Immunogene therapy combined with standard treatment is safe for patients with brain tumors

15 August 2011

A clinical trial has shown that a form of gene therapy is safe for treating a deadly form of brain cancer, even when combined with radiation therapy.

The phase 1b trial was conducted at the Ohio State University Comprehensive Cancer Center - Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC - James) and at Methodist at Hospital in Houston, TX.

The novel treatment uses an adenovirus vector called AdV-tk. The vector is taken up by cancer cells where it activates a drug that kills the cells. The vector is applied in the operating room after removing brain tumors such as glioblastoma multiforme, the most common and dangerous form of brain cancer.

The findings, published online in the *Journal of Clinical Oncology*, suggest that the therapy might also stimulate an immune response against the tumor.

"This is the first time that a gene therapy approach was combined with radiation in patients with newly diagnosed glioblastoma," says first author Dr. E. Antonio Chiocca, professor and chair of neurological surgery and co-director of the Dardinger Center for Neuro-oncology and Neurosciences at Ohio State.

"There had been a concern that combining these two treatments could be too toxic for patients, but this was not the case. We do not know yet if this will improve survival, but these findings are encouraging," he says.

Glioblastomas occur in about 18,500 Americans annually and kill nearly 13,000 of them yearly. Glioblastoma multiforme is the most common and lethal form of the malignancy, with an average survival of 15 months after diagnosis.

The tumors often recur because cancer cells typically migrate into adjacent brain tissue where they can give rise to a recurrent tumor. This study examines an immunogene therapy approach that is designed to kill these undetected cancer cells and prevent recurrence.

This clinical trial involved 10 patients with glioblastoma multiforme and two patients with anaplastic astrocytoma. The procedure works as follows:

- After removing the tumor, the neurosurgeon injects the tumor bed with 1 milliliter (1/30th oz) of a solution containing the AdV-tk vector. The vector carries a gene from herpes simplex virus for an enzyme called thymidine kinase (the '-tk' in AdV-tk). Cancer cells infected with the vector begin making the enzyme.
- Patients then take the anti-herpes virus drug valacyclovir for two weeks.
- Inside the cancer cells, the herpes thymidine kinase enzyme converts valacyclovir into DNA building blocks that the rapidly growing cancer cells cannot use to make DNA, and this kills them.
- Radiation therapy begins halfway through the course of valacyclovir. The radiation damages the DNA in the cancer cells, which then try to repair it, using the toxic valacyclovir building blocks.

In addition to improved overall survival, studies revealed a significant rise in the number of T lymphocytes in the tumors. This suggests that the gene therapy stimulated an immune response

against the tumor, producing an "immunogene therapy" effect.

Cancer immunogene therapy refers to genetically manipulating cancer cells to stimulate an immune response against a tumor. (Note: This differs from "immunotherapy," which attempts to stimulate the immune system directly against tumor cells.)

"If the results of another recently completed phase 2 efficacy trial are also encouraging, the next step will be to compare this therapy head-to-head with the current standard of care," Chiocca says.

Provided by Ohio State University Medical Center