A CAR T-Cell Therapy for Multiple Childhood Cancers?

Overall, the therapy worked very well in the mice used in the study. The first human clinical trial will be in adult brain cancers.

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An experimental CAR T-cell therapy may have potential as a treatment for several types of childhood cancer, results from a new study in mice suggest.

The CAR T cells, designed to bind to a protein called B7-H3 on the surface of cancer cells, eradicated tumors in mouse models of several different childhood cancers, including two forms of sarcoma and medulloblastoma.

The findings were reported January 17 in Clinical Cancer Research.

The treatment has yet to be tested in humans but is quickly moving toward clinical trials, said the study's lead investigator, Robbie Majzner, MD, of the Division of Pediatric Hematology-Oncology at the Stanford University School of Medicine.

One of the most promising aspects of this particular CAR T-cell therapy is that it targets a single protein, or antigen, that is present at high levels in numerous cancers. To date, CAR T-cell treatments have proven effective only against blood cancers like leukemia and l ymphoma, and those treatments target an antigen that is found at high levels in only those specific cancers.

But the B7-H3 CAR T cells target an antigen that is found in many non-blood cancers (i.e., solid tumors), including some pediatric cancers.

A single CAR T-cell treatment that could be used to treat multiple cancers, and thus more patients, could be particularly attractive for the therapy's continued development by the private sector, Majzner said. For childhood cancers, which are relatively rare, he added, "it would clearly be an advantage."

The data so far on B7-H3 CAR T cells are encouraging, said Stephen Gottschalk, MD, chair of the Department of Bone Marrow Transplantation and Cellular Therapy at St. Jude Children's Research Hospital in Tennessee, who was not involved in the research.

"This is a good step forward," Gottschalk said. "Looking at all of the preclinical data that's been

generated, this therapy deserves to be tested" in clinical trials.

Cell Surface Antigens: Identifying Elusive Targets

Two CAR T-cell therapies have been approved by the Food and Drug Administration (FDA) to treat leukemia and lymphoma, respectively. Both target an antigen known as CD19. A third CAR T cell that targets an antigen called BCMA is expected to be approved later this year to treat multiple myeloma.

The dramatic responses these treatments can induce—completely eradicating even highly advanced cancers in patients with perhaps only a few months to live, responses that in some cases have been sustained for months and even years—have generated intense enthusiasm and hope that CAR T-cell therapies could be developed for many more cancers.

However, CAR T cells have important limitations. One is that their target antigen must sit on the surface of the cancer cell, where the T cell's genetically engineered receptor—the chimeric antigen receptor, or CAR—can bind to it. Once the T cell is tethered to the cancer cell, it can then kill it.

But there's another related issue. "There are very few [antigens] on the [tumor cell] surface and that are unique to tumors," explained Marcela Maus, MD, PhD, director of Cellular Immunotherapy at the Massachusetts General Hospital Cancer Center, at a December 2018 NCI-sponsored workshop on cell-based immunotherapies.

If the target antigen is present on healthy cells as well, the CAR T cells could attack those cells.

The risk of harming healthy tissues is of particular concern with CAR T cells, Gottschalk said. "CAR T cells are not like a conventional drug," he explained. "They can dramatically expand in [the body]," unleashing powerful immune responses that can kill many cells.

However, as Maus pointed out, the antigen targets of the two FDA-approved CAR T-cell therapies, and the therapy moving toward approval, are also expressed on some types of normal cells. And by and large, she said, the side effects caused by these CAR T-cell therapies have been "clinically manageable."

B7-H3: A "Pan-Cancer Antigen" for Childhood Cancers?

With this new study, the research team began by performing what they believe is the largest effort to date to identify potentially targetable antigens in samples of solid cancers commonly diagnosed in children. The work began in NCI's Pediatric Oncology Branch, when Majzner was a pediatric hematology-oncology fellow, training under the study's senior author, Crystal Mackall, MD, who is also now at Stanford.

They focused their analysis on B7-H3 because previous studies had shown that it was found at high levels in a number of cancers.

And, indeed, their analysis showed that B7-H3 was present on the surface of cancer cells in many of the tumor samples, including samples of neuroblastoma, Wilms tumor, and a particularly difficult-to-treat form of brain cancer called DIPG.

The research team then developed a series of different CAR T cells that target B7-H3. In tests on cancer cell lines, one particular B7-H3 CAR stood out, showing the most cell-killing potency. That CAR incorporated a part of an antibody (called the single-chain variable fragment) from an investigational B7-H3-targeted drug already being tested in human clinical trials.

It was this CAR T cell that they then tested in mouse models of different childhood cancers.

In Mice, Shrinking Tumors

Overall, the therapy worked very well in the mice.

For example, in models of aggressive forms of osteosarcoma and Ewing sarcoma, a single treatment completely eradicated the tumors. A “control” CAR T cell that targets CD19 had little to no effect.

They saw similar results in medulloblastoma, a cancer that forms at the base of the brain near the top of the spinal cord.

The findings are very encouraging, Majzner said. In studies testing other CAR T cells against mouse models of solid tumors, he noted, the treatments often only prevent tumors from progressing.

“That’s not what we had here,” he continued. “Here we saw regression and clearance.”

The CAR T cells did not appear to attack cells that express low levels of B7-H3. This finding, Majzner said, suggests that there might be a “therapeutic window” for B7-H3 CAR T cells, in which the cells can eradicate tumors while having only minimal effects on healthy tissues.

In humans, B7-H3 is found at low levels on some types of immune cells and liver cells, as well as other tissues, he explained. However, early clinical trials of the B7-H3 targeted drug have not reported any serious side effects to date.

So, with B7-H3 CAR T cells, the potential for harm may be limited, Majzner said. “I think there could be a needle to thread.”

Moving Into Clinical Trials

Greater insight into the potential clinical value of B7-H3 CAR T cells may come soon, with early-stage clinical trials already being planned.

Although Majzner said his group intends to conduct trials in childhood cancers, the first trial out of the gate with the Stanford team’s B7-H3 CAR T cells will be in adult brain cancers.

Similar to what some other research groups have done in early-stage clinical trials of CAR T cells, they plan to administer the treatment directly into the brain, he noted, which could improve how well it works and possibly limit side effects.

At least two other research groups have developed B7-H3 CAR T cells and are also expecting to begin testing them in clinical trials, Gottschalk said.

“Expanding the use of CAR T cells beyond hematologic malignancies is an important next step for these therapies,” said Nirali Shah, MD, an associate research physician in NCI’s Pediatric Oncology Branch. Moving B7-H3 CAR T cells into clinic trials, Shah continued, “will help to further advance the potential of these therapies to treat solid tumors.”

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