Combining CAR T cells with existing immunotherapies may overcome resistance in glioblastomas

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Donald O'Rourke, MD, an associate professor of Neurosurgery at Penn. Credit: Penn Medicine

Genetically modified "hunter" T cells successfully migrated to and penetrated a deadly type of brain tumor known as glioblastoma (GBM) in a clinical trial of the new therapy, but the cells triggered an immunosuppressive tumor microenvironment and faced a complex mutational landscape that will need to be overcome to better treat this aggressive cancer, Penn Medicine researchers report in a new study this week in *Science Translational Medicine*.

Over the past two years, investigators from the Perelman School of Medicine at the University of Pennsylvania have reported results from a human trial in GBM using chimeric antigen receptor (CAR) T cell therapy, through which patients' own T cells were engineered to track down and kill cancer cells that express a tumor-specific protein known as EGFRvIII. A team led by principal investigator Donald M. O'Rourke, MD, an associate professor of Neurosurgery at Penn, and Marcela Maus, MD, PhD, showed that CART-EGFRvIII cells had an acceptable safety profile, crossed the blood-brain barrier, infiltrated the tumor, and prompted an immune response, resulting in reduction of the EGFRvIII tumor antigen in GBM cells. Maus - 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 - is the senior author on the study.

The new study includes full results from the first 10 patients treated. The paper identified two barriers: a wide variation in EGFRvIII expression in patients and a resistance in the tumor microenvironment, which

researchers showed became even more immunosuppressive following CAR T cell infusion. Although the former may require targeting additional antigens, the authors said, the latter may be overcome with existing drugs that target immunosuppressive molecules, such as checkpoint inhibitors used to successfully treat other cancers.

"This is an early stage trial, but we are encouraged by the fact that the cells got into the brain, proliferated, and reduced the level of antigen with very little toxicity to the patients," O'Rourke said. "We can build on this as a therapeutic option for these patients. It gives us clues on what to do next."

While no clinical benefit could be definitively determined from the study, one patient did achieve stable disease at the 18-month follow up, a response that remains today, following infusion of CART-EGFRvIII. Two other patients are alive but their disease progressed, as revealed via MRI imaging criteria. The additional seven patients lived incrementally longer than one would have predicted based on the number of previous treatments they received and the multifocal nature of the GBM tumor recurrences.

"This trial showed that there is a need to target additional antigens in glioblastoma, as well as overcome the immunosuppressive environment that the CAR T cells encountered in the tumor," Maus said.

Glioblastoma is diagnosed in more than 22,000 Americans each year. The tumors often develop resistance to existing therapies, and in general only 50% of people with the cancer live longer than 15 months. Notably, the trial included heavily treated, refractory patients with multi-focal, recurrent GBMs, a group whose overall survival is extremely poor.

The trial included three groups of patients: those who did not undergo surgery following infusion (three patients who had multi-focal and

recurrent tumors not amenable to surgical resection prior to infusion); those who underwent "late surgery" (three patients who had surgery once at either day 34, day 55, or day 104 following infusion); and those who underwent "early surgery" (four patients who had clear symptomatic progression leading to a combined regimen of CART infusion followed by clinically indicated surgery).

Within the first two weeks of infusion, a detectable number of CART-EGFRvIII cells trafficked to the tumors, with signs of activation in the four patients who had "early surgery", the researchers reported. All the infused patients also had detectable circulating CART-EGFRvIII cells in the blood in the first month after infusion. However, levels of the infused cells began to steadily decline after the two-week mark, and became undetectable after one month.

The immune activation from the CAR cells was also met with resistance mechanisms, including an upregulation of immunosuppressive pathways which may work against the patient and for the tumor, the researchers found.

"There is a dramatic expansion of inhibitory T cells in the tumors after the infusion, much more significant than what you see without the CAR T cells," O'Rourke said. "This tells us that we need to begin to modulate the microenvironment to make it more favorable."

"There may be a synergy between CAR T cells and inhibition of these pathways with small molecule drugs or checkpoint blocking antibodies," he added.

An evaluation of tumors removed from five of the patients who had surgery did reveal decreased levels of the target antigen EGFRvIII, a driver of growth found in about 30 percent of these tumors. However, an analysis of the samples showed a wide variation of EGFRvIII expression

in patients and over time and in different areas of their tumors. With so many variants at play, the authors suggest that using a single target to address a heterogeneous antigen may not suffice to achieve a durable clinical benefit.

The 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) which was successfully treated by antiepileptic medications.

Researchers did not observe dramatic tumor regression by MRI in any patients. Imaging assessments were difficult to interpret because potential treatment-related changes from the immunotherapy, such as inflammation, could not easily be distinguished from tumor progression.

"This is an important paper because it illustrates the potentially significant capabilities of CAR T cells in glioblastoma," O'Rourke said. "It also demonstrates the limitations: the antigen heterogeneity and the microenvironment's fight back. This points us and the rest of the field in the right direction."

More information: D.M. O'Rourke el al., "A single dose of peripherally infused EGFRvIII-directed CAR T cells mediates antigen loss and induces adaptive resistance in patients with recurrent glioblastoma," *Science Translational Medicine* (2017). stm.sciencemag.org/lookup/doi/ … scitranslmed.aaa0984

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