Antiangiogenic Agents for Nonmalignant Brain Tumors

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Abstract

Keywords

- brain tumor
- meningioma
- vestibular schwannoma
- vascular endothelial growth factor
- neurofibromatosis
- bevacizumab
- pazopanib

Objective To assess the treatment response and side effects for the use of antiangiogenic agents such as vascular endothelial growth factor (VEGF) inhibitors for patients with vestibular schwannomas and meningiomas.

Design and Methods Retrospective review of eight male and two female patients (ages 14 to 70, mean 36 years), treated with bevacizumab (9) or pazopanib (1). Six patients had neurofibromatosis type 2 (NF2) with bilateral vestibular schwannomas and meningiomas, and the four others had aggressive recurrent meningiomas.

Results During treatment (range 4 to 21 months, mean 9.1) with antiangiogenic agents, two patients with an atypical meningioma and radiation necrosis had dramatic partial response, the six NF2 patients had stable or slightly improved disease, and two meningioma patients had disease progression. Hearing was stable in three of the NF2 patients and was improved in three NF2 patients (one of whom received a cochlear implant). Minor toxicities included epistaxis, nausea, diarrhea, weight loss, and abdominal pain. No grade 3 or 4 toxicities were observed.

Conclusion Antiangiogenic agents appear to be safe for the treatment of patients with nonmalignant brain tumors, and in select cases may be efficacious.

Introduction

Surgical resection has historically been the mainstay of therapy for nonmalignant brain tumors such as vestibular schwannomas and meningiomas. However, there remains a

subset of patients who are not surgical candidates. Fractionated radiotherapy or radiosurgical techniques have provided some benefit for these patients but, unfortunately, in many cases, the tumors still progress.¹ Furthermore, most traditional chemotherapy regimens have had only modest, if any,

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effect on the growth of these nonmalignant brain tumors. For such patients, it is imperative to consider novel biologically based therapeutic agents in an effort to improve outcomes for patients with these nonmalignant brain tumors.

Vestibular schwannomas are slow-growing benign Schwann cell tumors that surround the vestibular division of the eighth cranial nerve.² Vestibular schwannomas can extend into the cerebellopontine angle and may cause mass effect on cranial nerves or adjacent structures to cause neurological symptoms. The incidence of sporadic vestibular schwannomas is 0.002% per year.^{3,4} Individuals with the neurofibromatosis type 2 (NF2) inherited cancer predisposition syndrome develop bilateral vestibular schwannomas, meningiomas, schwannomas affecting other nerves, and spinal cord ependymomas. Bilateral vestibular schwannomas in NF2 patients usually lead to bilateral deafness by adulthood. Surgical and radiotherapy options have potential detrimental neurological consequences in this patient population, including loss of function of the seventh or eighth cranial nerves and the risk of secondary malignancy. In this regard, systemic therapeutic agents may offer an advantage for some patients. Plotkin et al⁵ reported that the antiangiogenic agent bevacizumab (BEV), an anti-vascular endothelial growth factor A (VEGF_A) monoclonal antibody, reduced vestibular schwannoma tumor size in 9 out of 10 NF2 patients and improved hearing function in 5 of 7 of these patients. Mautner et al^{6,7} reported two patients in whom BEV reduced vestibular schwannoma size by 40% and improved hearing. These clinical studies are substantiated by histological studies that have shown that VEGF and VEGF receptor (VEGFR) expression in vestibular schwannomas correlates with tumor growth.^{8,9}

Antiangiogenic agents may also have a role in the treatment of other extra-axial nonmalignant tumors. Elevated expression of VEGF and its cognate receptors have been associated with recurrent meningiomas, which may respond to VEGF or VEGFR inhibitors.^{10–13} VEGF inhibitors can also significantly reduce meningioma-associated peritumoral edema¹⁴ and radiation necrosis.¹⁵ In this study, we present a retrospective review of patients with nonmalignant brain tumors that were treated with antiangiogenic agents.

Methods

Following approval from the Washington University School of Medicine Institutional Review Board, a retrospective case analysis was performed for 10 patients. Patient history, disease details, treatments, radiographs, and outcome data were collected. Radiographic information was ascertained directly from magnetic resonance imaging (MRI) images or from reports. Hearing results were obtained from audiograms. Side effects were graded based on the National Cancer Institute Common Toxicity Criteria (Version 2.0). Ranges, means, and standard deviations are shown.

Results

Ten patients received antiangiogenic agents (age range 14 to 70, mean 35.8 ± 19.2 years, eight men/two

women; ▶Table 1). Six of the patients treated had NF2 with bilateral vestibular schwannomas. Of the NF2 patients, six had vestibular schwannomas, five had meningiomas, and five had intramedullary spinal cord tumors. Prior to chemotherapy, Patient 1 had progressive enlargement of all tumors including schwannomas, meningiomas, and an intramedullary spinal cord tumor. Patient 2 demonstrated enlargement of vestibular schwannomas and an intramedullary spinal cord tumor. Patient 3 demonstrated enlargement of vestibular schwannomas, and Patients 4, 7, and 8 demonstrated progressive hearing loss. Patient 5, who had a remote history of a cerebellar astrocytoma treated with surgery and radiation, now had a progressing atypical petroclival meningioma (WHO II) that was previously treated with multiple operations, stereotactic radiosurgery (21.5 Gy), and RU486. Patient 6 presented with a meningioma that extensively involved his sagittal and transverse sinuses. Biopsy revealed atypical meningioma (WHO II), and he was treated with fractionated radiation (54 Gy). The meningiomas in Patients 5 and 6 were not amenable to gross-total resection and demonstrated tumor progression. Patient 9 had an enlarging atypical meningioma that had required multiple operations and radiation therapy. Patient 10 had progression of his lesion after surgery and proton beam therapy. Patient 2 was treated with pazopanib (PAZ), a tyrosine kinase inhibitor of VEGFRs that blocks tumor growth and inhibits angiogenesis. PAZ was initially dosed 800 mg per day and then reduced to 600 mg per day. The remaining patients were treated with BEV, and dosages ranged from 5 to 10 mg/kg every 2 to 3 weeks. Treatments ranged from 4 to 21 months (mean 9.1 ± 5.1 months).

Treatment with antiangiogenic agents led to improved or stable disease in all six NF2 patients. Antiangiogenic agents reduced vestibular schwannoma enhancement in one patient and improved hearing in two patients (▶Table 2). Clinical and radiographic disease was stable in the remaining patients. Patients 1 and 2 showed stable clinical and radiographic disease after treatment with antiangiogenic agents. Serial imaging revealed that these agents halted the progression of these two patients' vestibular schwannomas, meningiomas, and intramedullary spinal cord tumors. Patient 3 demonstrated decreased vestibular schwannoma enhancement and improvement in word recognition score from 56% to 80%. Patient 4 had improved hearing after a cochlear implant was placed followed by stable hearing with BEV treatment. Patient 7 showed stable radiographic disease but improved hearing for the 500-to-700-Hz range and the 4-to-8-kHz range. Right hearing was also slightly improved. Patient 8 showed stable hearing and radiographic disease with treatment.

Antiangiogenic agents improved clinical and radiographic disease in two of four meningioma patients (▶Table 2). Patient 6 showed dramatic partial response of his meningioma and surrounding T2 hyperintensity and clinical improvement (▶Fig. 1, ▶Table 2). Patient 10 remained neurologically stable and showed dramatic

Table 1 Patients with Antiangiogenic Agents

Case no.	Age (yr), sex	NF2	CNS neoplasms	Prior treatments	Progression prior to VEGF R _x	VEGF R _x	VEGF R _x duration (months)
1	22, M	Y	<ul style="list-style-type: none"> Meningiomas Vestibular schwannomas Nerve sheath tumors Intramedullary spinal cord tumor 	<ul style="list-style-type: none"> Craniotomy for vestibular schwannoma 	<ul style="list-style-type: none"> Increasing size of multiple tumors Reduced hearing 	BEV	12
2	23, F	Y	<ul style="list-style-type: none"> Meningiomas Vestibular schwannomas Other cranial nerve schwannomas Peripheral nerve neurofibromas Sacral nerve sheath tumor Intramedullary spinal cord tumor 	<ul style="list-style-type: none"> Multiple craniotomies for tumor resections SRS Sacral tumor resection Resection of peripheral nerve lesion. 	<ul style="list-style-type: none"> Increasing size of vestibular schwannoma Increasing size of intramedullary spinal cord tumor 	PAZ	10
3	24, M	Y	<ul style="list-style-type: none"> Meningiomas Vestibular schwannomas Nerve sheath tumors Spinal cord ependymoma Spinal schwannomas 	Resections of: <ul style="list-style-type: none"> Skull base meningioma Spinal cord ependymoma Cervical schwannoma 	<ul style="list-style-type: none"> Increasing size of vestibular schwannomas Reduced hearing (right) 	BEV	21
4	16, M	Y	<ul style="list-style-type: none"> Vestibular schwannomas Other cranial nerve schwannomas Spinal schwannomas 	<ul style="list-style-type: none"> Craniotomy for resection of right vestibular schwannoma Left cochlear implant 	<ul style="list-style-type: none"> Progressive hearing impairment 	BEV	12
5	46, M	N	<ul style="list-style-type: none"> Recurrent meningioma Cerebellar astrocytoma (remote) 	<ul style="list-style-type: none"> Multiple craniotomies SRS RU486 (<i>trial</i>) Resection of cerebellar astrocytoma (remote) fXRT for cerebellar astrocytoma (remote) 	<ul style="list-style-type: none"> Increasing size of meningioma 	BEV	7
6	61, M	N	<ul style="list-style-type: none"> Meningioma 	<ul style="list-style-type: none"> Biopsy fXRT 	<ul style="list-style-type: none"> Tumor progression with increasing surrounding T2 hyperintensity 	BEV	9
7	14, M	Y	<ul style="list-style-type: none"> Meningiomas Vestibular schwannomas Spinal cord ependymoma Other cranial nerve schwannomas 	<ul style="list-style-type: none"> Lovastatin (<i>trial</i>) 	<ul style="list-style-type: none"> Sensorineural hearing loss (left > right) 	BEV	5
8	38, F	Y	<ul style="list-style-type: none"> Meningioma Vestibular schwannomas Spinal cord ependymomas 	<ul style="list-style-type: none"> Craniotomy for left vestibular schwannoma 	<ul style="list-style-type: none"> Right tinnitus Right hearing loss 	BEV	5

Table 1 (Continued)

Case no.	Age (yr), sex	NF2	CNS neoplasms	Prior treatments	Progression prior to VEGF R _x	VEGF R _x	VEGF R _x duration (months)
9	44, M	N	• Meningioma	• Two craniotomies for tumor resections • fXRT • SRS • Endovascular embolization	• Tumor progression	BEV	6
10	70, M	N	• Meningioma	• Craniotomy for resection • Proton beam radiation • Biopsy	• Tumor progression and increased surrounding T2 hyperintensity.	BEV	4

Abbreviations: BEV, bevacizumab; CNS, central nervous system; fXRT, fractionated radiation therapy; PAZ, pazopanib; SRS, stereotactic radiosurgery; VEGF, vascular endothelial growth factor; VEGF R_x, vascular endothelial growth factor inhibitor.

reduction in tumor enhancement and surrounding T2 signal abnormalities with treatment. In contrast, meningioma Patients 5 and 9 showed progression of radiographic disease, and Patient 5 showed a decline in functional status despite treatment with BEV (►Table 2).

Treatment with antiangiogenic agents led to no side effects in one patient, National Cancer Institute Common Toxicity Criteria grade 1 side effects in three patients, and grade 2 side effects in two patients (►Table 3). Grade 1 side effects included anorexia, hypertension, chest pain, epistaxis, constipation, and confusion. Grade 2 side effects included abdominal pain, diarrhea, weight loss, and nausea. Side effects in Patient 2 led to dosage reduction. An episode of confusion in Patient 6 led to a brief pause in treatment. There were no grade 3, 4, or 5 side effects of treatment.

Discussion

Advances in our understanding of the molecular and cellular pathogenesis of brain tumors have facilitated the application of biologically-targeted therapies for difficult-to-treat cancers. One of the critical cellular targets for biologically targeted brain tumor treatment are factors that drive or maintain angiogenesis. Bevacizumab was the first clinically available angiogenesis inhibitor in the United States and has Food and Drug Administration (FDA) approval for the treatment of metastatic colon cancer, non-squamous non-small cell lung cancer, metastatic renal cell carcinoma, and recurrent glioblastoma.¹⁶ Several studies have also indicated that VEGF and VEGFR antagonists have roles in the treatments of other brain tumors, including vestibular schwannomas, meningiomas, and low-grade astrocytomas.^{5,7-9,11,12,17,18} Despite being nonmalignant brain tumors, vestibular schwannomas and meningiomas carry significant morbidity and risk of mortality for certain patients. Many but not all of these tumors can be treated with surgery or radiotherapy. Unfortunately, for schwannomas and meningiomas that recur after irradiation, there are no effective chemotherapies. In addition, temozolomide and other chemotherapies for malignant brain tumors are not clearly efficacious for nonmalignant brain tumors. Consequently, new therapeutic agents are needed. Here we report our experience with the use of VEGF and VEGFR inhibitors in schwannomas and meningiomas and demonstrate that in certain patients antiangiogenic agents can serve as a possible and safe treatment option for these tumors. In NF2 patients, antiangiogenic agents can slow or halt tumor growth and mitigate hearing loss. In some cases, antiangiogenic agents can even improve hearing. In meningioma patients, antiangiogenic agents may also play a role. Patients 6 and 10 both showed radiographic and clinical evidence of tumor progression of meningioma and possible radiation necrosis. Both had a dramatic radiographic and one had clinical improvement from BEV treatment. In contrast, the other meningioma patients had no response. It would be interesting to see if immunohistochemical stains for VEGF and

Table 2 Response to Antiangiogenic Agents

Case no.	Clinical	Radiographic
1	Stable hearing and neurological examination	Stable intracranial and spinal cord disease
2	Stable hearing and neurological examination	Stable intracranial and spinal cord disease
3	Improved hearing from 56% to 80% in word recognition score	Reduction in vestibular schwannoma tumor enhancement
4	Improved after cochlear implant followed by stable hearing; stable neurological examination	Stable disease
5	Decline in functional status	Continued tumor growth
6	Improved strength and functional status	Reduction in tumor enhancement and surrounding T2 hyperintensity
7	Left hearing improved slightly for 500–750 Hz and significantly for 4–8 Hz; right improved for 6–8 Hz; stable neurological examination	Stable disease
8	Stable hearing and neurological examination	Stable intracranial and spinal cord disease
9	Stable neurological examination	Continued tumor growth
10	Stable neurological examination	Reduction in tumor enhancement & surrounding T2 hyperintensity

VEGFRs could predict treatment response to VEGF and VEGFR inhibitors, respectively. Treatment with antiangiogenic agents is often associated with side effects, but in this report, we found no patients with high-grade side effects.

This case series carries implicit limitations in its retrospective nature, small patient number, and scope. Prospective clinical trials are now under way to further evaluate the efficacy of this treatment option. Future studies correlating

Figure 1 Response of atypical meningioma to bevacizumab (BEV). T1 axial and sagittal images with contrast are shown (A-B) before and (C-D) after 9 month treatment with BEV.

Table 3 Side Effects Antiangiogenic Agents

Case no.	Side effects (grade*)	Effect on treatment
1	Abdominal pain (2), diarrhea (2), weight loss (2)	None
2	Nausea (2), anorexia (1), Hypertension (1), weight loss (2)	Dose decreased from 800 to 600 mg daily
3	Hypertension (1)	None
4	Chest pain (1)	None
5	None	None
6	Hypertension (1), confusion (1)	Brief pause in treatment
7	Epistaxis (1)	None
8	None	None
9	Constipation (1), epistaxis (1)	None
10	None	None

*NCI CTC Toxicity scale Version 2.0.

VEGF and VEGFR expression with treatment response will also be helpful.

Conclusion

Antiangiogenic agents appear to be safe for the treatment of patients with benign brain tumors and in select cases may be efficacious.

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