Study: Vaccine targets malignant brain cancer antigens, significantly lengthens survival

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An experimental immune-based therapy more than doubled median survival of patients diagnosed with the most aggressive malignant brain tumor, Cedars-Sinai Medical Center researchers reported in *Cancer Immunology, Immunotherapy*, published online Aug. 3. Credit: Cedars-Sinai Medical Center

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Median survival in a Phase I clinical trial at Cedars-Sinai's Johnnie L. Cochran, Jr. Brain Tumor Center was 38.4 months, significantly longer than the typical 14.6-month survival of patients with newly diagnosed glioblastoma receiving standard therapy alone, which includes radiation

and chemotherapy.

Median progression-free survival – the time from treatment to tumor recurrence – was 16.9 months, compared to the typical 6.9 months with standard care.

The study included 16 newly diagnosed patients who could be properly evaluated between May 2007 and January 2010. At later follow-up, six patients (38 percent) – ranging from 49 to 66 months post-treatment – showed no evidence of tumor recurrence and were free of disease without current active treatment. Eight patients remained alive.

"Brain tumors evade the immune system to survive, and the vaccine is intended to alert the immune system to the existence of cancer cells and activate a tumor-killing response. We also are targeting cells that we believe generate and perpetuate cancers," said Keith L. Black, MD, chair and professor of Cedars-Sinai's Department of Neurosurgery, director of the Cochran Brain Tumor Center and director of the Maxine Dunitz Neurosurgical Institute, where the vaccine was researched and developed. Black is the Ruth and Lawrence Harvey Chair in Neuroscience.

The vaccine's latest version, ICT-107, targets six antigens (HER2/neu, TRP-2, gp100, MAGE-1, IL13R?2 and AIM-2) involved in the development of glioblastoma cells. All patient tumors had at least three of the targeted antigens; 74 percent of tumors had all six. Patients with tumors that expressed large amounts of MAGE-1, AIM-2, gp100 and HER2 had better immune responses and longer progression-free survival rates, suggesting that these antigens may be particularly vulnerable to the vaccine.

The researchers also found evidence that the vaccine attacks some brain cancer stem cells, considered the original source of tumor cells. These

self-renewing cells appear to enable tumors to resist radiation and chemotherapy and even regenerate after treatment. Cancer stem cells are especially appealing targets: killing the stem cells is believed to improve the chances of destroying a tumor and preventing its recurrence.

"The correlation of clinical responses to the level of antigen expression gives us confidence in our belief that a strong immunologic response is linked to clinical outcome. This finding supports our previous finding that immune responses are correlated to survival," commented John S. Yu, MD, vice chair of the Department of Neurosurgery, director of the Brain Tumor Center, professor of neurosurgery and senior author of the article.

Three of the tumor-associated antigens (HER2/neu, TRP-2 and AIM-2) are found not only on brain tumor cells but also on brain cancer stem cells, and the researchers reported that a protein (CD133) associated with cancer stem cells was decreased or eliminated from tumors of some vaccinated patients whose glioblastomas returned after treatment.

"Previous studies showed an increase in CD133 expression in patients who underwent treatment with radiation and chemotherapy. Our findings suggest that targeting antigens that are highly expressed by cancer stem cells may be a viable strategy for treating patients who have glioblastoma," said Surasak Phuphanich, MD, director of the Neuro-Oncology Program at the Cochran Brain Tumor Center and professor of neurology with Cedars-Sinai's Department of Neurosurgery and Department of Neurology.

Phuphanich and Christopher J. Wheeler, PhD, principal investigator in the Immunology Program at the Maxine Dunitz Neurosurgical Institute and associate professor of neurosurgery, are first authors of the article.

Cedars-Sinai's first dendritic cell vaccine began Phase I experimental

treatments in May 1998. With the ability of the latest version, ICT-107, to stimulate a targeted and controlled immune response established in this Phase I study, the vaccine moved into a Phase II multicenter, randomized, placebo-controlled trial in 2011. Enrollment in the Phase II trial is expected to be completed in September 2012.

Dendritic cells are the immune system's most powerful antigen-presenting cells – those responsible for helping the immune system recognize invaders. They are derived from white blood cells taken from the patient in a routine blood draw. In the laboratory, the cells are cultured with synthetic peptides of the six antigens – essentially training the dendritic cells to recognize the tumor antigens as targets.

When the "new" dendritic cells in the vaccine are injected under the patient's skin in the armpit, they are intended to seek and destroy lingering tumor cells. Vaccine is administered three times at two-week intervals after standard radiation and chemotherapy.

ICT-107 is a product of the biotechnology company ImmunoCellular Therapeutics, Ltd. Keith L. Black, MD, chair of Cedars-Sinai's Department of Neurosurgery, director of the Maxine Dunitz Neurosurgical Institute, director of the Johnnie L. Cochran, Jr. Brain Tumor Center and the Ruth and Lawrence Harvey Chair in Neuroscience, is chairman of the company's scientific advisory board. John S. Yu, MD, vice chair of the Department of Neurosurgery, director of the Brain Tumor Center, director of Surgical Neuro-Oncology and surgical director of the Gamma Knife Center at Cedars-Sinai, is chief scientific officer and chairman of the board. Yu and another author are salaried employees of the company and own stock in it; Black and another author are consultants for the company and stock owners. Certain rights in the dendritic cell vaccine technology and corresponding intellectual property have been exclusively licensed by Cedars-Sinai to ImmunoCellular Therapeutics, including subsequently developed

versions of the vaccine investigated in this clinical study. Cedars-Sinai also owns stock in the company.

More information: *Cancer Immunology, Immunotherapy*, "Phase I trial of a multi-epitope pulsed dendritic cell vaccine for patients with newly diagnosed glioblastoma," online Aug. 3, 2012.

Provided by Cedars-Sinai Medical Center

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