Therapeutic Vaccine for Brain Cancer Succeeds Using a Unique Approach

BY BOB CARLSON, MHA, *Senior Correspondent*

Senator Edward Kennedy's death from glioblastoma multiforme (GBM) in 2009 was a public reminder that this brain cancer is lethal. Less than 3 percent of glioblastoma patients who receive standard care survive five years. The incidence of GBM in the United States is about 11,000 diagnoses annually, and the prevalence is about 25,000.

"Dismal" is how a group of researchers at the Jonsson Comprehensive Cancer Center at the University of California–Los Angeles (UCLA) described the prognosis for patients with primary malignant brain tumors in a recent study (Prins 2011). Linda M. Liau, MD, PhD, who participated in that study, is the principal investigator in the clinical trials of DCVax[1] for brain cancer. DCVax is a dendritic cell vaccine for treating a wide variety of cancers, including GBM. Fourteen years after it first occurred to Liau to treat GBM with dendritic cells loaded with brain tumor antigens, DCVax is now being tested in a multicenter phase 2 trial. The idea of treating cancer with adjuvant immunotherapy wasn't new, but Liau was one of the first to try dendritic cell-based vaccines for GBM, a type of tumor that was thought to be "immune privileged" due to its location within the brain.

"Glioblastomas are very heterogeneous," says Liau, professor and vice chair of the UCLA department of neurosurgery and director of the UCLA brain tumor program at the David Geffen School of Medicine. These tumors, she explains, "don't have a well-defined antigen — at least not one that's uniformly expressed — and that's what makes them very difficult to treat based on single molecular targets. There are probably dozens of molecular targets within one tumor. So, I thought, why not just let the patient's own body decide what to attack and get the antigens from the tumor itself?"

The UCLA team's personalized vaccine concept worked in mice and rats. Brain tumors actually disappeared in a large percentage of the animals after treatment, and that led to three phase 1 clinical trials. In the most recent trial, 86 percent of the 23 GBM patients lived longer than the current standard of care. Six patients survived for more than 48 months, including one who had lived for more than 98 months at trial's end (Prins 2011) and is still alive.

Two months to live

Tom Jones (not his real name) was the third patient enrolled in that trial and has survived eight years since his diagnosis. He was a 33-year-old lifeguard when the first headache hit in 2003. Migraine meds did not help, so he went to his physician, who referred him to a neurologist. An electroencephalogram (EEG) identified an anomaly in the left side of his brain, and an MRI showed a tumor there. A tumor and craniotomy biopsy at nearby Torrance Memorial Hospital confirmed his diagnosis.

The surgeon who performed the biopsy advised him that surgery was not possible. The radiation oncologist at Torrance told him he had two months to live. His wife was pregnant with their second child and was due in less than two months. The radiation oncologist's boss suggested that Jones ask surgeons at UCLA and at the University of California–San Francisco (UCSF) whether any of the tumor could be removed, explaining that if it could, he might gain additional survival weeks so that he could hold his newborn son.

Mindful that GBMs can double in size in just two weeks, Jones and his wife grabbed MRI films and EEGs and visited UCLA and then flew to UCSF for a second opinion, all on the same day. Both hospitals said they could do the surgery, but Liau — a neurosurgeon and researcher of international stature — told him that he was a perfect candidate for the phase 1 DCVax trial.

Jones had a leukapheresis to harvest his adherent peripheral blood mononuclear cells, which were cultured with a variety of cytokines at the Jonsson Center for about 10 days to produce dendritic cells. So called because they have processes that look like neuronal dendrites, dendritic cells are the master calls of the immune system. They migrate to the lymph nodes, where they present antigens to T-cells and B-cells to initiate an adaptive immune response.

Eight years later

Liau resected Jones' tumor, which was about three quarters the size of a golf ball. Fresh tissue from this tumor was transported to the Jonsson Center, where it was minced, processed with enzymes, subjected to five freeze-thaw cycles, centrifuged, tested, and then frozen.

[1] DCVax is a registered trademark of Northwest Biotherapeutics.

The patients in the trial received the standard of care for GBM — surgery, temozolomide chemotherapy, and external beam radiation — plus a course of DCVax. One day before patients were scheduled to receive their DCVax injections, their processed tumor tissues were thawed and co-cultured, or pulsed, with their autologous dendritic cells to make their personalized DCVax vaccine. Two 1 mL intradermal injections of DCVax were administered, one in each arm near the armpit (and lymph nodes), once every two weeks over a six-week period. Thereafter, patients received booster shots every three months until tumor progression or until they ran out of tumor tissue to pulse with dendritic cells. Patients received an MRI every two months after the first injection.

Newly diagnosed patients (versus those with recurrent GBM) received their DCVax injections after completing the standard six weeks of postoperative chemotherapy and radiation but before starting adjuvant chemotherapy. Jones received his first DCVax injection in June 2003 and his last booster vaccination in February 2009.

"Seventy percent of people who are diagnosed with GBM are gone within a year and another 20 percent are gone within two — and I'm here more than eight years later," says Jones, who now coaches water polo at a midwest college.

Microarray gene-expression profiling revealed that Jones and the others in his trial who are still alive had tumors with mesenchymal gene-expression signatures. In the Prins study, an analysis of tumor tissue with a mesenchymal gene-expression signature showed that these tumors have a higher number of $CD3^+$ and $CD8^+$ tumor-infiltrating lymphocytes compared with glioblastomas with other gene-expression signatures. The authors theorized that "the mesenchymal gene-expression profile may identify an immunogenic subgroup of glioblastoma that may be more responsive to immune-based therapies."

Cancer vaccines gain ground

The usual personalized medicine approach is to identify the molecular markers that predict a patient's response to treatment. Liau and colleagues tried that. They analyzed GBMs for antigens and pulsed dendritic cells with the corresponding off-the-shelf synthetic peptides expressed by the tumors. Unfortunately, that trial did not improve patient survival.

But DCVax does. The unprecedented response by Jones and the other five surviving patients is encouraging, and so is the aggregate response of all patients enrolled in the phase 1 trial. Enrollees included 15 patients with newly diagnosed tumors and eight with recurrent disease — 16 men and 7 women, ranging in age from 26 to 74. For those who received DCVax at initial diagnosis, median overall survival was 35.9 months, with a mean follow-up time of more than four years. For those who enrolled in the trial at the time of recurrence, median overall survival was 17.9 months from the time of initial diagnosis, roughly double that of historical controls in the literature.

The phase 1 trials of DCVax were funded by UCLA, the National Institutes of Health, foundation grants, and Northwest Biotherapeutics. Northwest Biotherapeutics is funding the current multicenter phase 2 trial. Results are expected late next year. DCVax has been cleared for a phase 3 trial in 612 patients with prostate cancer.

"Dr. Liau is a leader in this field and we are pleased to be working closely with her as the clinical trial is carried out in 20 or more sites across the country," says Linda Powers, CEO of Northwest Biotherapeutics.

"Why not just let the patient's own body decide what to attack and get the antigens from the tumor itself?"

— Linda M. Liau, MD, PhD, David Geffen School of Medicine, UCLA

"This is groundbreaking personalized immune therapy. We are excited about the overall survival data and the absence of toxicity in patients who have used DCVax."

Cancer vaccines continue to gain ground as a relatively new subset of cancer treatments. Piribo, a London healthcare market research company, estimates that the worldwide market for cancer vaccines will exceed $7 billion by 2015.

"There's still a lot to learn about what works and what doesn't work for this type of cancer," says Liau.

"Patients should look for trials or treatments that aim to improve the current standard of care and for other options because that's the only way we're going to do better — to try things that potentially could work."

Reference

Prins RM, Soto H, Kankakit V, et al. Gene expression profile correlates with T-cell infiltration and relative survival in glioblastoma patients vaccinated with dendritic cell immunotherapy. *Clin Cancer Res.* 2011;17:1603–1615.

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