Peritumoral brain edema in intracranial meningiomas: the emergence of vascular endothelial growth factor–directed therapy

JACK HOU, M.D.,^{1,2} VARUN R. KSHETTRY, M.D.,² WARREN R. SELMAN, M.D.,¹
AND NICHOLAS C. BAMBAKIDIS, M.D.¹

¹Department of Neurological Surgery, University Hospitals Case Medical Center; and ²Department of Neurological Surgery, Cleveland Clinic, Cleveland, Ohio

Meningioma is the second most common type of adult intracranial neoplasm. A substantial subset of patients present with peritumoral brain edema (PTBE), which can cause significant morbidity via mass effect, complicate surgical management, and impact the safety of stereotactic radiosurgery. Recent studies suggest a close relationship between vascular endothelial growth factor-A (VEGF-A) expression and PTBE development in meningiomas. The authors performed a systematic review of the literature on the pathogenesis of PTBE in meningiomas, the effectiveness of steroid therapy, the role played by VEGF-A, and the current clinical evidence for antiangiogenic therapy to treat peritumoral brain edema. Mounting evidence suggests VEGF-A is secreted directly by meningioma cells to induce angiogenesis and edemagenesis of tumoral as well as peritumoral brain tissue. The VEGF-A cascade results in recruitment of cerebral-pial vessels and disruption of the tumor-brain barrier, which appear to be requisite for VEGF-A to have an edemagenic effect. Results of preliminary clinical studies suggest VEGF-directed therapy has modest activity against recurrent and progressive meningioma growth but can alleviate PTBE in some patients. A comprehensive understanding of the VEGF-A pathway and its modulators may hold the key to an effective therapeutic approach to treating PTBE associated with meningiomas. Further clinical trials with larger patient cohorts and longer follow-up periods are warranted to confirm the efficacy of VEGF-directed therapy.
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KEY WORDS • meningioma • brain edema • angiogenesis •
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MENINGIOMAS originate from arachnoid cap cells and are the second most common type of intracranial adult neoplasm, accounting for 20% of all intracranial tumors.^{17,66,96} According to the Central Brain Tumor Registry of the US, the annual incidence of meningiomas is 7.22 per 100,000 and increases with age even beyond 85 years without reaching a peak.²² Intracranial meningiomas outnumber spinal meningiomas by 10-fold and 85% occur supratentorially.⁷³ Females are twice as likely to be affected. However, higher-grade meningiomas occur more often in men.⁵³

The WHO classifies meningiomas into 9 low-grade (Grade I) subtypes and 3 subtypes each in Grade II and Grade III, which constitute 80%, 15%–20%, and 1%–3%

of cases, respectively. The most common subtypes are meningotheliomatous (63%), transitional or mixed type (19%), and fibrous (13%) meningiomas.⁷¹ Thus, most meningiomas are benign tumors with a 5-year recurrence rate of only 5% following gross-total resection.⁷¹

Although 97%–99% of meningiomas are slow-growing Grade I and II tumors, they can cause significant morbidity via edema production that exerts mass effect on neighboring structures. Indeed, 38%–67% of patients with intracranial meningioma present with a variable amount of peritumoral brain edema (PTBE),³⁰ which causes elevated intracranial pressure (ICP) and is associated with a shorter time to diagnosis and an increased likelihood of developing symptoms.^{5,21,90} Severe PTBE contributes significantly to the development of pre- and postoperative seizures.^{48,92} Peritumoral brain edema is often associated with pial blood supply to the meningioma and loss of a clean arachnoid dissection plane at the meningioma/brain interface.^{1,5} Consequently, meningiomas with PTBE are associated with a higher risk of postop-

Abbreviations used in this paper: ICP = intracranial pressure; NRP1-R = neuropilin-1 receptor; PFS = progression-free survival; PTBE = peritumoral brain edema; RT-PCR = reverse transcription polymerase chain reaction; VEGF = vascular endothelial growth factor; VEGFR = VEGF receptor.

erative intracranial hematoma, intracranial hypertension, receiving blood transfusion, and subsequently a longer hospital stay.^{1,92} As was reported by Sindou and Alaywan, meningiomas with PTBE, particularly located in eloquent areas, present a greater risk for postoperative neurological deficits.⁸⁰ Lastly, PTBE may impact the safety of stereotactic radiosurgery as well.⁴¹

Therefore, the ability to predict and alleviate PTBE in the management of meningiomas is paramount to improving patient outcomes. To date, several molecules, including vascular endothelial growth factor-A (VEGF-A), have been implicated in the development of PTBE. Disruption of the tumor-brain barrier as a result of tumor penetration of the arachnoid membrane may induce PTBE by introducing edemagenic substances into the brain parenchyma.^{38,76,87} In this review, we describe the current understanding of the pathophysiology underlying PTBE development in intracranial meningiomas and the basic science and clinical literature behind VEGF-directed therapy for treatment of PTBE.

Literature Search

A MEDLINE search via the PubMed interface was performed for all articles using the key words: “edema,” “meningioma,” “VEGF,” or “vascular endothelial growth factor.” Search result abstracts were reviewed for pertinent articles including reviews, laboratory investigations, and clinical series. Reference sections of reviewed articles were searched for additional articles not identified by the original MEDLINE search. Clinical laboratory studies investigating the correlation between VEGF expression and edema development were filtered by adding the supplementary key words “correlation” or “association.” Thirteen articles were identified that matched the eligibility criteria.

Articles relating to clinical VEGF-directed therapy in meningiomas were identified by adding the key words “therapy,” “treatment,” “clinical trial,” or “outcome.” We identified a total of 3 case reports and 3 case series. Five completed or ongoing clinical trials on VEGF-directed therapy in meningiomas were identified on the website www.clinicaltrials.gov using the key words “meningioma” and “VEGF” or “vascular endothelial growth factor.”

Theories on the Pathogenesis of PTBE in Meningiomas

Previous studies have attempted to correlate PTBE with a number of clinicopathological factors, such as age, sex, location of tumor, tumor size,^{11,14,15,29,40,49} histological subtypes,^{29,30,40,49} vascularity,¹² secretory activity,⁶¹ venous outflow obstruction,¹⁴ and expression of sex hormones and receptors.^{9,15,23} However, the results have been contradictory, and no clear etiology has emerged from these factors. Nevertheless, 4 theories have been proposed to explain PTBE development.

The secretory-excretory phenomenon states that meningiomas of different histological types produce eosinophilic and periodic acid–Schiff-positive inclusions that are secreted as perivascular proteinaceous substances,^{2,83}

which may induce edema formation in neighboring brain tissue directly through osmotic force or via an undetermined secondary mechanism.¹⁴ Secretory meningiomas in particular had been reported in multiple large series to be associated with severe PTBE exceeding tumor size in 35%–41% of patients and can involve the entire hemisphere.^{70,93} However, they account for only 1.1%–3.0% of all meningiomas^{18,67,70,89} and do not explain PTBE formation in the vast majority of cases. Beyond secretory meningiomas, no association between histological subtypes and the incidence or degree of PTBE has been found in a number of studies.^{29,49,52,60}

The cerebral compressive theory postulates that tumor size may play an important role. Larger tumors cause more severe brain compression leading to ischemia and subsequent cytotoxic edema.^{29,30,52} This theory would suggest that the incidence of PTBE should be less in elderly patients, who have some degree of brain atrophy to buffer an intracranial space-occupying mass. However, even very small meningiomas with benign histology may sometimes have extensive PTBE.⁴⁰ In recent series, using an edema index to measure PTBE relative to tumor size, no significant correlation was found with tumor volume or patient age.^{40,45,52,60} Therefore, the compressive effect on the brain alone may not be a major factor in PTBE development.

The vascular compression theory dictates that PTBE is higher in patients with meningiomas occluding major cerebral veins or dural sinuses. However, in the largest angiographic series to date by Bitzer and colleagues (n = 136), lesions involving the cortical and bridging veins and dural sinuses did not show higher PTBE incidence.¹¹ There is no doubt that for a small subgroup of meningiomas with involvement of major dural sinuses, obstruction of venous outflow may directly exacerbate preexisting PTBE,³⁶ but in the majority of meningiomas, compression of adjacent cortical veins may not be a major culprit for meningioma-related PTBE.

The hydrodynamic theory states that PTBE occurs in the presence of intratumoral congestion. One superselective angiographic analysis (n = 25) found hypoplasia of efferent draining veins from the meningioma itself to be associated with a significantly higher edema index (p < 0.001).⁸⁸ Thus, a growing meningioma secretes angiogenic factors when its blood supply becomes inadequate. Highly permeable immature vessels form and result in leakage of plasma proteins. Tumor swelling in an encapsulated space compresses its venous drainage, resulting in a further increase in intratumoral pressure, intratumoral congestion, and accumulation of angiogenic factors. Consequently, supratentorial meningiomas with PTBE were found to have a 2% significantly higher intratumoral water content than that derived from control brain tissue from temporal lobectomies.⁵⁵ In the presence of a tumor-brain communication,³⁸ fluid and angiogenic factors from the tumor could enter surrounding brain tissue, leading to further angiogenesis in the peritumoral brain.²⁰ Vasogenic substances increase the permeability of cerebral-pial capillaries and expansion of PTBE through vasogenic edema (Fig. 1). A range of angiogenic factors has been associated with growth and neovascularization of meningiomas, including VEGF-A, endothelin-1, and caveolin-1.⁷ Among

Fig. 1. Proposed mechanisms of PTBE development in intracranial meningiomas.

these factors, VEGF-A is considered to be a major factor in inducing meningioma angiogenesis and edemagenesis and is most consistently associated with PTBE formation in clinical and ex vivo studies.^{77,97} Consequently, VEGF-A may be a core element and a unifying component of the various theories presented above, asserting the multifactorial origin of edemagenesis.

Ineffectiveness of Steroid Therapy

Steroid therapy has been used in neurosurgery for more than 5 decades to reduce PTBE and thereby lessen symptoms and complications during craniotomy.^{27,28} Even though it is well established for patients harboring malignant intracerebral neoplasms, the effect of steroid therapy on PTBE associated with meningioma has yet to be demonstrated.⁷⁴

Few reports have investigated the level of ICP during such treatment. Skjoeth and Bjerre enrolled 5 patients with meningioma and 8 with glioblastoma or intracerebral metastases, all with a substantial amount of PTBE.⁸² Methylprednisolone 1.4 mg/kg/day was given over 5 days, and ICP was measured with an intraparenchymal monitor on the contralateral hemisphere of the tumor after patients were supine for 30 minutes. On Day 5, significant clinical improvement and diminished ICP was found in patients with malignant lesions but not in benign or atypical meningiomas. On the contrary, methylprednisolone treatment led to a substantial rise in ICP in all patients

with meningioma. These results were supported by those in the study of Andersen and colleagues, who used MR relaxation time imaging to measure PTBE resorption rate following dexamethasone treatment in 23 patients (13 with metastases, 10 with meningiomas) over 7 days. In metastatic tumors, a decrease of edema area and mean T1 relaxation time by 10.3% and 13.5%, respectively, was observed after 7 days, whereas meningiomas showed no change.³ Bodscho and colleagues (n = 60) found no change in the water content of biopsied meningioma tissue with increasing intratumoral dexamethasone concentrations, as opposed to malignant lesions in which there was a direct dose-response relationship.¹³ Later studies also demonstrated poor response to corticosteroid therapy in meningiomas.^{6,35,81} The exact reason for the failure of corticosteroid therapy to improve meningioma-associated PTBE is unclear.

The intense enhancement of meningiomas noted on contrasted CT or MRI is mediated by leakage of contrast material through highly permeable vessels of the tumor. The level of contrast enhancement in meningiomas is directly correlated with capillary transendothelial diffusion as expressed by a blood-to-tissue transport rate measured with MRI and a Gd-based volume distribution indicator.⁴ The proposed rationale for using corticosteroids for meningioma-associated PTBE is that they can reduce vessel permeability, resulting in a net reduction in edema fluid production.^{3,33,81} Theoretically, edema reabsorption would then exceed production with resulting attenuation in PTBE.³

Bodsch and colleagues found that the content of water and extravasated proteins in meningiomas are almost as high as in glioblastomas and metastases with a significantly smaller fraction of albumin, a relatively small plasma protein.¹³ An alternative hypothesis for the poor response to corticosteroids could be that the vessels of meningiomas exhibit larger fenestrations because meningiomas, in contrast to primary brain tumors, are of mesenchymal origin and therefore have no intrinsic tight blood-tumor barrier as would be expected to a certain degree for neuroepithelial tumors.^{37,91} Corticosteroids might be ineffective in obliterating larger fenestrations observed in meningiomas in comparison with glial tumor vessels, which exhibit a closed endothelial lining. Furthermore, the degree to which a tumor responds to corticosteroids also depends on the number of intracellular corticosteroid receptors.⁹⁹ Consequently, tumors such as metastases that respond favorably to corticosteroids have higher levels of corticosteroid receptors compared with tumors such as meningiomas, which respond poorly and are depleted of corticosteroid receptors.^{13,98}

Overview of VEGF

More than 2 decades of intense investigation has provided evidence that the VEGF pathway represents a critical rate-limiting step in physiological and pathological angiogenesis, such as that associated with tumor growth.²⁵ Vascular endothelial growth factor-A is an important member of a family of signaling molecules including VEGF-B, VEGF-C, and VEGF-D, expressed by a number of cells, such as meningioma stromal and endothelial cells in the presence of hypoxia.²⁰ Vascular endothelial growth factor-A is well documented to have the ability to induce growth of arterial endothelial cells, thereby promoting a powerful angiogenic response in vivo.⁴⁶ It was originally referred to as vascular permeability factor for its ability to facilitate leakage of plasma proteins with 1000 times the potency of histamine,⁷⁹ by inducing endothelial fenestrations⁷² and vasodilation from endothelial cell-derived nitric oxide.⁴³ Leakage of plasma proteins extracts water into the interstitial compartment and forms a provisional extracellular gel-like matrix that promotes the development of new blood vessels. Consequently, VEGF-A up-regulation, induced by ischemia as meningiomas outgrow their blood supply, was proposed to act as a critical factor in the development of PTBE.²⁴

Vascular endothelial growth factor-A interacts with two tyrosine kinase receptors: VEGFR-1 and VEGFR-2. The angiogenic and permeability-enhancing effects of VEGF-A are largely mediated by VEGFR-2.⁴⁷ However, in a membrane-bound or soluble form, VEGFR-1 is proposed to be a “decoy” to negatively modulate VEGF-A activity on the vascular endothelial cells by inhibiting the binding of VEGF-A to VEGFR-2.¹⁶

Among modulators of VEGFR-2, neuropilin-1 receptor (NRP1-R) is of particular importance. As with VEGF-A, NRP1-R expression is upregulated in ischemia.⁸⁵ Its ligand includes semaphorin-3A.⁵¹ When coexpressed in cells with VEGFR-2 in the absence of semaphorin-3A, NRP1-R acts as a coreceptor to enhance the

binding of VEGF-A to VEGFR-2 in a manner that augments the effectiveness of VEGFR-2-mediated signal transduction.⁸⁴ However, in the presence of semaphorin-3A when bound to NRP-1R, the VEGF-A-mediated angiogenic effect is attenuated.⁵⁴ Furthermore, semaphorin-3A in high concentrations repels endothelial cells and induces their apoptosis.³⁴ Thus, the ratio of VEGF-A to semaphorin-3A was postulated to regulate angiogenesis rather than VEGF-A alone, and may have prognostic and therapeutic implications in meningiomas.^{7,8}

Correlation Between VEGF-A Level and PTBE

Despite marked variation in VEGF detection/quantification methods over the past 15 years, the vast majority of data support a close relationship between VEGF-A expression and PTBE development (Table 1). Kalkanis and colleagues were the first to report the correlation between VEGF-A expression and PTBE development in meningiomas in 1996.⁴² VEGF-A mRNA was quantified using Northern blotting, and PTBE was evaluated with T2-weighted and Gd-enhanced T1-weighted MRI. A marked increase of 3.4-times the level of VEGF-A mRNA was found in meningiomas with PTBE compared with those without ($p < 0.001$). Subsequently, Goldman and colleagues investigated meningioma tissue samples from 37 patients.³¹ VEGF-A expression and PTBE were subjectively quantified on a 5-point scale with immunostaining and MRI, respectively. Similarly, a significantly positive correlation between VEGF-A staining intensity and MRI edema rating was demonstrated ($p = 0.0001$). In the study conducted by Ding and colleagues, PTBE was measured on MRI; VEGF-A protein and mRNA were quantified using Western blotting and reverse transcription polymerase chain reaction (RT-PCR), respectively.²⁰ Within meningioma tissue, the expression of both VEGF-A protein and mRNA were congruent and had a significant correlation with edema index ($p < 0.01$). Nassehi and colleagues in 2011 assessed only meningiomas affected by PTBE and quantified VEGF-A protein and mRNA level with an enzyme-linked immunosorbent assay-based method and PTBE with MRI.⁵⁵ VEGF-A protein ($p < 0.05$) and mRNA ($p < 0.05$) correlated positively with edema index. Multiple other studies have corroborated the relationship between VEGF-A and PTBE.^{10,56,59,60,65,68,75,78,97}

VEGF-A and Meningioma Vascularization

A number of studies have demonstrated that VEGF-A expression is associated with meningioma vascularity,^{63–65,68,77} while others did not find such an association.^{19,44,62} One of the possible explanations for this inconsistency is the method used to measure vascularity.

Nassehi and colleagues were the only group to have used a stereology-based method to estimate the total capillary length to correlate with VEGF expression in meningiomas.^{55,56} The mean capillary length was 3614 mm/mm³, 605 mm/mm³, and 229 mm/mm³ for angiomatous meningiomas ($p < 0.0001$ vs control), nonangiomatous meningiomas ($p = 0.014$ vs control), and control brain tissue, respectively.⁵⁶ Consistently, VEGF-A protein and mRNA

TABLE 1: Studies on VEGF-A expression and meningioma-associated PTBE development*

Authors & Year	No. of Patients	Angiomatous Meningiomas	High-Grade Meningiomas†	No. w/ Embolization	VEGF-A Expression		
					Evaluation Methods	Associated Parameters	Non-Associated Parameters
Kalkanis et al., 1996	31	0	2	not specified	Northern blotting	PTBE	none
Goldman et al., 1997	37	0	1	not specified	IHC	PTBE	histological subtypes of Grade I
Provias et al., 1997	18	0	0	not specified	Northern blotting	PTBE, MVD	none
Bitzer et al., 1998 [‡]	30	not specified	1	not specified	IHC	PTBE, pial blood supply	none
Yoshioka et al., 1999	73	10	7	not specified	IHC	PTBE‡	none
Paek et al., 2002	20	2	6	none	IHC, Western blotting	PTBE	PTBE,§ WHO grade
Pistolesi et al., 2002	35	0	5	not specified	IHC	PTBE, MVD, pial blood supply, expression of somatostatin receptors	none
Otsuka et al., 2004	118	2	4	not specified	IHC	PTBE	pial blood supply
Sakuma et al., 2008	40	3	6	13	ELISA, IHC	PTBE, WHO grade	histological subtypes of Grade I, embolization, pial blood supply, MVD
Ding et al., 2008	37	1	4	not specified	Western blotting, RT-PCR, IHC	PTBE	none
Schmid et al., 2010	79	1	0	not specified	IHC	PTBE¶	none
Nassehi et al., 2011	43	2	15	not specified	ELISA**	PTBE	histological subtypes of Grades I–III, steroid therapy, sex
Nassehi et al., 2013	62	22	0	not specified	ELISA**	PTBE, angiomatous meningiomas	none

* ELISA = enzyme-linked immunosorbent assay; IHC = immunohistochemistry; MVD = microvascular density.

† High-grade meningiomas = WHO Grades II and III.

‡ In meningiomas with cerebral-pial supply, edema index increased significantly, just as VEGF was strongly expressed ($p < 0.001$). In contrast, meningiomas without a cerebral-pial supply developed little or no PTBE and less VEGF expression.

§ Level of VEGF expression tended to be higher in moderate to severe edema on Western blotting.

¶ Only the occurrence of pial vascular supply and tumor VEGF expression was found to correlate with PTBE formation.

** ELISA-based methods were used to quantify protein and mRNA levels.

levels were highest in angiomatous meningiomas and lowest in control tissue.^{55,56} Lamszus and colleagues demonstrated that VEGF-A found in protein extracts from human meningioma tissue induced capillary-like tube formation and migration of endothelial cells *in vitro*.⁴⁴ These findings give reason to believe that VEGF-A is an important proangiogenic factor involved in angiogenesis in meningiomas.

Source of VEGF-A

Mounting evidence suggests that VEGF-A may be secreted by meningioma cells. Goldman and colleagues performed *in situ* hybridization of VEGF-A mRNA and localized these molecules in meningioma cells but not in peritumoral brain parenchyma, which indicates that PTBE may be a result of the ability of meningioma cells to produce VEGF-A locally, leading to increased tumor and peritumoral brain parenchyma vascularization and vascular permeability.³¹ Ding and colleagues compared peritumoral biopsied brain tissue ($n = 37$) with control brain tissue derived from temporal lobectomies performed for epilepsy.²⁰ In the peritumoral brain, Western blot results were inconsistent with results for RT-PCR. The VEGF-A protein level was 5 times higher than controls, but mRNA level, similar to control brain tissue, was almost undetectable. With increasing distance from the tumor, decreasing concentration of VEGF-A protein level was observed. These data indicate that even though VEGF-A protein level in peritumoral brain tissue is high and is correlated with edema index,²⁰ brain parenchyma does not produce VEGF-A, and VEGF-A signaling molecules are produced by meningiomas, which then enter peritumoral brain tissue and stimulate edema formation.

Tumor-Brain Barrier Disruption May Be an Essential Component of Edema Formation

Meningiomas, in contrast to glioblastomas and metastases, are encapsulated and are separated from the underlying normal cerebral cortex by the arachnoid membrane and pia mater. As a part of the blood-CSF barrier, the arachnoid membrane is impermeable to fluids.³⁹ Even though the pia mater is highly permeable to water and electrolytes, it is still far less pervious to macromolecules and proteins found in edema fluid.²⁹ Therefore, edema-inducing proteins from meningiomas are not expected to easily penetrate into the peritumoral brain tissue. Therefore, the mechanism by which VEGF-A secreted by meningiomas reaches peritumoral brain parenchyma needs elucidation.

Peritumoral brain edema almost always occurs in glioblastomas, and its severity has been directly correlated with the level of VEGF-A.⁸⁶ In contrast, it was reported that some meningiomas with high VEGF-A content did not develop PTBE.^{31,42,68,97} This disparity may be explained by the differences in blood supply. A meningioma is an extraaxial tumor perfused by blood vessels from the dural meninges, the pia mater, or both,^{12,40} whereas glioblastoma is an intracerebral tumor perfused solely by pial blood vessels. Thus, it appears that in meningiomas,

VEGF-A is a potent edemagenic factor only under specific circumstances, and some degree of pial vascular supply to the tumor may be a critical factor in PTBE formation.

Several authors have demonstrated a correlation between VEGF-A expression and the presence of pial vascular supply in meningiomas.^{10,63,65} Inamura and colleagues were the first to show in meningiomas that the edema index was associated with the existence of cerebral-pial vessels.⁴⁰ Subsequently, Bitzer and colleagues demonstrated on angiography that pial blush in meningiomas was strongly related to the incidence and degree of PTBE, and they proposed that cerebral-pial vessels may be a critical factor in edemagenesis.¹² Similarly, Yoshioka and colleagues demonstrated that the edema index increased in proportion to the degree of VEGF expression in the presence of a pial blood supply, whereas no such association was observed in those with only dural blood supply.⁹⁷ Lastly, Schmid and colleagues evaluated the vascular supply and arachnoid state intraoperatively, and revealed that only the presence of both pial vascular supply and VEGF-A expression found in tumors was clearly correlated with PTBE formation ($p < 0.002$).⁷⁸

These data indicate that angiogenesis of pial-tumor vessels is an important step in the development of PTBE, and VEGF-A likely plays an important role in the development of pial vascular supply to the tumor. VEGF-A is produced by meningioma cells to bind to VEGFR-2 on the endothelial lining of pial vessels and promotes the proliferation of these vessels to penetrate through the arachnoid membrane to perfuse the tumor. Through disruption of the arachnoid membrane, VEGF-A and other edema-inducing macromolecules can enter normal peritumoral brain tissue to induce further angiogenesis and enhance vascular permeability, giving impetus to edemagenesis. Alternatively, VEGF-A may also reach normal brain through an intact cerebral-tumor microcirculation and directly cause edema formation without the need for a tumor with a benign nature to invade its well-encapsulated meningeal borders.

Clinical Studies of VEGF Therapy

A robust association does not inevitably impose a causal relationship. The definitive proof of efficacy will require studies involving VEGF inhibition and evaluation of the effect on PTBE. To this point, 3 case reports and 3 retrospective case series have used systemic VEGF-directed therapy, in particular bevacizumab, in meningiomas (Table 2). Bevacizumab is a humanized monoclonal antibody that inhibits VEGF activity by binding directly to all VEGF isoforms, to form a complex that becomes incapable of binding to receptor sites.²⁶ It is currently approved by the US FDA for a variety of disorders, including glioblastoma.

In 2010, Puchner and colleagues presented the first case of bevacizumab use in meningioma.⁶⁹ Salvage therapy with bevacizumab (10 mg/kg body weight every 2 weeks) was initiated after the recurrence of an anaplastic meningioma following gross-total resection and postoperative adjuvant radiotherapy, and was well tolerated. Six weeks later, contrast-enhancing tumor regressed substan-

Peritumoral brain edema development

TABLE 2: Literature on systemic anti-VEGF therapy against meningioma*

Authors & Year	Treatment (dose)	No. of Patients	Median PFS (mos)	PTBE
Nayak et al., 2012	10 mg/kg every 2 wks	15 (6 w/ Grade II, 9 w/ Grade III)	6.5	40% regression; 60% stable
Lou et al., 2012	not specified	14 (5 w/ Grade I, 5 w/ Grade II, 3 w/ Grade III, 1 unknown)	15.8 (for Grade II/III meningiomas)	not specified
Nunes et al., 2013	5 mg/kg every 2 wks	15 (grade unknown)	20	not specified

* All studies were retrospective.

tially, and FLAIR and T2-weighted MRI showed reduced edema. These changes were sustained for 6 months after the cessation of therapy. Wilson and Heth reported regression of a partially resected Grade I meningioma after paclitaxel and bevacizumab was used to treat breast cancer for 6 months and 1 year, respectively.⁹⁵ Regression of the meningioma was maintained on follow-up MRI 1 year later. Goutagny and colleagues administered bevacizumab at a dose of 5 mg/kg body weight every 2 weeks for 15 months with the primary goal of treating a vestibular schwannoma in a patient with neurofibromatosis Type 2.³² Concomitantly, an unknown grade meningioma that measured 7.3 cm³ and grew 38% in volume over the preceding year decreased 22% in size throughout the course of the treatment.

In the first published case series, Nayak and colleagues administered bevacizumab with the primary aim of promoting regression of recurrent atypical and anaplastic meningiomas.⁵⁷ The cohort consisted of 15 patients with multiple prior surgeries (median = 3) and sessions of radiotherapy. The median number of recurrences was 4 per patient, and 7 patients received prior chemotherapy. A median of 9 doses of bevacizumab was given over 18 weeks. The median progression-free survival (PFS) was 6.5 months, and 6-month PFS was 44%. Two patients showed minor shrinkage of the enhancing part of the tumor while the remaining cohort had stable disease. Six patients exhibited reduction in peritumoral T2 hyperintense areas on MRI consistent with decreased PTBE. Five patients improved clinically, 9 remained unchanged, and 1 patient's condition deteriorated.

In a similar study, Lou and colleagues treated 14 patients with bevacizumab as salvage therapy where all had recurrent/progressive meningioma.⁵⁰ The primary end point was to assess 6-month PFS. Thirteen patients had previously undergone 1 or more resections, fractionated radiotherapy or stereotactic radiosurgery, chemotherapy, or biological targeted therapy, such as octreotide. Chemotherapy was used as an adjunct in 71% of patients. One patient with multifocal disease demonstrated partial response according to the criteria for malignant gliomas, as established by the Response Assessment in Neuro-Oncology.⁹⁴ While disease in 2 patients progressed, 11 patients exhibited stable disease. Median PFS and 6-month PFS were 12.2 months and 80%, respectively, for patients with Grade I meningiomas, and 15.8 months and 87.5% for patients with Grade II/III meningiomas, respectively. The therapeutic effect on PTBE was not reported.

In a more recent report by Nune and colleagues, 15 patients neurofibromatosis Type 2 harboring a total of 48

meningiomas of unknown grade were given bevacizumab (5 mg/kg body weight) every 2 weeks.⁵⁸ Although the effect on PTBE was not described, 29% of meningiomas showed radiographic response with a 15-month median time to regression. The median PFS and 6-month PFS was 20 months and 93% on a per-patient basis, respectively.

To date, limited data have been published describing the antiedemagenic and antitumoral activity of VEGF-directed therapy for meningioma. However, several retrospective studies suggest that bevacizumab may be an efficacious treatment. Even though the patient population was heterogeneous and most patients in the aforementioned series were heavily pretreated, the outcome compared favorably to that achieved using other salvage systemic therapies. In the Phase II trials of hydroxyurea, temozolomide, irinotecan, imatinib, erlotinib/gefitinib, interferon- α , tamoxifen, mifepristone, and octreotide for recurrent meningiomas, the median PFS ranged from 2 to 15 months.⁵⁰ A decrease in PTBE on T2-weighted MRI was noted in 40% of patients, but all patients that had a decrease in PTBE demonstrated clinical improvement or remained stable.⁵⁷ The lack of response in the remaining cohort emphasizes that VEGF-directed therapy is only beneficial under specific conditions, such as in the presence of a cerebral-pial blood supply and high VEGF-A to semaphorin-3A ratio. Further evaluation of this issue is warranted to determine which patients will respond best to therapy.

Ongoing Trials

Several clinical trials based on VEGF-A- or VEGFR-2-directed therapy for patients with recurrent or progressive meningiomas are ongoing. Phase II trials evaluating bevacizumab as monotherapy (clinicaltrials.gov identifier: NCT01125046) or in combination with everolimus, a mammalian target of rapamycin inhibitor (clinicaltrials.gov identifier: NCT00972335), are currently recruiting. Small molecules inhibiting VEGFR-2 and platelet-derived growth factor receptor signal transduction, such as sunitinib (clinicaltrials.gov identifier: NCT00589784) and vatalanib (clinicaltrials.gov identifier: NCT00348790), are also under Phase II investigation. Lastly, we await the results of a Phase II study on bevacizumab for reducing CNS side effects in patients who have undergone radiation therapy for intracranial meningiomas (clinicaltrials.gov identifier: NCT00492089).

Conclusions

Intracranial meningiomas are often complicated by

PTBE. To date, no reliable chemotherapeutic option exists for this complication. Naturally, the cause of edema generation is eliminated with tumor removal, but in most cases presurgical elimination or reduction in PTBE is desirable to reduce surgical morbidity. In addition, reduction of PTBE may decrease complications associated with radiation for meningiomas. Mounting evidence suggests PTBE may be the result of a cascade of events triggered by tumor VEGF-A production leading to increased microvascular permeability and neovascularization of tumoral and peritumoral brain tissue, causing extravasation of plasma proteins and ultimately PTBE. Understanding the VEGF-A and PTBE formation pathways may hold the key to a perioperative therapeutic approach to treating meningiomas with PTBE. Thus, a targeted inhibition of VEGF-A, VEGFR-2, or one of its substrates along the signal transduction pathway, and targeted activation of negative modulators of VEGF-A activity, may one day improve patient outcomes from PTBE-related complications of meningiomas.

Disclosure

Dr. Selman has direct stock ownership in Surgical Theater and Osteoplastics II.

Author contributions to the study and manuscript preparation include the following. Conception and design: all authors. Acquisition of data: Hou, Kshetry, Selman. Analysis and interpretation of data: all authors. Drafting the article: Hou, Kshetry. Critically revising the article: Bambakidis, Hou, Selman. Reviewed submitted version of manuscript: Bambakidis, Hou. Approved the final version of the manuscript on behalf of all authors: Bambakidis. Administrative/technical/material support: Hou.

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Address correspondence to: Nicholas C. Bambakidis, M.D., Department of Neurological Surgery, University Hospitals Case Medical Center, 11100 Euclid Ave., Cleveland, OH 44106. email: nicholas.bambakidis2@uhhospitals.org.