Triple therapy revs up immune system against common brain tumor

4 August 2014

A triple therapy for glioblastoma, including two types of immunotherapy and targeted radiation, has significantly prolonged the survival of mice with these brain cancers, according to a new report by scientists at the Johns Hopkins Kimmel Cancer Center.

Mice with implanted, mouse-derived glioblastoma cells lived an average of 67 days after the triple therapy, compared with mice that lasted 24 days when they received only the two immunotherapies. Half of the mice who received the triple therapy lived 100 days or more and were protected against further tumors when new cancer cells were re-injected under the animals' skins.

The combination treatment described in the July 11 issue of *PLOS One* consists of highly focused radiation therapy targeted specifically to the tumor and strategies that lift the brakes and activate the body's immune system, allowing anti-cancer drugs to attack the tumor. One of the immunotherapies is an antibody that binds to and blocks an immune checkpoint molecule on T cells called CTLA-4, allowing the T-cells to infiltrate and fight tumor cells. The second immunotherapy, known as 4-1BB, supplies a positive "go" signal, stimulating anti-tumor T cells.

None of the treatments are new, but were used by the Johns Hopkins team to demonstrate the value of combining treatments that augment the immune response against glioblastomas, the most common brain tumors in human adults. The prognosis is generally poor, even with early treatment.

"We're trying to find that optimal balance between pushing and pulling the immune system to kill cancer," said Charles Drake, M.D., Ph.D., an associate professor of oncology, immunology and urology, and medical oncologist at the Johns Hopkins Kimmel Cancer Center.

The researchers speculate that when radiation destroys tumor cells, the dead tumor cells may release proteins that help train immune cells to recognize and attack the cancer, said Michael Lim, M.D., an associate professor of neurosurgery, oncology at the Johns Hopkins University School of Medicine and member of Johns Hopkins' Institute of NanoBiotechnology.

"Traditionally, radiation is used as a definitive therapy to directly kill cancer cells," said Lim, who also serves as director of the Brain Tumor Immunotherapy Program and director of the Metastatic Brain Tumor Center at Johns Hopkins Medicine. "But in this situation we're using radiation as kind of kindling, to try to induce an immune response."

Lim says if further studies affirm the value of the triple therapy in animals and humans, the radiation could be delivered a few days before or after the immunotherapies and still achieve the same results. Lim said this leeway "could make applications of this therapy in patients possible."

The researchers say they were also encouraged to see that the triple therapy created "immune memory" in mice that were long-term survivors. When brain tumor cells were re-introduced under the skin of the animals, their immune systems appeared to protect them against the development of a new brain tumor.

Drake said since the immune system usually doesn't generate a memory when foreign (tumor) cells are still present in the body. "But the idea that this combination treatment was successful at generating immunological memory really suggests that we could do this in patients and generate some long-term responses."

The researchers are developing a variety of clinical trials to test combination therapies against brain tumors.

More information: *PLOS One*, www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0101764

Provided by Johns Hopkins University School of Medicine