Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 5, pp. 2018–2024, 2012

0360-3016/$ - see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2010.12.074

CLINICAL INVESTIGATION **Central Nervous System Tumor**

SAFETY AND EFFICACY OF STEREOTACTIC RADIOSURGERY AND ADJUVANT BEVACIZUMAB IN PATIENTS WITH RECURRENT MALIGNANT GLIOMAS

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Purpose: Patients with recurrent malignant gliomas treated with stereotactic radiosurgery (SRS) and multiagent systemic therapies were reviewed to determine the effects of patient- and treatment-related factors on survival and toxicity.

Methods and Materials: A retrospective analysis was performed on patients with recurrent malignant gliomas treated with salvage SRS from September 2002 to March 2010. All patients had experienced progression after treatment with temozolomide and radiotherapy. Salvage SRS was typically administered only after multiple post-chemoradiation salvage systemic therapies had failed.

Results: 63 patients were treated with SRS for recurrent high-grade glioma; 49 patients had World Health Organization (WHO) Grade 4 disease. Median follow-up was 31 months from primary diagnosis and 7 months from SRS. Median overall survival from primary diagnosis was 41 months for all patients. Median progression-free survival (PFS) and overall survival from SRS (OS-SRS) were 6 and 10 months for all patients, respectively. The 1-year OS-SRS for patients with Grade 4 glioma who received adjuvant (concurrent with or after SRS) bevacizumab was 50% vs. 22% for patients not receiving adjuvant bevacizumab ($p = 0.005$). Median PFS for patients with a WHO Grade 4 glioma who received adjuvant bevacizumab was 5.2 months vs. 2.1 months for patients who did not receive adjuvant bevacizumab ($p = 0.014$). Karnofsky performance status (KPS) and age were not significantly different between treatment groups. Treatment-related Grade 3/4 toxicity for patients receiving and not receiving adjuvant BVZ was 10% and 14%, respectively ($p = 0.58$).On multivariate analysis, the relative risk of death and progression with adjuvant bevacizumab was 0.37 (confidence interval [CI] 0.17–0.82) and 0.45 (CI 0.21–0.97). KPS >70 and age <50 years were significantly associated with improved survival.

Conclusions: The combination of salvage radiosurgery and bevacizumab to treat recurrent malignant gliomas is well tolerated and seems to be associated with improved outcomes. Prospective multiinstitutional studies are required to determine efficacy and long-term toxicity with this approach. © **2012 Elsevier Inc.**

Stereotactic radiosurgery, Glioma, Bevacizumab, Vascular endothelial growth factor-A.

INTRODUCTION

The diagnosis of malignant glioma carries a poor prognosis, with few long-term survivors. Long-term local control in high-grade gliomas is difficult to achieve because of the infiltrating nature of the disease and its relative resistance to targeted and cytotoxic systemic therapies. Standard treatment for a newly diagnosed malignant glioma includes surgical resection followed by radiation therapy with concurrent temozolomide. This treatment yields a median overall survival (OS) of 12 to 15 months (1). Most malignant gliomas recur locally within a year after the completion of initial treatment (2–4), and recurrent disease is difficult to manage, given the morbidity associated with re-excision (5, 6) or large-volume reirradiation (7) and the limited options for systemic therapy (8–10).

Stereotactic radiosurgery (SRS) offers the potential to obtain local control in recurrent high-grade gliomas with minimal morbidity. Several case series, retrospective studies, and prospective studies have shown the potential efficacy and acceptable toxicity of radiosurgery for this disease (4, 11–15). Although radiation is often thought to destroy tumor vasculature, preclinical studies have demonstrated that radiation can paradoxically stimulate angiogenesis via a hypoxia-inducible-factor-1α—mediated pathway (16).

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Presented at the 51st Annual Meeting of the American Society for Radiation Oncology, Chicago, IL, November 1-5, 2009.

Conflict of interest: none.

Received Sept 2, 2010, and in revised form Dec 20, 2010. Accepted for publication Dec 31, 2010.

Thus, it might be useful to combine radiation with an agent that inhibits this paradoxic effect.

Bevacizumab is a humanized murine monoclonal antibody that targets vascular endothelial growth factor-A (VEGF) and inhibits angiogenesis (17, 18). This agent has been approved for use by the U.S. Food and Drug Administration for colorectal cancer, non–small-cell lung cancer, renal cell carcinoma, and recently for recurrent high-grade gliomas. Grade 4 gliomas overexpress VEGF, and higher VEGF expression is associated with a poorer prognosis (19, 20). A recent Phase II trial showed efficacy and minimal toxicity for bevacizumab and irinotecan in the treatment of recurrent high-grade gliomas (21, 22). The current study examined the safety and efficacy of salvage SRS and systemic agents, including bevacizumab, in a retrospective series of patients with recurrent malignant gliomas. These patients were heavily pretreated before undergoing SRS, and most patients received additional courses of systemic therapy immediately after SRS.

METHODS AND MATERIALS

Patient selection

Between September 2002 and March 2010, 63 patients with a diagnosis of a recurrent malignant glioma of the brain were treated with salvage SRS at Duke University Medical Center using a linear accelerator–based system. All patients had pathologic results reviewed and confirmed at our institution. Patients were treated at the time of initial diagnosis with a gross or near total resection followed by adjuvant external-beam radiation and temozolomide. Recurrence was confirmed by surgical pathologic analysis and/or neuroimaging, including magnetic resonance imaging (MRI) and/or positron emission tomography. All patients in the study had experienced progression after primary treatment with concurrent temozolomide and external-beam radiotherapy, and salvage systemic therapy had been unsuccessful in nearly all patients before SRS was performed. Most of the patients received additional systemic therapy after SRS was administered. Only patients with World Health Organization (WHO) Grade 3/4 gliomas were included in the analysis. This retrospective study was approved by the Institutional Review Board of Duke University Medical Center.

SRS technique

All radiosurgical procedures were performed with linear-accelerator–based systems. Radiosurgical procedures before March 2008 were performed using a Radionics X-Knife system (Burlington, MA) with a Brown-Roberts-Wells stereotactic head frame for immobilization. Radiosurgical procedures after March 2008 were performed using a Novalis Tx system (Varian, Palo Alto, CA, and BrainLAB, Munich) with a custom U-frame mask for immobilization, a high-definition micromultileaf collimator, and cone-beam computed tomography for image guidance. All patients underwent a simulation computed tomography scan, which was fused to thin-slice, contrast-enhanced T1-weighted MRI. The gross tumor volume was defined based on T1-weighted contrast-enhanced axial MRI images, occasionally with guidance by positron emission tomography. Before March 2008, patients were treated using multiple arcs with conical collimators or six to nine static conformal beams. After March 2008, lesions 3 cm in diameter or smaller were typically treated using four to five dynamic conformal arcs, and larger lesions were treated with intensity-modulated static beams. Doses were prescribed to the isodose line fully encompassing the planning target volume, and single-fraction treatments were limited by the volume-based guidelines established in Radiation Therapy Oncology Group 90-05. Most patients received a short prophylactic course of dexamethasone after SRS.

Systemic therapies and toxicity

A review of patient medical records was performed to determine which systemic therapies each patient received before and after salvage SRS. Systemic therapy administration was directed by the Preston Robert Tisch Brain Tumor Center at Duke University. Many of the patients included in this analysis had previously been treated according to therapeutic protocols approved by the Institutional Review Board. Many of the systemic agents were given in combination. Toxicity was determined based on the Common Terminology Criteria for Adverse Events (version 4). Toxicity was defined as new symptoms or worsening of previous symptoms after salvage radiosurgery was administered. Symptoms occurring after 3 months from salvage radiosurgery that were attributable to disease progression were excluded.

Statistical analysis

Actuarial survival was calculated using the Kaplan-Meier method. Endpoints for analysis included OS from the time of initial (primary) diagnosis, OS from the time of radiosurgery (OS-SRS), and progression-free survival (PFS) from the time of radiosurgery. Patients were censored at the time of the last follow-up visit. Student's *t* test was used to compare grade, age, Karnofsky performance status (KPS), number of therapies, time from diagnosis to SRS, and tumor volume between groups. Survival curves were compared using the Wilcoxon (Mann-Whitney *U*) rank sum test. Multivariate analyses of OS-SRS and PFS in patients with a WHO Grade 4 glioma were performed using a Cox proportional hazards model. Variables used in the analysis included the use of adjuvant bevacizumab, KPS >70, age >50 years, and tumor volume greater than the median (5 cc). Adjuvant bevacizumab was defined as bevacizumab given at the time of SRS or afterward. Statistical calculations were performed using JMP statistical software (version 8, SAS, Cary, NC). The toxicity analysis included all patients who received salvage radiosurgery for a malignant glioma. Survival analysis focused on the subset of patients with a WHO Grade 4 glioma, for consistency with previous reports.

RESULTS

Patient characteristics

Table 1 shows the characteristics of the patients in the study. Of the 63 patients included in the analysis, 45 were men and 18 were women. The median age at the time of radiosurgery was 47 years (range, 19–76 years). Forty-nine patients had a WHO Grade 4 glioma, and 14 patients had a WHO Grade 3 glioma. Six of the 14 patients with a WHO Grade 3 glioma were originally diagnosed with a WHO Grade 1 or 2 glioma, which later dedifferentiated. All of the patients with a WHO Grade 4 glioma had a *de novo* tumor. The median time from initial diagnosis to salvage SRS was 20 months. The median SRS dose was 15 Gy (range, 12.5–25 Gy). Twelve patients received 25 Gy in five equal fractions, all using the Novalis Tx system, and the remaining patients were treated with a single fraction.