Role of a second chemotherapy in recurrent malignant glioma patients who progress on bevacizumab

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Bevacizumab is a humanized monoclonal antibody against vascular endothelial growth factor (VEGF) that has efficacy in recurrent malignant gliomas, particularly in combination with irinotecan. However, responses are rarely durable. Continuation of bevacizumab in combination with another chemotherapeutic agent may demonstrate some activity. In this article we present a retrospective review of 54 patients with recurrent malignant gliomas who progressed on a bevacizumab-containing regimen and were then treated with an alternate bevacizumab-containing regimen. All patients received intravenous bevacizumab (5–10 mg/kg) every 2 weeks alone or in combination with an additional chemotherapeutic agent, such as irinotecan. There was no limit on the number of prior therapies. Clinical characteristics and outcomes were reviewed. Tumor progression was determined by a combination of clinical status and radiographic changes. Patients were 33 men, 21 women (median age, 50 years; range, 23–72 years) with a median KPS score of 80 prior to the first bevacizumab-containing regimen and 70 prior to the second regimen; median prior chemotherapy regimens including the first bevacizumab-containing regimen was 3 (range, 2–5). Median progression-free survival (PFS) on the first

bevacizumab-containing regimen was 124 days (95% confidence interval [CI], 87–154 days); 6-month (6M)-PFS was 33%. Median PFS on the second bevacizumab-containing regimen was 37.5 days (95% CI, 34–42 days); 6M-PFS was 2%. Ten patients on the first regimen and 12 patients on the second regimen suffered grade 3/4 toxicities. Those patients with malignant gliomas who progressed despite a bevacizumab-containing regimen rarely responded to the second bevacizumab-containing chemotherapeutic regimen. In such patients, alternate therapies should be considered. *Neuro-Oncology* 11, 550–555, 2009 (Posted to *Neuro-Oncology* [serial online], Doc. D08-00204, March 30, 2009. URL <http://neuro-oncology.dukejournals.org>; DOI: 10.1215/15228517-2009-006)

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Malignant gliomas are the most common primary brain tumors in adults. Despite optimal treatment, the median survival for malignant glioma remains poor: 12–15 months for glioblastomas, 2–3 years for anaplastic astrocytomas and anaplastic oligoastrocytomas without 1p/19q deletions, and 6–7 years for anaplastic oligodendroglioma with 1p/19q loss.¹ When tumors recur, the treatment options are very limited. The median time to tumor progression is only 9 weeks for glioblastomas and 13 weeks for anaplastic gliomas.²

Bevacizumab is a humanized monoclonal antibody that targets vascular endothelial growth factor-A (VEGF-A),

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thereby preventing activation of the VEGF receptor and the subsequent signaling cascade involved in tumor angiogenesis. Recent studies suggest that it has promising activity in recurrent malignant gliomas, especially in combination with irinotecan.^{3–6} These studies have produced response rates of 67% and 6-month progression-free survival (6M-PFS) of 56% for recurrent anaplastic gliomas,⁷ and response rates of 21.2%–61% and 6M-PFS of 30%–51% for recurrent glioblastomas.^{3,7,8} However, most patients eventually progress despite this salvage therapy. The optimal therapy for these patients is unknown. Frequently, they are maintained on bevacizumab and the concurrent chemotherapeutic agent is changed. We reviewed our experience with this therapeutic strategy in heavily pretreated patients with recurrent malignant gliomas.

Materials and Methods

We retrospectively reviewed records at Dana-Farber Cancer Institute between November 2005 and March 2008. During this period, 124 patients with high-grade gliomas were treated with a bevacizumab-containing regimen; 11 patients received a non-bevacizumab-containing regimen after the first bevacizumab-containing regimen, 7 patients did not receive any further treatment following the first bevacizumab regimen, and 19 patients died while on the first bevacizumab-containing regimen. We included only patients who progressed on a bevacizumab-containing regimen and were subsequently treated with an alternate bevacizumab-containing regimen. Sixty-eight patients with high-grade gliomas met this inclusion criteria, but five patients had not yet progressed on the second bevacizumab regimen, three patients were lost to follow-up, three patients changed the first bevacizumab-containing regimen without evidence of radiographic or clinical progression as described below, two patients did not have pathologically proven high-grade gliomas, and one patient was unable to obtain MRIs. We reviewed the charts of the remaining 54 patients who progressed on a bevacizumab-containing regimen and were subsequently treated with an alternate bevacizumab-containing regimen. All patients were older than 18 years of age. There was no limit on the number of prior therapies. One patient received intravenous bevacizumab 5 mg/kg every 2 weeks throughout the course of his treatment. The remainder received intravenous bevacizumab 10 mg/kg every 2 weeks. As the initial bevacizumab-containing regimen, 39 patients received irinotecan, 9 bevacizumab alone, 3 carboplatin, 2 carmustine, and 1 temozolomide. As the second bevacizumab-containing regimen, 36 patients received carboplatin, 12 irinotecan, 3 carmustine, 1 lomustine, 1 etoposide, and 1 erlotinib. Clinical characteristics and outcomes were reviewed. Brain MR images with contrast were obtained every 8 weeks or sooner. Tumor progression was determined by a combination of clinical status and radiographic changes. Laboratory tests, including complete blood count, serum electrolytes, and liver function, were assessed every 4 weeks or at closer intervals depending on results. Toxicities

were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0 (http://ctep.cancer.gov/reporting/ctc_v30.html). The end points were median PFS, 6M-PFS, and radiographic response as determined by the modified Macdonald criteria.⁹ In addition to the standard response criteria, patients were considered to have tumor progression if there was clinical deterioration or if there was a clear increase in T2/fluid-attenuated inversion-recovery (FLAIR) signal not attributable to radiation changes and associated with mass effect on stable or decreasing doses of corticosteroids, even if the contrast enhancement was stable. This takes into account the phenomenon observed in a subset of malignant glioma patients treated with bevacizumab in which the contrast scans appear stable but there is progression of nonenhancing tumor.⁴ These radiographic criteria were applied to patients receiving both regimens. This study was approved by the Dana-Farber/Harvard Cancer Center Office for the Protection of Research Subjects.

Statistical Methods

Overall survival and PFS estimates and curves were computed using the Kaplan-Meier method. Time to progression was calculated for each patient twice: from the start date of first treatment to first progression and from the start date of second treatment to second progression. These times to progression sets of observations were used for the estimation and comparison of survival curves for each treatment; that is, these two sets of progression times were compared as though they came from two independent groups.

Results

We studied 54 patients (33 men, 21 women; Table 1). The median age was 50 years (range, 23–72 years). The median KPS score prior to receiving the first regimen was 80 (range, 60–100) and prior to receiving the second regimen was 70 (range, 40–100). Thirty-five patients had a histologic diagnosis of glioblastoma, nine anaplastic astrocytoma, five anaplastic oligoastrocytoma, one anaplastic oligodendroglioma, and four high-grade glioma (grade 3 or 4 was not specified). Forty-three patients presented with their high-grade glioma *de novo*; the remainder were initially diagnosed with a low-grade glioma that subsequently progressed to a higher grade. The median number of chemotherapy regimens prior to the second bevacizumab-containing regimen was 3 (range, 2–5). Ten patients (19%) on the first regimen and 12 patients (22%) on the second regimen suffered grade 3–5 adverse events (Table 2). One patient (2%) died from an intracranial hemorrhage while on the second bevacizumab-containing regimen. On the first regimen, five patients (9%) developed thromboembolic complications (venous thrombosis and/or pulmonary embolism). On the second regimen, two patients (4%) developed a pulmonary embolism. Grade 3 hypertension was experienced by two patients (4%) on the first regimen and

Table 1. Patient characteristics

Characteristics	Cases (Second Bevacizumab Regimen), <i>n</i> = 54	Controls (Second Non-Bevacizumab Regimen), <i>n</i> = 11
Age, years [median (range)]	50 (23–72)	48 (34–60)
Sex [<i>n</i> (%)]		
Male	33 (61)	7 (64)
Female	21 (39)	4 (36)
Histology [<i>n</i> (%)]		
Glioblastoma	35 (65)	7 (64)
Anaplastic astrocytoma	9 (17)	1 (9)
Anaplastic oligoastrocytoma	5 (9)	0
Anaplastic oligodendroglioma	1 (4)	0
High-grade glioma (grade 3 or 4 not specified)	4 (6)	3 (27)
KPS score [median (range)]		
Prior to first regimen	80 (60–100)	80 (70–100)
Prior to second regimen	70 (40–100)	80 (60–90)
No. chemotherapy regimens prior to second regimen [<i>n</i> (%)]		
Median	3	2
1	0	1 (9)
2	17 (31)	4 (36)
3	21 (39)	3 (27)
4	11 (20)	3 (37)
5	5 (9)	0

one patient (2%) on the second regimen. Most of the remaining grade 3 or 4 adverse events were hematologic toxicities on bevacizumab alone or in combination with irinotecan, carboplatin, or carmustine. Median PFS on the first bevacizumab-containing regimen was 124 days (95% confidence interval [CI], 87–154 days); 6M-PFS was 33%. Median PFS on the second bevacizumab-containing regimen was 37.5 days (95% CI, 34–42 days); 6M-PFS was 2%. The difference in PFS between the two regimens is significant (p -value < 0.0001; Fig. 1). There was no significant difference in the median PFS between those patients who received a second bevacizumab-containing regimen and the 11 patients who received a second regimen that did not contain bevacizumab.

Thirty-five of the 54 patients received bevacizumab plus irinotecan as the first bevacizumab-containing regimen followed by bevacizumab plus carboplatin as the second regimen. In this subgroup, median PFS was 135

days (95% CI, 88–196 days) on the first regimen and 35 days (95% CI, 30–58 days) on the second regimen (p -value < 0.0001). 6M-PFS was 37% on the first regimen and 3% on the second regimen.

At the time of last follow-up, 37 patients had died and 17 were alive. The median overall survival from time of diagnosis was 2.54 years (95% CI, 2.24–6.56 years). The median overall survival from discontinuing the second bevacizumab-containing regimen was 82 days (range, 0–287 days). Among the 37 patients who died, 13 had been treated with a third bevacizumab-containing regimen, and 9 with a chemotherapy regimen that did not contain bevacizumab; 15 did not receive any further therapy. For patients who received a third bevacizumab-containing regimen, the median overall survival from discontinuing the second bevacizumab-containing regimen was 116 days (range, 32–287 days). For the nine patients who received a chemotherapy regimen that did not con-

Table 2. Grade 3, 4, or 5 toxicities during treatment [*n* (%)]

Toxicity	During First Bevacizumab-Containing Regimen, <i>n</i> = 54	During Second Bevacizumab-Containing Regimen, <i>n</i> = 54
Neutropenia	3 (6)	2 (4)
Thrombocytopenia	1 (2)	4 (7)
Pulmonary embolism	2 (4)	2 (4)
Venous thrombosis	3 (6)	0
Intracranial hemorrhage	0	1 (2) ^a
Hypertension	2 (4)	1 (2)
Elevation in aspartate transaminase and/or alanine transaminase	1 (2)	1 (2)

^aFatal in one patient.

Fig. 1. Kaplan-Meier progression-free survival (PFS) comparing the first bevacizumab-containing regimen (solid line) to the second bevacizumab-containing regimen (dashed line). PFS decreased on the second regimen (p -value < 0.0001).

tain bevacizumab, the median overall survival was 91 days (range, 30–165 days). The median overall survival for the remaining 15 patients who did not receive further treatment was 35 days (range, 0–248 days). The one patient who survived 248 days without further therapy had an anaplastic glioma. Only limited data are available regarding clinical and radiographic outcomes after switching to a non-bevacizumab-containing regimen. At least three of the nine patients required higher doses of dexamethasone. One patient declined rapidly on the non-bevacizumab-containing regimen, but no imaging was pursued to document whether this person had developed progressive disease and/or rebound edema.

Increased or new enhancement on the postcontrast brain MRI was the most common cause for changing or stopping treatment regimens. Two patients died on the second regimen due to clinical progression and did not have restaging brain MRI at the time of death. One patient on the second regimen died from an intracranial hemorrhage demonstrated on noncontrast head CT. Of

the patients who had restaging brain MRI at the time of progression, six patients on the first regimen and five patients on second regimen changed treatments based on clinical progression without changes on the postcontrast images. Almost all these patients (four of six on the first regimen and four of five on the second regimen) developed increases in T2/FLAIR signal abnormality on MRI while on stable or increased dexamethasone doses. Two patients on each regimen changed treatments based on increased T2/FLAIR signal abnormality even though they were clinically stable. On retrospective review of radiographic images, 53 of 54 patients could be assessed for radiographic response (Table 3). Radiographic images were no longer available for review for the remaining patient. No patients achieved a complete response on either regimen. On the first regimen, 15 patients (28%) achieved a partial response, 30 patients (57%) had stable disease, and 8 patients (15%) had progressive disease. On the second regimen, no patients achieved a partial response, 27 patients (51%) had stable disease, and 26 patients (49%) had progressive disease at first follow-up MRI.

Discussion

Malignant gliomas are highly vascular tumors producing VEGF¹⁰ and represent potentially promising targets for anti-VEGF therapies.^{11,12} In addition to inhibiting angiogenesis, anti-VEGF treatments may also improve the efficacy of chemotherapies by normalizing abnormal vasculature, reducing interstitial pressure, and improving delivery of the drugs to the tumor.¹³ The promising results of the preliminary studies with bevacizumab and irinotecan have led to widespread use of this regimen in patients with recurrent malignant gliomas.^{3–5,7,8} These studies have produced response rates of 67% for recurrent anaplastic gliomas⁷ and 21.2%–61% for recurrent glioblastomas.^{3,7,8} For anaplastic gliomas, the 6M-PFS is 56%, and for glioblastomas it has been increased to 30%–51%. In comparison, a retrospective review of negative phase II trials in recurrent malignant gliomas found a 6M-PFS of 15% in glioblastomas and 31% in anaplastic gliomas,² while temozolomide produced a 6M-PFS of 21% in recurrent glioblastomas and 46% in recurrent anaplastic gliomas at first relapse.^{14,15}

Despite the benefit of bevacizumab and irinotecan,

Table 3. Radiographic response rates [n (%)]

	During First Bevacizumab-Containing Regimen				During Second Bevacizumab-Containing Regimen			
	AG ($n = 14$)	HGG ($n = 4$)	GBM ($n = 35$)	Total ($n = 53$)	AG ($n = 14$)	HGG ($n = 4$)	GBM ($n = 35$)	Total ($n = 53$)
Best Radiographic Response ^a								
Complete response	0	0	0	0	0	0	0	0
Partial response	5 (36)	2 (50)	8 (23)	15 (28)	0	0	0	0
Stable disease	9 (64)	1 (25)	20 (57)	30 (56)	8 (57)	1 (25)	18 (51)	27 (51)
Progressive disease	0	1 (25)	7 (20)	8 (15)	6 (42)	3 (75)	17 (49)	26 (49)

Abbreviations: AG, anaplastic glioma; HGG, high-grade glioma (grade not specified); GBM, glioblastoma.

^aDefined by Macdonald criteria.

almost all patients eventually develop recurrent disease. Currently, the optimal therapy for patients progressing on the first bevacizumab-containing regimen is unknown. Most centers continue patients on bevacizumab and change the chemotherapeutic agent, in the hope that bevacizumab will continue to enhance the therapeutic benefit of the chemotherapeutic agent. This therapeutic strategy was previously reviewed in a small cohort of patients.⁴ However, the present study expands on the prior cohort to verify preliminary findings. To our knowledge, this is the largest study to date to review the therapeutic efficacy of this common clinical practice.

In this study, the 6M-PFS was 33% on the first bevacizumab-containing regimen, suggesting that the regimen provides some benefit in this relatively heavily pretreated group of patients. The 6M-PFS in our study is slightly lower than in prior published studies. This may be because our patients were generally more heavily pretreated, with 68% of patients receiving bevacizumab for the first time at their second relapse. The overall 6M-PFS was only 2% with the second bevacizumab-containing regimen. The majority of patients received the combination of bevacizumab and carboplatin for their second regimen. In this group of patients the 6M-PFS was only 3%. Thirty-six percent of patients with anaplastic gliomas, 50% with high-grade gliomas (grade 3 or 4 not specified), and 23% with glioblastomas achieved partial responses on the first regimen. There were no partial responses on the second regimen. These results suggest that patients who progress on a bevacizumab-containing regimen respond poorly in general to a second chemotherapy combined with bevacizumab.

Thirty-seven patients had died at time of last follow-up. Median time to death from stopping the second regimen was 82 days. There was no difference in survival between patients who received a third bevacizumab-containing regimen and patients who received another chemotherapy that did not contain bevacizumab (116 days vs. 91 days, respectively). This lends credence to our suspicion that patients who progress on a bevacizumab-containing regimen do not respond well to additional bevacizumab regimens.

Therapy with bevacizumab in combination with the chemotherapeutic regimens was generally well tolerated. The number of patients suffering grade 3 or 4 adverse events was similar between the two groups. A total of seven patients (13%) developed thromboembolic complications, comparable to numbers reported in phase II clinical trials of bevacizumab plus irinotecan in recurrent high-grade gliomas.^{7,8} One patient died from an intracranial hemorrhage. Radiographic treatment response in clinical trials is often measured by the "Macdonald criteria," which relies on the cross-sectional area of the tumor from postcontrast images.⁹ Some of our patients developed clinical progression without any changes on postcontrast images. In almost all these cases, MRI demonstrated increased T2/FLAIR signal abnormality not attributable to changes in dexamethasone dosing. Norden et al.⁴ hypothesized that this T2/FLAIR signal

abnormality may represent infiltrating tumor, although results were not conclusive. This is supported by preclinical studies suggesting that anti-VEGF therapy may force tumor cells to co-opt and grow along existing blood vessels, resulting in an infiltrative phenotype that may be more difficult to treat.¹⁶⁻¹⁸

Conclusions from our study must be guarded for several reasons. A retrospective review has inherent limitations, including selection bias and outcome criteria. Patients changed regimens at the discretion of their treating physician. Therefore, progression as defined in our study did not always meet the standards of the Macdonald criteria. In this study we considered patients to have progressive disease if they had clinical progression and increased T2/FLAIR signal not due to changes in corticosteroid doses. We feel that this more accurately reflects tumor progression than an evaluation based only on the extent of enhancing tumor. Our population did not all receive the same bevacizumab-containing chemotherapy regimens. However, subgroup analysis of 35 patients who received the same two regimens (bevacizumab plus irinotecan followed by bevacizumab plus carboplatin) demonstrated median PFS and 6M-PFS similar to that of the overall population. Another, although less likely, explanation for our results is that bevacizumab in combination with irinotecan is a better treatment than bevacizumab in combination with carboplatin. Since most of the patients in this study received irinotecan followed by carboplatin, bias regarding the order of treatments may potentially account for the differences in PFS between the two groups. However, since single-agent irinotecan has only very limited activity in recurrent malignant gliomas,^{19,20} it seems unlikely that our results can be explained by the fact that irinotecan is significantly more effective than carboplatin. At present, most physicians begin with irinotecan in combination with bevacizumab, so this study reflects current clinical practices. Further studies are needed to conclusively determine if irinotecan or carboplatin is the better chemotherapeutic choice in combination with bevacizumab. The number of patients receiving other types of chemotherapeutic agents was too small to determine whether a particular chemotherapeutic agent was more effective in combination with bevacizumab.

Despite these limitations, our study offers insight into a common clinical practice. A bevacizumab-containing regimen may be an effective initial treatment in recurrent, heavily pretreated malignant gliomas. However, continuation of bevacizumab in combination with another chemotherapeutic agent was generally not an effective salvage therapy. Other therapeutic options should be considered for these patients.

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