RESEARCH—HUMAN—CLINICAL TRIALS

Phase I Trial of Radiosurgery Dose Escalation Plus Bevacizumab in Patients With Recurrent/Progressive Glioblastoma

Mahmoud Abbassy, MD
Symeon Missios, MD
Gene H. Barnett, MD, MBA
Cathy Brewer, RN
David M. Peereboom, MD
Manmeet Ahluwalia, MD
Gennady Neyman, PhD
Cathy Brewer, RN
David M. Peereboom, MD
Manmeet Ahluwalia, MD
Gennady Neyman, PhD
Michael A. Vogelbaum, MD, PhD

*Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center, Department of Neurosurgery, Neurological Institute, Cleveland Clinic, Cleveland, Ohio; ¶Department of Hematology and Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, Ohio; ‡Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, Ohio; §Department of Neurosurgery, Alexandria University, Alexandria, Egypt

Correspondence: Michael A. Vogelbaum, MD, PhD, Cleveland Clinic, 9500 Euclid Ave, ND40, Cleveland, OH 44195. E-mail: vogelbm@ccf.org

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BACKGROUND: The effectiveness of stereotactic radiosurgery (SRS) for recurrent glioblastoma (rGBM) remains uncertain. SRS has been associated with a high risk of radionecrosis in gliomas.

OBJECTIVE: To determine the safety of dose escalation of single-fraction radiosurgery for rGBM in the setting of bevacizumab therapy.

METHODS: We conducted a prospective trial to determine the safety and synergistic benefit of higher doses of SRS administered with bevacizumab for rGBM. A single dose of bevacizumab was given prior to SRS and continued until progression. Dose-limiting toxicity was evaluated in successive cohorts of 3 patients.

RESULTS: Seven males and 2 females entered the study. The maximum linear diameter of the enhancing tumor was 2.58 cm (2.04-3.09). Prescription dose was escalated from 18 to 22 Gy. The radiosurgery target was chosen before the first dose of bevacizumab, about 1 wk prior to SRS treatment. Pre-SRS bevacizumab treatment was associated with a reduction of the mean volume of the enhancing lesion from 4.7 to 2.86 cm³ on the day of SRS (P = .103). No patient developed an acute side effect related to SRS treatment. The combination of SRS and bevacizumab resulted in a partial response in 3 patients and stable disease in 6 patients. Median progression-free and overall survival were 7.5 and 13 mo, respectively.

CONCLUSION: A single dose of bevacizumab prior to SRS permitted safe prescription dose escalation up to 22 Gy for rGBM. Further evaluation of the efficacy of SRS for rGBM should be performed in the setting of bevacizumab treatment.

KEY WORDS: Recurrent glioblastoma, Bevacizumab, Gamma Knife radiosurgery, Glioblastoma radiosurgery

Glioblastoma (GBM) has been one of the most challenging pathologies in oncology because of its devastating prognosis.1 The median overall survival (OS) remains close to 15 mo, with little change since the establishment of the efficacy of external beam radiation therapy by Walker and colleagues in the 1970s.2,4

The current management of newly diagnosed GBM was defined by a phase III trial from the European Organization of Research and Treatment of Cancer and the National Cancer Institute of Canada, led by Stupp and colleagues.5,6 Patients were randomized to receiving a daily dose of temozolomide (75 mg/m²) concurrently with a radiation therapy (60 Gy/30 fractions) followed by conventional adjuvant temozolomide (200 mg/m²) from the first to the fifth day of a 28-d cycle vs radiation therapy alone. This study demonstrated that the combined radiation and chemotherapy regimen produced a median OS of 14.6 mo vs 12.1 mo in the group that received radiation treatment alone.

Unfortunately, despite the success of this first-line treatment regimen, nearly all patients with GBM experience tumor progression or recurrence. The prognosis at recurrence is grim, with a median OS of 4 mo despite the use of a variety of salvage or investigational chemotherapy regimens.7 The
blood–brain barrier, widespread tumor infiltration, and intrinsic resistance of GBM cells to conventional cytotoxic agents have limited the availability of effective treatments for recurrent GBM.

Vascular endothelial growth factor (VEGF) promotes both angiogenesis and invasion of cancer, and GBM cells express high levels of VEGF. Bevacizumab is humanized monoclonal antibody against VEGF (VEGF-A). The biological effects of bevacizumab include inhibition of the VEGF-induced proliferation of human endothelial cells in Vitro and the decrease of microvessel density and interstitial pressure in tumor xenografts in Vivo. This drug has demonstrated remarkable anticancer activity in renal cell carcinoma, non-small cell lung cancer, and colorectal cancer alone or in combination with other cytotoxic agents because of its synergistic effect. It also delays efficacy in terms of delaying further progression in recurrent GBM.

Radiotherapy is one of the most important and effective adjuvant modalities in the management of GBM. Because patients with recurrent GBM have previously received a high dose of fractionated radiation, stereotactic radiosurgery (SRS) has been considered as an alternative modality at recurrence, as most of the tumor cell density is present in the enhancing area of the tumor and more than 80% of subsequent recurrences are within 2 cm of the enhancing edge. One prospective study (RTOG 93-05), which included SRS before radiotherapy for newly diagnosed GBM, failed to show survival advantage related to the addition of SRS. Of note, the dosing of SRS used in RTOG 93-05 was determined by an earlier Radiation Therapy Oncology Group (RTOG) study (RTOG 90-05) that evaluated the maximum tolerated dose of single fraction SRS with the dose limits defined by radiation toxicity. However, no prospective, randomized studies of SRS in the recurrent setting have been published, and 2 American Society of Therapeutic Radiation and Oncology reviews have concluded that the data are insufficient to make any definitive recommendations regarding the use of this modality.

Adverse radiation effect, or radiation necrosis, is a common complication in the radiation therapy of GBM, with a frequency of 1% to 24%. It is also one of the primary concerns associated with the use of SRS. On the other hand, SRS dosing also has been shown to influence local control of metastatic tumors, so there is interest in increasing the dose of SRS in order to achieve more effective tumor control in gliomas. Bevacizumab has demonstrated remarkable reduction of the radiographic volume of necrosis-associated cerebral edema in patients with radiation necrosis and improvement of their neurological symptoms. We conducted a prospective trial with the aim of determining the safety and the potential synergistic benefit of dose escalation of single fraction SRS when administered in conjunction with bevacizumab to patients with recurrent GBM.

METHODS

Eligibility and Exclusion Criteria

Patients with recurrent, histologically proven GBM were included in this phase I trial. Inclusion criteria also included completion of the standard concurrent conventional fractionated radiotherapy plus daily temozolomide (75 mg/m²/day), and radiographic evidence of tumor recurrence/progression as defined by a contrast-enhanced magnetic resonance imaging (MRI) at least 3 mo after the completion of the radiation therapy. All patients were required to have a unifocal enhancing mass with maximum diameter between 2 and 3 cm and a Karnofsky performance score of >60 at the beginning of the study. Patients were not permitted to receive any chemotherapeutic or investigational agents within 6 wk of registration.

Exclusion criteria included the following: prior invasive malignancy unless disease free for ≥3 yr, presence of more than one focus of enhancement, involvement of the brain stem, prior use of any intratumoral or intracavitary chemotherapeutic agents/wafers, prior treatment with bevacizumab, or severe, active comorbidity.

An Institutional Review Board (IRB)-approved, study-specific written informed consent was signed by all patients. The study was registered on ClinicalTrials.gov.

Administration of Bevacizumab and SRS Prescription Dose Determination

Patients received a single dose of bevacizumab (10 mg/kg) followed within 10 to 14 d by SRS.

SRS dose escalation was performed with a 3 + 3 design. The first cohort was started at 18 Gy, which is considered the maximum tolerated dose as defined by RTOG 90-05, and escalated by 2 Gy for each cohort, with a planned maximum of 3 cohorts if none develop dose-limiting toxicity.

SRS Technique and Target Volume Determination

All patients were treated using the Gamma Knife Perfexion unit (Elekta, Stockholm, Sweden). An MRI obtained within 1 wk before administration of bevacizumab was used for SRS target definition and planning to avoid undertreating the bulk tumor due to the pseudoresponse that is often observed following the administration of bevacizumab. The pre-bevacizumab MRI was coregistered to a stereotactic localization computed tomography (CT) done on the day of treatment after the Leksell frame had been placed. An MRI was also performed after frame placement. Planning was performed and isodose distributions were generated with the use of Gamma Plan (Elekta). Dose prescription was set to the lowest isodose line that achieved 100% coverage of the target volume (enhancing tumor margin), with a minimum prescription isodose line of the 50th percentile to maintain a conformity index of less than or equal to 2.

After SRS treatment, patients were continued on a conventional schedule of bevacizumab (10 mg/kg IV every 2 wk). Toxicity evaluation was done by clinical assessment and radiological evaluation. Clinical assessment for radiation toxicity was performed using the Common Terminology Criteria of Adverse Events version 4.0 (US Department of Health and Human Services, National Institutes of Health, 2009). Unacceptable toxicity was considered to be irreversible grade 3 (severe), any grade 4 (life threatening), or grade 5 (fatal) central nervous system toxicity that was considered to be related to radiosurgery occurring within 90 d of protocol radiosurgery. Radiological evaluation was based upon the evaluation of brain MRIs. The first follow-up MRI was done 6 wk after treatment and continued every 3 mo until progression. Dose escalation was not performed until all patients in each cohort had been evaluated for at least 90 d.
### TABLE 1. Patient Demographic and Baseline Clinical Data

<table>
<thead>
<tr>
<th>Factor</th>
<th>Cohort 1 (18 Gy) n = 3</th>
<th>Cohort 2 (20 Gy) n = 3</th>
<th>Cohort 3 (22 Gy) n = 3</th>
<th>All patients N = 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in yr mean (range)</td>
<td>52 (28-71)</td>
<td>48 (41-58)</td>
<td>58 (59-65)</td>
<td>52.7 (28-71)</td>
</tr>
<tr>
<td>Gender M:F</td>
<td>3:0</td>
<td>2:1</td>
<td>2:1</td>
<td>7:2</td>
</tr>
<tr>
<td>Time from primary diagnosis to enrollment</td>
<td>49.7</td>
<td>19.8</td>
<td>12.7</td>
<td>27.4</td>
</tr>
<tr>
<td>mean in mo (range)</td>
<td>(40.1-66.7)</td>
<td>(12.7-31.8)</td>
<td>(9.0-17.5)</td>
<td>(9.0-66.7)</td>
</tr>
<tr>
<td>Progression free survival after radiosurgery</td>
<td>27.5</td>
<td>12.4</td>
<td>8.6</td>
<td>9.7</td>
</tr>
<tr>
<td>median in mo (range)</td>
<td>(3.1-57.1)</td>
<td>(3.4-12.5)</td>
<td>(6.8-9.7)</td>
<td>(3.1-57.1)</td>
</tr>
<tr>
<td>Total volume of visible disease* on</td>
<td>26.5</td>
<td>63.9</td>
<td>95.5</td>
<td>50.9</td>
</tr>
<tr>
<td>pre-bevacizumab MRI mean in cm³ (range)</td>
<td>(15.2-31.7)</td>
<td>(24.6-130.6)</td>
<td>(34.5-67.3)</td>
<td>(15.2-130.6)</td>
</tr>
<tr>
<td>Sum of 2 dimensions on pre-bevacizumab MRI</td>
<td>31.0</td>
<td>53.7</td>
<td>44.0</td>
<td>42.9</td>
</tr>
<tr>
<td>mean in cm (range)</td>
<td>(25.0-38.0)</td>
<td>(47.0-63.0)</td>
<td>(35.0-60.0)</td>
<td>(25.0-63.0)</td>
</tr>
<tr>
<td>KPS before enrollment median (range)</td>
<td>90</td>
<td>80</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>(70-90)</td>
<td>(70-90)</td>
<td>(70-90)</td>
<td>(70-90)</td>
</tr>
</tbody>
</table>

*Total volume of visible disease: enhancing T1 + T2 hyperintense region

### TABLE 2. SRS Planning Data

<table>
<thead>
<tr>
<th>Factor</th>
<th>Cohort 1 (18 Gy) n = 3</th>
<th>Cohort 2 (20 Gy) n = 3</th>
<th>Cohort 3 (22 Gy) n = 3</th>
<th>All patients N = 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment volume at prescription dose mean cm³ (range)</td>
<td>4.4 (2.1-8.8)</td>
<td>5.13 (4.38-6.47)</td>
<td>4.64 (2.54-6.62)</td>
<td>4.72 (2.1-8.8)</td>
</tr>
<tr>
<td>Maximum dimension of target mean in cm (range)</td>
<td>2.35 (2.10-2.74)</td>
<td>2.70 (2.53-2.90)</td>
<td>2.69 (2.04-3.09)</td>
<td>2.58 (2.04-3.09)</td>
</tr>
<tr>
<td>Isodoseline mean percentile (range)</td>
<td>54.0 (51.0-56.0)</td>
<td>52.3 (50.0-55.0)</td>
<td>50.3 (50.0-51.0)</td>
<td>52.2 (50.56)</td>
</tr>
<tr>
<td>Conformality ratio mean (range)</td>
<td>1.64 (1.35-1.91)</td>
<td>1.71 (1.54-1.98)</td>
<td>1.53 (1.32-1.78)</td>
<td>1.63 (1.32-1.98)</td>
</tr>
<tr>
<td>SRS side effects</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

### Outcomes Evaluations

Response to treatment was determined according to the revised assessment in neurooncology (RANO) criteria by way of volumetric measurement of the total volume of visible disease, which included the enhancing lesion on T1 plus the surrounding T2 hyperintensity. OS and progression-free survival (PFS) were calculated from the time of study entry.

### Statistical Analysis

Statistical analysis was performed with the use of paired samples of t-test. OS and PFS were calculated using the Kaplan–Meier method.

### RESULTS

Seven males and 2 females entered the study. Mean and median ages were 52.7 and 55.5 yr (range: 28-71). The mean and median times from the initial diagnosis of GBM to enrollment were 27.4 and 17.8 mo (9.0-66.7; Table 1).

After initial surgery and conventional concomitant chemoradiotherapy (with a total radiotherapy dose of 60 Gy), the median PFS was 9.7 mo (3.1-57.1).

The mean maximum linear diameter of the enhancing recurrent tumor was 2.58 cm (2.04-3.09). The recurrences for all patients were within the previous external beam radiotherapy field in 8 out of 9 cases. The prescription dose for the first cohort was 18 Gy, and dose escalation occurred to the protocol-defined limit of 22 Gy. Prescription doses were set at the margin of the enhancing tumor, which resulted in a mean isodoseline of 52.2% (50%-56%) and a mean conformality ratio of 1.63 (1.32-1.98; Table 2).

No patient developed an acute side effect related to SRS treatment, and hence only 3 patients were treated in each dose cohort (Table 2). Because we did not plan to escalate beyond a prescription dose of 22 Gy, our results indicate that the maximum tolerated dose for SRS in the setting of bevacizumab is at least 22 Gy.
TABLE 3. Bevacizumab Treatment Data

<table>
<thead>
<tr>
<th>Factor</th>
<th>Cohort 1 (18 Gy) n = 3</th>
<th>Cohort 2 (20 Gy) n = 3</th>
<th>Cohort 3 (22 Gy) n = 3</th>
<th>All patients N = 9a</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPS at first cycle</td>
<td>90 (70 to 90)</td>
<td>80 (70 to 90)</td>
<td>80 (70 to 90)</td>
<td>80 (70 to 90)</td>
</tr>
<tr>
<td>median (range)</td>
<td>4 (4 to 14)</td>
<td>6 (6 to 8)</td>
<td>7 (6 to 7)</td>
<td>6 (4 to 14)</td>
</tr>
<tr>
<td>Number of cycles</td>
<td>90 (70 to 90)</td>
<td>70 (70 to 90)</td>
<td>80 (60 to 90)</td>
<td>80 (60 to 90)</td>
</tr>
<tr>
<td>median (range)</td>
<td>1.8 (0.5 to 3.6)</td>
<td>3.7 (1.7 to 6.3)</td>
<td>3.4 (1.3 to 7.0)</td>
<td>2.9 (0.5 to 7.0)</td>
</tr>
<tr>
<td>Enhancing tumor volume after first dose of bevacizumab</td>
<td>–60.1 (% range)</td>
<td>–28.8 (% range)</td>
<td>–33.7 (% range)</td>
<td>–40.8 (% range)</td>
</tr>
<tr>
<td>mean cm³</td>
<td>(–78.3 to –42.9)</td>
<td>(–67.5 to 43.8)</td>
<td>(–58.0 to 5.7)</td>
<td>(–78.3 to 43.8)</td>
</tr>
<tr>
<td>Percent change in enhancing volume after first dose of bevacizumab</td>
<td>–60.1</td>
<td>–28.8</td>
<td>–33.7</td>
<td>–40.8</td>
</tr>
<tr>
<td>mean % (range)</td>
<td>(–78.3 to –42.9)</td>
<td>(–67.5 to 43.8)</td>
<td>(–58.0 to 5.7)</td>
<td>(–78.3 to 43.8)</td>
</tr>
<tr>
<td>Side effects</td>
<td>Fatigue</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Cognitive</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Seizure</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephrotic</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension Tinnitus</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reason for termination</td>
<td>Side effects</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Progression</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>7</td>
</tr>
</tbody>
</table>

KPS, Karnofsky performance score

*P-value = .103

Bevacizumab treatment was associated with the following side effects: fatigue (5 patients), cognitive dysfunction (3), proteinuria (1 patient), nephrotic syndrome (1 patient), and hypertension (1 patient). Other complications that were considered not to be related to SRS or bevacizumab included seizures in a patient with pre-existing seizure disorder and tinnitus. Bevacizumab was terminated in 2 patients due to side effects (1 persistent, generalized weakness, 1 wound dehiscence 7 mo after prior cranial surgery). The other 7 patients terminated bevacizumab due to progressive disease (Table 3).

The radiosurgery target was determined on an MRI performed immediately before the first dose of bevacizumab, about 1 wk prior to the SRS treatment. A second MRI was performed on the day of treatment, but this exam was not used to plan the treatment. In comparing these 2 MRIs, we found that the single dose of bevacizumab resulted in a reduction of the mean volume of the enhancing lesion from 4.7 to 2.86 cm³ on the day of SRS (P = .103; Table 3). The first MRI after SRS was obtained at a median of 45 d (42-47). Evaluation of this first post-SRS MRI indicated that the combination of SRS and bevacizumab resulted in a partial response (by RANO) in 3 patients and stable disease in 6 patients (Table 4). The mean change of the total tumor volume (volume of all visible disease including the enhancing lesion and T2 hyperintensity) was −44.9% (−96.4 to 16.1; Figure 1).

The median PFS and OS were 7.5 mo and 13 mo, respectively (Figure 2). The pattern of recurrence was variable: 5 patients had local recurrence within the field of radiosurgery (55.6%), 3 patients had diffuse enhancement outside of the radiosurgical target (33.3%), and 1 patient had multifocal recurrence (11.1%). For the patients with in-SRS field recurrence, the distinction between radiation necrosis and tumor recurrence was made with use of cerebral blood volume (MRI perfusion) imaging in 3 out of 5 cases and with repeat radiographic imaging in 2 out of 5 cases. Each of these cases was reviewed by a multidisciplinary brain tumor board.

DISCUSSION

SRS is a conformal method for delivering high-dose radiation in a single session. This conformal approach is intended to deliver an ablative dose of radiation to the target, in this case the enhancing tumor mass, while minimizing the likely neurocognitive effects that would result from reirradiation of GBM.33 Although RTOG 93-05 did not show any survival advantage associated with the use of SRS for newly diagnosed GBM,18 many other retrospective and prospective studies have demonstrated favorable local control and median OS (13-26 mo) benefit in patients with recurrent high-grade gliomas. These results have
TABLE 4. Follow-up Data

<table>
<thead>
<tr>
<th>Factor</th>
<th>Cohort 1 (18 Gy)</th>
<th>Cohort 2 (20 Gy)</th>
<th>Cohort 3 (22 Gy)</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>TV at first follow-up MRI mean in cm³ (range)</td>
<td>16.1 (7.5 to 27.6)</td>
<td>33.8 (0.9 to 42.5)</td>
<td>33.6 (19.0 to 59.9)</td>
<td>27.8 (0.9 to 59.9)</td>
</tr>
<tr>
<td>% Change in TV compared to pre-bevacizumab MRI mean (range)</td>
<td>–41.4 (–58.6 to –15.1)</td>
<td>–45.3 (–96.4 to 16.1)</td>
<td>–48.0 (–61.9 to –37.3)</td>
<td>–44.9 (–96.4 to 16.1)</td>
</tr>
<tr>
<td>Sum of 2D mean in cm (range)</td>
<td>16.0 (15.0 to 17.0)</td>
<td>32.0 (26.0 to 40.0)</td>
<td>19.3 (13.0 to 26.0)</td>
<td>22.4 (13.0 to 40.0)</td>
</tr>
<tr>
<td>% Change in the 2D compared to pre-bevacizumab MRI mean (range)</td>
<td>–47.1 (–55.3 to –36.0)</td>
<td>–40.6 (–49.0 to –36.2)</td>
<td>–50 (–78.3 to –25.7)</td>
<td>–46.2 (–78.3 to –25.7)</td>
</tr>
<tr>
<td>Response according to RANO criteria</td>
<td>PR 2 / SD 1</td>
<td>PR 0 / SD 3</td>
<td>PR 1 / SD 2</td>
<td>PR 3 / SD 6</td>
</tr>
</tbody>
</table>

PR, partial response; RANO, response assessment in neurooncology; SD, stable disease; TV, total volume of visible disease which includes T1 enhancement and T2 hyperintense region; 2D, 2 perpendicular dimensions of enhancing disease

*P-value = .017
#P-value = .001

FIGURE 1. Left: pre-bevacizumab/radiosurgery T1 + Gd and T2-weighted axial MRI images. Center: day of SRS axial T1 + Gd MRI showing the 22 Gy isodose line. Right: follow-up T1 + Gd and T2-weighted axial MRI images obtained 45 days after the SRS.
helped to maintain interest in the use of SRS for recurrent high-grade glioma, especially in patients with unifocal GBM. 18,34-45

Radiation necrosis is a common complication associated with radiotherapy and radiosurgery. VEGF is considered the principal mediator for the dysfunction of the blood–brain barrier and the development of the cerebral edema that is associated with radiation necrosis. 29,46 This association between VEGF release and risk of radiation necrosis, and the ability of bevacizumab to sequester VEGF, has led to interest in the use of bevacizumab to reduce the side effects associated with the radiation therapy in general and radiosurgery in particular. 47,48

The first description of the use of reirradiation and bevacizumab in the management of recurrent GBM came in 2009 from Gutin et al, 47 who showed a median PFS and OS for 25 patients of 7.3 and 12.4 mo, respectively. In 2011, Cuneo et al 49 evaluated patients who received bevacizumab before or after linear accelerator-based SRS and compared their outcomes to those of patients who underwent radiosurgery alone. These investigators found a significant difference in PFS and OS favoring the patients who received bevacizumab (median PFS was 5.2 vs 2.1 mo, and median OS was 11.2 vs 3.9 mo). In 2012, Park et al 55 also performed a salvage treatment of recurrent GBM with a combination of bevacizumab and SRS in a case-control study. The control group included patients who received SRS alone. The median prescription dose was 16 Gy (13-18 Gy) with a 50% prescription isodose. In that study, the bevacizumab was administered after the SRS, as opposed to the pre- and post-SRS bevacizumab dosing that we used in our study. A significant improvement in survival was observed in the bevacizumab arm in comparison to the control group. The reported PFS and OS results were 14.9 mo and 17.9 mo in the bevacizumab-SRS-treated patients compared to 6.7 mo and 12.2 mo in the SRS only control group (P values: .035 and .05).

We hypothesized that radioprotective effect of bevacizumab would allow us to use a higher prescription dose for the SRS treatment, and this study was constructed to evaluate the safety of dose escalation. Specifically, we provided the first dose of bevacizumab before radiosurgery. While we further hypothesized that the use of pre-SRS bevacizumab potentially could improve the efficacy of SRS due to vascular normalization, 50 this study...
was not sufficiently powered or designed to specifically test that hypothesis. One of the anticipated consequences of the use of pre-SRS bevacizumab was that the enhancement characteristics of the target tumor would change in the interval between the first dose of bevacizumab and the SRS treatment, thereby complicating target definition on the day of SRS.51,52 Accordingly, we used the pre-bevacizumab MRI coregistered to the CT scan obtained on the day of SRS (with the frame in place) for target delineation. We also obtained an MRI on the day of treatment, and saw a notable trend towards a decreased size of the enhancing volume; however, this observation did not reach statistical significance, likely due to the small sample size and lack of consistency of the effect.

Radiographic response criteria developed by Macdonald et al53 in 1990 have been widely used for the determination of progression in cases of high-grade gliomas. These criteria, which were based upon CT imaging, include 2-dimensional measurements of the enhancing lesion only. They do not include an assessment of the nonenhancing part of the tumor.32 Also, they were developed prior to the use of bevacizumab and the ensuing recognition that the antiangiogenic effect of bevacizumab can markedly decrease contrast enhancement as early as 1 to 2 d after the initiation of treatment due to normalization of the permeability of the abnormal tumor vessels, thereby resulting in what is termed “pseudoprogression.”51,52 Recognition of these limitations to the Macdonald criteria led to the development of the RANO response assessment criteria.32 The RANO criteria include consideration of the use of corticosteroids and the progression of edema on fluid-attenuated inversion-recovery/T2 sequences, and they provide a way to assess patients with multifocal or diffuse disease. These considerations have led us to evaluate the total volume of disease (enhancing volume plus volume of edema on T2 sequence) for the determination of the initial response.

The median OS in the current study was 13 mo, which is comparable to other studies conducted on the efficacy of SRS as a salvage treatment of high-grade gliomas.38,39,43-45 This study was not designed to evaluate the full benefit of combined bevacizumab and SRS on survival, but it provides evidence that a higher dose than that specified in RTOG 90-05 can be used safely, and it provides the basis for further evaluation of the efficacy of this approach in a phase 2 trial. While this study was restricted to patients with recurrent GBM, one could reasonably hypothesize that the protective effect of bevacizumab could extend to SRS dose escalation for brain metastases, particularly those larger than 2 cm or for those in the brainstem, where dose reduction is typically performed.

CONCLUSION

Bevacizumab prior to SRS for recurrent GBM permitted safe SRS prescription dose escalation to 22 Gy for a target volume of 2 to 3 cm in maximum diameter. Furthermore, we observed a 33% partial response rate and 67% stable disease rate, with use of the RANO criteria. These results provide justification for a phase 2 study of the overall efficacy of this higher SRS dose, when given with bevacizumab before and after SRS, in recurrent GBM.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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