Glioblastoma is the most common primary intracranial tumor, accounting for approximately 17,000 cases per year in the US. The standard treatment generally involves maximum safe resection, followed by radiation therapy and concomitant temozolomide therapy, usually with temozolomide. The results of the EORTC trial showed that the median PFS and median OS in newly diagnosed patients treated with this approach are 6.9 and 14.6 months, respectively.22

Glioblastoma is highly angiogenic and is known to express VEGF. For this reason, VEGF has been identified as an important therapeutic target in the context of GBM growth and clinical or radiological progression. Bevacizumab (Avastin, Genentech) is a monoclonal antibody against VEGF-A. Currently, it is approved by the Food and Drug Administration for the treatment of recurrent GBM. The median OS in patients with recurrent GBM treated with bevacizumab in Phase II studies ranges between 8 and 9 months.4,19,23

A clinical trial of bevacizumab, temozolomide, and radiation for newly diagnosed glioblastoma

Clinical article

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Object. The presence of angiogenesis is a hallmark of glioblastoma (GBM). Vascular endothelial growth factor (VEGF), which drives angiogenesis, provides an additional target for conventional therapy. The authors conducted a prospective clinical trial to test the effectiveness of bevacizumab, an inhibitor of VEGF, in newly diagnosed GBM.

Methods. From 2006 through 2010, 51 eligible patients with newly diagnosed GBM were treated with involved-field radiation therapy and concomitant temozolomide (75 mg/m² daily for 42 days) along with bevacizumab (10 mg/kg every 2 weeks), starting 29 days after surgery. This was followed by 6 cycles of adjuvant temozolomide therapy (150 mg/m² on Days 1–7 of a 28-day cycle) with bevacizumab administered at 10 mg/kg on Days 8 and 22 of each 28-day cycle.

Results. The 6- and 12-month progression-free survival (PFS) rates were 85.1% and 51%, respectively. The 12- and 24-month overall survival (OS) rates were 85.1% and 42.5%, respectively. Grade III/IV toxicities were noted in 10 patients (19.6%). No treatment-related deaths were observed. Asymptomatic intracranial bleeding was noted in 5 patients.

Conclusions. The addition of bevacizumab to conventional therapy in newly diagnosed GBM appears to improve both PFS and OS in patients with newly diagnosed GBM, with acceptable morbidity. A shift toward diffuse relapse was noted in a significant number of patients. Ongoing Phase III clinical trials will show the true benefit of this antiangiogenic approach. (DOI: 10.3171/2011.9.JNS11656)

Key Words • glioblastoma • bevacizumab • radiation therapy • temozolomide • oncology

Abbreviations used in this paper: EORTC = European Organization for Research and Treatment of Cancer; GBM = glioblastoma; KPS = Karnofsky Performance Scale; OS = overall survival; PFS = progression-free survival; UCLA = University of California, Los Angeles; VEGF = vascular endothelial growth factor.
patients with GBM treated with radiation, temozolomide, and bevacizumab was 19.6 months.\textsuperscript{11} This regimen was generally well tolerated with few dose-limiting toxicities.\textsuperscript{11} Preliminary data from our own institution looking at the feasibility of this regimen resulted in a 1-year PFS of 59.3\% and 1-year OS of 86.7\% with acceptable morbidity.\textsuperscript{15} In light of these promising results, we conducted a clinical trial to test the feasibility of combining bevacizumab with radiation therapy and temozolomide in patients with newly diagnosed GBM.

Methods

This was an open-label, single-arm clinical trial involving patients with newly diagnosed, histologically proven GBM, who were treated with involved-field radiation therapy, temozolomide, and bevacizumab between 2006 and 2010. Institutional review board approval was obtained for this study at Overlook Hospital (Summit, New Jersey). All eligible patients were at least 18 years of age and had a KPS score of 70 or higher. Patients who were pregnant, who had a history of myocardial infarct or stroke within 6 months of diagnosis or other significant vascular disease, had infection, or who had significant trauma within 28 days prior to receiving the first dose of bevacizumab were excluded from this study.

All patients underwent maximum surgical debulking with functional preservation. Involved-field radiation therapy was delivered with conformal technique to the surgical bed with a 2-cm margin at 1.8 Gy/fraction, to a total dose of 59.4 Gy. Radiation therapy, temozolomide (Temodar, Schering-Plough) treatment, and bevacizumab treatment were all initiated 29 days after surgery. Bevacizumab was administered intravenously 29 days after surgery at 10 mg/kg over 30 minutes every 2 weeks, and temozolomide was administered orally at 75 mg/m\textsuperscript{2} from Day 1 to Day 42 (that is, from 29 to 70 days after surgery). If postradiation MR imaging showed improvement or no change and the patient was clearly stable, treatment with temozolomide and bevacizumab was continued as follows: temozolomide was administered at 150 mg/m\textsuperscript{2} on Days 1–7 of a 28-day cycle for 6 cycles, and bevacizumab was administered on Days 8 and 22 of each cycle.

To assess response to therapy, we employed modified Macdonald criteria using maximum cross-section T1-weighted contrast-enhanced MR images, as well as T2-weighted FLAIR sequences. Progressive disease was defined as a 25\% or greater increase in contrast-enhancement, T2 FLAIR signal, appearance of a new lesion, or neurological deterioration that could not be attributed to other causes. The National Cancer Institute Common Toxicity Criteria (Version 3.0) were used to grade toxicity. Grade IV toxicities were considered a contraindication to treatment with further cycles. Evidence of temozolomide allergy, including rash, was considered a contraindication to further temozolomide chemotherapy.

The primary end point of the study was PFS, calculated from the time of original diagnosis. Assuming that the PFS rate at 6 months is binomial, a maximum of 54 patients was needed with an alpha of 0.05 and 80\% power. The secondary end points were toxicity, radiographic response, OS, and pattern of relapse. Kaplan-Meier estimates were used to calculate PFS and OS. A p value < 0.05 was considered statistically significant. All analyses were performed using the PASW software program, version 18 (SPSS, Inc.).

Results

Patient Characteristics

Fifty-one patients who met all the eligibility criteria were enrolled in the study. Seventeen patients who were screened after a diagnosis of GBM during the study period did not meet the criteria and were excluded from the study. Patient demographics and treatment characteristics are listed in Table 1. All patients had tumors with WHO Grade IV histology. The median patient age was 54 years. Gross-total resection was achieved in 36 patients (70.6\%). The median KPS score at the start of treatment was 90 (range 70–100). All but one of the patients completed planned radiation without any interruption. The median number of bevacizumab cycles given, defined as 2 infusions per cycle, was 7 (range 1–14 cycles).

Toxicity

Table 2 summarizes the selected Grade II, III, and IV toxicities observed during the course of treatment. Seven patients (13.7\%) had Grade III toxicities and 3 (5.9\%) had Grade IV. There was no symptomatic intracranial bleeding, although blood products were observed on the MR images obtained in 5 patients after the start of treatment. Involved-field radiation therapy was not stopped in any patient due to toxicity, but treatment was temporarily stopped and later resumed in 1 patient with severe thrombocytopenia. Chemotherapy was stopped in 8 patients due to toxicities experienced during the study, namely thrombocytopenia (in 1 patient), pulmonary embolism (in 1), deep vein thrombosis (in 2), and temozolomide allergy (in 4).

Progression-Free Survival

Thirty-five (68.6\%) of 51 patients have experienced relapse as of this writing. The median PFS was 13 months (Fig. 1). The 6- and 12-month PFS rates were 85.1\% and 51\%, respectively.

Overall Survival

Twenty-one patients (41.2\%) have died. The median overall duration of survival was 23 months (Fig. 2). The 12- and 24-month OS rates were 85.1\% and 42.5\%, respectively.

Relapse Pattern

Of the 35 patients who experienced a relapse, 20 (57.1\%) had diffuse recurrence, defined by the presence of contrast-enhancing disease and/or FLAIR changes in more than 2 lobes. The values for PFS and OS in patients with diffuse relapse did not differ significantly from those in patients with local relapse. Neurological morbidity and quality of life were also similar in both groups.
Bevacizumab for newly diagnosed glioblastoma

Table 1: Summary of patient characteristics in 51 cases

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
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<td></td>
</tr>
<tr>
<td>male</td>
<td>31</td>
</tr>
<tr>
<td>female</td>
<td>20</td>
</tr>
<tr>
<td>age (yrs)</td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>54</td>
</tr>
<tr>
<td>range</td>
<td>26–75</td>
</tr>
<tr>
<td>op</td>
<td></td>
</tr>
<tr>
<td>GTR</td>
<td>36</td>
</tr>
<tr>
<td>STR</td>
<td>9</td>
</tr>
<tr>
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<tr>
<td>KPS score</td>
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</tr>
<tr>
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<td>90</td>
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<tr>
<td>range</td>
<td>70–100</td>
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<tr>
<td>no. of bevacizumab cycles</td>
<td></td>
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<tr>
<td>median</td>
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</tr>
<tr>
<td>range</td>
<td>1–14</td>
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<tr>
<td>duration of FU (mos)</td>
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</tr>
<tr>
<td>median</td>
<td>16</td>
</tr>
<tr>
<td>range</td>
<td>2–34</td>
</tr>
</tbody>
</table>

* Values represent number of patients unless otherwise indicated. Abbreviations: FU = follow-up; GTR = gross-total resection; STR = subtotal resection.

Table 2: Summary of toxicities in 51 patients

<table>
<thead>
<tr>
<th>Sign or Sx</th>
<th>Grade II</th>
<th>Grade III</th>
<th>Grade IV</th>
<th>Combined</th>
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<tr>
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<td>0</td>
<td>1</td>
<td>0</td>
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<tr>
<td>bleeding</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>5 (9.8)</td>
</tr>
<tr>
<td>thrombocytopenia</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>5 (9.8)</td>
</tr>
<tr>
<td>nausea</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>deep vein thrombosis</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2 (3.9)</td>
</tr>
<tr>
<td>pulmonary embolism</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>drug allergy</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>4 (7.8)</td>
</tr>
</tbody>
</table>

* Values in parentheses represent percentages of cases.

Discussion

The prognosis for patients diagnosed with high-grade gliomas, including GBM, continues to remain poor. The addition of temozolomide has improved both PFS and OS, but it has brought only a small improvement in comparison to the survival outcomes in patients who were treated with radiation therapy only.22 Interest in VEGF and other angiogenic factors started with Folkman’s seminal paper in 1971.3 Since then, the role of VEGF in GBM has been investigated heavily in both in vitro and in vivo settings. Expression of VEGF has been shown to correlate heavily with vascularity in high-grade astrocytomas, most notably in GBM.14 Levels of VEGF-A were shown to be approximately 30-fold higher in GBM than in lower-grade astrocytic tumors.22 Devascularization in these tumors likely contributes to the increased levels of VEGF observed.22 Preclinical data from Massachusetts General Hospital demonstrated that administration of bevacizumab contributes to the pruning of abnormal blood vessels, as well as the normalization of vasculature in GBM.4 Phase I/II trials were initiated, investigating the feasibility and efficacy of bevacizumab in recurrent GBM. Studies conducted at Duke, UCLA, and the National Cancer Institute, as well as our own institution, demonstrated an improvement in PFS and OS in patients treated with bevacizumab and irinotecan.10,16,19,23 Preclinical and clinical data on bevacizumab have shown the effect of radiosensitization in various solid tumors.24 There is the possibility that it could potentiate the effects of involved-field radiation therapy as well as enhance chemosensitivity by inhibiting the action of VEGF, a phenomenon that has been shown in various solid tumors.2,24 In addition, reducing hypoxia at initial diagnosis through the normalization of blood vessels with bevacizumab could produce a more pronounced decrease in angiogenesis.25 Vessel normalization could also allow for better drug delivery by reducing vessel permeability and improving perfusion.8 However, normalization is sustained only within a short window of opportunity, during which radiation has been found to be especially effective.9

This lends support to the idea of using antiangiogenic therapies in frontline chemoradiation treatment. Our preliminary data investigating the feasibility of combining bevacizumab with chemoradiation in 15 patients with newly diagnosed GBM showed a 12-month PFS rate of 59.3% and a 12-month OS rate of 86.7%.15 An update to these data in 25 patients showed a median PFS of 12 months and a median OS of 24 months, with a 12-month OS rate of 85%.6 The mature results of our trial and a study recently conducted at UCLA have shown a median
PFS of 13 and 13.6 months, respectively. This reflects a near doubling of PFS compared with the 6.9 months in the EORTC trial of Stupp and colleagues, in which temozolomide was used alone. However, the improvement in OS seen in our study and the UCLA study (with a median OS of 23 and 19.6 months, respectively) was more moderate relative to the EORTC trial (median OS of 14.6 months).

In several well-done Phase II and retrospective trials, use of bevacizumab in recurrent gliomas in combination with irinotecan resulted in a radiological response rate of 28%–71%. The median PFS ranged from 4 to 6 months, and the median OS ranged from 8 to 10 months. Additionally, patients treated with bevacizumab were able to maintain a stable steroid dosage or decrease the dosage over time. However, the benefit may not be due to the antitumor effects of bevacizumab, but rather, to its ability to reduce edema. To maximize the radiation-sensitizing effects of bevacizumab observed in preclinical trials, we chose to use it in an upfront setting in combination with radiation and temozolomide in patients with newly diagnosed GBM.

In the present study, 57% of patients had a diffuse pattern of recurrence compared with a historical rate of around 10% in patients treated with conventional chemotherapy alone. In recurrent high-grade glioma treated with bevacizumab therapy, we have reported an incidence of diffuse recurrence of 48.1%. Other studies have found incidence rates as high as 31%, with 11% of these recurrences manifesting as non–contrast-enhancing tumors. These results suggest that antiangiogenic therapy may increase invasiveness. A preclinical study by Nowicki and colleagues demonstrated that lithium blocks invasion in glioma cells by blocking glycogen synthase kinase-3 (GSK-3). This forms the basis of an ongoing Phase II trial at our institution, investigating the use of lithium in combination with chemotherapy with temozolomide and bevacizumab, in patients with newly diagnosed GBM.

The Radiation Therapy Oncology Group is currently conducting a Phase III randomized trial investigating the efficacy of bevacizumab in combination with upfront chemoradiation treatment with temozolomide in more than 900 patients with newly diagnosed malignant astrocytomas. Additionally, a large Phase III trial involving over 900 patients is currently being conducted by Roche (AVAglio, BO21990, NCT00943826) to evaluate bevacizumab as frontline therapy. Mature data from these adequately powered studies should be available in the next 2–3 years. These studies will help determine the true benefit of using bevacizumab in newly diagnosed patients.

Conclusions

The use of bevacizumab in conjunction with radiation and chemotherapy in patients with newly diagnosed GBM is feasible. Both PFS and OS appeared to improve, with acceptable morbidity, in this clinical trial. A shift toward diffuse relapse was noted in a significant number of patients, but the clinical significance is unclear at this time. Ongoing large Phase III clinical trials will show the true benefit of such an antiangiogenic approach.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Narayana, D Gruber, M Gruber. Acquisition of data: D Gruber, Golfinos, Parker, Zagzag, Eagan, M Gruber. Analysis and interpretation of data: D Gruber, Kunnakkat, Raza, M Gruber. Drafting the article: Narayana, D Gruber, Kunnakkat, Raza, M Gruber. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Narayana. Statistical analysis: Kunnakkat, Raza, M Gruber. Administrative/technical/material support: Narayana, D Gruber, Golfinos, Parker, Zagzag, Eagan, M Gruber. Study supervision: Narayana, D Gruber, M Gruber.

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