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Companies Rush to Develop 'Utterly Transformative' Gene Therapies

The approval of gene therapy for leukemia, expected in the next few months, will open the door to a radically new class of cancer treatments.

Companies and universities are racing to develop these new therapies, which re-engineer and turbocharge millions of a patient's own immune cells, turning them into cancer killers that researchers call a "living drug." One of the big goals now is to get them to work for many other cancers, including those of the breast, prostate, ovary, lung and pancreas.

"This has been utterly transformative in blood cancers," said Dr. Stephan Grupp, director of the cancer immunotherapy program at the Children's Hospital of Philadelphia, a professor of pediatrics at the University of Pennsylvania and a leader of major studies. "If it can start to work in solid tumors, it will be utterly transformative for the whole field."

But it will take time to find that out, he said, at least five years.

This type of treatment is now also being studied in glioblastoma, the aggressive brain tumor that Senator John McCain was found to have this week. Results of a study at the University of Pennsylvania, published Wednesday, were mixed. In the first 10 patients treated there, one has lived more than 18 months with what the researchers called "stable disease." Two other survivors have cancer that has progressed, and the rest have died.

. Researchers plan to try giving the cell treatment to children with earlier stages of leukemia than in the past, combining it with other treatments and developing new types of cell therapy. One new version, with human trials just starting, uses immune cells extracted not from the patient, but from samples of umbilical-cord blood donated by mothers when they give birth.

The products closest to approval so far have a limited focus — to treat blood cancers like leukemia (for which an F.D.A. advisory panel recommended approval of the first treatment last week) and lymphoma, as opposed to the solid tumors that form in organs like the breasts and lungs and cause many more deaths. About 80,000 people a year have the kinds of blood cancers that the first round of new treatments can fight, out of the 1.7 million cases of cancer diagnosed annually in the United States.

The new treatments are expected to cost hundreds of thousands of dollars, and they come with risks. Patients in the earliest studies nearly died from side effects like raging fever, low blood pressure and lung congestion. Doctors have learned how to control those reactions, but experts

also have concerns about possible long-term effects like second cancers that could in theory be caused by the disabled viruses used in genetic engineering. No such cancers have been seen so far, but it is too soon to rule them out.

Emily Whitehead was the first child to be treated for leukemia with genetically engineered T-cells, which were made by researchers at the University of Pennsylvania. Credit T.J. Kirkpatrick for The New York Times

The new leukemia treatment involves removing millions of white blood cells called T cells — often referred to as the soldiers of the immune system — from the patient's bloodstream, genetically engineering them to recognize and kill cancer, multiplying them and then infusing them back into the patient. The process is expensive because each treatment has to be made separately for each person.

Solid tumors are less amenable to treatment with these altered cells — which scientists call CAR-T cells — but studies at various centers are trying to find ways to use it against mesothelioma and cancers of the ovary, breast, prostate, pancreas and lung.

"These solid tumors are like Fort Knox," Dr. Grupp said. "They don't want to let the T cells in. We need combination approaches, CAR-T plus something else, but until the something else is defined we're not going to see the same kind of responses."

The pioneering T-cell therapy for leukemia was created at the University of Pennsylvania, which licensed it to Novartis. The F.D.A. panel recommended approval of it for a narrow subset of severely ill patients, only a few hundred a year in the United States: those ages 3 to 25 who have B-cell acute lymphoblastic leukemia that has relapsed or not responded to the standard treatments. Those patients have poor odds of surviving, but in clinical trials, a single T-cell treatment has produced long remissions in many and possibly even cured some.

Novartis plans to request another approval later this year of the same treatment (which it calls CTL019 or tisagenlecleucel) for adults who have a type of lymphoma — diffuse large B-cell lymphoma that has relapsed or resisted treatment. A competitor, Kite Pharma, has also filed for approval of a T-cell treatment for lymphoma. Another competitor, Juno, suffered a setback when it shut down a T-cell study in adults after five patients died from brain swelling. Kite has also reported one such death.

Novartis is studying several other types of T-cells, with different genetic tweaks, to treat chronic lymphocytic leukemia, multiple myeloma as well as glioblastoma.

Some of the more promising work so far involves efforts to make the existing gene treatments even more effective in blood cancers. For lymphoma patients, the T cells are being given along with a drug, ibrutinib, and the combination seems to work better than either treatment alone.

At the Children's Hospital of Philadelphia, there are not enough study spots for all the patients who hope to receive T-cell treatment, and the waiting time can stretch to months, longer than

some can afford to wait. Waiting times should decline after the treatment is approved and becomes more widely available.

Dr. Grupp said that one encouraging avenue of research involved giving the T-cells at an earlier stage of the disease, instead of very late, as rules now require. He said a study was being planned at multiple centers that he hoped would start within the next six months or so. The patients would be children with early signs that the usual chemotherapy — which cures many — is not working well for them.

“We could deploy the treatment considerably earlier and before they get so sick,” he said. He added, “That is another big step in terms of trying to figure out how to use these cells appropriately.”

Earlier treatment, he said, might help some patients avoid bone-marrow transplant, a grueling, last-ditch treatment. Children with less advanced disease also tend to have milder side effects from the T-cell treatment.

Studies in children are also underway to combine T-cell treatment with the immunotherapy drugs called checkpoint inhibitors, which help unleash the cancer-killing power of T cells. There will be many such studies, Dr. Grupp predicted, but, he said, “It’s early days.”

The T cells in the Novartis products, and in the earliest ones its competitors are developing, have been engineered to seek and destroy cells that display on their surfaces a protein called CD19 — a characteristic of many leukemias and lymphomas.

Identifying other targets would be a boon, Dr. Grupp said, because sometimes leukemic cells lacking CD19 proliferate, escape the treatment and cause relapse.

A patient’s white blood cells are frozen after collection before the white blood cells are separated. Credit Brent Stirton/Novartis

Another target is being studied, and Dr. Grupp said the next step, which he called “superimportant,” would be to attack two cellular targets in the same patient.

In the next year or so, he said, that approach will also be studied in both children and adults who have acute myeloid leukemia, which he described as a “tough disease.”

Researchers at the University of Texas MD Anderson Cancer Center in Houston are trying a completely different approach to engineering cells, one that they hope might eventually yield an “off the shelf” treatment that would not have to be tailored to each individual patient and that might be less expensive.

Instead of using T cells, the team uses natural killer cells, another component of the immune system, one that has a powerful ability to fight anything it recognizes as foreign. Instead of extracting the cells from patients, the researchers, Dr. Katy Rezvani and Dr. Elizabeth Shpall,

remove the natural killers from samples of umbilical-cord blood donated by women who have just given birth.

They use natural killer cells because T cells from one person cannot be safely given to another, lest they attack the host's tissue, causing graft-versus-host disease, which can be fatal. Natural killer cells do not cause that deadly reaction, so it is safe to use such cells from a newborn's cord blood to treat patients.

The natural killer cells are genetically engineered to attack CD19, and also to produce a substance that activates them and helps them persist in the body. They also have an "off switch," a gene that will let the researchers shut down the cells with a certain drug if they cause dangerous side effects that cannot be controlled.

After promising studies in mice, the researchers have opened a study for adults with relapsed or treatment-resistant chronic lymphocytic leukemia, acute lymphocytic leukemia or non-Hodgkin lymphoma. The first patient was to be treated this week, Dr. Rezvani said.

One unit of cord blood yields enough cells to treat five patients, she said, and in two weeks the natural killer cells can be expanded 500-fold, to a billion cells.

"We plan to make the product and infuse it fresh to the patient, but we are also working on optimizing the freezing process so we can make the product, freeze it and keep it, so that when patients need it, we can give it."