FEATURE

Trial to assess feasibility, safety of CAR T-cell therapy for relapsed pediatric central nervous system tumors

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Nicholas A. Vitanza

A clinical trial is underway to examine the role of chimeric antigen receptor T-cell therapy for children and young adults with relapsed or refractory HER-2-positive central nervous system tumors.

“[Although] survival rates have improved for pediatric brain and spinal cord tumors, many of the children we care for have no life-saving therapy options if their disease recurs,” **Nicholas A. Vitanza, MD,** neuro-oncologist at Seattle Children’s Hospital, said in a press release. “We have to find a way to give them a life after they recur and, ultimately, be able to offer initial treatments with fewer long-term side effects.”

The BrainChild-01 trial is designed to enroll at least 18 patients into one of two groups.

All patients’ chimeric antigen receptor (CAR) T cells will be reprogrammed to target HER-2. After that, patients in the first group will have their T cells infused through a catheter into the tumor resection cavity. Patients in the second group will have their T cells infused through a catheter into their central nervous system (CNS) ventricular system.

HemOnc Today spoke with Vitanza about the trial, the need for new and more effective treatments for this patient population, and the implications of this approach if it is proven effective and safe.

Question: How did this trial come about?

Answer: Clinical trials for brain and spinal cord tumors are a big need in pediatric oncology. A lot of what we have discovered within the past decade in pediatric neuro-oncology has been the molecular subgrouping of different tumors. The 4,000 diagnoses of brain and spinal cord tumors that occur annually in pediatrics is broken down into very small groups. It has been very exciting to learn more about the biology in targeted and molecular approaches. However, it also has meant that it has been hard to write clinical trials for such small groups and have something like a next-generation therapy that can help so many children. **Michael Jensen, MD,** director of Ben Towne Center for Childhood Cancer Research at Seattle Children’s Research Institute, and **Rebecca Gardner, MD,** attending physician at Seattle Children’s Hospital, have both been very successful in developing our PLAT pipeline of clinical trials. They have been interested in trying to find someone who can transition those into pediatric neuro-oncology. This, along with my own interest to reach more children, were the big instigators of this project.

Q: How will you conduct the trial?

A: We have identified HER-2 as a good target that is expressed on some of the tumors and not on the brain. To circumvent the blood-brain barrier, catheters are placed either into where the tumor was (ie, the resection bed) or into a fluid compartment (ie, the ventricles) in their brain. Then the CAR T cells will be injected directly into the catheter that sits directly under their scalp so we have the best chance to get the T cells to the tumor. When a tumor develops in the body, we know the white blood cells have already failed to deal with the problem and will not be able to get rid of the tumor. Still, the immune system is a powerful weapon. To harness this weapon, but also make it better, we take out a patient’s T cells and then re-engineer them to fight a target on the tumor. In leukemia, this has been done by targeting a molecule known as CD19, which is present on almost all leukemia cells. Because leukemia is a cancer that forms in the blood, our leukemia PLAT trials inject the CAR T cells back into the patients’ bloodstream. With this approach, we have been able to get 93% of children with recurrent leukemia and with an otherwise difficult prognosis into another remission with one single dose. The challenge associated with applying this system to brain tumors is that they are not a total clonal population of cells — not all cells are identical. We need to be smart [and make sure] the targets we pick are on the majority of cells, but also not on a normal brain.

Q: Can you elaborate on the need for new or more effective treatments for this patient population?

A: CNS tumors — like medulloblastoma, the most common malignant brain tumor — can spread throughout the brain and spine. They require very aggressive therapy, including radiation and chemotherapy. Fifty or 60 years ago, this was a fatal disease. Patients now have about a 75% chance for cure. Yet, we have about 25% of children who still have the tumor recur. We also have other diseases, such as glioblastoma, from which only about 10% of patients survive upfront. In both cases, there are almost no curative options when there is a recurrence.

Q: Why might this approach be effective?

A: A lot of what we have been doing for a long time in pediatric cancer is finding the pathways that are activated inside the cell and trying to block them. This means we have to get a drug inside a patient's body, into the cells, at the right concentration, and then hope it is the right pathway to which the cell will not become resistant. A much simpler approach is to evaluate if each tumor has a molecule on it and to target that. Even if a patient's white blood cells are not able to see that molecule because the tumor is hiding from the immune system, we can engineer those white blood cells to be able to fight that target. We work hard to find targets on tumor cells but not anywhere else in the body, so the system works like a heat-seeking missile that only goes to a specific location. This can sound like science fiction, but it is actually quite practical. There is no better biological killer in the world than the human immune system.

Q: What are the implications if this approach works?

A: Hundreds of children die every year of pediatric brain and spinal cord tumors that either did not have good therapies initially or had no curative options when they recurred. The thousands of children we do cure usually have to go through radiation or chemotherapy, which leaves them with long-term side effects that can be fatal. We hope this will be a curative option for patients if their tumors recur, but we ultimately hope this could be a strategy to use upfront to offer patients a curative approach with fewer side effects from our conventional treatments.

Q: What is the timeline for results?

A: We are open and enrolling children. We plan to enroll enough patients within 2 to 3 years to know the safety of this treatment approach. Hopefully we will have an answer within the next 2 years about whether this is a safe approach that we can feasibly do, and then we will continue to open other trials simultaneously. We have BrainChild-02, targeting the EGFR molecule, which is being reviewed by the FDA now and hopefully will be open in a few months. Within the next 5 years, we will be opening other studies that will combine these targets to look to cure more children. – *by Jennifer Southall*

For more information:

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Disclosure: Vitanza reports no relevant financial disclosures.