune system into a disease-fighting weapon, this new field of medicine adds innovative technologies that transform healthy cells into "super" cells that can more effectively combat disease.

Several studies presented during the meeting detail results using one method known as chimeric antigen receptor (CAR) cell engineering. The CAR process starts when T cells (naturally occurring immune cells) are extracted from the blood of an individual and outfitted with two powerful features: a receptor on the outer cell surface that recognizes a

protein called CD19 present on most leukemic cells and a powerful mechanism inside the cell that triggers it to expand and proliferate once attached to the targeted protein. With these new engineered features, the T cells are injected back into the patient, now primed to seek and destroy cancer cells.

Studies on the CAR approach provide data on both adult and pediatric patients with leukemia who have responded well to this treatment strategy. In addition to the abstracts detailed below, two additional data sets are being presented on this research program during the meeting [abstracts 4162 and 873 (both by David Porter, MD)].

Preliminary studies have found that this process may generate responses in as many as two-thirds of cases in which all other treatment options have failed. Further, because the cells are derived from the patient, there is an inherently lower risk of toxicity because the cells are less likely to attack the host tissue than cells introduced from a foreign body.

Other advances in cell engineering reported today include a new generation of gene "vector" therapy that self-destructs once it delivers critical, missing genetic material to a patient, solving the issue of T cell overgrowth observed in previous studies. Finally, genetic modifications of haploidentical (or half-matched) stem cells prior to transplant could expand the utility of this treatment approach to a much wider range of patients in the coming years by reducing the risk of transplant infections.

"It's exciting to see these encouraging initial results with engineered immune cells, particularly such a durable response among patients who have very aggressive disease that has relapsed after standard treatments," said Laurence Cooper, MD, of The University of Texas MD Anderson Cancer Center in Houston. "With the right technology and laboratory expertise, the process of cell engineering is feasible for many patients. One remaining challenge is determining why some patients benefit and

others have less durable responses. Does 'one size fits all' therapy work or do we need personalized or individualized T cell treatments? Further, we need to extend these studies to other tumor types, particularly solid tumors, to evaluate their potential in other clinical settings."

Removal of Alpha/Beta+ T Cells and of CD19+ B Cells From the Graft Translates Into Rapid Engraftment, Absence of Visceral Graft-Versus-Host Disease and Low Transplant-Related Mortality in Children With Acute Leukemia Given HLA-Haploidentical Hematopoietic Stem Cell Transplantation [157]

Transplants of haploidentical, or half-matched, blood-forming stem cells may be an effective option for patients in need of a transplant without a fully matched donor; however, in the past, in comparison to transplant from a fully matched donor, this treatment has been associated with an increased risk of infection and disease recurrence. This study tested the effectiveness of manipulating in the lab these half-matched donor stem cells.

In this process, the team selectively removed the alpha/beta-positive T cells and CD19-positive B cells from the donor graft, as those are more likely to trigger donor cells to attack recipient cells, resulting in a dangerous complication known as graft-versus-host disease (GVHD). At the same time, the process preserved healthy, mature, immune-active cells known as natural killer and gamma/delta-positive T cells that help prevent disease relapse and protect against infection. A total of 45 patients with acute leukemia were treated with genetically engineered stem cells from one of their parents. Transplants engrafted in 44 of the 45 patients, with a 29 percent cumulative incidence of mild GVHD. One month after transplant, follow-up analyses showed that transplanted cells had persisted in the patients and demonstrated potential anti-leukemic activity, which continued to increase over time.

"Our results, which demonstrate that transplantation of selectively modified, half-matched donor stem cells boasts success rates equivalent to those of a fully matched transplant, preventing GVHD and reducing transplant-related death, help continue to establish this approach as a viable option for patients without a matched donor," said study author Alice Bertaina, MD, of the Bambino Gesu Children's Hospital in Rome, Italy. "This has the potential to make this lifesaving treatment more accessible to a much larger population of patients who may not have a perfect donor match."

Immune Reconstitution and Preliminary Safety Analysis of 9 Patients Treated With Somatic Gene Therapy for X-Linked Severe Combined Immunodeficiency (SCID-X1) With a Self-Inactivating Gammaretroviral Vector [715]

Previous studies have investigated the potential for gene therapy using a retroviral vector to treat children with the fatal inherited disease, X-linked severe combined immunodeficiency (SCID-X1, or "bubble boy disease"). The vector works by latching to the surface of the T cell and injecting genetic material that helps "train" the cells to properly produce their own immune cells. While successful in earlier studies, in some cases the children developed leukemia when new corrective genetic material was inserted near a trigger in the children's DNA, predisposing T cells to turn into cancer cells.

Aiming to overcome this challenge and achieve immune recovery in these patients without provoking the development of leukemia, investigators considered an approach with a modified version of the vector that was designed to insert the genetic material but not encourage overgrowth of the cells. Enrolling nine boys with SCID-X1, investigators removed some of the boys' bone marrow stem cells and engineered them with this new version of the vector and infused the engineered cells back into the bloodstream. After the cell infusion and adequate observation,

eight of the nine boys remained alive and healthy; one patient died of advanced viral infection that was present when he entered the study. Seven are showing signs that their bodies are properly producing healthy T cells. Analysis of insertion pattern in the blood of these children shows much less insertion of the corrective gene near trigger points for cancer compared to children enrolled on the previous trial.

"We have preliminary evidence that using this new vector approach is just as effective but may eliminate the long-term risk of leukemia in these children," said study author Sung-Yun Pai, MD, of Dana-Farber/Boston Children's Cancer and Blood Disorders Center in Boston, Mass. "We will need to closely monitor these patients to evaluate their long-term risks, but at this point we are hopeful given the excellent response so far."

Long-Term Functional Persistence, B Cell Aplasia and Anti-Leukemia Efficacy in Refractory B Cell Malignancies Following T Cell Immunotherapy Using CAR-Redirected T Cells Targeting CD19 [163]

These research results provide an overview of patient response in a clinical research program evaluating treatment of pediatric and adult leukemia patients with experimental CAR genetically engineered T cells. A series of treatment cohorts were included in the analysis, including pediatric and adult patients with high-risk, treatment-resistant acute lymphocytic leukemia and adult patients with advanced relapsed and/or treatment-resistant chronic lymphocytic leukemia. The focus of this research effort was to understand how the engineered cells responded in patients with time, and how that response correlated with anti-leukemia activity. To accurately estimate the quantity, lifespan, and activity of the engineered cells in the patients, researchers developed a number of highly accurate tests. The researchers observed that those patients with the greatest expansion of T cells (above 5% of the total of all of their T

cells) were very likely to achieve complete response; 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. In complete responders, the engineered T cells were usually detectable many months after the infusion and continued to show functional activity in the body.

"These new and expanded data provide significant proof that T cells engineered to express cancer-targeting chimeric antigen receptors 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," said study author Michael Kalos, PhD, of the University of Pennsylvania Perelman School of Medicine in Philadelphia. "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."

T Cells Engineered With a Chimeric Antigen Receptor (CAR) Targeting CD19 (CTL019) Produce Significant In Vivo Proliferation, Complete Responses and Long-Term Persistence Without GVHD in Children and Adults With Relapsed, Refractory ALL [67]

This study report, which provides select results from a group of cell therapy trials conducted by investigators at the Children's Hospital of Philadelphia and the University of Pennsylvania, used the chimeric antigen receptor (CAR) cell engineering approach to manipulate the T cells of 22 children and five adults with relapsed, treatment-resistant acute lymphocytic leukemia. After treatment with their own cells re-engineered to seek, attack, and kill leukemic cells, 24 patients (19 children, five adults) achieved a complete response (CR). One patient

has remained in remission for a year and had detectable engineered cells at 18 months post infusion, indicating that the cells show potential to persist in the body. Of those who achieved CR at one month, six (five children, one adult) have since relapsed. No patients experienced immediate infusion-related toxicities or graft-versus-host disease. The most significant toxicity each patient experienced was a complication known as delayed cytokine release syndrome, characterized by high fever, muscle pain, and nausea, which developed as a result of successful T cell expansion, driven by the interaction between engineered T cells and the patients' leukemic cells.

"Our results serve as another important milestone in demonstrating the potential of this treatment for patients who truly have no other therapeutic options," said study author Stephan Grupp, MD, PhD, of the Children's Hospital of Philadelphia, Abramson Cancer Center and the Perelman School of Medicine at the University of Pennsylvania in Philadelphia. "These data also demonstrate that these engineered hunter cells greatly expand and then persist in patients, allowing for long-term disease control. This allays previous concerns that infused cells only survive for a limited time. 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 and we look forward to continuing to evaluate their long-term response."

Effective Treatment of Chemotherapy-Refractory Diffuse Large B Cell Lymphoma With Autologous T Cells Genetically-Engineered to Express an Anti-CD19 Chimeric Antigen Receptor [168]

This abstract reports on the treatment of 15 patients with anti-CD19 CAR-expressing T cells, all of whom had advanced B cell malignancies, and eight of whom had large B cell lymphomas. This is the first report of successful treatment in patients with chemotherapy-refractory primary

mediastinal B cell lymphoma and diffuse large B cell lymphoma. In the trial, the 15 adult patients with varying types of lymphoma or leukemia received an infusion of their own genetically modified T cells following a chemotherapy conditioning regimen of cyclosphamide and fludarabine. Six patients achieved complete remission and six achieved partial remission. Acute toxicities such as fever, low blood pressure, focal neurologic deficits, and delirium resolved in less than three weeks.

"Our data provide the first true glimpse of the potential of this approach in patients with aggressive lymphomas that, until this point, were virtually untreatable," said study author James Kochenderfer, MD, of the Experimental Transplantation and Immunology Branch of the National Cancer Institute at the National Institutes of Health in Bethesda, Md. "We are particularly encouraged by the partial and complete responses that we observed in a number of patients with diffuse large B cell lymphomas who had exhausted all other treatment options. This approach offers an option for patients with chemotherapy-refractory large B cell lymphomas who are not generally thought to be good candidates for hematopoietic stem cell transplantation. This approach is still an early-stage experimental therapy, and we will continue our research to further improve the protocol and evaluate its value in additional patients with treatment-resistant disease."

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