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Spotlight

This is the first article in a two-part series on an immune-boosting therapy for cancer called adoptive cell transfer (ACT). Part one focuses on a form of ACT that uses tumor-infiltrating lymphocytes to treat advanced melanoma.

In the May 15 NCI Cancer Bulletin, the second article will describe a form of ACT that uses genetically engineered T cells and is being investigated for the treatment of a variety of cancers. It will also explore the challenges of moving ACT from small clinical trials to everyday use in the clinic.

A Transfer of Power: Harnessing Patients' Immune Cells to Treat Their Cancer

"These patients are probably cured" is not something most oncologists get to say about their patients with advanced cancer. Yet that's exactly how NCI's Dr. Steven Rosenberg describes a number of patients with advanced melanoma treated in three small clinical trials he has led at the NIH Clinical Center.

The patients in these trials—most of whom had tumors throughout their body (metastatic disease) and had nearly exhausted other treatment options—underwent a procedure known as adoptive cell transfer (ACT).

ACT involves removing some of a patient's own



Before and after pictures of a patient with melanoma who underwent treatment with tumor-infiltrating lymphocytes. Within 2 weeks of treatment, the large tumor had disappeared.

immune-system cells, growing billions of them in the laboratory, and infusing the cultured cells into the patient. The idea is to provide an invading force of immune cells that can attack tumors in a way that the immune system was incapable of doing on its own.

"The results in melanoma have been impressive," said Dr. Rosenberg, who, along with his colleagues, is in the Surgery Branch of NCI's Center for Cancer Research, has done pioneering work on ACT for more than a decade.

Based in large part on the Surgery Branch's success, a small but growing group of research centers in the United States and abroad have launched their own programs to study ACT for melanoma and, increasingly, other cancers.

To date, only a few hundred patients have been treated with some form of ACT, but with the results reported thus far the treatment is gaining more attention and raising hopes among researchers in the field that it can one day be available to many more patients.

When TILs Attack

The ACT approach used in the three NCI trials entails collecting lymphocytes from patients' tumor samples, known as tumor-infiltrating lymphocytes (TILs), performing tests to identify the cells with the greatest antitumor activity, and then growing those particular cells in the laboratory over a period of several weeks.

In this one-time-only treatment, the newly grown lymphocytes, composed primarily of T cells, are infused into the patient along with a cytokine (an immune-stimulating agent) called interleukin-2 (IL-2).

At high enough doses, IL-2 on its own can be a highly effective, even curative, treatment for a small proportion of patients with melanoma and advanced kidney cancer, explained Surgery Branch investigator Dr. James Yang. (IL-2 is approved by the Food and Drug Administration for certain cancer indications.) But it is difficult to administer and can have significant side effects, which have limited its use in clinical practice.

Before receiving the expanded TIL cells, patients also undergo lymphodepletion that consists of chemotherapy and, in one of the treatment's current forms, whole-body radiation. The lymphodepletion "prepares patients to receive the infused lymphocytes without impediment from other immune cells that can thwart the incoming T-cell flood," Dr. Yang said.

The results to date are impressive. Of the 93 patients treated in the three trials, 20 have seen their tumors disappear completely (complete response); 19 of those 20 have remained tumor-free for longer than 12 months.

years. (Most of these patients' tumors had not responded to other immunotherapy treatments.) Tumors shrank substantially in 52 patients.

The idea [behind adoptive cell transfer] is to provide an invading force of immune cells that can attack tumors in a way that the immune system was incapable of doing on its own.

Several of the complete responses have extended years. "In my view, that's good evidence that we probably cure some patients with metastatic melanoma," Dr. Rosenberg said. "And I don't use the term

At the University of Texas MD Anderson Cancer Center, Dr. Patrick Hwu, who trained in NCI's Surgery Branch, has seen similar results in a small clinical trial of adoptive cell transfer in metastatic melanoma. Half of the 50 patients at MD Anderson have had partial or complete tumor

reported.

TIL therapy "is clearly one of the best treatments for metastatic melanoma," said Dr. Hwu. "The use of adoptive cell transfer and other forms of ACT beyond NCI was an important step for the field, he stressed. "We hope that this approach could be done at other centers."

As part of that process, researchers at established immunotherapy programs such as those at MD Anderson consult with their colleagues at other centers that are in the process of or hope to start their own programs. Dr. Hwu and his colleagues, for example, worked with researchers at the University of Florida Cancer Center in Florida to establish its immunotherapy program.

TIL therapy has moved overseas as well. Dr. Jacob Schachter leads a TIL therapy program at the Weizmann Institute Medical Center in Israel that is seeing similar results in patients with metastatic melanoma. Of 21 patients treated to date, 6 have had complete responses, 15 have had partial responses, and 10 others have stable disease.

"Seventy percent of the clinical responders are still alive 2 years after treatment," he said.

Making Improvements

As promising as this treatment approach is, there are hurdles to overcome. Like other cancer treatments, TIL therapy has side effects. In addition to toxicities associated with IL-2 and the lymphodepleting regimen, the infusion of billions of T cells can trigger massive immune responses that can be potentially fatal, problems for patients. And for some patients, an army of T cells can't be grown in the lab.

Dr. Schachter's group is attempting to address the latter problem by focusing their efforts on

TILs, meaning that the lymphocytes removed from patients' tumors are grown for a shorter laboratory and are not selected for expansion based on whether they exhibit antitumor activity tests.

These "young" TILs, which Surgery Branch researchers are also investigating, "are relatively compared to the 'selected TILs,'" Dr. Schachter explained, which has allowed the researchers to successfully formulate treatments for more patients.

Surgery Branch researchers have launched a trial of TILs that are genetically engineered to express cytokine interleukin-12 when the TILs lock onto their molecular target on cancer cells. Some results have been seen in the first few patients to receive the treatment.

Dr. Hwu and his colleagues at MD Anderson are combining TIL therapy with other immunotherapies such as dendritic cell vaccines and ipilimumab (Yervoy). They are also engineering TILs to express receptors to molecules known as chemokines that help guide them to cancer cells.

A major focus of his program's work, Dr. Hwu said, is to standardize the entire process. "We want to grow TIL cells successfully for every patient," he said. "So we're constantly looking for ways to improve the end product better and to grow cells for a higher percentage of patients."

There are clearly challenges to making TIL therapy more broadly available, Dr. Rosenberg acknowledged. But with further research, support, and experience, they can be overcome, he said.

"If you have a deadly disease like melanoma and a treatment that can induce durable complete regressions of disease," he said, "people are going to want the treatment."

—Carmen Phillips

From the Lab to the Clinic and Back

The TIL therapy regimen used by NCI's Surgery Branch serves as the foundation for the clinical treatments being studied at other centers around the world and has been refined based on laboratory and mouse model studies led by Surgery Branch researchers.

For example, mouse model studies led by Dr. Nicholas Restifo showed that more intense lymphodepletion with a radiation regimen made the treatment more effective, a finding that led to similar changes in the TIL regimen used in the NCI-led human trials. Of the three trials, the one that used the highest dose of radiation had the highest complete response rate: 10 of 11 patients.

9 of whose responses have persisted for at least 5 years.

Dr. Rick Morgan led the laboratory and mouse model studies of TILs engineered to express IL-12—an important advance because, although IL-12 can potentially kill tumors in mice, it is toxic and potentially fatal when administered systemically in humans.

The iterative nature of the process is a cornerstone of the Surgery Branch's work. "I think a really unique feature of the NIH Clinical Center and the NIH intramural program," said I "We can sit together at lunch, talk about results we're seeing in the clinic and how they apply to lab studies. [We talk about] what's happening with our lab studies and how they should be approached in the clinic. It's as quick and productive as anything I've ever been involved in."

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