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Bevacizumab therapy for adults with recurrent/progressive meningioma: a retrospective series

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Abstract

Intracranial meningiomas are often indolent tumors which typically grow over years to decades. Nonetheless, meningiomas that progress after maximum safe resection and radiation therapy pose a significant therapeutic challenge and effective therapies have yet to be identified. Preclinical studies implicate angiogenesis in the pathophysiology of more aggressive meningiomas, suggesting that anti-angiogenic therapies may be of utility in this setting. We performed a retrospective review of fourteen patients with recurrent meningioma treated at Duke University Medical Center with bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor, administered either alone or in combination with chemotherapy. Most patients were heavily pre-treated. Progression-free survival at 6 months was 86 % and was comparable regardless of meningioma grade and whether bevacizumab was administered as monotherapy or in combination with chemotherapy. Most toxicities were mild however single patients developed CNS hemorrhage (grade 1) and intestinal perforation (grade 4), respectively. Bevacizumab can be administered safely to patients with meningioma and appears to be associated with encouraging anti-tumor effect when administered as either a single agent or in combination with chemotherapy. Phase II trials investigating bevacizumab in patients with progressive/recurrent meningioma are warranted.

Keywords

Meningioma; Angiogenesis; Vascular endothelial growth factor; Bevacizumab

Introduction

Meningiomas account for 33.8 % of all primary brain tumors, and therefore are the most common primary tumor of the central nervous system. According to the Central Brain Tumor Registry of the United States (CBTRUS), 53,455 patients developed meningiomas between 2004 and 2006 and the annual incidence is estimated at 6.29 cases per 100,000 person-years [1]. Eighty percent of meningiomas are benign (World Health Organization [WHO] grade I), while nearly 20 % are atypical (WHO grade II) and 1–2 % are anaplastic (WHO grade III) [2]. Initial therapy for symptomatic or growing benign meningiomas is maximum safe resection, while radiation therapy is usually added for atypical and anaplastic lesions or for inoperable, progressive grade I lesions [3, 4]. Nonetheless, effective therapy for meningiomas that recur following radiation therapy has not been identified. In particular, overall outcome for patients with progressive grade II and III meningiomas remains poor, with most series reporting 5-year survival rates of 28–61 % [5]. Results with several chemotherapy agents have been disappointing, although hydroxyurea has demonstrated modest anti-tumor activity in some series [6–11]. Targeted therapies that inhibit specific activators of growth factor signaling pathways, such as the epidermal growth factor receptor (EGFR) and platelet-derived growth factor receptor (PDGFR), have proven ineffective in clinical trials to date among non-enriched progressive meningioma patients [12, 13]. In summary, effective therapy for patients with meningiomas that recur or progress following

resection and radiotherapy remains a major challenge and a current unmet need in neuro-oncology.

Angiogenesis, or the process of new blood vessel formation, is a critical adaptation of aggressive cancers [14] and is predominantly mediated by vascular endothelial growth factor (VEGF) [15]. Growing evidence also supports the role of VEGF-mediated angiogenesis among some meningiomas, particularly higher grade subtypes [16, 17]. The rationale for targeting angiogenesis therapeutically for recurrent/progressive meningioma patients is based on several factors. First, as described above, effective therapies for such patients are currently lacking. Second, bevacizumab is effective for most patients with recurrent glioblastoma, another highly aggressive primary CNS tumor [18]. Third, levels of VEGF, VEGF-R, and microvessel density increase with meningioma grade and may provide prognostic significance [16, 19, 20]. Pistolesi et al. [16] performed reverse transcriptase polymerase chain reaction (RT-PCR) and immunohistochemical staining (IHC) on 40 samples of intracranial meningioma, and determined that microvessel density and VEGF expression were significantly associated with grade II and III meningiomas. Interestingly, Maiuri et al. [21] demonstrated a lack of correlation of VEGF expression with recurrence among patients with grade I meningiomas following complete resection. This study however, excluded patients with grade II or grade III meningiomas, as well as patients whose resection was subtotal.

Levels of VEGF and VEGF-R have also been positively correlated with extent of peritumoral brain edema in meningioma patients [20, 22–26]. Ding et al. evaluated biopsy material from areas of associated peritumoral edema adjacent to intracranial meningiomas obtained from 37 patients. The biopsy material was tested for VEGF mRNA and protein. Of note, VEGF mRNA was essentially absent, but the protein was present, suggesting that VEGF produced and secreted by the tumor may extend outward into the associated tumor microenvironment [27]. We performed a retrospective review of all patients with meningioma who received bevacizumab therapy at our institution in order to assess whether formal evaluation of bevacizumab-based therapy for recurrent/progressive meningioma patients is warranted.

Materials and methods

We retrospectively reviewed records of all patients with histopathologically confirmed meningioma treated at Duke University Medical Center between December 2008 and January 2011. During this time period, fifteen patients with recurrent/progressive meningioma were prescribed bevacizumab. One of these patients was lost to follow-up after the initial recommendation of bevacizumab therapy. Administration of bevacizumab could not be confirmed and hence this patient is not included in the current analysis. The remaining fourteen patients were confirmed to have received bevacizumab therapy and their medical records were reviewed for demographic and prior treatment characteristics, adverse events and outcome.

All patients were over 18 years of age and had radiologic evidence of either progressive or recurrent tumor after prior therapy. All patients submitted archival tumor material for histopathologic confirmation of tumor and grade assessment (R. E. M., neuropathologist). There was no limit on the number or type of prior treatment. Patients who received prior radiation therapy including radiosurgery were not required to have histologic confirmation of tumor prior to initiating bevacizumab salvage therapy. Patients received bevacizumab according to published dosing guidelines, with or without chemotherapy [28, 29]. Patients were evaluated by physical examination and MRI scans every 8 weeks. Assessment of response was based on Radiologic Assessment in Neuro-Oncology (RANO) criteria for

malignant gliomas that included evaluation of both enhancing and non-enhancing imaging findings as well as clinical changes [30]. Routine laboratory studies were assessed each month or sooner if medically indicated. Toxicities were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0 (evs.nci.nih.gov/ftp1/CTCAE/About.html).

Statistical methods

The primary objective was to estimate 6-month progression-free survival (PFS-6) among adults with progressive/recurrent meningioma treated with bevacizumab. Secondary objectives included evaluation of the safety and tolerability of this regimen and of radiographic response, PFS and overall survival (OS) in this patient population.

Kaplan–Meier curves were generated to describe PFS and OS, with each measured from the date bevacizumab therapy began. Progression-free survival was defined as the time until death, initial disease progression, or last follow-up, assuming the patient remained alive without disease progression. Overall survival was defined as the time until death.

Results

Fourteen patients (8 female; 6 male) with recurrent/progressive meningioma were initiated on bevacizumab treatment (Table 1). The median age at bevacizumab initiation was 53.5 years (range, 20–70 years). Nearly 80 % of patients had a Karnofsky performance status (KPS) ≥80 as well as 1–2 meningioma tumors. Twenty percent of patients had 3 or more meningiomas. Five patients (36 %) had grade I meningioma, five (36 %) had grade II (atypical) meningioma, and three patients (21 %) had grade III (anaplastic) meningioma. One patient had a confirmed histologic diagnosis of meningioma, but grade was not possible to specify.

Most patients were heavily pretreated. All patients had undergone prior surgical resection including four patients (29 %) with one prior resection, seven patients (50 %) with two prior resections and three patients (21 %) with three prior resections. Ten patients (77 %) had received prior fractionated radiotherapy and seven patients (50 %) had also undergone stereotactic radiosurgery. Nine patients (64 %) had received prior chemotherapy including five patients treated with one prior chemotherapeutic, 3 patients who received two prior chemotherapies and one patient who was treated with three prior chemotherapies. Seven patients (50 %) received prior biologic targeted therapy including octreotide (n = 3) or pasireotide (SOM230), a multi-ligand somatostatin receptor analogue (n = 1), imatinib mesylate (n = 6), tamoxifen (n = 1) and cele-coxib (n = 1). Only one patient received bevacizumab therapy without prior radiation, chemotherapy or biologic therapy.

Bevacizumab was administered as single agent in four patients (29 %), while ten patients (71 %) received bevacizumab with chemotherapy. Chemotherapeutic agents combined with bevacizumab included daily etoposide (n = 5), daily temozolomide plus sirolimus (n = 1), and temozolomide (5-day schedule, n = 3; daily schedule, n = 1).

The median follow-up for all patients was 21.8 months (95 % CI, 9.2, 27.3). At the time this manuscript was prepared, four patients (29 %) were continuing on bevacizumab therapy while ten patients (71 %) had discontinued bevacizumab. The reason for bevacizumab discontinuation included progressive disease (n = 6), toxicity (n = 3) and lack of compliance (n = 1). Although no patients achieved a complete response (CR), one patient with multifocal disease achieved a partial response (PR; Fig. 1), 11 patients achieved stable disease (SD) and 2 patients had progressive disease (PD) as their best response. Clinically, neurologic function and KPS were preserved in general among patients who achieved stable

disease or radiographic response. The median PFS and PFS-6 were 17.9 months (95 % CI: 8.5, ∞) and 85.7 % (95 % CI: 53.9, 96.2), respectively. Median PFS and PFS-6 were 12.2 months (95 % CI: 1.1, 27.2) and 80 % (95 % CI: 20.4, 96.9), respectively, for patients with grade I meningiomas, and 15.8 months (95 % CI: 5.5, 17.9) and 87.5 % (38.7, 98.1) for patients with grade II/III meningiomas, respectively. The median PFS and PFS-6 were 15.8 months (95 % CI: 12.2, ∞) and 100 %, respectively for patients treated with single-agent bevacizumab (n = 4), and 17.9 (95 % CI: 1.1, 27.2) and 80 % (95 % CI: 40.9, 94.6), respectively for patients treated with bevacizumab plus chemotherapy (n = 10). Median OS for all patients has not been reached (Fig. 2). Due to the heterogeneity of the patient population we examined, it is difficult to speculate how and if specific prior treatments and varying histologic grades impacted response to treatment with bevacizumab. There is a general trend toward increased PFS in patients who had received stereotactic radiotherapy as part of their prior treatment regimen; in general these patients (7 total) seemed to do well on bevacizumab. As nearly half of the patients have not yet demonstrated disease progression as of this writing, the long-term implications and associations are yet to be determined.

Hematologic toxicity was limited to grade 1 thrombocytopenia (n = 1) attributed most likely to prior extensive chemotherapy treatment and grade 3 thrombocytopenia (n = 1) which was attributed to concurrent temozolomide therapy. Non-hematologic toxicity included proteinuria (grade 1, n = 3; grade 2, n = 3), hypertension (grade 1, n = 4; grade 2, n = 1) and craniotomy site cellulitis (grade 2, n = 1) which responded to oral antibiotics. In addition, five patients experienced hemorrhage while receiving bevacizumab. All of these events were grade 1, and included hematochezia (n = 1), microscopic hematuria (n = 3) and bleeding into a meningioma along the vermis (grade 1; n = 1). Bevacizumab was discontinued in three patients (21 %) due to toxicity including the previously described patient with hemorrhage into a vermis meningioma, a patient with grade 4 intestinal perforations and one patient with grade 5 pneumonia/sepsis.

Discussion

Meningiomas are the most common primary CNS tumor [1]. Most meningiomas are grade I and respond durably to surgical resection [4]. Atypical and anaplastic meningiomas account for 20–30 % of these tumors and usually recur following surgery and radiation therapy [2]. Currently there are no effective therapies for meningiomas that recur after surgery and radiation therapy, thus such patients represent an unmet need in oncology at present. In the current report, we describe the outcome of fourteen recurrent meningioma patients treated with bevacizumab.

Limited data have been reported to date describing the anti-tumor activity of anti-angiogenic agents among patients with recurrent/progressive meningioma. Puchner et al. reported significant regression of an anaplastic meningioma that recurred following prior surgery and radiation therapy that was durable and ongoing after 6 months of bevacizumab therapy [31]. DeBoer recently reported preliminary results of a phase II trial incorporating PTK787, an oral tyrosine kinase inhibitor against VEGF-R2 and PDGFR, among twelve patients with recurrent grade II/III meningioma. One patient (8 %) achieved a radiographic response and nine patients (69 %) achieved stable disease with a median time-to-progression of 15.7 weeks, and a median PFS-6 of 46 % [32].

Our retrospective review of fourteen recurrent meningioma patients suggests that bevacizumab may have activity in this indication. Most patients in our series were heavily pretreated, having undergone multiple prior surgical resections as well as treatment with conventional external beam radiotherapy and chemotherapy. In addition, half of the patients received prior stereotactic radiosurgery and half also were previously treated with biological

targeted therapies. The median PFS and PFS-6 compare favorably to outcome achieved using salvage chemotherapy [33–37], targeted therapeutics against PDGFR [12] and EGFR [13], interferon-α [38], somatostatin inhibitors [39, 40] and hormonal agents (Table 2) [41, 42]. Nonetheless, conclusions from our series are limited by its small size and retrospective nature. We also elected to utilize RANO criteria to assess response. This choice poses further potential limitations of our findings given that the RANO criteria were specifically drafted to assess response among malignant glioma patients and not meningioma patients. Nonetheless, given the complexity of response assessment observed among malignant glioma patients treated with bevacizumab, we felt that our assessment should include both the enhancing as well as non-enhancing radiographic components of the tumors, as is specified in the RANO criteria. An additional limitation of our findings is that patients, who received prior radiotherapy, including radiosurgery, may have had radionecrosis rather than true tumor progression at the time bevacizumab therapy was initiated.

Advanced-grade meningiomas express higher levels of VEGF and exhibit increases in microvessel density [16, 19, 20], thus potentially making them more susceptible to VEGF inhibition with bevacizumab. This correlation has been demonstrated in preclinical studies to be most prominent in grades II and III meningiomas [16]. In addition, alleviation of peritumoral brain edema, which may propagate VEGF distribution in vivo [27], may also be alleviated by bevacizumab. We hypothesize the patients with higher grade meningioma tumors respond most effectively to bevacizumab due to higher levels of VEGF expression and subsequent response to inhibition. Further examination of this issue is warranted and may provide utility in prognostication and determination of which patients will respond most effectively.

Most patients in our series tolerated bevacizumab well and observed toxicities were similar in type, severity and frequency to those reported among GBM patients treated with bevacizumab [28, 29]. Serious toxicities leading to bevacizumab discontinuation in our study occurred in 3 patients (21 %) including one intracranial hemorrhage (grade 1), one episode of intestinal perforation (grade 4) and one episode of pneumonia/sepsis (grade 5).

There are currently several ongoing clinical trials incorporating VEGF/VEGFR-directed therapy for patients with recurrent, progressive meningioma, including a multicenter phase II trial combining bevacizumab with the mTOR inhibitor everolimus (Clinicaltrial.gov identifier: NCT00972335), and separate phase II study evaluating single-agent bevacizumab (Clinicaltrials.gov identifier: NCT01125046. Additional clinical trials evaluating multikinase inhibitors targeting VEGFR and PDGFR, including sunitinib and vatalanib, are also underway for recurrent/progressive meningioma patients.

In summary, effective therapy for patients with recurrent/progressive meningioma after surgery and radiation therapy represents an unmet need in neuro-oncology. Pre-clinical studies have suggested that microvessel density and VEGF expression appear to increase with increasing meningioma grade [16, 21], suggesting that anti-VEGF therapies may be active in this setting. Our retrospective series of recurrent/progressive meningioma patients suggests that bevacizumab, administered as single-agent or in combination with chemotherapy, has activity for these patients and can be safely administered. However, our findings are limited by the overall small number of patients evaluated and the retrospective nature of our analysis. Prospective studies of anti-VEGF/VEGFR therapeutics are warranted for recurrent/progressive meningioma patients.

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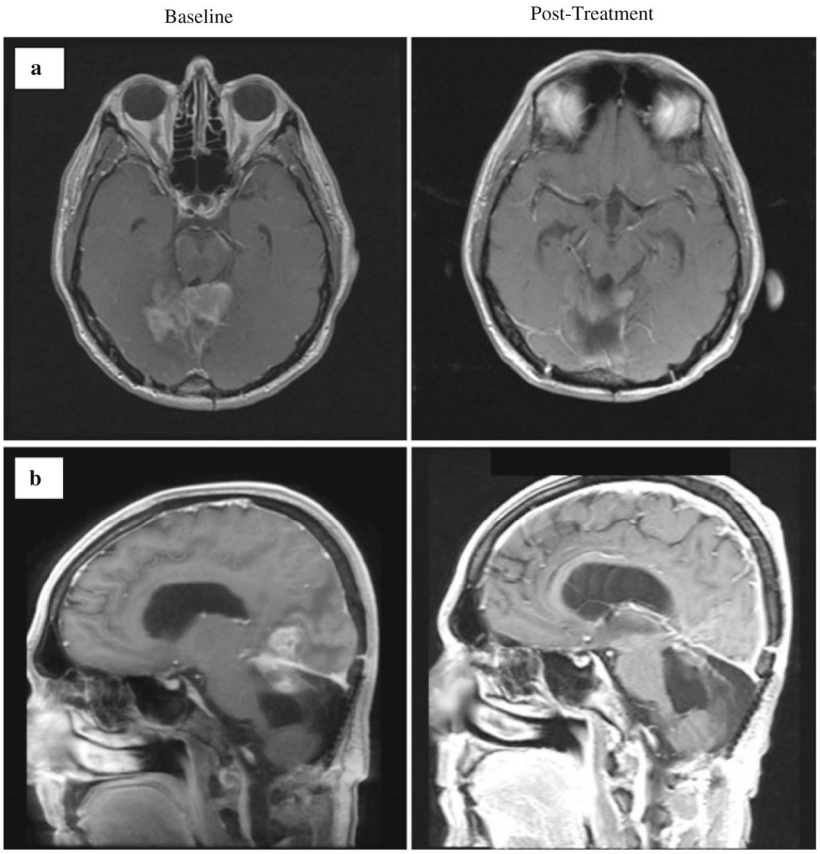

Fig. 1.

Magnetic resonance imaging demonstrating a partial response of a patient with recurrent atypical (grade II) meningioma following four cycles of bevacizumab with daily oral etoposide. The patient (Patient 13, Table 1) initially presented with grade I fibroblastic meningioma treated with resection, adjuvant imatinib/hydroxyurea, and then temozolomide following first progression and did not receive prior radiotherapy. **a** Post-contrast axial T1-weighted images. **b** Post-contrast sagittal T1-weighted images

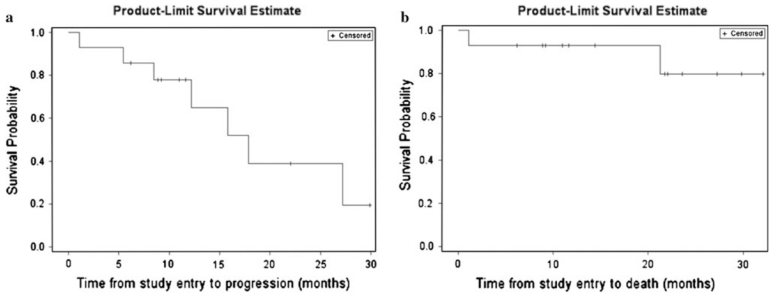

Fig. 2.
Kaplan–Meier plots of progression-free survival (**a**) and overall survival (**b**) for all patients

Table 1

Patient characteristics and treatment outcome

Patient	Age at diagnosis (years)	Grade	Number lesions	Age BV treatment (years)	KPS	Prior therapies	BV partner	Months of BV treatment	Reason BV discontinued	Time to progression (months)
1	30	I	2	45	80	Resection × 3, tamoxifen/RT, imatinib/ hydroxyurea, SRS, octreotide/celebrex	Etoposide	29.5	PD	29.5
2	44	III	1	53	90	Resection × 3, temozolomide/RT, octreotide, imatinib/hydroxyurea, 5-day temozolomide	Etoposide, sirolimus	5.9	PD	5.9
3	51	II	1	57	80	Resection × 3, hydroxyurea, SRS, imatinib, pasireotide	Etoposide	7.0	Ongoing	None
4	28	III	1	43	90	Resection × 2, RT, SRS, 5-day temozolomide	Etoposide	19.4	PD	19.4
5	52	II	1	54	80	Resection × 2, temozolomide/RT, SRS	Etoposide	2.5	Compliance	None
6	46	II	1	54	80	Resection × 1, RT, SRS	Temozolomide (daily)	10.0	Ongoing	None
7	53	I	1	57	90	Resection × 2, imatinib/hydroxyurea, daily temozolomide	None	13.3	PD	13.3
8	47	III	3	52	80	Resection × 2, temozolomide/RT, etoposide/5-day temozolomide, imatinib/hydroxyurea	None	17.1	PD	17.1
9	30	I	4	50	70	Resection × 2, RT, octreotide	Temozolomide (5-day)	9.2	PD	9.2
10	65	II	1	66	70	Resection × 2, RT/temozolomide	None	7.0	Ongoing	None
11	42	Unknown	1	59	80	Resection × 2; RT; SRS	None	7.0	Toxicity	None
12	19	I	1	20	90	Resection; SRS; RT	Temozolomide (5-day)	8.0	Ongoing	None
13	37	I	3	51	60	Resection; imatinib/hydroxyurea; temozolomide	Etoposide	0.5	Toxicity	None
14	77	II	1	79	90	Resection	Temozolomide (5-day)	0.5	Toxicity	None

BV bevacizumab, *KPS* Karnofsky performance status, *NA* not applicable, *PD* progressive disease, *RT* radiation therapy, *SRS* stereotactic radiosurgery

Table 2

Outcome of systemic therapies from selected published recurrent meningioma series

Treatment	Study type	Number patients	Median PFS (months)	PFS-6 (%)	Citation
Bevacizumab	Retrospective	14	18	86	Current series
Hydroxyurea	Phase II	12 (grade 1, n = 12)	13	NR	Loven et al. [10]
Hydroxyurea	Retrospective	60 (grade I)	4	10	Chamberlain and Johnston [34]
Hydroxyurea + RT	Phase II	21 (grade I, n = 13; grade II/III, n = 4; unknown grade, n = 4)	15	NR	Hahn et al. [36]
Temozolomide	Phase II	16 (grade I, n = 16)	5	0	Chamberlain et al. [37]
Irinotecan	Phase II	16 (grade I, n = 16)	5	6	Chamberlain et al. [35]
Imatinib	Phase II	23 (grade I, n = 13; grade II, n = 5; grade III, n = 5)	2	29	Wen et al. [12]
Imatinib + Hydroxyurea	Phase II	21 (grade 1, n = 8; grade II, n = 9; grade III, n = 4)	7	62	Reardon et al. [33]
Erlotinib/Gefitinib	Phase II	25 (grade I, n = 8; grade II, n = 9; grade III, n = 8)	2.5	28	Norden et al. [13]
Interferon-α	Phase II	35 (grade I, n = 35)	7	54	Chamberlain and Glantz[38]
Tamoxifen	Phase II	19 (grade not reported)	15	NR	Goodwin et al. [41]
Mifepristone	Phase II	90 (grade unknown)	10	NR	Grunberg et al. [42]
Octreotide	Phase II	11 (grade I, n = 3; grade II, n = 3; grade III, n = 5)	4	NR	Johnson et al. [39]
Sandostatin LAR	Phase II	16 (grade I, n = 8; grade II, n = 3; grade III, n = 5)	5	44	Chamberlain et al. [40]

n Number, *NR* not reported, *PFS* progression-free survival, *PFS-6* progression-free survival at 6 months, *RT* radiation therapy