Patients' own genetically altered immune cells show promise in fighting blood cancer

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July 20, 2015. In recent years, immunotherapy has emerged as a promising treatment for certain cancers. Now this strategy, which uses patients' own immune cells, genetically engineered to target tumors, has shown significant success against multiple myeloma, a cancer of the plasma cells that is largely incurable. The results appeared in a study published online today in *Nature Medicine*.

Patients received an infusion of altered immune cells known as T-cells - roughly 2.4 billion of them - after undergoing a stem cell transplantation of their own stem cells. In 16 of 20 patients with advanced disease, there was a significant clinical response. The scientists found that the T-cell therapy was generally well-tolerated and that modified immune cells traveled to the bone marrow, where myeloma tumors typically are found, and showed a long-term ability to fight the tumors. Relapse was generally associated with a loss of the engineered T-cells.

"This study suggests that treatment with engineered T-cells is not only safe but of potential clinical benefit to patients with certain types of aggressive multiple myeloma," says first author Aaron P. Rapoport, MD, the Gary Jobson Professor in Medical Oncology at the University of Maryland School of Medicine. "Our findings provide a strong foundation for further research in the field of cellular immunotherapy for myeloma to help achieve even better results for our patients."

The trial is the first published use of genetically modified T-cells for treating patients with multiple myeloma. The approach has been used to

treat leukemia as well as lymphoma, according to Dr. Rapoport, who is the Director of the Blood and Marrow Transplant Program at the University of Maryland Marlene and Stewart Greenebaum Cancer Center.

More than 77,000 people in the United States have multiple myeloma, with about 24,000 new cases diagnosed each year. Patients are treated with chemotherapy and in many cases an autologous stem cell transplant, but long-term response rates are low, and median survival is three to five years.

"The majority of patients who participated in this trial had a meaningful degree of clinical benefit," Dr. Rapoport notes. "Even patients who later relapsed after achieving a complete response to treatment or didn't have a complete response had periods of disease control that I believe they would not have otherwise experienced. Some patients are still in remission after nearly three years."

The research is a collaboration between the University of Maryland School of Medicine, the Perelman School of Medicine at the University of Pennsylvania and Adaptimmune, a clinical stage biopharmaceutical company which owns the core T-cell receptor technology and funded the study. Dr. Rapoport and co-authors Edward A. Stadtmauer, MD, of the University of Pennsylvania Abramson Cancer Center, and Gwendolyn K. Binder-Scholl, PhD, of Adaptimmune, contributed equally to the research. Dr. Rapoport is the study's principal investigator.

In the clinical study, patients' T-cells were engineered to express an affinity-enhanced T-cell receptor (TCR) specific for a type of tumor antigen, or protein, known as a cancer-testis antigen (CT antigen). The target CT antigens were NY-ESO-1 and LAGE-1. Up to 60 percent of advanced myelomas have been reported to express NY-ESO-1 and/or LAGE-1, which correlates to tumor proliferation and poorer outcomes.

According to Adaptimmune, the trial is the first published study of lentiviral vector mediated TCR gene expression in humans.

Of the 20 patients treated, 14 (70 percent) had a near complete or complete response three months after treatment. Median progression-free survival was 19.1 months and overall survival was 32.1 months. Two patients had a very good partial response three months post treatment. Half the patients were treated at the University of Maryland Greenebaum Cancer Center and half at the University of Pennsylvania Abramson Cancer Center. Researchers note that the response rate was better than would be expected for a standard autologous stem cell transplant. In addition, patients did not experience side effects which have been associated with another type of genetically engineered T-cells (chimeric antigen receptors, or CARS) used to treat other cancers.

The study was originally developed by Carl H. June, MD, of the University of Pennsylvania Abramson Cancer Center, and Dr. Rapoport, who have been research collaborators for 18 years.

"Multiple myeloma is a treatable but largely incurable cancer. This study reveals the promise that immunotherapy with genetically engineered T-cells holds for boosting the body's ability to attack the cancer and provide patients with better treatments and control of their disease," says E. Albert Reece, MD., PhD, MBA, vice president for medical affairs at the University of Maryland and the John Z. and Akiko K. Bowers Distinguished Professor and dean of the University of Maryland School of Medicine. "This trial is also an excellent example of significant scientific advances that result from collaborations between academic medical institutions and private industry."

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