Results from clinical trial of personalized cellular therapy in brain tumors

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Immune cells engineered to seek out and attack a type of deadly brain cancer known as glioblastoma (GBM) were found to have an acceptable safety profile and successfully migrate to and infiltrate tumors, researchers from Penn Medicine and Harvard University reported at the AACR Annual Meeting 2016 (Abstract LB-083).

The phase I study tested an investigational chimeric antigen receptor (CAR) therapy made from patients' own T cells engineered in a specialized laboratory to target a tumor-specific protein known as EGFRvIII, which is found in about 30 percent of GBM patients' tumors. In contrast to other CAR therapies that also target some healthy cells, EGFRvIII is found only on tumor tissue, which the study's leaders believed would minimize side effects of the new therapy.

Results from nine patients treated so far on the trial, led by Donald M. O'Rourke, MD, an associate professor of Neurosurgery at the Perelman School of Medicine at the University of Pennsylvania, were presented by Marcela Maus, MD, PhD, a former Penn faculty member who is now the Director of Cellular Immunotherapy at the Massachusetts General Hospital Cancer Center and an assistant professor of Medicine at Harvard Medical School.

The CAR therapy was found to have an acceptable safety profile in all patients, with no clinical or laboratory signs of systemic cytokine release syndrome, a potentially serious toxicity that has been observed in other CAR trials. One patient experienced a seizure (non-convulsive status

epilepticus); however, it was successfully treated by antiepileptic medications. All patients had significant expansion of CART-EGFRvIII cells in their blood between 7 and 10 days after infusion. Also, a pathologic evaluation of tumors surgically removed from five patients between 6 and 120 days after infusion revealed focal areas which showed infiltration of both CAR positive and CAR negative T cells with signs of activation, the researchers reported.

"One of the main questions in the field of T cell therapies is: can we make this work in solid tumors?" Maus said. "The barriers to CAR T cells in solid tumors are identifying targets with acceptable safety profiles, proving that T cells can get out of the blood, and that they can successfully target the tumor cells expressing the antigen without being turned off by the tumor environment.

"Here, we demonstrated that targeting EGFRvIII has an acceptable safety profile, , that CAR T cells do actually find their way and get into the tumor—even crossing the blood-brain barrier—and are able to eliminate the target."

The new study was born of an interdisciplinary collaboration: neurosurgeons, neuro-oncologists, neuropathologists, immunologists, and transfusion medicine experts have all played key roles in developing the investigational therapy. Penn is the first institution to open a trial utilizing this type of CAR T cell therapy for glioblastoma, and a second study site is now open at the University of California, San Francisco.

The phase I trial will include a total of 12 adult patients whose tumors express EGFRvIII.

After some of each patient's T cells are removed via an apheresis process similar to dialysis, the cells are engineered using a viral vector that programs them to hunt for cancer cells that express EGFRvIII. Then, the

new cells are infused back into the patient's bodies, where a signaling domain built into the CAR promotes rapid growth of these cells, building an army of tumor-killing cells that have been shown in studies of blood cancer patients to persist in the body. The investigators believe the cells may then serve as a vaccine-like protection against tumor recurrence.

More than 22,000 Americans are diagnosed with GBM each year. Patients whose tumors express the EGFRvIII mutation tend to have more aggressive cancers: Their tumors are less likely to respond to standard therapies.

"We now need to see in the next set of patients if we can augment the effects of the CAR infiltration into the brain and determine optimal timing and combination of this therapy with other established therapies," O'Rourke said. "In this manner, we believe this highly personalized T cell therapy will begin to show clinical efficacy in a reproducible manner with all patients containing EGFRvIII-positive GBMs."

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