Joseph E. Kerschner, MD

CAR T-cell Immunotherapy Bringing Hope Where None Existed

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Clinicians who treat cancer patients have long battled the dual need to eradicate malignancy while doing the least amount of harm to the patient through side-effects of their treatment. Each of the traditional forms of cancer therapy – surgery, chemotherapy, and radiation therapy – often have left clinicians wanting new modalities that produce excellent cures with fewer difficulties. Recently, along with an increasing number of "targeted" pharmaceuticals, advances in immunotherapy have created an increasing promise to also deliver new treatment possibilities. Immunotherapy enlists and strengthens the power of a patient's immune system to attack malignancies.

Adoptive cell transfer (ACT), in which the patient's own immune cells are collected, modified, and then used to treat the patient's cancers, has several variations, but the one that has advanced the furthest in clinical development is chimeric antigen receptor (CAR) T-cell therapy.[1]

Although the majority of CAR T-cell therapy innovations are being conducted at academic medical centers through clinical trials with relatively small enrollments for the treatment of hematologic malignancies, the Food and Drug Administration recently approved two broader CAR T-cell therapies – one for the treatment of children with acute lymphoblastic leukemia and the other for adults with advanced lymphomas. "Immuno-oncology using T-cell treatments shows incredible promise for patients with cancer," according to Parameswaran Hari, MD, MS, professor of medicine at the Medical College of Wisconsin (MCW) and chief of hematology and oncology, who specializes in treating individuals with myeloma, leukemia, and lymphoma at the Froedtert & MCW Clinical Cancer Center.

The most common procedure for CAR T-cell therapy starts with the extraction of T cells from the patient, in a process called leukapheresis. The T cells are genetically modified to express a CAR, multiplied in the laboratory, and then infused back into the patient, where they further multiply to a number that will allow a potent immunologic response. The CAR on the modified T cells is a receptor that normally would not be present on the T cell and has the express purpose of recognizing a protein (antigen) on the surface of the malignant cells. Once this receptor recognizes the antigen, the T cell then initiates its usual immunologic response to eradicate the tumor cells. There are currently more than 240 CAR T-cell clinical trials in progress internationally.[2]

One such historic clinical trial was announced on February 1, 2018, by physicians and researchers from MCW, Froedtert Hospital, Children's Hospital of Wisconsin, and BloodCenter of Wisconsin. In this announcement, the clinical and research team reported a successful, innovative CAR T-cell treatment developed by MCW researchers to combat lymphoma in a Wisconsin man who had failed all other forms of "traditional" therapy.

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> *—Nirav Shah, MD*

This patient was diagnosed with mantle cell lymphoma, a cancer of the immune system. Despite chemotherapy, stem cell transplants, and other directed pharmaceutical intervention in clinical trials, his lymphoma kept returning. He received the CAR T-cell dose in late October 2017, and just 6 weeks later, his lymphoma was in full remission.

"The patient's results from the CAR T-cell immunotherapy have been phenomenal,"

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said Nirav Shah, MD, principal investigator of the trial and assistant professor of medicine (hematology and oncology) at MCW who specializes in lymphoma and stem cell transplant at Froedtert & MCW Clinical Cancer Center. Doctor Shah is a member of the Blood and Marrow Transplant (BMT) and Cellular Therapy team. "We are harnessing this knowledge from years of research and creating improved outcomes for patients. There is amazing potential here for the future of cancer treatment, and a healthier world is closer than ever," he added.

This success was a first-in-human clinical trial for a novel dual-targeted CAR T cell against CD19 and CD20 antigens. The team utilized innovative new technology[3] that allowed a very rapid, onsite development of the CD19 and CD20 T-cell CARs, such that following leukapheresis the modified T cells were reinfused within 14 days. Precious time was saved for the patient by being able to perform the entire process at the Froedtert & MCW laboratories on the academic medical center campus. And the treatment also was able to be performed at substantively reduced cost.

The CAR T-cell therapy clinical trial is a wonderful example of how our researchers rapidly translate basic research into clinical applications – a unique ability provided at academic medical center and a substantial benefit to all members of the community and beyond. The successful launch of this clinical trial is the result of decades of collaborative cancer and cellular immunotherapy research at our BMT program. Pioneers in the field of immunotherapy, these researchers helped discover and develop how the body's own immune system has the power to fight cancer cells, leading to innovative ideas of alternatives to chemotherapy, radiation, and transplants.

This unique immunotherapy clinical trial – simultaneously targeting CD19 and CD20 – is continuing as the research team tracks the progress of the second participant, who received a dose of CAR T cells in December 2017. A third patient began treatment in February 2018, with 1 new participant being dosed every 6 weeks. Additionally, this trial also has been extended to pediatric patients, with a first patient expected to begin treatment at Children's Hospital of Wisconsin later this year.

This clinical trial is a great leap forward in personalized medicine and the future of cancer treatment – not just in our region but around the globe. It is our expectation that a significant number of patients will soon be benefiting from this discovery – a discovery that happened because of the linkage of research and clinical care at an academic medical center.

REFERENCES

1. National Cancer Institute. CAR T Cells: Engineering Patients' Immune Cells to Treat Their Cancers https://www.cancer.gov/about-cancer/treatment/research/car-t-cells. Accessed March 7, 2018.

2. A Cure for Cancer? How CAR-T Therapy is Revolutionizing Oncology. https://labiotech.eu/car-t-therapy-cancer-review/. Accessed March 7, 2018.

3. The CliniMACS Prodigy device. http://www.miltenyibiotec.com/en/clinical-applications/clinimacs-system/clinimacs-instruments/clinimacs-prodigy.aspx. Accessed March 7, 2018.

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