Dendritic Cell Vaccine Shows Promise in GBM

BY KERRI WACHTER
Senior Writer

CHICAGO — Combining dendritic cell vaccination with imiquimod for the treatment of glioblastoma more than doubled survival in an intervention group compared to a conventionally treated control group in a small phase I trial presented as a poster at the annual meeting of the American Society of Clinical Oncology.

Two-year survival—the primary clinical end point—for 19 patients treated with the dendritic cell vaccines was 68%, and 3-year survival was 43%. In comparison, only 26% of control patients at the University of California, Los Angeles, survived to 2 years, and only 20% survived to 3 years.

To date, the median progression-free survival and median overall survival in the vaccinated group are 18 months and 34 months, respectively. This compared with 7 months and 15 months, respectively, for control patients from the published literature.

Dr. Linda Liau, a neurosurgeon at UCLA, and her colleagues presented immunologic response data for 13 patients with newly diagnosed glioblastoma multiforme (GBM). Patients underwent resection, followed by a 6-week course of radiation and chemotherapy with temozolomide. Two weeks prior to the first immunization, patients underwent MRI. One week before the first immunization, patients underwent leukapheresis and immunologic assays.

The vaccines were composed of autologous dendritic cells that have been pulsed with lysates from GBM tumor cells. Preclinical studies have demonstrated that dendritic cells are preferentially responsible for the sensitization of naive T cells in their first exposure to antigen.

Each patient initially received three vaccinations at 2-week intervals. Four patients received 1 million dendritic cells per immunization; four others received 5 million dendritic cells per immunization, and the remaining five received 10 million dendritic cells per immunization.

Patients without tumor progression subsequently received booster injections every 3 months combined with topical administration of imiquimod, which is a toll-like receptor-7 agonist that enhances both the innate and acquired immune response. Imiquimod (Aldara) is indicated for the treatment of actinic keratosis, superficial basal cell carcinoma, and external genital and perianal warts.

Immunologic responses to tumor antigens were monitored using several methods. Clinical tumor growth was monitored by MRI every 2 months.

The control group consisted of a total of 191 patients with GBM at UCLA, who received standard treatment. The average age of the patients in the vaccinated and control groups was 51 and 49 years, respectively.

"It appears that vaccination approaches in general are very successful," said Dr. Albert Wong of Stanford University Palo Alto, Calif., who reviewed the poster during a discussion session.

Almost all of the patients had de novo infiltration of T lymphocytes into CNS tumors. In addition, CNS tumors were found to be expressing known tumor-associated antigens. Five patients also had an increase in tumor antigen-specific CD8-positive T cells with vaccination.

The relationship between response to tumor antigens and patient survival was somewhat disappointing. "In my opinion, there was not a strong correlation between the response to these defined tumor antigens and patient response," Dr. Wong said.

In general there is a need for better surrogate markers to assess immune response. Perhaps the best may be the infiltration of T cells into the tumor, he added.

In terms of safety, no grade 3 or 4 adverse events were reported. The most frequent adverse events were low-grade fever, injection-site itching and pain, and arthralgia and myalgia. Seizures also occurred that were possibly related to the vaccines; however, seizures are also typical in GBM patients.

An important next step is to identify what the true tumor antigens are, in order to better refine the vaccine. Dr. Wong likened the current generation of dendritic cell vaccines to using foxglove to treat "x," when it would really be better to extract and use the active component, digitalis.

Dr. Liau did not disclose any conflicts of interest. The study was sponsored in part by Northwest Biotherapeutics Inc., which is developing the technology behind the vaccines. A phase II clinical trial, sponsored by Northwest Biotherapeutics Inc., is underway. ■

Temozolomide/Vaccination Combo May Work as Glioblastoma Therapy

BY KERRI WACHTER
Senior Writer

CHICAGO — Temozolomide may not be incompatible with immunologic approaches for the treatment of glioblastoma, based on data from a small analysis presented at the annual meeting of the American Society of Clinical Oncology.

Vaccinating patients who have glioblastoma multiforme (GBM) with dendritic cells and either acid-eluted peptides or an antigen-specific peptide has shown promising results in extending patient survival. Likewise, temozolomide (Temodar) has been shown to prolong survival in these patients and has become part of a standard treatment regimen.

However, temozolomide also often induces a profound and long-lasting lymphopenia that could limit immunotherapeutic approaches, such as vaccination.

"This preliminary experience suggests that sequential administration of chemotherapy and immunotherapy may not be deleterious," wrote Dr. John H. Sampson, who is an associate professor of surgery at Duke University in Durham, N.C., and his colleagues.

This analysis involved patients from two ongoing trials, who are newly diagnosed with GBM, are epidermal growth factor receptor variant III (EGFRvIII)–positive, and have had complete resection.

In the ACTIVATE trial, patients received radiation (approximately 60 Gy) and concurrent temozolomide (50-75 mg/m^2 per day), followed by vaccination with EGFRvIII-specific peptide. In the ACT II trial, patients received the same radiation and temozolomide regimen. Vaccination was given on day 21 of repetitive 28-day temozolomide cycles.

Peripheral blood counts were monitored in patients. Grade 2 lymphopenia (less than 800 lymphocytes per mcL of blood) was induced in all patients receiving temozolomide after the first cycle. Grade 3 lymphopenia (less than 500 lymphocytes per mcL of blood) was induced in 70% of patients after the first cycle of temozolomide. However, lymphocyte counts returned to normal after treatment with the drug was stopped.

Regulatory T cells increased from 5% to 12% after the combination of temozolomide and radiation. Cycles of temozolomide do not appear to have diminished EGFRvIII-specific CD3-positive/CD8-positive T cells producing interferon-gamma. EGFRvIII-specific IgG responses were induced and maintained during temozolomide.

Dr. Sampson did not report having any relevant conflicts of interest. ■

Preoperative System Characterizes Hemispheric Low-Grade Gliomas

BY JEFF EVANS
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WASHINGTON — A new preoperative grading system for adult hemispheric low-grade gliomas produced accurate prognoses for disease stage, Dr. Edward F. Chang said at the annual meeting of the American Association of Neurological Surgeons.

"There are few standards for guiding both the medical and surgical management of low-grade gliomas," said Dr. Chang, a third-year resident in the department of neurologic surgery at the University of California, San Francisco. To construct a system, Dr. Chang reviewed 280 patients who had undergone operations for histologically confirmed grade 2 gliomas (from biopsy to maximal surgical resection) during 1989-2005 at UCSF.

Median patient age was 38 years at presentation. Most (88%) had seizures. A majority had a Karnofsky Performance Scale score of 100 or 90. Most tumors were in the frontal (72%) or temporal lobe (34%); median diameter was 4.5 cm.

In the follow-up period, patients survived for a median of 12 years; 65 died. A total of 134 events of progression or recurrence occurred. The median time of progression-free survival was 6 years.

The investigators used four variables highly predictive of lower survival in their grading. (See box.) The strongest was the presence of tumor in "eloquent" brain regions, particularly the sensorimotor cortex (specifically the pre- and postsensory gyri), perisylvian dominant language areas, insular areas, basal ganglia-internal capsule, thalamus, and hypothalamus. Tumor presence in an area of eloquence was the only significant, independent predictor of progression or recurrence.

The interobserver reliability of the grading system had a kappa value of 0.86 between a neurosurgery resident and an attending neurosurgeon blinded to the outcome of a subset of 200 random cases from the study.

When the study sample was graded, the median survival fell from 16 years for patients with low risk to nearly 11 years for those with intermediate risk and 8 years high risk. The median period of progression-free survival dropped as risk grew.

The researchers also analyzed predictors of the extent of resection. Tumors in an area of eloquence had a diameter greater than 4 cm with diffuse borders on MRI; tumors in the temporal lobe were significantly more likely to be treated with subtotal resection; parietal tumors were significantly more likely to undergo gross total resection.

The grading system currently is undergoing external validation. ■

Low-Grade Glioma Grading System

- ▶ Age 50 years or older
- ▶ Karnofsky Performance Scale score less than 90
- ▶ Maximum tumor diameter more than 4 cm
- ▶ Tumor located in "eloquent" area

A "yes" answer is given a score of 1 and a "no," a score of 0. The categories for risk of death or progression were defined as:

Low = 0-1
Intermediate = 2
High = 3-4

Source: Dr. Chang