Q&A: CAR T cell therapy offers a novel approach to pediatric cancer treatment

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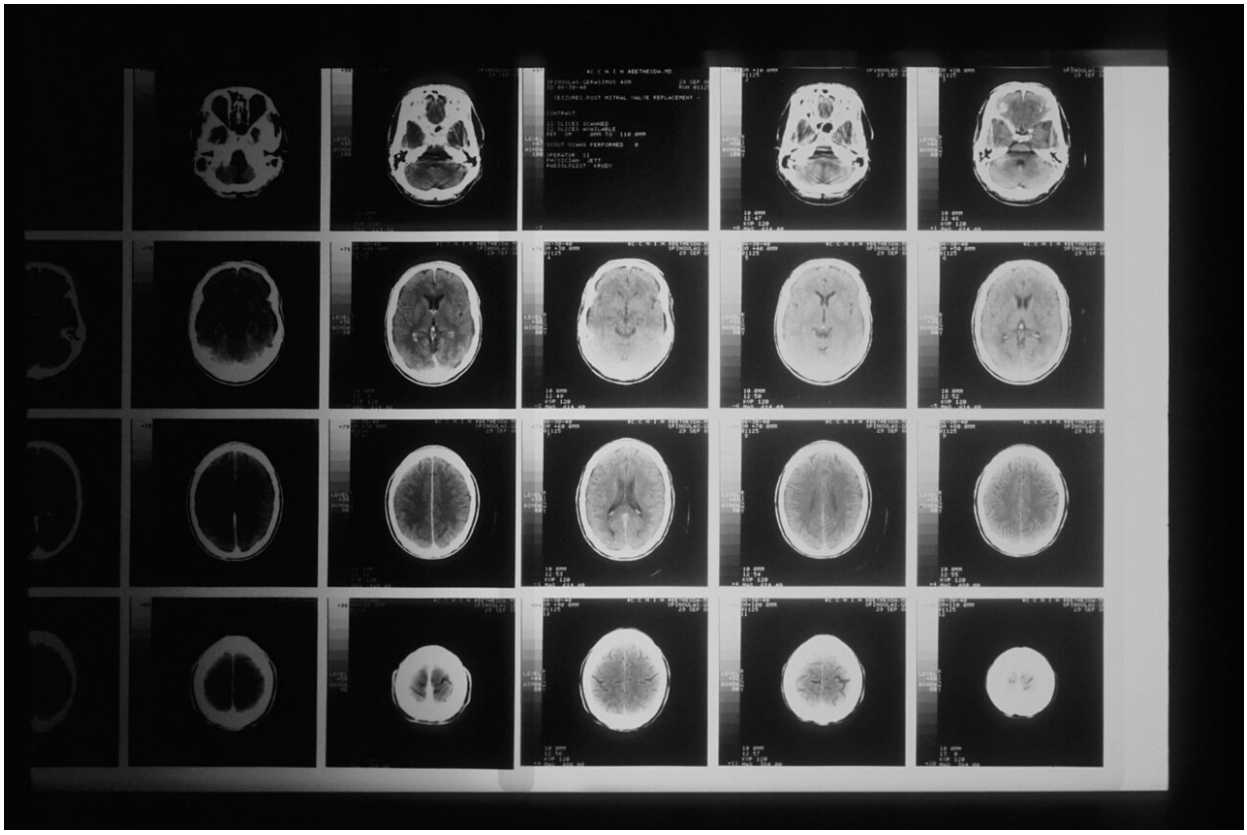

Brain cancer cat scan. Credit: Pediatric Cancer Research Foundation

One of the most innovative treatments for pediatric cancer today is a novel form of targeted immunotherapy that was recently developed and is now increasingly being applied to pediatric cancer treatment: chimeric

antigen receptors (CAR) T cell therapy. This technology harnesses the power of a patient's own immune system to directly target and kill cancer cells and has shown great promise for a variety of cancer types.

In 2001, the Pediatric Cancer Research Foundation began supporting the work of Dr. Laurence Cooper and other pioneers. The Foundation's investment helped fuel the launch of the first in-human protocol using T cells to target leukemia. This groundbreaking work proved that when CAR T cells are infused back into the same patient, they can mount full-blown immune attacks on tumor cells and helped lay the foundation for the cascade of research that has followed.

Two pediatric oncology experts answered questions about CAR T Cell Therapy. Dr. Nicholas Vitanza, Attending Pediatric Neuro-Oncologist and Associate Professor, Hematology/Oncology at Seattle Children's Hospital, who is leading a clinical trial of CAR T therapy for pediatric brain tumors and Dr. Navin Pinto, Attending Pediatric Oncologist at Children's Hospital Colorado and Professor of Pediatrics at Colorado University Anschutz School of Medicine, who is an authority on CAR T cell therapy for patients with relapsed and refractory cancer.

What is CAR T cell therapy?

"CAR T cells are immune cells that are created by collecting immune cells (T cells) from patients and genetically engineering them to express a novel protein receptor (CAR) on their surface. When a CAR T cell engages with its protein target on a tumor cell, it activates natural pathways in the T cell to release chemicals capable of killing target tumor cells," says Dr. Pinto.

This is why CAR T cell therapy is a type of ongoing targeted immunotherapy that harnesses the power of the body's own immune system to directly attack cancer cells.

As Dr. Pinto describes it, "CAR T cell therapy is a "living drug" that, when effective, is able to survive in the patient, serially kill cancer cells and then perform surveillance for recurrent cancer cells."

Dr. Vitanza expands on this idea, "When we think about tumors and what ways to target them, for generations we focused on killing rapidly dividing cells through a variety of means and then we transitioned to targeted therapies. But most of that was molecularly targeted, which has challenges because [most cancers] are not clonal diseases like leukemia.

"CAR T cells offer a targeted approach by leveraging somebody's own immune system to better fight a tumor, with the thinking that some things that the immune system should be doing besides fighting infection, which it's most famous for, is also eliminating abnormal cells of your own that could become cancer."

What can CAR T cell therapy treat / what are your trials?

Dr. Pinto explains, "CAR T cells were first tried in B-cell malignancies [cancers that affect immune cells in the blood], namely pre-B ALL and B-cell lymphoma, and were highly successful in inducing remissions, even in heavily pretreated patients.

"Most of the successes have been in the B-cell space (B-ALL, B-lymphoma, multiple myeloma), but success has been very limited in brain and solid tumors as well as other leukemias, such as acute myeloid leukemia." Dr. Pinto's work has focused on CAR T cell therapy for a variety of pediatric malignancies, including hematologic and solid tumors, as well as the auto-immune disease lupus.

Specifically, the University of Colorado is currently running three CAR

T cell trials:

- CD19 CAR T cell for relapsed pediatric B-cell leukemia lymphoma
- CD19 CAR T cell for adult patients with minimal residual disease positivity with B-cell leukemia
- CD19xCD22 CAR T cell for adults with relapsed/refractory B-cell lymphoma

Future trials at University of Colorado include:

- CD19xCD22 CAR T cell for pediatric patients with relapsed/refractory B-cell malignancies
- CD64 CAR T cell for acute myeloid leukemia (AML)
- CD19 CAR T cell for treatment refractory lupus (our first non-cancer CAR T study)
- B7H3 CAR T cells for patients with relapsed/refractory solid tumors

In contrast, Dr. Vitanza works on CAR T cell therapy targeting pediatric brain tumors and has a keen perspective on the potential efficacy of this approach given the history of the development of CAR T cell therapy for hematologic malignancies.

To echo Dr. Pinto's response, "In around 2011, CHOP and Seattle Children's pioneered using CAR T cells for leukemia. Children with recurrent leukemia would have some of their white blood cells removed, that are then genetically engineered to have a new receptor on their surface and then those cells are grown into the hundreds of millions in the lab.

"That one bulk dose of CAR T cells was given back to the patient in the blood, so they got their own white blood cells back, just with a new

receptor on the surface. It's not enough of a change that their immune system rejected these modified cells and instead had a group of viable T cells that could attack their tumor."

While this technology was very exciting, its efficacy in attacking brain tumors was limited due to the intact blood brain barrier, which prevents most materials, including toxins like chemotherapeutic drugs and foreign cells, from entering into brain tissue. Despite this, researchers were not daunted.

"What we learned, I would say primarily through the City of Hope experience in LA with adults, is that you can give CAR T cells for brain tumors directly into the brain," says Dr. Vitanza. This discovery led to the development of trials of CAR T therapy for brain tumors.

He explains, "When we started treating [pediatric brain tumor] patients in 2018, and were the first center with intracranial dosing, our hypothesis was, 1) that it was possible to generate a CAR T cell product, and 2) instead of that one bulk dose like leukemia patients get, we could divide it into multiple doses and that it would be safe to administer intracranially.

"Based on animal data, and then the City of Hope adult data, we hypothesized that this might be a superior approach rather than giving the therapy into the blood. And so, it's really that initial leukemia process, but with modifications to optimize it for CNS tumors."

Seattle CAR T trials include:

- BrainChild-01 (targeting HER2)
- BrainChild-02 (targeted EGFR)
- BrainChild-03 (targeting B7-H3)
- BrainChild-04 (multi-antigen targeting of HER, EGFR, B7-H3,

and IL-13ra2
- BrainChild-03 and BrainChild-04 continue to actively enroll patients

What is the process of CAR T cell therapy delivery for children? What are the potential side effects?

For systemic hematologic (blood) cancers and solid tumors, CAR T cells are delivered into the systemic circulation intravenously, like conventional chemotherapy. In contrast, for brain tumor treatment, Dr. Vitanza describes their treatment protocol.

First, trial participants are treated by their neurosurgery team, who surgically place a reservoir into the lateral ventricle of the brain to facilitate direct drug delivery.

"We bring patients to clinic and dose the lateral ventricle by infusing over about three minutes, and then flush the catheter with preservative free saline to ensure the full dose. That's the whole dosing strategy. Kids are awake. It's quite quick."

Given that this is an experimental therapy, Dr. Vitanza and his team were keenly attentive to any potential side effects.

"We were worried there would be allergic reactions or some immediate side effect, so we observe kids in clinic for three hours. So far we've treated over 100 kids and given over 500 doses and we haven't seen any immediate negative effects."

Dr. Vitanza continues, "The most common side effects appear in the six to 18 hour range. It's usually a fever, they're not like feeling flu-like, but if you check their temperature they have a fever." This makes sense

given that CAR T cell therapy stimulates activity of the immune system response.

"Sometimes kids have headaches after dosing, especially the children who have baseline bad headaches, so we admit these children to the hospital for observation. The majority of kids don't need to be admitted and most are back to school and normal activities the next day."

Interestingly, one thing Dr. Vitanza's team hypothesized, which has been true, is that CAR T cells administered directly into the brain do not traffic to the systemic circulation.

Indeed, "We don't get systemic toxicity, you don't get immunocompromised, you don't get any of those changes. Kids with leukemia who get systemic dosing get severe, sometimes even fatal neurologic complications, likely from systemically driven inflammation that goes to the brain. Because we don't have that huge systemic inflammation [with direct intracranial dosing], we haven't seen any patients with global diffuse neurologic changes," says Dr. Vitanza.

These findings speak to the differential mechanism of CAR T cell action and efficacy based on delivery approach and demonstrate the need for further scientific inquiry and discovery into this novel biology.

Notably, CAR T therapies have been used by at least 27,000 patients since it was first approved by the FDA in 2017. Since then, the FDA has reported the occurrence of about 25 cases of suspected hematologic malignancies by federal health officials to have been caused by CAR T treatments, so now requires all CAR T manufacturers to place a boxed warning that the treatment itself may cause cancer.

However, more investigation is still needed to demonstrate a definitive link. The FDA still recommends that the benefits of CAR T therapy

outweigh the risks because patients receiving CAR T treatments tend to have few options left and a secondary cancer would be exceedingly rare.

Are there markers of CAR T cell therapy vulnerability and response?

Being able to measure vulnerability to a particular therapy, and the response to that therapy, is a valuable tool for clinicians to help guide therapy. We asked our experts if there are any existing biomarkers of disease or treatment response for CAR T cell therapy for pediatric cancer.

Dr. Vitanza states, "Different things are involved in T cell trafficking activation that we analyze. We have a partnership with Dr. Mandy Paulovich at the Hutch who runs targeted mass spectroscopy on the CSF samples from our brain tumor patients. We showed preliminary data in 2023 of predictive biomarkers in cerebrospinal fluid (CSF). Our goal is to overlie some of this information to identify early responders or failures since time is the most important thing to all these families."

What are the challenges in delivering CAR T cell therapy to children?

Inherent to the complexities of our clinical and medical research institutional enterprise, progress can sometimes be slow and certainly there are aspects of pediatric cancer research that present significant obstacles and hindrances. Application of CAR T cell therapy to pediatric cancers is no exception.

Academic and industry buy-in is a significant challenge.

Dr. Pinto explains, "It is expensive to genetically engineer these cells.

Further, pediatric cancer is rare, [and in the case of most hematologic malignancies], most patients are cured with upfront therapy, so relapsed/refractory cancer is even rarer in this patient population. Finding uniform populations of patients, who all express the same protein target on their tumor, further subdivides patients into rarer and rarer subgroups," making it exceedingly difficult to identify targeted therapies.

Sadly, "Because of this rarity, there is not a huge financial incentive by pharma to develop these therapies."

Further, there is a perception in the community that CAR T cell therapy is controversial, given some of the observed side effects.

"When CAR T cells are effective and activated, and even sometimes when they are ineffective, they release chemicals that can cause severe symptoms: fevers, chills, low blood pressure, neurologic disturbances and even death," Dr. Pinto states.

"Another controversy is that engineering these cells to express a CAR currently involves using viruses that insert the CAR DNA randomly into the T cell's genome. One concern is that this could lead to insertional mutagenesis and potentially create a second malignancy."

Specifically, the concern is that the presence of genetically engineered CAR DNA in the body could lead to changes in T cell biology that could promote cancer development.

Despite this concern, families are still eager to access this treatment for their children. As Dr. Vitanza shares, "Just this morning I have a family from Brazil, another family from Italy and one from Tokyo who all want to do everything for their child. I obviously would too and these families are ready to move to wherever they can get CAR T cells. I think that the

current feeling in the field is, 'I just need to get my kid on a CAR T cell trial.'"

Dr. Vitanza continues, "I spend a lot of time talking to families. I appreciate their enthusiasm; I would want to do whatever is the newest thing coming up for my kid as well and understand that perspective. But these are still Phase I trials. I spend a lot of time really being thoughtful with families: Is this the best option? Do you really want to be away from home? Does this make the most sense? Is the timing right for this? I think there are still controversies in the field: What's the best way to make CAR T cells? Do you need repeated dosing? How often?"

Until researchers know more about this promising therapy, optimism must be tempered with the desperate need for more effective treatments for these devastating pediatric cancers.

Currently, researchers are exploring the use of CAR T cells in treating high-grade gliomas and other brain tumors, understanding which genes are involved in a phenomenon called CAR T cell exhaustion and how to build better CAR T cells to achieve more robust antitumor immune responses.

More information: To stay up to date with news about these projects, and all the latest news shaping the future of pediatric cancer treatment. Don't forget to follow the Pediatric Cancer Research Foundation Profectus Blog.

Provided by California NanoSystems Institute

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