Biotech Innovations

"Off-the-Shelf" CAR T-Cell Therapy Tested in Pediatric B-Cell Leukemia

Experimental allogeneic gene-edited T cells may provide an "off-the-shelf" alternative to autologous chimeric antigen receptor (CAR) T-cell therapies for children with recurrent or refractory B-cell acute lymphoblastic leukemia, reducing treatment delays and costs, according to a study in Science Translational Medicine. In a phase 1 clinical trial, 4 of 6 children treated with the allogeneic CAR T cells achieved remission, paving the way for them to receive allogeneic hematopoietic stem cell transplants.

T cells from healthy adult donors were edited at multiple gene sites using a next-generation CRISPR-Cas9 (clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9) lentiviral method. One edit enables the T cells to target CD19 receptors expressed by diseased lymphocytes. Another reduces rejection risk by disrupting a receptor chain that promotes graft-vs-host disease. A third edit enhances edited T-cell survival by eliminating a receptor targeted by alemtuzumab, a monoclonal antibody commonly used to kill lymphocytes before stem cell transplants. The edited cells were expanded and purified, producing enough to treat several dozen patients, and cryopreserved before infusion.

For the 6 patients who were treated, 2 had refractory disease after the edited T-cell infusion. They did not receive stem cell transplants and eventually died. The remaining 2 children were still in remission at 12 and at 3 months after receiving stem cell transplants. Historically, the 3-year event-free survival in similar high-risk cohorts is about 15%.

Overall toxicities were similar to previous CAR T-cell therapies targeting CD19 receptors, meeting the trial's primary end point for safety. Although the study was not designed to evaluate efficacy, "salvage of 2 of 6 patients treated under this approach is encouraging, and further data from larger cohorts and their long-term outcomes will be required," the authors wrote. The possibility of eliminating allogeneic stem cell transplant after the edited T-cell treatment may also be investigated, they added.

Investigational RSV Vaccine Given During Pregnancy Protects Newborns

As respiratory syncytial virus (RSV) infections surged, a maternal vaccine was found to be 82% effective in preventing severe medically attended lower respiratory tract infections due to RSV in newborns up to 90 days after birth, and 69% effective for the first 6 months after birth, reaching 1 of 2 primary efficacy end points in a phase 3 clinical trial. The top-line results were announced by Pfizer and have not yet been published elsewhere, though the firm intends to submit them for peer review.

During Pregnancy Protects Newborns

Designated RSVpreF, the vaccine blocks the RSV prefusion F protein, preventing the virus from entering human cells. Administered during the late second to third trimester of pregnancy, it elicits neutralizing antibodies that are passed to the fetus. A phase 3 clinical trial of RSVpreF for preventing lower respiratory infections among adults aged 60 years or older is also underway.

Researchers Use Plasmid Gene Editing to Personalize Solid Tumor T-Cell Therapy

A gene editing method using bacteria-derived plasmids rather than viral vectors could program patients' own T cells to attack multiple tumor antigens specific to their cancers, a first-in-human study suggests. The study's authors say the approach could open up thousands of unique tumor antigens as targets, potentially personalizing cancer immunotherapy and making it more effective against solid tumors. The study was presented at the Society for Immunotherapy of Cancer meeting and published in Nature.

For the second efficacy end point, the vaccine reduced all RSV-related medically attended lower respiratory tract infections by 57% for 90 days and 51% for 6 months after birth. Although these results did not meet the established statistical end point, the company's press release noted that they are clinically significant.

Pfizer stopped enrollment in the clinical trial in light of the results, and in consultation with the study's independent data monitoring committee and the US Food and Drug Administration (FDA). The firm plans to file for FDA approval based on these results by the end of this year.

The ongoing trial involves about 7400 pregnant individuals who are followed up for safety through 6 months after delivery and whose infants are monitored for safety and efficacy through 1 year. About half of the infants have been followed up for 2 years. No safety concerns have been identified for either the vaccinated individuals or their newborns, according to the release.

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In a phase 1 clinical trial involving 16 patients, the approach delivered edited T cells to solid tumor targets. The tumors regressed in 2 patients and remained stable in 5 despite clinically suboptimal dosing.
Two patients had adverse reactions possibly related to T-cell therapy though all reacted to lymphodepleting chemotherapy used to prepare them for the edited T-cell infusion.

Potential tumor antigen targets were identified by comparing tumor DNA with blood DNA for every patient. Gene sequences targeting antigens displayed only by tumor cells were inserted into T cells and tested for their affinity, specificity, and activity against the intended targets. Of 127 gene sequences tested, 73 were confirmed as specific and sufficiently functional for product use, and 37 of these were edited into autologous T cells infused into the 16 patients.

Compared with viral gene editing, plasmid editing with CRISPR-Cas9 (clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9) may reduce potentially dangerous off-target effects while increasing the genetic load delivered to edited cells, the authors wrote. And by allowing multiple knockout and knock-in edits in a single cell, it could enable edited T cells to not only target tumor-specific antigens but to resist exhaustion, avoid immunosuppressive factors in the solid tumor microenvironment, and possibly even ensure cell expansion without the need for lymphodepleting chemotherapy. Such enhanced immunotherapy capabilities could result in complete and durable responses for patients with solid tumors, the authors concluded.

— Howard Larkin

Note: Source references are available through embedded hyperlinks in the article text online.