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 aggressive 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 lymphomas and stem cell transplants.

"CAR T-cell therapy uses advances 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 leukemias."

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 against other cancers. Currently available for adults, the pediatric program will launch for children with acute lymphoblastic leukemia under the direction of Dr. Niketa Shah in the spring of 2019.

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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 by introducing a disarmed virus that stimulates the cells to produce new surface receptors called chimeric antigen receptors (CARs). "The lab basically inserts a code into the T-cell's genome," 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 an antigen called CD19, which is common on lymphomas and leukemias.

Next the lab grows these genetically-modified T-cells into an army 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 step: infusion of the CAR T-cells.

"Once these cells are put back into the body," said Dr. Seropian, "if they're going to work, they really take off. The therapy can put someone into remission almost immediately or within weeks."

This intense response, however, can be also accompanied by intense side 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." One of the main toxicities is called cytokine release syndrome (CRS). As T-cells do their work, they 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.

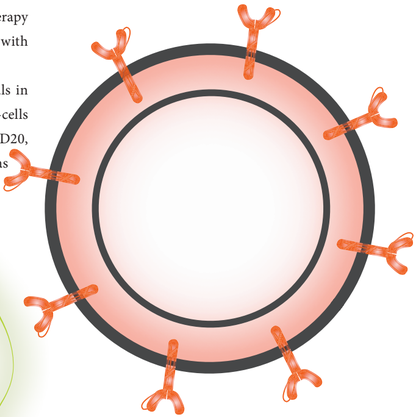
"The patient's blood pressure drops," said Dr. Isufi, "and they can develop high fever and respiratory issues and require intensive care." The other main side effect is neurologic toxicity, manifested by mental confusion and even seizures. These side effects, though usually brief and temporary, are dangerous, and are the reason the program at Smilow took a year to begin.

"A lot 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, neuro-oncologists, and the epilepsy team are involved in the management of the patients, so we were sure to train and include them. And of course we had to train all the nursing staff and the hospitalists and the fellows who might be caring for the patients on the floor at 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, so 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 far 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 could 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 related clinical trials in 2019 where the team will test new types of CAR T-cells that target antigens beyond CD19, in particular CD20, found in certain lymphomas and leukemias, as well as BCMA, common in multiple myeloma. They are also participating in a trial to test a chimeric T-cell receptor that binds to an antibody instead of targeting one protein on the surface of a cancer cell. They will test this antigen on solid tumors as well, an area where existing CAR T-cells have been disappointing so far, perhaps because such tumors are more complex and difficult to penetrate.



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 new varieties 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.