Phase II Data Show Remissions

Regimen *from page 1*

of lead investigator Dr. James J. Vredenburgh, medical director of adult clinical services at the center, in this work.

All patients had failed standard-of-care treatment (radiotherapy, temozolamide), with a median of two progressions. Patients received bevacizumab and irinotecan intravenously every 2 weeks for 6 weeks; bevacizumab was administered at 10 mg/kg, and the irinotecan dose was adjusted according to whether patients were taking enzyme-inducing antiepileptic drugs. Patients with evidence of intracranial hemorrhage on initial brain MRI were excluded, as were patients who had failed more than three previous treatments. Patients underwent imaging at baseline and then every 6 weeks.

For the 34 patients with grade III tumors, the mean progression-free survival (PFS) was 42 weeks, compared with 22 weeks for historical benchmark controls comprising 125 patients; 6-month PFS was 61%, compared with 46%. For the 34 patients with grade IV tumors, mean PFS was 23 weeks (vs. 12 weeks), and 43% (vs. 21%) had 6-month PFS.

A complete response/partial response (CR/PR) occurred in 22 of 34 grade III patients (65%); 32% had stable disease, and 3% had progressive disease. For the 34 grade IV patients, 53% had CR/PR, 41% had stable disease, and 6% had progressive disease.

Historically, chemotherapy response rates run about 10% in advanced glioma, said Dr. Vredenburgh in a presentation of the same study at a meeting of the American Society of Clinical Oncology in Chicago earlier this summer. Without commenting on the implications, he reported that investigators took 12 patients off treatment after positron emission tomography (PET) scans showed their tumors to be hypometabolic. "They had a cold PET scan," he explained afterward in an interview. "Given the toxicity and the risk involved, we thought that was a reasonable time to stop their treatment."

Dr. Vredenburgh added that Five patients have not progressed in more than a year; one returned to graduate school.

The four mechanisms by which bevacizumab achieves its efficacy are: a direct anti-tumor effect, an antiangiogenic effect, normalization of tumor vasculature with decreased interstitial pressure leading to improvement in hypoxia, and an anti-tumor stem cell effect. "Clearly, it is the bevacizumab making a difference. It's not the irinotecan," he noted.

During his presentation, Dr. Reardon said that some clinicians have questioned whether the radiographic responses to the bevacizumab/irinotecan therapy should actually be considered a "glorified steroid" effect. He disagreed, noting that, unlike the results reported here, steroids do not produce a durable antitumor response.

The treatment was associated generally manageable toxicity, said Dr. Reardon. Fatigue, hypertension, and proteinuria were common grade 2 events. One CNS hemorrhage occurred, six patients developed deep venous thromboses or pulmonary emboli, and one cerebrovascular accident was reported. There were no grade 4 or 5 events.

Dr. Reardon showed evidence using dynamic contrast-enhanced MRI that the bevacizumab/irinotecan treatment induces an almost-immediate response. In a subgroup of 20 patients from the therapeutic trial above, changes in the K^{trans} (a parameter that reflects the ability of contrast agent to pass between blood and extravascular extracellular space) were noted within 1 day in 10 patients and in 19, or 95%, of patients by the end of their first cycle of treatment. The goal of this research is to develop a biomarker to identify treatment responders and nonresponders.

Malignant gliomas are among the most vascular tumors, said Dr. Reardon. Vascular endothelial growth factor (VEGF) is a key mediator of glioma angiogenesis. Bevacizumab, a humanized monoclonal antibody against VEGF, is FDA-approved for use in both colorectal cancer and lung cancer based on its ability to significantly enhance the antitumor activity of chemotherapy.

"Many clinical trials [for antiangiogenic agents] excluded brain tumor patients, primarily because of concern for intracranial hemorrhage and toxicity. To me, it is encouraging but paradoxical to find that brain tumor patients are some of the most responsive to this class of agents," Dr. Reardon said.

In an interview, Dr. Daniel P. Barboriak, a neuroradiologist from Duke University who also collaborated on the work with Dr. Reardon, said that although the bevacizumab/irinotecan combination is not a cure, its effectiveness in patients who have failed previous therapies is dramatic and encouraging. It also may change the reluctance of funding agencies to invest research dollars in a disease once thought to be incurable.

The trial reported research support from Genentech, the developer of bevacizumab (Avastin). ■

Jane Salodof MacNeil contributed to this story.

Treatment Information for Cancer Patients

Cancer Monthly publishes information about the side effects of hundreds of cancer treatments and is designed to help patients and their families make informed decisions about brain tumors as well as other types of cancer. This online resource lets patients see survival rates for each type of cancer as well as quality of life measures for different cancer therapies. It offers physicians' contact information and a list of 260 hospitals where new therapies have been performed. It also provides patients with access to cancer news, clinical trials, medical scientific reports, and alternative and integrative approaches. For additional information, visit the Cancer Monthly Web site at www.cancermonthly.com. ■

Imaging Biomarker Can Help To Assess Glioma Malignancy

BY AMY ROTHMAN SCHONFELD
Contributing Writer

Chicago — Measurement of cerebral blood flow volume in a patient with glioma is a sensitive predictor of disease stability or progression, according to Dr. Meng Law, who presented his findings at the annual meeting of the American Society of Neuroradiology.

Using dynamic susceptibility contrast perfusion magnetic resonance imaging (DSC-MRI), Dr. Law found that gliomas with a high relative cerebral blood volume (rCBV) showed significantly more rapid time to progression than did gliomas with a low rCBV. This information gained at the time of diagnosis can impact treatment decisions, including the extent of neurosurgical resection, or the choice of postoperative radiation or chemotherapy protocols.

Patients who progressed and patients who died had much higher mean rCBV values than did patients with either a complete response or stable disease.

This 10-year, retrospective study included 189 patients with histologically proved gliomas: low-grade astrocytomas (28), low-grade oligodendrogliomas (14), low-grade oligoastrocytomas (11), anaplastic astrocytomas (72), anaplastic oligoastrocytomas (12), and glioblastoma multiforme (52).

Patients underwent DSC-MRI, and measurements of rCBV were obtained by choosing the highest regional intratumoral rCBV after excluding large intratumoral vessels. Patients were followed up clinically and with MRI (median follow-up 3.2 years).

Dr. Law, currently of Mount Sinai Medical Center, New York, conducted this research while on the faculty of New York University.

Patients who progressed had a mean rCBV of 4.84 (n=130) and for patients who died the mean value was 3.82 (n=36), values that were much higher than in those who showed a complete response (1.41, n=4) or who had stable disease (2.36, n=41). *P* values from logistic regression demonstrated that age and rCBV were significant predictors of disease progression and death.

Patients with higher rCBV scores showed more rapid time to progression (TTP), as seen in the image, below. Those patients with an rCBV greater than 1.75 had a mean TTP of 265 days, compared with 3,585 days for those with an rCBV less than 1.75.

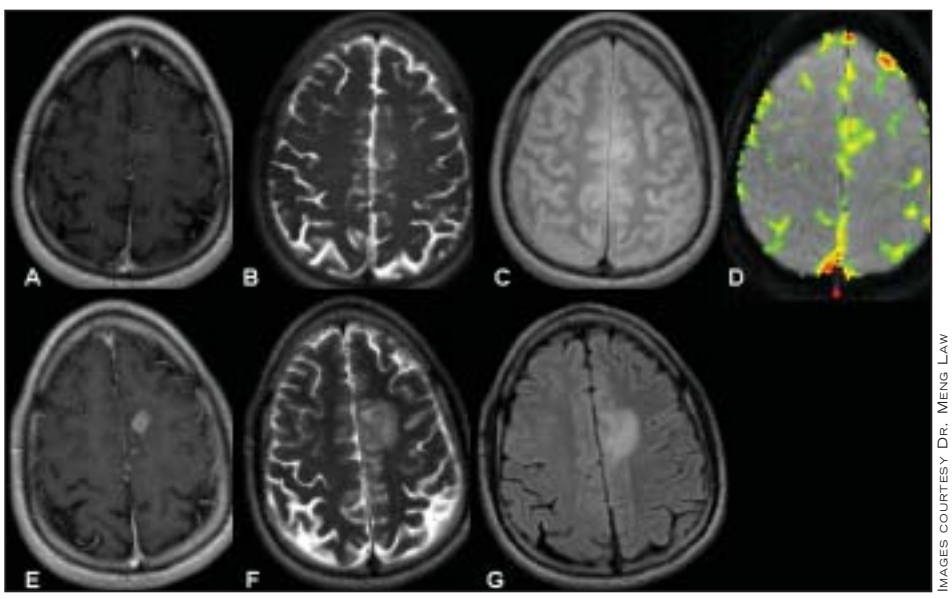
These values were derived from Kaplan-Meier Progression Free Survival curves. The 1.75 threshold for rCBV has a sensitivity of about 90% for distinguishing low-grade from high-grade tumors, said Dr. Law.

DSC-MRI is a technique that can provide physiologic information about vascular endothelial proliferation, vascular density, and angiogenesis. Since vascular proliferation is an important factor in the biology of gliomas, Dr. Law said, it is not surprising that DSC-MRI can provide an accurate means of characterizing tumor biology.

According to Dr. Law, while histopathology is the standard reference for determining glioma tumor biology and making prognostic decisions, histopathology has significant limitations. These include sampling errors, inter- and intraobserver variability, and dynamic changes as the tumor progresses.

Since patients with misclassified gliomas may not receive optimum treatment, Dr. Law suggested that measuring cerebral blood volume may be as sensitive, or even more sensitive, a predictor than pathology when assessing glioma outcomes.

He is investigating this further in a multicenter study using perfusion in predicting patient outcome; the study is being funded by the nonprofit Accelerate Brain Cancer Cure in Washington. ■



Images courtesy Dr. Meng Law

Imaging shows disease progression over a 6-month period in a man with a pathology-proven low-grade astrocytoma but a high baseline relative cerebral blood volume (rCBV). Dr. Law said that while histopathology is the standard reference for determining glioma biology and making prognostic decisions, it has limitations.