Survival Doubled at 2 Years

Glioblastoma *from page 1*

Organisation for Research and Treatment of Cancer (EORTC) Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group.

Participants had a World Health Organization performance status of 2 or better. "They were independent for activities of daily living but were not working," explained Dr. Henson, attending neuro-oncologist, Massachusetts General Hospital, Boston.

Median survival was 12.1 months with radiation alone versus 14.6 months in the combination treatment group. Two-year survival was 10.4% in the radiation alone group but 26.5% in the radiation/chemotherapy group—"really a remarkable result in glioblastoma," said Dr. Henson, also of Harvard Medical School, Boston.

Results of the phase III trial were published in March 2005 (N. Engl. J. Med. 2005;352:987-96). Dr. Henson was not an author of the study, and has no conflict of interest to disclose regarding Schering-Plough.

The improved 2-year survival of concomitant radiation and temozolomide is a rationale for widespread use of this radiation/chemotherapy regimen, Dr. Henson said. In March 2005, the Food and Drug Administration approved a new indication for temozolomide: treatment of adult patients with newly diagnosed high-grade glioblastoma multiforme concomitantly with radiotherapy and then as an adjunctive treatment. The FDA first approved the drug in 1999 for treatment of adults with refractory anaplastic astrocytoma.

"Glioblastoma remains a deadly disease, but this study represents a new beginning," Dr. Henson said. "For the first time, a very exciting result for our patients and our field."

Temozolomide may work by silencing the O^6-methylguanine–DNA methyltransferase (*MGMT*) DNA-repair gene. Once the *MGMT* gene is silent, the ability of tumor cells to repair themselves is impaired, and temozolomide treatment becomes more effective. Participants with a silenced *MGMT* gene had a median survival of 21 months compared with 15 months for patients with a nonsilenced *MGMT* gene.

All participants received fractionated focal irradiation in daily fractions of 2 Gy given 5 days for 6 weeks, for a total of 60 Gy. Participants in the dual-treatment group also received 7 days per week of temozolomide 75 mg/m^2 body surface area per day during radiation treatment, then adjuvant temozolomide 150-200 mg/m^2 for 5 days during each 28-day treatment cycle.

There were grade 3 or 4 hematologic toxic effects in 7% of patients taking temozolomide. Patients in this group discontinued treatment because of toxicity (5%) and progression of disease (4%). Overall, the agent was well tolerated, he said.

One of the study's limitations is its failure to distinguish between value of concomitant and adjuvant temozolomide. Most often in patients with multiforme blastoma chemotherapy is adjuvant, given after radiation therapy.

Use of the agent in the concomitant phase alone cost $10,000, he said in response to an audience question. ■

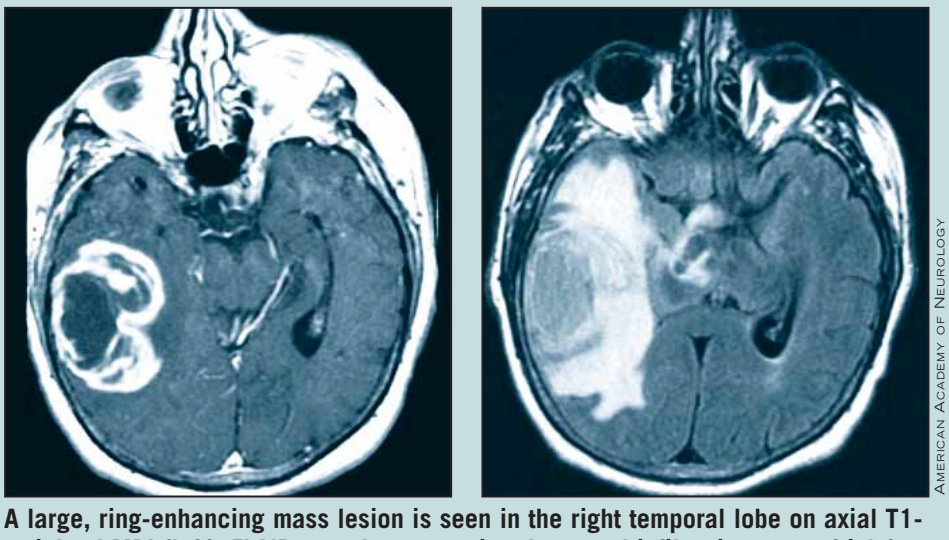
Case Illustrates Typical Aggressiveness Of Glioblastoma Multiforme Tumor

A 66-year-old executive presented to Dr. Henson with the complaint that he had been having headaches and feeling fatigued for several weeks.

The man reported difficulty performing routine tasks of daily living, such as buttoning his shirt, beginning during the week preceding his first visit to Dr. Henson. A shuffling gait lasting for several days prompted the patient to seek evaluation for stroke. The patient was fully oriented on a neurologic examination and his family history was negative for cancer. MRI showed a right temporal lobe mass surrounded by hyperintense signals. There was some infiltration of tumor cells into his optic tract visible on fluid attenuated inversion recovery (FLAIR) image. The lesion appeared severely necrotic, a diagnostic feature of glioblastoma multiforme, he said.The patient had surgery, followed by oral temozolomide and radiation.

"As is common with these patients, he had asymptomatic recurrence 12 months following diagnosis," Dr. Henson said.

Repeat surgery uncovered malignant glioma. The patient died 18 months after diagnosis.



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A large, ring-enhancing mass lesion is seen in the right temporal lobe on axial T1-weighted MRI (left). FLAIR reveals vasogenic edema and infiltrating tumor (right).

Temozolomide, Wafers Added To CNS Cancer Guidelines

BY DIANA MAHONEY
New England Bureau

HOLLYWOOD, FLA. — Oral temozolomide should be added to radiotherapy for adults newly diagnosed with glioblastoma multiforme, according to updated guidelines for the management of central nervous system cancers.

Recent studies have shown that including the oral alkylating agent in the management of glioblastoma multiforme results in a clinically meaningful, statistically significant survival benefit with minimal additional toxicity, Steven Brem, M.D., said at the annual conference of the National Comprehensive Cancer Network (NCCN).

The new central nervous system cancer guidelines, issued in March, were developed by the NCCN, which comprises 19 member institutions that have been designated as comprehensive cancer centers by the National Cancer Institute. Last updated in 2004, the guidelines also recommend the use of chemotherapeutic polymer implants following glioblastoma resection, said Dr. Brem, chair of the central nervous system guidelines writing panel.

Where brain metastases were often viewed as fatal, we now consider them treatable. Focused radiation can improve median survival time.

The inclusion of temozolomide in the updated guidelines comes on the heels of the Food and Drug Administration's (FDA's) March 16 approval of the drug for use in combination with radiotherapy for newly diagnosed glioblastoma, the most common type of primary brain tumor in adults, said Dr. Brem, leader of the neuro-oncology program at H. Lee Moffitt Cancer Center in Tampa, Fla.

Both the FDA approval and NCCN guideline update are based in large part on safety and efficacy data from a phase III study by the European Organisation for Research and Treatment of Cancer (EORTC) in which 573 patients newly diagnosed with glioblastoma were randomized to receive radiotherapy alone or in conjunction with temozolomide (N. Engl. J. Med. 2005;352:987-96). The temozolomide group saw a median survival improvement of 2.5 months—"a significant gain and one that can be built upon," according to Dr. Brem.

With respect to polymer implants, the guidelines state that BCNU wafers (biodegradable 1,3-bis 2-chloroethyl-1-nitrosourea) should be implanted into the cavity created following glioblastoma resection. As the small white wafers erode, they release the chemotherapy agent carmustine directly to the tumor site over an extended period of time. The FDA approved the wafers for use in patients with newly diagnosed glioblastoma in February 2003 based on results of a series of randomized trials. The NCCN treatment update reflects these results as well as the findings of a 2003 phase III trial out of the University Hospital Eppendorf, Hamburg (Germany), in which 240 patients were randomized to receive either BCNU or placebo wafers at the time of primary surgical resection, followed by postoperative external beam radiation. The BCNU group had a median survival improvement of 2.3 months and a 28% reduction in death risk. Additionally, time-to-decline and neuroperformance measures were significantly improved, and adverse events were comparable, with the exception of increased risk for cerebrospinal fluid leak and intracranial hypertension in the BCNU group (Neuro-oncol. 2003;5:79-88).

For patients in whom the wafers are not implanted, radiation therapy and treatment with temozolomide should be used, he said.

The updated guidelines also recommend aggressive treatment of metastases to the brain from other cancers. In general, surgery is indicated when there are fewer than four resectable metastatic lesions—depending on such factors as histologic type, location, and neurologic function. This recommendation is based on studies that have associated surgery via various modern techniques—image-guided navigation, functional mapping, awake craniotomy for eloquent area, and minimally invasive microneurosurgery—with a median drop in surgical mortality from 11% to 0%, said Dr. Brem. When there are more than three metastases or when surgery is not indicated, whole-brain radiation therapy—which has a 40%-60% response rate, depending on the tumor—should be used. "Where brain metastases were often viewed as fatal, we now consider them treatable. Where radiation [to the brain] was often perceived as too harmful, we now know that focused radiation can improve median survival time," he said.

For patients with pain and disability resulting from metastatic spine tumors, the guidelines recommend reconstructive spinal surgery over medical management because the former is associated with better quality of life outcomes, said Dr. Brem.

The guidelines also outline the use of imaging as an accurate biomarker for monitoring central nervous system disease progression and recurrence, as well as treatment efficacy, he said. ■

The updated guidelines are posted at www.nccn.org/professionals/physician_gls/default.asp.