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CLINICAL INVESTIGATION **Brain**

SAFETY AND EFFICACY OF BEVACIZUMAB WITH HYPOFRACTIONATED STEREOTACTIC IRRADIATION FOR RECURRENT MALIGNANT GLIOMAS

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Purpose: **Preclinical studies suggest that inhibition of vascular endothelial growth factor (VEGF) improves glioma response to radiotherapy. Bevacizumab, a monoclonal antibody against VEGF, has shown promise in recurrent gliomas, but the safety and efficacy of concurrent bevacizumab with brain irradiation has not been extensively studied. The objectives of this study were to determine the safety and activity of this combination in malignant gliomas.**

Methods and Materials: **After prior treatment with standard radiation therapy patients with recurrent glioblastoma (GBM) and anaplastic gliomas (AG) received bevacizumab (10 mg/kg intravenous) every 2 weeks of 28-day cycles until tumor progression. Patients also received 30 Gy of hypofractionated stereotactic radiotherapy (HFSRT) in five fractions after the first cycle of bevacizumab.**

Results: **Twenty-five patients (20 GBM, 5 AG; median age 56 years; median Karnofsky Performance Status 90) received a median of seven cycles of bevacizumab. One patient did not undergo HFSRT because overlap with prior radiotherapy would exceed the safe dose allowed to the optic chiasm. Three patients discontinued treatment because of Grade 3 central nervous system intratumoral hemorrhage, wound dehiscence, and bowel perforation. Other nonhematologic and hematologic toxicities were transient. No radiation necrosis was seen in these previously irradiated patients. For the GBM cohort, overall response rate was 50%, 6-month progression-free survival was 65%; median overall survival was 12.5 months, and 1-year survival was 54%.**

Discussion: **Bevacizumab with HFSRT is safe and well tolerated. Radiographic responses, duration of disease control, and survival suggest that this regimen is active in recurrent malignant glioma.** **© 2009 Elsevier Inc.**

Malignant gliomas, Glioblastoma, Bevacizumab, Anti-angiogenesis, Intensity-modulated radiation therapy.

INTRODUCTION

Radiotherapy (RT) has been shown to be the most effective adjuvant treatment for malignant gliomas but has only limited benefit in these tumors because of intrinsic radioresistance and the limited radiation tolerance of surrounding normal brain (1, 2). Attempts to improve the therapeutic index of brain tumor irradiation by localized dose escalation, altered fractionation, and radiosensitization have failed to affect survival of patients with malignant gliomas significantly (3).

Malignant gliomas are innately hypoxic tumors with strong endogenous expression of hypoxia-inducible factor-1 (HIF-1), vascular endothelial growth factor (VEGF), and VEGF receptors and consequently demonstrate vigorous angiogenesis (4–7). Tumor xenografts, including U87 gliomas, induce VEGF expression in response to irradiation, which may serve to protect their endothelium (8, 9). Furthermore, adding VEGF to cultures of human umbilical endothelial cells enhances radioresistance (8).

Bevacizumab, a humanized monoclonal antibody to VEGF, has been used with safety and clinical success with

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This study has been presented in part at the 2007 Annual Meeting of the American Society of Clinical Oncology (Chicago, June 1–5, 2007) at the 49th Annual Meeting of the American Society for Therapeutic Radiology and Oncology (Los Angeles, October 28–November 1, 2007), at the 16th Annual Meeting of the International Society for Magnetic Resonance in Medicine (Toronto, May 3–9, 2008), and at the 46th Annual Meeting of the American Society of Neuroradiology (New Orleans, May 31–June 5, 2008).

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concomitant chemotherapy in solid tumors (10–12). In recurrent malignant gliomas, it has been used alone and in combination with irinotecan (13–15). Bevacizumab has been successfully used in patients undergoing radiotherapy and chemotherapy for solid tumors, including glioblastomas (16–19). Reasons to combine bevacizumab and RT include the ability of antiangiogenic agents to sensitize tumor endothelium to RT by depletion of VEGF and reduction of its pro-survival signaling (8, 20). It is known that blockade of the VEGF receptor-2 by the monoclonal antibody DC101 can lower the dose of radiation needed to control 50% of tumor xenografts, including the glioblastoma U87 (21). Recent evidence points to a population of radioresistant glioma stem cells residing within vascular niches. These stem cells may be a nidus for regrowth following RT, but, promisingly, this niche can be disrupted by bevacizumab in xenograft brain tumor models (22, 23). Garcia-Barros *et al.* (24) have found that at a single dose threshold of approximately 8–10 Gy, the endothelium in tumor xenografts undergoes apoptosis, legitimizing tumor endothelium as an additional target for radiotherapy. Early clinical trials have shown efficacy of stereotactic high-dose fraction irradiation for paraspinal and brain metastases, lung cancer, pancreatic cancer, and renal cancer (25–32). The threshold for endothelial apoptosis in glioblastoma endothelium is not clear; therefore, we chose an aggressive fractionation scheme to optimize the antiendothelial impact, particularly because bevacizumab could maximize the effects of radiation on this target (8).

We hypothesized that a combined approach of hypofractionated stereotactic radiotherapy (HFSRT) with VEGF inhibition would be an effective strategy for malignant glioma. The study was performed in previously irradiated patients with recurrences as a pilot to assess the safety of bevacizumab used during RT for glioma treatment in general and also the potential of this regimen in particular for patients at all stages of disease. Correlative markers of response to anti-angiogenic therapy are being actively sought (33); perfusion MRI was performed in some patients to assess changes in tumor perfusion after bevacizumab administration.

METHODS AND MATERIALS

Patient eligibility

Patients were recruited from March 2006 to February 2008. Adult patients (aged $\geq$ 18 years) with histopathologic confirmation of malignant glioma who had recurrent or progressive tumor and had failed prior RT were eligible. Brain MRI needed to show a circumscribed enhancing tumor $\leq$ 3.5 cm in its largest diameter; surgery for recurrent malignant glioma could be offered before enrollment in this protocol, but at least 4 weeks had to elapse between the surgery and first dose of bevacizumab. Additional eligibility criteria included Karnofsky Performance Status (KPS) $\geq$ 70, adequate bone marrow function (hemoglobin $\geq$ 10g/dL, absolute neutrophil count $\geq$ 1,500/mm^3, platelet count $\geq$ 100,000/mm^3), adequate liver function (bilirubin < 1.5 times the upper limit of normal [ULN], aspartate aminotransferase and alanine aminotransferase $\leq$ 3 times ULN, alkaline phosphatase $\leq$ 2 times ULN), adequate renal function (blood urea nitrogen and creatinine < 1.5 times ULN), and life expectancy $\geq$ 12 weeks. At least 4 weeks must have elapsed from major surgery, open biopsy, or significant traumatic injury; 1 week from minor surgical procedures; 6 weeks from RT; 4 weeks from prior cytotoxic therapy; and 1 week from noncytotoxic agents; patients must have recovered from all toxicities of prior therapies. Patients who received prior treatment with bevacizumab or who had any history of hypertensive crisis or hypertensive encephalopathy, stroke, transient ischemic attack, symptomatic peripheral vascular disease, or Grade 2 congestive heart failure were excluded. Patients with unstable angina or myocardial infarction within 12 months of enrollment or peptic ulcer, abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months of enrollment were excluded. Additional exclusion criteria included blood pressure > 150/100 mm Hg, ongoing use of anticoagulant or antiplatelet agents, pregnant or nursing women, urine protein:creatinine ratio $\geq$1.0 at baseline, nonhealing wound, ulcer or bone fracture, and prior spontaneous central nervous system (CNS) hemorrhage as determined from clinical history or preoperative CT or MRI scan. Agreement to use an acceptable method of birth control was required for men and women with reproductive potential.

Study design

The study was approved by the Memorial Sloan-Kettering Cancer Center (MSKCC) Institutional Review Board, and written informed consent was obtained from all patients. Baseline evaluation included gadolinium-enhanced brain MRI with gradient echo sequence and perfusion, complete physical and neurological examination, and blood and urine tests within 2 weeks before treatment. Patients received bevacizumab 10 mg/kg every 14 days on Days 1 and 15 of 28-day cycles until treatment failure. After completion of the first cycle, patients underwent a physical and neurological examination and a repeat brain MRI with gradient echo sequence and perfusion for RT planning. If patients had a response or stable findings on MRI, they proceeded to radiation therapy.

Radiation technique

Patients underwent an MRI with 1.5-mm slices within 1 week of a treatment planning CT with 3-mm slices. MRI was fused with the treatment planning CT, and a gross tumor volume (GTV) was designed based on the contrast enhancing lesion. The planning treatment volume (PTV) typically was defined as the GTV plus a 5-mm margin. At the time of the treatment planning CT, an immobilization device was created for each patient. The first 11 patients were immobilized with a Gil-Thomas-Cosman (GTC) frame, and the subsequent 13 patients were immobilized with a 7-point face-mask system. Treatment planning was performed with either the BrainLAB system for the patients with a GTC frame or the MSKCC treatment planning system for patients treated with a facemask. A single isocenter plan was used for each patient, and intensity-modulated radiation therapy with a sliding window technique was used.

A total dose of 30 Gy (6 Gy $\times$ 5 fractions) was prescribed to the 100% isodose line for all plans. HFSRT started on Days 7–10 of Cycle 2 and was delivered over a 2.5-week period. A median number of 9 beams (range, 2–11 beams) were used. The median planning target volume was 34 cm^3 (range, 2–62 cm^3). Brain MRI was repeated every two cycles after cycle 2.

Response and toxicity evaluation

Response to treatment was evaluated by brain MRI and neurological status according to the Macdonald criteria (34). Toxicity was evaluated using the National Cancer Institute's Common Toxicity