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Review Article

Role of bevacizumab for treatment-refractory meningiomas: A systematic analysis and literature review

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Abstract

Background: Meningiomas are the most prevalent primary tumor of the central nervous system (CNS), and although the majority of these neoplasms are classified as benign, nearly one fourth of the lesions display an aggressive profile characterized by pleomorphic histology, high recurrence rates, and overall resistance to standard treatment. Despite the ubiquitous nature of these tumors, no adjuvant therapeutic regimen has been identified which effectively controls disease recurrence and progression after surgery and radiation, leading to a dismal prognosis in this patient population. The primary focus of this research study is, hence, to assess the recently emerging use of bevacizumab, an anti-angiogenic agent, in the treatment of meningiomas. This systematic literature review analyzes the efficacy and safety of therapeutic bevacizumab for treatment-refractory meningiomas.

Methods: A systematic PubMed search was conducted according to PRISMA guidelines to identify all relevant reports investigating the anti-angiogenic agent bevacizumab in the treatment of intracranial meningiomas. The reported parameters from pertinent retrospective reviews, prospective studies, and case studies were volumetric reduction, radiographic response, clinical stability, overall survival (OS), and progression free survival (PFS) measured at 6 and 12 months postinitiation of treatment. Complications were cataloged based on the range and severity of the therapy-related toxicities.

Results: A total of 11 articles, 5 retrospective series, 2 prospective trials, and 4 case reports, reporting on a total of 92 patients, were included in this review. The use of bevacizumab therapy for intracranial meningiomas demonstrated median overall PFS of 16.8 months (range: 6.5-22 months) and PFS-6 of 73% (range: 44%-93%).

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Conclusions: Therapeutic bevacizumab, either alone or with combination chemotherapies, for select patient populations with recurrent or progressive meningiomas, offers a treatment option that confers improved overall progression-free survival. To assess OS parameters, larger randomized controlled trials assessing the use of anti-angiogenic agents for recurrent/progressive meningiomas are warranted.

Key Words: Avastin, bevacizumab, meningioma, outcomes, systematic analysis

INTRODUCTION

Meningiomas account for 35.8% of all brain tumors making them the most common primary tumor of the central nervous system (CNS).[31] With regard to overall tumor response and increased patient survival, general outcomes for patients with progressive World Health Organization (WHO) grade II and III meningiomas remain poor, with the average reported 5-year survival ranging from 30% to 60%.[18] Although the majority of intracranial meningiomas are benign (WHO grade I) and with a relatively low recurrence risk of 7% to 20% at 10-year follow-up, approximately 20% are diagnosed as atypical (WHO grade II), and 1% to 3% are classified as anaplastic (WHO grade III). Atypical and anaplastic meningiomas are characteristically more aggressive in nature and are associated with a high recurrence risk of 29%–52% and 50%–94%, respectively.[24,40] Despite such a high incidence of meningiomas among the general population, an efficacious therapy for recurrent meningiomas following surgery and radiation therapy has yet to be discovered.

Surgery remains a mainstay of treatment for meningiomas that have either grown on sequential imaging or those that cause symptoms. Typically, surgery is performed with curative intent by aiming for a Simpson Grade 1 resection (gross total resection with excision of the dural tail and overlying invaded cranium). In the event that such gross total resection is not attainable, clinicians may opt for a subtotal resection and adjuvant radiotherapy. The decision to use adjuvant radiation therapy is based on the extent of resection and certain characteristics of the histological analysis of the tumor, and is generally performed as adjuvant therapy in cases of atypical and anaplastic lesions as well as inoperable yet progressive Grade I lesions.[2,40] Unfortunately, when patients fail to respond to the initial standard therapy, further treatment options are currently limited and the morbidity and mortality among these patients increase significantly. The latter is mainly due to neurological deterioration secondary to aggressive growth leading to compression of neural structures by the tumor and by peritumoral edema. In summary, the need to find effective therapeutic agents for patients with recurrent or progressive meningiomas following resection and radiotherapy (RT) is needed to improve the prognoses of these patients.

Clinical trials investigating various chemotherapeutic agents, immunotherapies, and hormonal agents for recurrent meningiomas have been unfruitful, offering finite survival benefit with substantial drug toxicity.[40] Although the preliminary results using hydroxyurea were promising,[38] further studies revealed that a sustained radiographic response in meningiomas was uncommon with this agent.[25,27] PDGF (platelet-derived growth factor), EGF (epidermal growth factor), VEGF (vascular endothelial growth factor), IGF (insulin-like growth factor), and TGF-β (transforming growth factor-beta) have been shown to be highly expressed in some vascular tumors such as certain meningiomas. However, clinical trials with such targeted therapies against EGFR and PDGFR have as of now not proven to be effective.[29,35,41] Despite these earlier studies, inhibiting tumor angiogenic pathways using the VEGF pathways has shown some promise in early studies.[29,35] Angiogenesis, the formation of new blood vessels, is considered a primary contrivance that tumors of the human body use not only for growth and progression but also to gain access to systemic circulation thus giving them metastatic potential.[5] In this process of neovascularization, the signal protein VEGF contributes a vital role. Bevacizumab was engineered as a humanized monoclonal antibody to VEGF receptors and interferes with the binding and signal transduction necessary for tumor vascularization leading to a regression of tumor blood supply.[26] Currently, several studies show promise regarding the efficacy of targeting VEGF-regulated angiogenesis in meningiomas, especially in patients with higher grade/recurrent meningiomas; however, data have not been conclusive.[32,37] Therefore, we have conducted a systematic review of the literature to comprehensively assess the efficacy and safety of bevacizumab for treatment-refractory meningiomas.

MATERIALS AND METHODS

Study selection

Using the MeSH database system of PubMed, a systematic literature search was performed between the years 2003 and 2017 for all articles containing the terms meningioma and bevacizumab (("Meningioma [Mesh]") AND "Bevacizumab [Mesh]") following the PRISMA guidelines [Figure 1]. Article search was limited to English with humans as the only study participants.

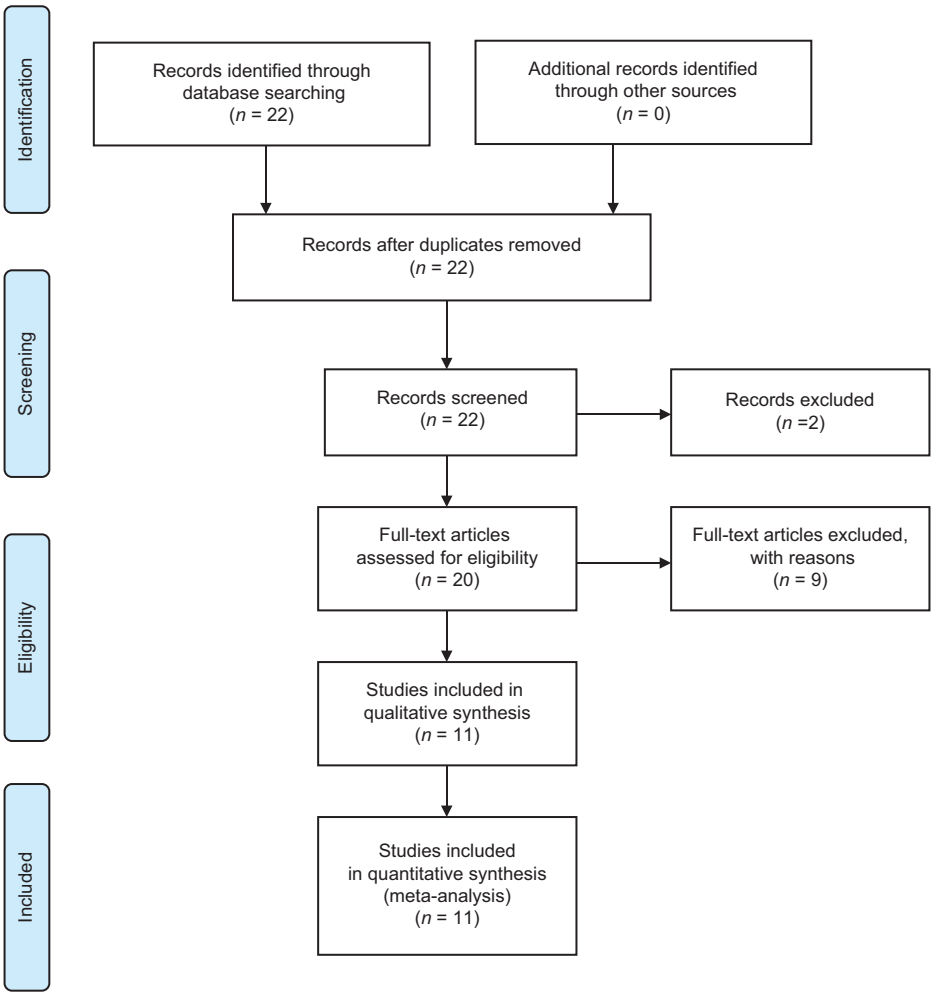

Figure 1: Demonstrates the Prisma guidelines and how they were used for our assessment of the literature regarding the use of bevacizumab for recurrent meningiomas

In addition, the article types were specified as case reports, retrospective patient studies, clinical trials, and randomized controlled trials while reviews, editorials, and commentaries were excluded. In total, 22 articles were identified that matched the eligibility criteria. These results were then manually scrutinized to identify those studies that included patients who were given bevacizumab as adjuvant treatment for surgery/radiation resistant meningiomas. Nine of the studies found were retrieved by this initial inclusion criterion. The results excluded from this review include five studies whose primary focus was the utilization of bevacizumab for radiation necrosis and peritumoral edema, and two studies reviewing toxicity comparisons among anti-angiogenic therapies, rather than endpoints regarding survival or tumor response. We also included two additional case reports that focused on bevacizumab treatment for primary tumors and the consequential response of the meningioma in those patients. A brief search was also conducted on other Internet databases, using the same criteria. Studies providing supplementary information for this review were obtained via bibliographic review of the reports identified during the systematic search. The ClinicalTrials.gov database was searched on June 1, 2017, for active studies using bevacizumab as therapy for meningiomas. Currently, two phase II prospective trials for patients with sporadic recurrent or progressive meningiomas are underway, one using monotherapy bevacizumab (NCT01125046) and the other studying a combination of bevacizumab and optune-delivered electric field therapy (NCT02847559).

Data extraction

The analysis conducted on the results from each of the studies was based on the treatment cohort, pathological tumor diagnosis, any form of pretreatment received prior to the bevacizumab therapy, specifics of the administration protocol, clinical and radiographic response, and any adverse effects experienced during the adjuvant therapy. However, two case reports detailed the response rates in meningiomas when bevacizumab was used to treat other primary tumors, one breast cancer and one vestibular schwannoma. Some of the parameters established to assess the efficacy of bevacizumab therapy were tumor

volumetric reduction, achievement of a radiographic response, clinical patient stability, overall survival (OS), and progression free survival (PFS) measured at defined points in time after initiation of treatment (i.e. at 6/12 months). Data review and analysis was used to assess the safety parameters of the treatment by looking at the range and severity of reported adverse effects experienced in patients during therapy protocol. Of note, neither did all of the studies in this review assess treatment efficacy using identical end-point parameters nor did some of the reports include the etiology of toxicities experienced. Due to these discrepancies among data protocols, our analysis has certain limitations in reporting comparative results (see below). All patient and treatment data available from the studies were included in this literature review.

RESULTS

Study selection

The preliminary literature search for studies using PubMed yielded 22 results. After selectively narrowing the criteria required of the studies, 11 articles and a total of 92 patients were included in our review. Five retrospective clinical trial series, two prospective trials, and four single patient case reports were included in this analysis. Patient demographics, specific diagnosis, pretreatment regimens, adjuvant drug therapy, and therapeutic bevacizumab doses and schedule of these studies are described in detail in Table 1.[1,4,13,15,19,23,28,30,34,39,42]

Pretreatment recurrences/treatments

Nine of the studies, comprised of 76 patients, summarized in this review reported some form of prior meningioma treatment before starting patients on bevacizumab therapy. Among the participants in the studies retrieved, various combinations of pretreatment tumor management modalities were administered. The data show that 69 out of 76 (91%) patients from these nine studies underwent prior treatment with surgery. Of those, 30 patients underwent multiple surgeries for meningioma resection. Stereotactic radiosurgery was used in the pretreatment (pre-bevacizumab) regimen of 28 patients (37%). In all, 51 patients (72%) received fractionated RT prior to the start of bevacizumab; however, the dosing, regimen, and margins of RT varied among studies. Of note, 22 patients (29%) had received prior treatment with various chemotherapeutic and biological agents including imatinib mesylate (7), hydroxyurea (12), pasireotide (SOM230), a multi-ligand somatostatin receptor analogue (2), temozolomide (7), sunitinib (2), sandostatin (3), octreotide (3), tamoxifen (1), RU-486 (1), lovastatin (1), celecoxib (1), and etoposide (1) [Figure 2].

Bevacizumab dosage

Nine of the studies reported the administered dosage and schedule for the employed bevacizumab therapy.

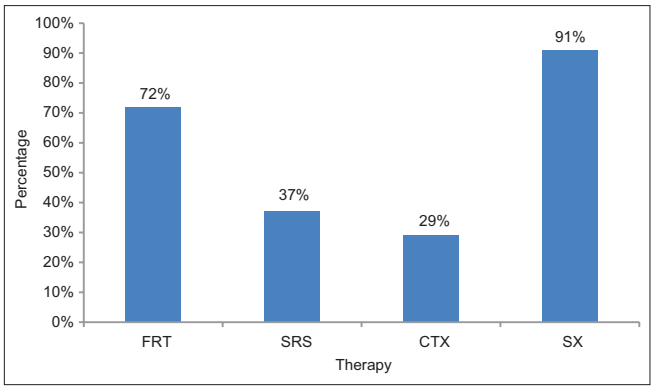

Figure 2: This is a diagram indicating percentage of patients and treatment prior to bevacizumab therapy

Bevacizumab was administered every 2 weeks, with four studies administering the drug at a dose of 5 mg/kg,[4,13,15,30] three studies administering a dose of 10 mg/kg,[28,34,39], and one study administering either 5 mg/kg or 10 mg/kg.[19] The Alanin *et al*. study administered bevacizumab 10 mg/kg every 2 weeks for 6 months and then 15 mg/kg every 3 weeks.

Pathology

In evaluating the differences in tumor responses among patients, we must take into account the grade of the tumors treated and their susceptibility to anti-angiogenic therapy. In the case studies reported by Puchner *et al*. and Bostrom *et al*., the tumors had histological features of a grade III (anaplastic) meningioma, whereas the case report by Wilson *et al*. reported a grade I tumor. The retrospective series of Lou *et al*. included 14 patients: five (36%) with grade I meningioma, five (36%) had grade II (atypical) meningioma, three (21%) had grade III (anaplastic) meningioma, and one patient had a confirmed histologic diagnosis of meningioma, but of unspecified grade. The series identified by Nayak *et al*. reported 15 patients: six (40%) had grade II (atypical) meningioma and nine (60%) had grade III (anaplastic) meningioma. The prospective trial by Furuse *et al*. included six patients: two with grade I meningioma, one with grade II (atypical) meningioma, and three with anaplastic (grade III) meningioma. Finally, the phase II prospective trial by Shih *et al*. included 17 patients: five with grade I meningioma, seven with grade II meningioma, and four with grade III meningioma.

Survival

Using Kaplan–Meier survival curves, PFS and OS were documented for the patient cohorts, with both endpoints measured from the initiation of bevacizumab therapy. PFS was defined as the time from induction of therapy until death, initial disease progression, or last follow-up, assuming the patient remained alive without disease progression. OS was defined as the time from the

Table 1: Bevacizumab study data

Author and year	Type of study	No. of Pts.	Avg age + range (yrs.)	Patients with prior resections	WHO Grade	Treatment Dose	Outcomes
Puchner *et al*. (2010)[34]	CRp.	1	52	1	Anaplastic (Grade III)	Bevacizumab IV (10 mg/kg) q 2 weeks	T1 MRI (6 months.)- PR; T2 & FLAIR HIL- MR
Goutagny *et al*. (2011)[17]	CRp.	1	51	N/A⊥	Unknown	Bevacizumab IV (5 mg/kg) q 2 weeks for 15 months	Tumor volume decreased by 22% (7.3 cm3 to 5.69 cm3) Last follow up at 15months and no PR
Wilson *et al*. (2011)[18]	CRp.	1	57	1	Grade I	Bevacizumab (12 mos.) + Pacitaxel (6 mos.)	PR (N/A⊥)
Lou *et al*. (2012)[19]	RS	14	53.5 (20-70)	14	Grade I: *n*=5; Grade II: *n*=5; Grade III *n*=3; Unknown: *n*=1	N/A⊥	Med. PFS: 12.2 months (WHO Grade I tumors) 15.8 months (WHO Grade II/III tumors) PFS- 6 mo. - 80% (Grade I) 86% (Grade II/III)
Nayak *et al*. (2012)[20]	RS	15	55 (16-36)	15	Atypical (Grade II): *n*=6, Anaplastic (Grade III): *n*=9	Bevacizumab IV (10 mg/kg) q 2 weeks	Median PFS: 6.5 months (95% CI, 10-29 weeks) Median OS: 15 months (95% CI, 10-22 mo.) PFS- 6 months: 43.8% (95% CI, 15.7-69.1%)
Nunes *et al*. (2013)[21]	RS	15	29.5 (11-78)	N/A⊥	15 NF-2 pts with a total of 48 meningiomas (Unknown Grade)	Bevacizumab IV (5 mg/kg) q 2 weeks	Per pt analysis: Median PFS- 20 months; PFS- 6/12 months: 93%/79% Per tumor analysis: Median PFS- 15 months; PFS- 6/12 months: 85%/62%
Hawasli *et al*. (2013)[22]	RS	9	37.2 (14-70)	7	Unknown	Bevacizumab IV 5-10 mg/kg q2-3 weeks	2 patients with response 5 patients with stable disease 2 patients with disease progression
Bostrom *et al*. (2014)[23]	CRp	1	80	1	Anaplastic (Grade III)	Bevacizumab IV 5 mg/kg q2 weeks	T1MRI decrease in lesion
Alanin *et al*. (2014)[24]	RS	12	34 (23-78)	8	Unknown	Bevacizumab IV 10 mg/kg q2 weeks for 6 months, then bevacizumab 15 mg/kg q3 weeks	Radiological response in 6/12 patients (50%), 4/12 had continued response 6 months later
Furuse *et al*. (2015)[25]	P	6	60.8 (46-76)	6	Grade I: *n*=2 Grade II: *n*=1 Grade III: *n*=3	Bevacizumab IV 5 mg/kg q2 weeks	Average 52.5% reduction via FLAIR
Shih *et al*. (2016)[26]	P	17	59 (29-84)	16	Grade I: *n*=5 Grade II: *n*=7 Grade III: *n*=4 Unknown: *n*=1	Bevacizumab IV 10 mg/kg D1 and d15 q28d with Everolimus 10 mg q28d	Median PFS: 22 months (95% CI, 4.5-26.8) Median OS 23.8 months (95% CI 9.0-33.1) PFS-6 months 69%

Acronyms: CRp: Case report, RS: Retrospective study, P: Prospective study, ⊥Study did not specify, NF: Neurofibromatosis, PR: Progression, PFS: Progression Free Survival, OS: Outcome Survival, CI: Confidence Interval

therapy start date until death. Results analyzed from the studies (61 patients) demonstrated median overall PFS of 16.8 months (range: 6.5-22 months) and that 73% of patients were progression free at 6 months (PFS-6) (range: 44%-93%).

Bevacizumab safety

Overall, the majority of patients tolerated the dosage of bevacizumab used in these series with minimal complications. Evaluating the data reported for complication rates for the 92 patients included in this pooled cohort; grade III events were reported in 9.8% of patients, grade IV events in 4.3%, and two patients (2.1%) had a grade V event, of which the causality is uncertain in one. When comparing the dosages of bevacizumab (5 mg/kg vs. 10 mg/kg), there were no statistically significant differences in the frequencies of side effects between the two groups.

DISCUSSION

Although meningiomas are the most common primary CNS tumor, there is a paucity of data to support the use of most adjuvant chemotherapies, and no effective medical treatment currently exists for recurrent tumors after resection and radiation. Among the available FDA approved drugs is bevacizumab, a monoclonal antibody that binds to VEGF receptors forming a complex that inhibits binding of ligands and subsequently blocks angiogenesis.[26] This review is directed at evaluating all current data regarding the efficacy and safety of bevacizumab for the treatment of recurrent intracranial meningiomas. A comprehensive literature review revealed five retrospective series, four case reports, and two prospective trials using this systemic VEGF-directed therapeutic modality. Individual patient data were tabulated and available for 45.6% (42/92) patients.

Five studies, with a total of 40 patients, in this review evaluated the tumors' best radiographic response using the RANO (Response Assessment in Neuro-Oncology) criteria.[18-20,22,23] Calculations of tumor response under the RANO criteria include the assessments of both enhancing and nonenhancing imaging measuring the maximal cross-sectional area with consideration of FLAIR abnormalities and clinical outcome. The observed tumor responses were categorized as having a complete response (all target lesions have disappeared), partial response (tumor decreased ≥50% from baseline value), stable disease (<50% decrease to <25% increase), or progressive disease (increased by ≥25% from nadir value). Interpretations of best tumor response from the radiographic imaging showed 32 patients (80%) with stable disease, 4 patients (10%) achieved a partial response, and 4 patients (10%) were found to have a progressive disease. From these five studies, no patients achieved a complete response.

The other six studies, with a total of 52 patients, used a percentage of volumetric change as measurement criteria for radiographic response. Radiographic response was defined as volumetric regression (decrease ≥20%), progression (increase ≥20%), or stable disease as any volumetric change in between. Regression analysis showed 12 patients (23%) had a radiographic response. In all, 26 patients (50%) had a stable disease, while 12 patients (23%) progressed. Two patients (4%) died prior to repeat imaging evaluation, and no patients had complete response.

Nayak *et al*. observed six patients with magnetic resonance imaging (MRI) findings of decreased T2 hyperintensities around the tumor, consistent with a reduction in peritumoral edema. After six weeks of therapy, FLAIR and T2-weighted MRI data reported by Puchner *et al*. exhibited regression in the hyper-intense lesions; both in the peritumoral edema zone and the center of the tumor. These observed radiographic responses were maintained at follow-up, 6 months after treatment cessation.

The Nayak review recorded the OS with a median OS of 15 months (95% CI: 10, 22 months). Due to the higher incidence of multifocal disease in patients with NF-2, Nunes *et al*. analyzed their data on a per-tumor as well as per-patient basis. The reported rates for the per-tumor PFS-6 and PFS-12 were 85% and 62%, respectively. The rates calculated for the per-patient PFS-6 and PFS-12 analyses were 93% and 79%, respectively, which accounts for multiple intracranial abnormalities. Lou and colleagues further analyzed the data and dichotomized the results based on WHO tumor grade and therapeutic treatment arms. The patient cohort with grade I meningiomas had a median PFS and PFS-6 of 12.2 months (95% CI: 1.1, 27.2) and 80% (95% CI: 20.4, 96.9), respectively, and 15.8 months (95% CI: 5.5, 17.9) and 87.5% (95% CI: 38.7, 98.1) for patients with grade II/III meningiomas, respectively. The four patients receiving treatment with bevacizumab as a single-agent therapy had a median PFS and PFS-6 of 15.8 months (95% CI: 12.2, ∞) and 100%, respectively, and 17.9 (95% CI: 1.1, 27.2) and 80% (95% CI: 40.9, 94.6), respectively, for the combination of bevacizumab plus chemotherapy group (n = 10). The Shih *et al*. phase II study was the only other study which showed OS. The median OS was 23.8 months (95% CI: 9.0-33.1), with median PFS of 22 months (95% CI: 4.5-26.8). PFS-6, 12, and 18-month rates were 69%, 57%, and 57%, respectively.

Most patients tolerated bevacizumab well, and the observed adverse effects were similar in type, severity, and incidence to those reported in patients treated with bevacizumab for glioblastoma (GBM).[12,22] Most toxicities experienced were hematologic, including thrombocytopenia (grade 1), anemia (grade 1-2), and intratumoral hemorrhage (grade 1-3). Although one patient did present with grade 3 thrombocytopenia, this was most likely attributed to concurrent irinotecan chemotherapy. Nonhematologic toxicity included proteinuria (grade 1-3), hypertension (grade 1-3), fatigue (grade 1-3), elevated liver enzymes (grade 3), mucositis (grade 1-2), diarrhea (grade 1-3), hypercholesterolemia (grade 1-3), epistaxis (grade 1-2), headache (grade 1-2), and a report of a craniotomy site cellulitis (grade 2), which was responsive to oral antibiotics. Although rare, some more serious (grade ≥ 4 and/or requiring therapy discontinuation) treatment-related concerns were intestinal perforation, wound healing delays, and a report of pneumonia complicated by sepsis.

Potential uses of bevacizumab for meningiomas

The use of bevacizumab for patients with recurrent meningiomas is a matter of debate. However, its use may

be most beneficial in special circumstances such as the ones listed below:

1. Treatment refractory/high-grade/high-vascularity cases
   In certain cases where treatment fails to prevent recurrence or progression, we advocate for the use of an adjuvant therapeutic agent such as bevacizumab. Although surgery and radiosurgery may be potential options for relapsing meningiomas, bevacizumab may delay recurrence and may also serve as a potential neoadjuvant option to radiation/surgery.

   Case illustration

   First patient is a 40-year-old female with a history of progressive left-sided hemiparesis and nausea and vomiting who presented to our institution with a large parasagittal meningioma extending over the central sulcus. Patient received a subtotal resection and adjuvant radiation therapy. After 5 years, tumor progression was noted in the surgical site, and a new lesion was noted along the anterior falx [Figure 3]. The patient was subsequently taken for a second round of surgery aiming at gross total resection of both lesions. Histology revealed a grade III malignant meningioma with sarcomatous features.

   Case illustration

   Second patient is a 46-year-old male with a history of resection of an anterior parasagittal meningioma, who presented with progressive headaches 6 months later. Imaging revealed a large anterior frontal parasagittal meningioma along the anterior two thirds of the superior sagittal sinus. Patient was taken for surgery and a Simpson grade 3 resection was achieved. Histology at that time revealed a WHO grade III anaplastic meningioma. Over the next year, serial imaging revealed a left convexity meningioma [Figure 4].
2. Multiple meningiomas
   Patients with symptomatic multiple meningiomas are often difficult to treat due to the complexity of surgery, distance between lesions, and predisposition to recur. Resection is typically limited to the largest most symptomatic lesion and to surgically accessible lesions; therefore, adjuvant treatment such as radiation treatment (external beam RT or radiosurgery) or chemotherapy (bevacizumab) may be potential options for patients with meningiomas that continue to grow.

   Case illustration

   The patient is a 66-year-old female who presented with a lower cranial nerve palsies and left-sided hearing loss. MRI imaging revealed a large petroclival meningioma that continued to increase in size. The patient was taken for left suboccipital craniotomy (translabyrinthine approach), in which a subtotal resection was achieved. Subsequently, the patient underwent gamma knife radiosurgery, which failed to achieve control tumor. Two years later, the patient underwent another resection of residual tumor, again considered to be a gross total resection. However, the patient began to experience left-side radicular thoracic pain five years after the initial diagnosis. Subsequent imaging revealed multiple intradural extramedullary lesions in the thoracic spine from T3-T5 and T9-T10.
3. Radiation-induced meningiomas

   Case illustration

   The patient is a 47-year-old male with a history of an intraparenchymal low-grade glioma (treated with gross total resection and RT 25 years prior) who presented with a new-onset seizure. MRI revealed a right frontal convexity radiation-induced meningioma;

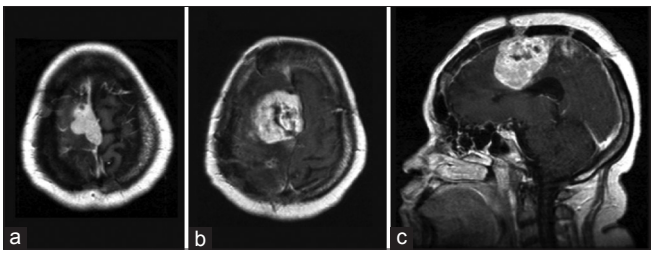

Figure 3: Preoperative Post contrast T1 axial (a) MRI image indicating a vertex meningioma. Post contrast T1 MRI images axial (b) and coronal (c) demonstrating large recurrent lesion 3 years after surgery at operative site

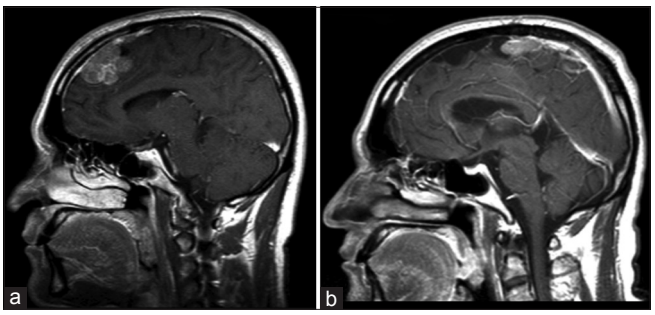

Figure 4: T1 sagittal post contrast MRI image revealing falx meningioma (a). 2 years after surgery T1 sagittal post contrast MRI image indicating new meningioma posterior to the operative cavity (b)

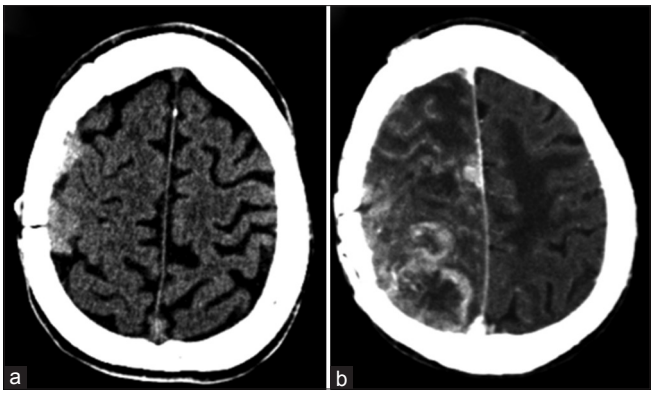

Figure 5: CT image indicating right frontal convexity meningioma (a). Follow up ct scan with contrast indicating recurrence of the tumor (b)

the patient subsequently had the surgery and a gross total resection was achieved. However, the tumor recurrence was noted after 2 years, and the patient was taken again for surgery [Figure 5].

Study limitations

As with all review studies, certain limitations exist that must be taken into account when interpreting pooled results. To begin with, the conclusions drawn from the individual series are restricted due to the small number of patients enrolled and the retrospective nature of the reports. Another finding limiting our analysis is the use of RANO criteria, which analyzes both enhancing and nonenhancing radiographic components, to assess tumor response to therapy. This response assessment paradigm was created to measure changes in malignant gliomas, not meningiomas, as was the case in our studies. An additional constraint in the interpretation of these studies comes from the fact that many patients received radiation and/or stereotactic radiosurgery prior to initiating bevacizumab therapy. This may have induced radionecrosis, which radiographically is indistinguishable from tumor progression. Furthermore, there was variation among the individual studies with respect to the dosage of bevacizumab administered, as well as differences in latency and duration of therapy. Finally, this review includes varying meningioma pathologies, some of which may grow at different rates and may require longer follow-up period to fully understand the pathophysiological changes observed. This may result in response rates that are blurred across various pathologies.

Future directions

The overall findings of these studies, even in the absence of survival parameters in some, offer encouraging results which warrant further investigations via large, prospective randomized control trials [Table 2]. The results of our clinical endpoint analysis of the available data were promising; the achieved median PFS and PFS-6 compare favorably with the results of other trials using PDGFR,[35,41] EGFR,[29] and multi-tyrosine kinase[21] targeted agents; salvage chemotherapy;[8-10,17,36] interferon-α;[6] somatostatin inhibitors;[7,20] and therapeutic hormone agents.[14,16]

The observation that advanced meningiomas, grades II and III, has been associated with increased VEGF expression and hypervascularity,[3,32,33] and hypothetically offers the advantage of tumor susceptibility to anti-angiogenic agents, such as bevacizumab. Further support for agents with this mechanism of action stem from its potential to effectively reduce peritumoral edema, thus deterring any further promulgation of VEGF and tumor cells.[11]

The molecular hypothesis guiding the rationale for using bevacizumab, and agents with comparable mechanisms of action, is based on the notion that VEGF as a key mediator of angiogenesis and edema formation has been shown to be expressed in 67% to 84% of meningiomas.[40] However, results from the Nunes *et al.* study demonstrate considerable heterogeneity among tumors in their expression of angiogenic factors as well as microvascular density.[30] In addition, by using immunohistochemical (IHC) analysis, these investigators were able to better define the contents of the tumor-associated molecular environment, and to identify factors driving angiogenesis. Specifically, the IHC analysis looked at expression of VEGF, SEMA3 (a potent inhibitor of angiogenesis), and VEGF/SEMA3 ratios, revealing variable expression on both tumor

Table 2: This is a table looking at other agents and data for the treatment of recurrent/progressive meningiomas

	Wen[9]	Norden[10]	Reardon[30]	Kaley[29]	Johnson[36]	Raizer[11]
Targeted Therapy & MOA	Imatinib PDGFR Inhibitor	Gefitinib (n=16); erlotinib (n=9) EGFR Inhibitor	Imatinib + Hydroxyurea	Sunitinib TKI Inhibitor	Octreotide Somatostatin analogue	VEGFR and PDGFR Inhibitors
n	23	25	21	36	12	21
Overall Results	Med. PFS: 2 months PFS-6: 29.4%	Med. PFS: 2.5 months Med OS: 23 months PFS-6: 28%	Med. PFS: 7 months PFS-6: 61.9%	N/A	Med. PFS: 4.25 months Med OS: 32.4 months PFS-6: 28%	Med. PFS: 5.9 months PFS-6: 47%
WHO Grade I	Med. PFS: 3 months PFS-6: 45%	Med. PFS: 2.25 months OS: 13 months PFS-6: 25%	Med. PFS: 13.9 months Med OS: 66 months PFS-6: 87.5%	N/A	N/A	N/A
WHO Grade II/III	Med. PFS: 2 months PFS-6: 0%	Med. PFS: 4 months OS: 33 months PFS-6: 29%	Med. PFS: 5.3 months Med OS: 20.9 months PFS-6: 46.2%	Med. PFS: 4.6 months PFS-6: 36%	N/A	Med. PFS: 3.7/3.6 Med OS: 22.9/19.6 months PFS-6: 39/43%
Radiographic Tumor Response	SD: 40%	SD: 32%	SD: 31%	SD: 61% PR: 3%	SD: 75%	SD: 71% PR: 5%

markers and microvascular density among meningiomas. These tumor-associated molecular markers are recent findings which may offer a pragmatic explanation to why such variation in response to bevacizumab therapy exists between tumors. Further research on this issue is warranted and may help in identifying patients who will more likely respond to these targeted therapies, thereby gaining maximum benefit.

Currently, there are several clinical trials underway using therapeutic agents targeting VEGF-directed pathways in patients with recurrent/progressive meningiomas. Notably, the multi-institutional phase II trial evaluating the combination therapy of bevacizumab and optune delivered electric field therapy (NCT02847559) and the phase II trial using bevacizumab as a single-agent therapy (NCT01125046), the former of which is still recruiting.

Further studies are required to identify medical therapies for patients who have progressed on avastin therapy. It is unclear whether these patients will benefit from continued avastin therapy or whether such therapy should be discontinued. KPS scores should also be included in these studies to further allow to ascertain the benefit of such therapies in the patient subgroups.

CONCLUSION

Patients with recurrent meningiomas currently have limited treatment options once they experience either recurrence or progression following the maximal surgical treatment and adjuvant radiation therapy. Given the overall morbidity with recurrent tumors and the subsequent poor survival, there is a critical need for effective therapies for these patients. The studies in this review, though limited by their small size and retrospective nature, offer encouraging efficacy and safety results with the use of bevacizumab, either alone or with combination chemotherapies, for selected patients. The data from these studies to date warrant further investigation in larger, prospective, randomized control trials evaluating the use of anti-angiogenic agents for recurrent/progressive meningiomas.

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Conflicts of interest
There are no conflicts of interest.

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