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Outcome after bevacizumab clinical trial therapy among recurrent grade III malignant glioma patients

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Abstract

Although outcome following bevacizumab among recurrent grade IV malignant glioma patients is documented as poor by several analyses, outcome for recurrent grade III patients following bevacizumab therapy has not been specifically evaluated. We performed a pooled analysis of 96 recurrent grade III malignant glioma patients enrolled on three consecutive phase II bevacizumab salvage trials to evaluate overall outcome following bevacizumab trial discontinuation. Outcome on the three bevacizumab trials, which included similar eligibility, treatment and assessment criteria, was comparable. Forty-nine patients who progressed on bevacizumab trial therapy and remained alive for at least 30 days elected to receive additional therapy. These patients achieved a median PFS-6 and OS of 30.6% (95% CI: 18.4, 43.6) and 10.3 months (95% CI: 5.2, 11.7), respectively. Among patients who continued bevacizumab therapy ($n = 23$) after study progression, PFS-6 and median OS were 39.1% (95% CI: 19.9, 58.0) and 9.2 months (95% CI: 5.2, 13.6), respectively, compared to 23.1% (95% CI: 9.4, 40.3; $P = 0.51$) and 10.3 months (95% CI: 2.5, 14.4; $P = 0.91$) for patients who initiated non-bevacizumab containing therapy ($n = 26$). Outcome after discontinuation of bevacizumab therapy for recurrent grade III malignant glioma patients is associated with improved outcome compared to historical data for recurrent grade IV malignant glioma patients. Salvage therapies following bevacizumab failure have modest activity for grade III malignant glioma patients that is independent of further bevacizumab continuation.

Keywords

Malignant glioma; Angiogenesis; Bevacizumab; Vascular endothelial growth factor; Anaplastic astrocytoma

Introduction

WHO grade III malignant gliomas include a number of histologically diverse tumor types including anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO) and mixed anaplastic oligoastrocytoma (AOA). Despite multimodality therapy including surgery, radiation therapy and in many cases, temozolomide chemotherapy, median overall survival (OS) for newly diagnosed AA patients is only 3–5 years, while that of AO and AOA patients is modestly better [1, 2]. Growing evidence links outcome to specific genetic and epigenetic factors including co-deletion of chromosomes 1p and 19q [3], promoter methylation of the methylguanine methyltransferase (MGMT) DNA repair enzyme gene [4, 5], and mutation of the isocitrate dehydrogenase 1 or 2 (IDH1 or IDH2) genes [4–7]. Importantly, salvage therapies following progression after radiation therapy and temozolomide chemotherapy have historically yielded disappointing results including median progression-free survival at 6 months of 24–28% and median OS of 38–39 weeks [8, 9].

Due to the overall low activity of salvage therapies, our group and others have evaluated bevacizumab, a humanized monoclonal antibody targeting vascular endothelial growth factor (VEGF), among patients with recurrent grade III malignant glioma. Of note, bevacizumab was recently granted accelerated approval by the US Food and Drug Administration (FDA) for recurrent GBM [10, 11]. Among recurrent grade III malignant glioma patients, encouraging evidence of bevacizumab activity as well as acceptable safety have been noted [12–18]. Although most patients benefit, essentially all patients ultimately progress. Outcome after bevacizumab progression has not been specifically evaluated, although small numbers of grade III patients have been included in some retrospective series of primarily recurrent grade IV patients which have consistently documented dismal outcome for therapies administered after bevacizumab progression [16, 19, 20]. Thus, we performed a pooled analysis of all completed clinical trials evaluating bevacizumab for recurrent grade III malignant glioma patients performed at our institution over the past five years [17, 21, 22] in order to better define outcome after bevacizumab-based therapy for these patients. We also sought to identify clinical characteristics associated with subsequent salvage therapy outcome.

Materials and methods

Patient inclusion

All patients treated on three consecutive, single-arm, phase II, bevacizumab trials for recurrent malignant glioma patients conducted at our institution were included in this study (Supplementary Table 1). This pooled analysis, as well as the three associated therapeutic studies, were approved by the Duke University Institutional Review Board. The current analysis reflects patient follow-up through January 1, 2011. Enrollment on the three bevacizumab trials occurred between July, 2005 and July, 2010. Entry criteria across the therapeutic studies were similar as previously published and included institutional confirmation of histopathology for study eligibility.

Bevacizumab (10 mg/kg every two weeks) was combined in each trial with a partner therapeutic that was administered according to previously determined guidelines including irinotecan [23], oral etoposide [24, 25], or erlotinib [26, 27]. General dose modification and re-treatment guidelines as well as study discontinuation parameters were similar across the studies. Study therapy was planned to continue for twelve months or until progressive disease, excessive toxicity or non-compliance.

Patients were evaluated with a full physical examination and contrast-enhanced neuro-imaging (computed tomography (CT) was permitted if MRI was contraindicated) every 2 months. Response assessment was based on clinical status combined with MRI findings that included evaluation of both enhancing and T2/fluid-attenuated inversion recovery (FLAIR) sequences as recently described by the Radiologic Assessment in Neuro-Oncology (RANO) criteria [28].

Following discontinuation of bevacizumab study therapy, subsequent treatment options including clinical trial participation as well as best clinical management chemotherapy regimens were offered as appropriate to patients. The specific choice of subsequent treatment after bevacizumab study discontinuation was made for each individual patient by the treating oncologist based on relevant clinical, psychosocial and practical considerations following a discussion with the patient and their caregivers, and was not based on a pre-designed algorithm or protocol. Subsequent treatment and associated evaluations were performed at either the study center or locally depending on the preference of each patient. All subsequent treatments were tabulated for each patient and the time to progression for the

first subsequent treatment after bevacizumab discontinuation was assessed by the study center staff for all patients. All patients were followed for OS.

Statistical methods

The reason bevacizumab was discontinued and the initial subsequent treatment type were cross-tabulated. Overall survival was defined as time between initiation of treatment after bevacizumab study discontinuation and death, or last follow-up for surviving patients. Progression-free survival was defined as time between initiation of treatment after bevacizumab study discontinuation and first occurrence of disease progression or death. Kaplan–Meier methods were used to produce OS and PFS estimates.

Among patients who received additional therapy following progression on bevacizumab study therapy, and remained alive at least 30 days after bevacizumab termination, a Cox proportional hazards model was used to compare OS for patients that received further bevacizumab therapy and those who received non-bevacizumab therapy after adjustment for covariates. In addition to the full model, a reduced model of covariates was generated by using the backwards elimination method with a 0.1 significance level for variable inclusion. The following covariates were considered in this analysis: age at initiation of subsequent treatment (≤ 50 years; >50 years); KPS at progression on bevacizumab trial therapy (<90, ≥90); specific bevacizumab trial therapy; number of prior disease progressions (<2, ≥2); time since initial diagnosis (≤ 18 months, >18 months); duration of bevacizumab trial treatment (≤ 6 months, >6 months); corticosteroid use at the time of bevacizumab study progression; the specific type of subsequent treatment; whether patients received initial subsequent therapy or therapy evaluations at the study center; proximity to the study center (<200 vs. ≥200 miles); and residence in an urban environment.

Results

Initial bevacizumab study therapy

Characteristics of patients enrolled in the three bevacizumab trials were comparable (Supplementary Table 2). Patients were moderately pre-treated with over half enrolled at second or third progression and over one-third having received 3 or more prior treatments, however 61% had a KPS of 90–100. Outcome was comparable across the studies and approximately 25–40% of patients progression-free for 12 months and alive at 2 years (Supplementary Table 3).

Treatment and outcome following bevacizumab trial progression

Sixty-three patients (66%) discontinued bevacizumab study therapy due to progressive disease (Fig. 1). Forty-nine of these patients received additional therapy and remained alive for at least 30 days. The characteristics of these patients, the constituency analyzed in the current report, are summarized in Table 1. Two patients underwent a subtotal resection prior to initiating subsequent therapy; in both of these patients, subsequent therapy did not include bevacizumab. Initial treatment for 23 of these patients (47%) included bevacizumab while 26 patients (53%) began non-bevacizumab therapy. Of note, clinical characteristics and degree of prior treatment did not differ significantly between patients who received bevacizumab continuation compared to those who received non-bevacizumab therapy. Since the choice of therapy was made by the treating oncologist and not according to defined guidelines or protocol, we sought to evaluate other factors that may have impacted treatment choice including proximity to our institution, whether treatment or evaluations were conducted at our institution and whether patients lived in an urban environment (which may have affected the sophistication of their subsequent treatment). Of note, these factors also

appeared equally distributed between patients who received bevacizumab compared to those who received non-bevacizumab therapy.

Table 2 and Fig. 2 summarize outcome for all patients who received additional therapy after bevacizumab trial progression and remained alive for at least 30 days, based on whether initial subsequent salvage therapy included bevacizumab. Overall outcome was poor for all patients. Although there was a trend of improved PFS for those who continued bevacizumab, the difference did not achieve statistical significance ($P = 0.5082$). There was no difference in OS among these patients based on whether initial subsequent therapy after bevacizumab study progression included bevacizumab ($P = 0.9103$). The results of an analysis that included all patients who received additional therapy regardless of whether they survived at least 30 days, yielded the same results. We extended this analysis to evaluate patients ($n = 39$) who received at least two salvage regimens following progression on bevacizumab study therapy. Among these patients, again there was no difference in OS between those who received bevacizumab ($n = 28$) compared to those who received non-bevacizumab therapy ($n = 21$).

We evaluated the impact of several factors on outcome for treatment after progression on bevacizumab study therapy including age, number of prior episodes of progression, time from original diagnosis, bevacizumab trial, duration on bevacizumab trial therapy, proximity to the study center, whether subsequent treatment or evaluations were conducted at the study center and residence in an urban environment. The type of subsequent treatment, proximity to the study center (<200 vs. 200 miles) and residence in an urban environment were not assessed as covariates due to lack of distribution among patients in that 91% received chemotherapy as subsequent therapy, 86% lived greater than 200 miles from the study center and 83% did not live in an urban environment. Multivariate analysis (Table 3) revealed that dexamethasone therapy at the time of bevacizumab study therapy was the only independent predictor of outcome (HR: 3.83; 95% CI: 1.87, 7.86; $P = 0.0002$). Of note, continuation of bevacizumab therapy was not associated with OS (HR: 0.762; 95% CI: 0.40, 1.47; $P = 0.418$).

Discussion

Although bevacizumab provides benefit for recurrent GBM patients, essentially all will eventually progress and the identification of effective therapies after bevacizumab failure remains elusive. Specifically, several reports document PFS-6 and median OS rates of 0–4% and 2–5 months, respectively for GBM patients who progress on bevacizumab [11, 19, 20, 29–32]. A growing number of retrospective series and prospective studies have evaluated bevacizumab for recurrent grade III malignant glioma patients primarily based on the encouraging response to this agent observed in recurrent GBM patients and the lack of durable, effective therapy following progression on conventional treatment [12–18, 21].

However, the outcome of recurrent grade III malignant glioma patients after progression on bevacizumab therapy has not been specifically studied, although a small number of patients have been reported in primarily recurrent GBM series [16, 19, 20]. Thus, we performed a pooled analysis of three consecutive single-arm phase II studies of bevacizumab-based therapy conducted at our center for recurrent grade III malignant glioma patients in order to better define the outcome of these patients following bevacizumab progression. We also sought to evaluate potential factors associated with outcome. Importantly, the population for this pooled analysis was relatively homogeneous due to consistent eligibility criteria, treatment guidelines and evaluation parameters across our institutional single-arm, phase II bevacizumab trials. Characteristics of patients enrolled on these studies and outcome while on study and after study discontinuation did not differ between the studies.

Progression of underlying tumor was the overwhelming reason for bevacizumab trial discontinuation. Among those who progressed on bevacizumab study therapy, 79% of patients elected to receive additional therapy, while 30% pursued palliative/hospice care. Because there is currently no effective therapy for malignant glioma patients who progress on bevacizumab, the treatment choice for patients who elected to receive further treatment was made between the treating oncologist and the patient/their caregivers on a case-by-case basis after careful consideration of individual clinical and quality of life factors. Although no predetermined guidelines or protocol were prospectively defined to determine subsequent therapy, the individualized, patient-centric approach employed for these patients reflects current “real-world” practice.

Following bevacizumab study progression, 49 patients received further therapy and remained alive for at least 30 days. Overall outcome with subsequent therapy was poor, including a PFS-6 of 30.6% (95% CI: 18.4, 43.6) and a median OS of 10.3 months (95% CI: 5.2; 11.7). Nonetheless, these results were similar to those reported in two recent meta-analyses of cooperative group clinical trials, even though the meta-analyses did not include bevacizumab salvage therapies [8, 9]. Relative to the meta-analyses outcome data, our pooled analysis results suggest that outcome of salvage therapies for recurrent grade III malignant glioma patients after bevacizumab progression is comparable to outcome after non-bevacizumab therapy.

Utilizing a cox proportional hazards model, we attempted to identify demographic, clinical or treatment criteria which may have been associated with outcome to treatment administered after bevacizumab study progression. This analysis was limited by a small sample size but identified dexamethasone administration at the time of bevacizumab study progression as the only independent predictor of OS (HR: 3.83; $P=0.0002$). This finding is not unexpected and likely reflects patients with more aggressive and/or larger tumor burdens.

We also attempted to determine whether bevacizumab continuation improved outcome following bevacizumab study progression for recurrent grade III malignant glioma patients. Although a randomized, prospective study has yet to be performed among recurrent GBM patients who progress on bevacizumab therapy, small single-arm studies and retrospective series consistently report a dismal outcome for treatment, regardless of whether it includes bevacizumab, among GBM patients who progress on bevacizumab [11, 16, 19, 20, 29, 31, 32]. Nonetheless, pending the identification of effective therapy for such patients, a randomized prospective study should be considered to definitively address this question. Although involving a different cancer indication, two large registries of colorectal cancer patients have noted improved survival for patients who continue bevacizumab following bevacizumab progression [33, 34]. Our analysis was limited by a small sample size, but nonetheless did not detect a difference in outcome for recurrent grade III patients who had progressed on bevacizumab based on whether subsequent therapy included bevacizumab.

Caution should be exercised in the interpretation of our study findings due to the retrospective design of our analysis and the lack of randomized control patients. Although patients included in this pooled analysis were relatively homogeneous with regard to demographics, study treatment and outcome assessment, and we attempted to identify any potential differences among patient cohorts, inherent biases associated with retrospective analyses may have affected our findings. Another potential limitation is that our analysis of outcome focused only on the first two therapies administered after bevacizumab study therapy. However, the impact of subsequent therapies was not possible to evaluate accurately due to a steep decrease in the number of patients who received more than two subsequent therapies. Third, since all three trials included bevacizumab in combination with

another therapeutic and since bevacizumab continuation after bevacizumab study progression was always administered with a chemotherapeutic, our study analyses cannot address the impact of single-agent bevacizumab for these patients. Finally, sufficient archival tumor material was not available to incorporate an analysis of relevant tumor markers such as chromosome 1p/19q deletion, IDH mutation or markers potentially associated with anti-angiogenic therapy outcome. Although this deficiency represents a major missed opportunity, future prospective studies to evaluate outcome for malignant glioma patients who progress on bevacizumab should consider including these important correlative analyses.

Although bevacizumab is approved for recurrent GBM and is not currently approved for recurrent grade III malignant glioma patients, it is likely that an increasing number of recurrent grade III malignant glioma patients will receive bevacizumab therapy, particularly given the lack of alternative effective therapies. This retrospective pooled analysis evaluating outcome for recurrent grade III malignant glioma patients who progressed on three consecutive single-arm, phase II bevacizumab studies, demonstrates that subsequent therapy is associated with modest benefit that is independent of bevacizumab continuation. The overall poor outcome of such patients underscores the critical need to identify more effective therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
Derivation of patients included in the current analysis

Fig. 2. Kaplan–Meier estimates of progression-free survival (**a**) and overall survival (**b**) for patients based on treatment after progression on bevacizumab clinical trial

Characteristics of patients who progressed on bevacizumab trial, received subsequent therapy and remained alive for at least 30 days

Table 1

	Initial subsequent treatment						All	
	Non-BV			BV				
	N	%	N	%	N	%	N	%
Total patients	26	53	23	47	49	100		
Age at start of initial subsequent therapy	9	35	8	35	17	35		
Age 40								
Age >40	17	65	15	65	32	65		
Mean (SD)	45 (10)		45 (12)		45 (11)			
Median (range)	46 (25–62)		46 (24–68)		46 (24–68)			
Gender								
Female	10	38	6	26	16	33		
Male	16	62	17	74	33	67		
Time since diagnosis at start of initial subsequent therapy								
36 months	12	46	12	52	24	49		
>36 months	14	54	11	48	25	51		
Mean (SD)	51 (40)		66 (74)		58 (58)			
Median (range)	45 (7–169)		35 (7–274)		45 (7–274)			
BV Trial								
BV irinotecan	8	31	1	4	9	18		
BV erlotinib	8	31	12	52	20	41		
BV etoposide	10	38	10	43	20	41		
Duration of BV trial therapy								
6 months	17	65	13	57	30	61		
>6 months	9	35	10	43	19	39		
Mean (SD)	6 (5)		7 (6)		7 (5)			
Median (range)	5 (1–19)		6 (2–26)		6 (1–26)			
KPS at BV trial failure								
<90	19	73	16	70	35	71		
90	7	27	7	30	14	29		

	Initial subsequent treatment						All	
	Non-BV			BV				
	N	%	N	%	N	%	N	%
Type of initial subsequent therapy								
Biologic	–	–	2	9	–	–	–	–
Chemotherapy	26	100	21	91	–	–	–	–
Number of prior PDs at start of initial subsequent therapy								
2	12	46	11	48	23	47		
>2	14	54	12	52	26	53		
On dexamethasone at BV trial failure								
No	17	65	16	70	33	67		
Yes	9	35	7	30	16	33		
Initial subsequent therapy at study center								
No	25	96	17	74	42	86		
Yes	1	4	6	26	7	14		
Initial subsequent treatment evaluation at study center								
No	17	65	6	26	23	47		
Yes	9	35	17	74	26	53		
Live <200 miles from study center								
No	22	85	18	78	40	82		
Yes	4	15	5	22	9	18		
Live in urban environment								
No	16	62	15	65	31	63		
Yes	10	38	8	35	18	37		

BV bevacizumab, KPS Karnofsky performance status, SD standard deviation

Table 2
Outcome with subsequent salvage therapy after progression on bevacizumab trial therapy

Group	Total	# Failed	Median survival in months (95% CI)	6-month survival (95% CI)	12-month survival (95% CI)	24-month survival (95% CI)	Log-Rank <i>P</i> value
OS from initiation of subsequent treatment							
Non-BV Therapy	26	21	10.3 (2.5, 14.4)	57.7 (36.8, 73.9)	38.5 (20.4, 56.3)	26.9 (11.9, 44.5)	0.9103
BV Therapy	23	18	9.2 (5.2, 13.6)	69.6 (46.6, 84.2)	31.4 (13.4, 51.3)	15.7 (4, 34.5)	
PFS from initiation of subsequent treatment							
Non-BV Therapy	26	24	1.9 (1.2, 4.1)	23.1 (9.4, 40.3)	11.5 (2.9, 26.7)	11.5 (2.9, 26.7)	0.5082
BV Therapy	23	22	3.8 (2.1, 6.9)	39.1% (19.9%, 58%)	17.4 (5.4, 35)	NE	

BV bevacizumab, *CI* confidence interval, *NE* not-evaluable, *OS* overall survival, *PFS* progression-free survival

Table 3

Multivariate Cox model for overall survival (reduced model using backward elimination)

Parameter	Parameter estimate	Standard error	Hazard ratio	95% Hazard ratio confidence limits	P
Age (>40 vs. 40 years)	-0.16226	0.44322	0.850	0.357	2.027
Time since diagnosis (>36 months vs. 36 months)	-0.42626	0.37292	0.653	0.314	1.356
KPS at BV trial failure (<90 vs. 90)	-0.41382	0.40504	0.661	0.299	1.462
Duration of BV trial therapy (>6 months vs. 6 months)	-0.33763	0.41237	0.713	0.318	1.601
# Prior PDs (>2 vs. 2)	-0.25001	0.45354	0.779	0.320	1.894
On dexamethasone at BV trial failure (yes vs. no)	1.58367	0.48019	4.873	1.901	12.489
Initial subsequent therapy/evaluation at study center (yes vs. no)	-0.29484	0.45638	0.745	0.304	1.821
BV trial (erlotinib vs. irinotecan)	-0.95862	0.64796	0.383	0.108	1.365
BV trial (etoposide vs. irinotecan)	-0.36252	0.59093	0.696	0.219	2.216
Initial subsequent therapy (BV vs. Non-BV)	-0.01183	0.45374	0.988	0.406	2.405
Reduced Model					
On dexamethasone at BV trial failure (yes vs. no)	1.34387	0.36597	3.834	1.871	7.855
Initial subsequent therapy (BV vs. Non-BV)	-0.27128	0.33482	0.762	0.396	1.470

BV bevacizumab, *KPS* Karnofsky performance status, *PD* progressive disease