Excitement Over CAR-Engineered T-cells in Leukemia and Lymphoma

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NEW ORLEANS — There is palpable excitement here at American Society of Hematology (ASH) 55th Annual Meeting over results that are being reported with a new approach to treatment, engineered T cells. Although the results come from pilot clinical trials conducted in a small number of patients with leukemia and lymphoma, these are patients with very aggressive and refractory disease, and yet some of them have shown dramatic responses to the therapy, going into complete remission and no longer showing visible signs of tumor on computed tomography (CT) scans.

"It looks like the disease has disappeared after a single infusion of these engineered T cells," commented James Kochenderfer, MD, from the Experimental Transplantation and Immunology Branch of the National Cancer Institute (NCI) in Bethesda, Maryland.

However, he cautioned that there is a significant patient variation in both efficacy and toxicity with this approach.

Several groups in the United States are working on this approach to treatment, and some have teamed up with pharmaceutical companies. The T cells developed at NCI have been licensed to Kite Pharmaceuticals, and a similar approach developed at the University of Pennsylvania, which has the most clinical data so far, has been licensed to Novartis.

Some observers say that this pharmaceutical company involvement, as well as accelerated approval for an urgent medical need, could result in these therapies becoming available as early as 2016, but others forecast a longer development time and suggest the therapies will not be available for clinical use until 2020.

Like a Smart Bomb

The novel approach to therapy involves extracting T cells from the patient, subjecting the cells to chimeric antigen receptor (CAR) cell engineering, and then infusing the engineered T cells back into the patient.

The engineering, which takes about 10 days, changes the T cell in 2 ways. First, it adds a receptor that targets the CD19 antigen that is found on most leukemic cells; when the cells are inserted back into the patient's body, they home in on this antigen, latch on and destroy the leukemic cell. Second, the process inserts a viral vector mechanism into the cells which – once the cells have latched on to the leukemia – triggers these T cells to expand and proliferate, so that they seek out and destroy all the remaining leukemic cells.

There is tremendous excitement over this approach, because it acts like a smart bomb, said Mary Horowitz, MD, scientific director at the Center for International Blood and Marrow Transplant Research and chief of the Division of Hematology and Oncology at the Medical College of Wisconsin, in Milwaukee. Whereas bone marrow transplantation is like carpet bombing of a city in order to destroy a specific building, these CAR cells are like smart bombs that seek out and destroy just the building, she commented to *Medscape Medical News*.

The clinical results have been dramatic and unprecedented in such advanced disease.

Results in Lymphoma

Dr. Kochenderfer presented results from 15 adult patients with advanced B cell lymphomas (abstract 168), including 9 patients with chemotherapy-refractory large cell lymphoma such as primary mediastinal B cell lymphoma and diffuse B cell lymphoma. They received reduced-intensity conditioning with cyclophosphamide and fludarabine and then an infusion of their own T cells that had been CAR engineered.

Thirteen of the 15 patients treated were evaluable for response, and 12 of those 13 responded: 7 patients had complete remissions, and 5 had partial remissions, Dr. Kochenderfer said. The remaining patients had stable disease.

Dr. Kochenderfer gave details of one of the patients who had a complete remission, showing CT scans with visible tumor in the liver and abdomen prior to the treatment, and none visible after treatment. This was a patient who had undergone 10 prior therapies, including many different combinations of rituximab plus chemotherapy regimens, and the disease progressed a month after chemotherapy finished, so she was "clearly refractory," he said.

"Our data provide the first true glimpse of the potential of this approach in patients with aggressive lymphomas that, until this point, were virtually untreatable," Dr. Kochenderfer told journalists at an ASH press briefing at which these novel therapies were highlighted.

"We are particularly encouraged by the partial and complete responses that we observed in a number of patients with diffuse large B cell lymphomas who had exhausted all other treatment options…and who are not generally thought to be good candidates for hematopoietic stem cell transplantation," he added.

However, he tempered his enthusiasm by adding that "this approach is still an early-stage experimental therapy."

Severe but Reversible Adverse Events

In addition, this treatment approach can cause severe adverse events, which may require that the patient stay in an intensive care unit, although these reactions are temporary. Once the T cells start to expand in the body, nearly all patients develop a delayed cytokine release and macrophage activation, which can result in acute toxicity, including a high fever, hypotension, breathing difficulties, delirium, aphasia, and neurologic toxicity.

However, patients recover quickly, usually within 2 days, and these symptoms have resolved within about 3 weeks, Dr. Kochenderfer said.

These reactions are not surprising, commented Laurence Cooper, MD, from the University of Texas MD Anderson Cancer Center, Houston, who was moderating the press briefing. The T cells' expanding and proliferating represents a massive assault on the immune system, and some of the reactions can be dramatic, but they are temporary and reversible, he added. They are manageable, he said, and he also emphasized that these are patients who are already very ill and who have exhausted all other treatment options.

Stephen Grupp, MD, PhD, of the Children's Hospital of Philadelphia and the University of Philadelphia in Pennsylvania, who has been conducting trails with engineered T cells in acute lymphocytic leukemia (ALL), says that some of the adverse events resulting from delayed cytokine release can be severe. However, they can be managed with the monoclonal antibody tocilizumab, which acts as an antagonist of interleukin-6, one of the cytokines that is released when the T cells expand and proliferate in the body. This drug has been a "game changer" for controlling the toxicity seen with these engineered T cell, he said. He also noted that there has been no graft vs host disease seen.

At the meeting, Michael Kalos, PhD, from the University of Pennsylvania, presented a summary of the clinical results from this group to date (abstract 163), which come from adult patients with advanced relapsed or treatment-refractory chronic lymphocytic leukemia (CLL) and both adult and pediatric patients with treatment-refractory ALL.

Results in CLL

Adult CLL patients have been treated in 2 studies that included a total of 32 patients. Partial responses were seen in 15 patients, and complete responses were seen in 7 patients. All of these complete responses are ongoing, Dr. Kalos reported.

Further details of the CLL results will be reported at the meeting (abstracts 4162 and 873) by David Porter, MD, professor in leukemia care excellence and director of blood and marrow transplantation at the University of

Pennsylvania's Abramson Cancer Center. In a statement, he said: "We are tremendously excited about these results. About half of our CLL patients responded to this therapy, with most of them having several pounds of tumors eradicated by the genetically modified T cells."

"We've now seen remissions lasting for more than 3 years, and there are clues that the T cells continue to kill leukemia cells in the body for months after treatment. Even in patients who had only a partial response, we often found that all cancer cells disappeared from their blood and bone marrow, and their lymph nodes continued to shrink over time. In some cases, we have seen partial responses convert to complete remissions over several months," Dr. Porter added.

Results in ALL

Also at the University of Pennsylvania, ALL has been treated in 22 pediatric patients, of whom 19 achieved a complete response, and this is ongoing in 14 patients (5 have relapsed).

In addition, ALL was treated in 5 adult patients, of whom 5 had a complete response, and in 4, this is ongoing (the remaining patient went on to have an allogeneic transplant).

Further details on the clinical results in ALL patients were presented (abstract 67) by Dr. Grupp, who noted that the ongoing complete responses have continued out to 18 months.

"Our results demonstrate the potential of this treatment for patients who truly have no other therapeutic option," Dr. Grupp said. "In the relatively short time that we've observed these patients, we have reason to believe that this treatment could become a viable therapy for their relapsed, treatment-resistant disease," he added.

Not all patients respond, however.

Dr. Kalos noted that the patients who had the best clinical responses were the ones who showed the greatest expansion and proliferation of engineered T cells (which at their peak accounted for more than 5% of the overall T cell total). The patients who did not respond demonstrated "minimal in vivo expansion," he said.

"Our results show that we can potentially measure and track the activity of these engineered cells in a way as to monitor treatment, an exciting finding considering that this treatment is often the last hope for these patients," he said.

These engineered T cells are "poised to replace bone marrow transplants with a therapy that is less expensive and is more widely available," Dr. Kalos said.

American Society of Hematology (ASH) 55th Annual Meeting: Abstracts 67, 163, and 168 presented 8 December; abstract 4162 to be presented on December 9; and abstract 873 to be presented on December 10, 2013.

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