new IMMUNOTHERAPY for Blood Cancers

Steve Kemper writer
In late 2018, after nearly a year of preparation, Yale Cancer Center and Smilow Cancer Hospital launched an innovative new immunotherapy program for patients with certain blood cancers. Chimeric Antigen Receptor (CAR) T-cell therapy reprograms a patient’s own T-cells to target tumor antigens. CAR T-cell therapy has shown complete remission rates of 80 to 90 percent in patients with B-cell acute lymphoblastic leukemia and multiple myeloma, and 40 percent in patients with a rare form of B-cell non-Hodgkin’s lymphomas who have failed multiple prior lines of treatment. CAR T-cells target an antigen called CD19, which is common on lymphoblasts and lymphocytes.

The Yale program will offer both of the FDA-approved CAR T-cell therapies to give patients with blood cancer more ways to target their disease. In the therapies approved by the FDA so far, CAR T-cells target galactosyl ceramide, which is found in certain lymphomas and leukemias. CAR T-cells are suddenly infused into the bloodstream, to target tumor antigens. CAR T-cell therapy has shown complete remission rates of 80 to 90 percent in patients with B-cell acute lymphoblastic leukemia and multiple myeloma, and 40 percent in patients with a rare form of B-cell non-Hodgkin’s lymphomas who have failed multiple prior lines of treatment. The therapy is new and currently available in only a handful of leading cancer centers. No other hospital in Connecticut offers it.

The program’s Co-Directors are Stuart Seropian, MD, Associate Professor of Medicine, and Iris Isufi, MD, Assistant Professor of Medicine. Dr. Seropian runs Smilow Cancer Hospital’s Stem Cell Transplant Program. Dr. Isufi specializes in lymphoma and stem cell collection.

“CAR T-cell therapy was an advancement in our knowledge of genetics and in the science of immune cells to empower the immune system to fight certain cancers,” said Dr. Seropian. “It’s the next big success story in treating B-cell lymphomas and B-cell leukemia.”

“T-cells target a unique antigen, so there’s no overlap between CAR T-cells against other cancers. Currently available CAR T-cells target the B-cell lymphoma and leukemia with CD19, and the pediatric program will focus on multiple myeloma with a unique antigen called CD38. Adult patients with multiple myeloma and B-cell non-Hodgkin’s lymphoma have had a lot of success,” said Dr. Isufi.

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For the moment, the therapy is FDA-approved only for patients with either childhood acute lymphoblastic leukemia, the most common cancer in children, or adult B-cell non-Hodgkin’s lymphoma. To be eligible, patients must have failed two forms of standard treatment. The Yale program will offer both of the FDA-approved treatments while also conducting clinical trials to test new CAR T-cells to target antigens. Currently available CAR T-cells target the B-cell lymphoma and leukemia with CD19, and the pediatric program will focus on multiple myeloma with a unique antigen called CD38. Adult patients with multiple myeloma and B-cell non-Hodgkin’s lymphoma have had a lot of success,” said Dr. Isufi.

The science behind the therapy is fascinating. Blood is drawn from the patient so that T-cells, the workhorses of the immune system, can be filtered out and collected. These cells are sent to a lab where they are genetically engineered into a desired strain. Then the T-cells are used as CAR T-cells, genetic engineers insert a new type of receptor into the T-cells gene pool,” explained Dr. Seropian.

“That produces a new receptor with a different external portion, an antibody that targets whatever you want it to target,” in the therapies approved by the FDA so far, CAR T-cells target galactosyl ceramide, which is common on lymphoblasts and lymphocytes.

Neither the lab gives these genetically modified T-cells into an array of millions, which takes several weeks. This mass of cells is frozen and returned to the patient’s treatment center. Typically the patient will receive chemotherapy to increase the effectiveness of the next steps: infusion of the CAR T-cells.

“Once these cells are put back into the body,” said Dr. Isufi, “what the T-cells do is very complex. They start to work, they really take off. The therapy can put someone into remission almost immediately or within weeks.”

The immune response, however, can be also adversely affected by adverse effects as the T-cells proliferate and expand in the body. The “therapy is very effective,” said Dr. Isufi, “but it is also potentially very toxic.” In the two CAR T-cell therapies currently used, cytokine release syndrome (CRS) and T-cells on their work, release cytokines to excite the immune system. When millions of CAR T-cells are suddenly infused into the bloodstream, they produce a torrent of cytokines.

“The patient’s blood pressure drops down,” said Dr. Isufi, “and they can develop high liver and kidney toxicity and requires intensive care.” The other main side effect is neurologic toxicity, manifested by mental confusion and cranial nerve damage. These side effects, though generally brief and temporary, are dangerous, and are the reason the program at Smilow took a year to begin.

“Any kind of effort has gone into hiring and training personnel in the lymphoma and transplant teams,” said Dr. Isufi, “but also the medical intensive care unit team, critical care physicians, pharmacists, nurses-oncologists, and the endocrinology team involved in the management of the patients, so we were ready to treat and include them. And of course we had to train all the nursing staff and the pharmacies and the nurses who might be caring for the patient,” added Dr. Isufi. “And the night, because patients can get sick very quickly, and early identification of the toxicities is crucial so that the interventions can be given. It’s been a multidisciplinary hospital-wide educational effort. Everyone who could potentially touch the patient, at every level, needed to become familiar with the therapy and how to manage the toxicities.”

Patients generally are discharged within two weeks after infusion, but the risk of side effects continues, for the first month, CAR T-cell patients must stay within two hours of the cancer center in case they need specialized care. That’s another reason Drs. Seropian and Isufi are so pleased that Yale now offers the therapy, so their patients don’t have to leave the state to receive it elsewhere.

The treatment’s advantages outweigh its risks, especially for patients who have run out of options. Aside from the strong possibility of remission, which in the majority of patients seems durable, the therapy is also relatively brief compared to the standard regimen for blood cancer—six months of chemotherapy. Dr. Seropian mentions that CAR T-cell therapy may function as a bridge treatment for some patients, putting them in remission long enough to qualify for a stem cell transplant that can cure them. Dr. Isufi adds that CAR T-cell therapy may even cure some patients, making a transplant, with all its attendant dangers, unnecessary.

They expect to start several clinical trial in 2019 where the team will look at new types of CAR T-cells that target antigens beyond CD19, in particular CD38, found in certain lymphomas and leukemias, as well as RSCAs, common in multiple myeloma. They are also participating in a trial to a different CAR T-cell receptor that binds to an antibody instead of targeting one proteins on the surface of a cancer cell. They will test this antigen on solid tumors as well, as any interest in CAR T-cells have been disappointing so far, perhaps because such tumors are more complex and difficult to enumerate.

Another clinical trial planned for patients with multiple myeloma will test a new method of introducing the chimeric antigen receptor into the T-cells transiently rather than permanently, thereby potentially reducing the risk of cytokine release and neurologic toxicity.

As research advances, Drs. Seropian and Isufi expect CAR T-cell therapies to be approved for a wider array of lymphomas and leukemias, and expanded to include all age groups. They also expect that now variations of CAR T-cells will target multiple antigens and will be used in combination with each other as well as with other therapies to give patients with blood cancer more ways to achieve remission.

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