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Management of treatment-associated toxicites of anti-angiogenic therapy in patients with brain tumors†

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Anti-angiogenic therapies, including bevacizumab, are being used with increasing frequency in the management of malignant glioma. Common clinically significant toxicities include hypertension and proteinuria, poor wound healing, and the potential for thromboembolic events. Literature related to the use of bevacizumab in malignant glioma, reported toxicities in this patient population, and management of these toxicities was reviewed. Recommendations for assessment and management are provided. Anti-angiogenic therapies will continue to have a role in the treatment of malignant glioma. Further studies of the prevention, assessment, and management of these toxicities are warranted.

Keywords: brain tumors, chemotherapy, toxicity.

Malignant gliomas remain difficult to treat, and standard approaches are associated with poor survival. Despite level 1 evidence of a survival benefit for those patients treated with concurrent temozolomide and radiation, followed by adjuvant temozolomide in patients with glioblastoma (GBM), the overall median survival, even with this therapy, was only 14.6 months.[1] Even for patients who receive a diagnosis of anaplastic gliomas (World Health Organization [WHO] grade 3), median survival is only 2–4 years.[2–4] For all high-grade gliomas, achieving response after the tumor has recurred is difficult and survival is poor. In recurrent GBM, using temozolomide, response rates of 5% and 6-month progression-free survival of 21% have been reported.[5,6] Therefore, effective salvage therapies for patients with GBM are needed.

Angiogenesis and Tumor Growth

Previous preclinical and clinical investigations have established that most solid tumor growth beyond several millimeters is dependent on angiogenesis.[7,8] Angiogenesis is a physiologic process involving a balance of angiogenic factors and inhibitors that control microvessel sprout growth and proliferation of endothelial cells.[9] The importance of this increased vasculature in glioma was first observed by Virchow during the 19th century[10,11] and was recognized to be integral to tumor growth. The profound importance of angiogenesis in brain tumor biology is highlighted by the recognition that endothelial proliferation is a hallmark of GBM and is considered to be a major criterion in conferring the histopathological diagnosis. GBM cells are known to produce angiogenic factors, such as basic fibroblast growth factor, hepatocyte growth factor/scatter factor, and vascular endothelial growth factor-A (VEGF-A).[11–13] In addition, endothelial cells in tumor express VEGFR2 (KDR), resulting in a paracrine loop. These signaling pathways work with other important pathways and glioma stem-like cells to result in new vessel formation supporting continued tumor growth.

Anti-Angiogenic Therapy

Because of the importance of vascular proliferation in the biology of GBM, targeting angiogenesis may be an

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important treatment for malignant gliomas. Several agents are under investigation, targeting different components of the angiogenesis pathway. There are several potential therapeutic advantages of targeting angiogenesis in the treatment of malignant gliomas. These include tumor selectivity because of selective vulnerability of the newly formed vasculature; less concern about drug delivery as the primary targets of these therapies because the endothelial cells are in the microvascular niche, which is outside of the blood-brain barrier; and minimal myelotoxicity permitting combination with conventional cytotoxic agents (although other systemic toxicities have been reported).

The first anti-angiogenic inhibitor approved for clinical use in brain tumors is bevacizumab, a recombinant humanized IgG1 monoclonal antibody.[14,15] Bevacizumab was first approved in 2004 as first-line treatment for metastatic colorectal cancer in combination with conventional cytotoxic chemotherapy. Later, bevacizumab was approved for the treatment of lung and breast cancer in combination with cytotoxic chemotherapy and with interferon in renal cancer. In malignant gliomas, there are several retrospective and prospective trials in patients with recurrent GBM.[16–25] Two pivotal prospective trials, AVG3708g, an open-label multicenter trial and, NCI 06-C-0064E, led to accelerated approval by the United States Food and Drug Administration for use in brain tumors in May 2009 as a monotherapy in patients with GBM who progressed after first-line therapy. Recent and ongoing phase II and phase III trials are evaluating use of bevacizumab both in the up-front setting and in combination with a variety of agents for recurrent disease.

Although the clinical trials demonstrate the apparent efficacy of bevacizumab, there are several issues related to the administration of anti-angiogenic agents that may complicate their use in the population with malignant glioma. Concerns have been raised regarding the clinical significance of reduction of contrast enhancement, the standard metric of objective response that can occur within hours or days after administration of anti-angiogenic agents (i.e., bevacizumab and cediranib). It remains uncertain whether the reduction in contrast enhancement is the result of true tumor response, treatment-induced reduction of blood-brain barrier permeability, or a combination of both.[26] Preclinical models suggest that alterations in blood-brain barrier permeability may be the dominant effect.[27] Furthermore, there is concern that the use of anti-angiogenic agents may change tumor biology, resulting in alterations in pattern of tumor spread to a more infiltrative pattern that is highly refractory to salvage treatments.

In addition to the aforementioned issues related to the use of anti-angiogenic agents, treatment-associated toxicities further complicate care. Common toxicities include hypertension and proteinuria, poor wound healing, and the increased risk for venous and arterial thromboembolic events. These toxicities have specific implications for patients with brain tumor because of the inherent increased risk of thrombosis and issues with wound healing related to chronic corticosteroid use. These toxicities further complicate care by influencing further neurosurgical intervention and tolerance of other therapies. Understanding the incidence and diagnostic and management strategies for toxicities from anti-angiogenic therapy for the population with malignant glioma is an important component of care.

Hypertension

The mechanism of arterial hypertension associated with anti-VEGF therapy is complex and almost certainly multifactorial. Nitric oxide, which helps maintain the balance between vasoconstriction and vasodilation, is a major contributor. VEGF normally increases endothelial transcription of nitric oxide synthase, and anti-VEGF agents decrease nitric oxide production, resulting in vasoconstriction.[28,29] At the renal level, this vasoconstriction produces sodium retention, adding further to hypertension.[28] A reduction in density of microvascular beds, a phenomenon termed "rarefaction," increasing systemic vascular resistance and blood pressure may be a second mechanism.[28] Recent human studies support bevacizumab- and sunitinib-mediated rarefaction as a component of hypertension.[30,31] Finally, endothelial oxidative stress has been implicated as a factor in the development of hypertension, and upregulation of VEGF and VEGFR-2 plays a role in protecting the endothelium from reactive oxygen species. Therefore, treatment-induced diminution of this protective mechanism may predispose to hypertension.[28]

Bevacizumab treatment is associated with a high incidence of hypertension. However, it is important to recognize that most published studies reporting on hypertension with anti-VEGF agents have used Common Terminology Criteria for Adverse Events (CTCAE), version 2.0 or 3.0 and not version 4.0, which was recently modified to bring their criteria into line with the Seventh Report of the Joint National Commission on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7).[32] A meta-analysis of clinical trials that randomized patients with multiple tumor types to chemotherapy with or without bevacizumab determined that low-dose ($<$10 mg/kg/dose) bevacizumab increased the incidence of any grade hypertension by 3-fold and that high-dose ($\geq$10 mg/kg/dose) bevacizumab increased such incidence by 7.5-fold.[33] A subsequent meta-analysis found that 24% of patients receiving bevacizumab developed any grade of hypertension and 8% developed grade 3+ hypertension (relative risk [RR], 5.3).[34] The incidence of bevacizumab-associated hypertension in glioblastoma appears to be similar; the BRAIN study reported an all-grade rate of 31% and grade 3+ hypertension in 5% of patients.[20] VEGFR tyrosine kinase inhibitors (TKIs) induce hypertension at similar rates, with figures of 22% and 23% for sunitinib and sorafenib.[35,36] Risk factors for development of hypertension with bevacizumab remain to be elucidated.[29,37]

Although long-term hypertension is an important risk factor for the development of coronary artery and chronic renal disease, ischemic stroke, and intracranial hemorrhage, the typically limited life expectancy of patients with malignant glioma who are receiving anti-VEGF therapy may render these complications as secondary concerns in treatment decision-making. Nonetheless, there are compelling reasons to treat hypertension. In some patients, blood pressure elevation is dramatic and, if untreated, may preclude continued anti-VEGF agent administration. Moreover, hypertension-related adverse events sometimes have a rapid onset with anti-VEGF therapy. Finally, a modest but increasing percentage of patients with glioblastoma become long-term survivors and, therefore, more vulnerable to the chronic effects of hypertension. Consequently, determination of the cardiovascular risk of hypertension in a given patient is advised, including assessment of risk factors, such as diabetes mellitus, known cardiovascular disease, chronic kidney disease, tobacco use, hyperlipidemia, obesity, family history, and advanced age. In patients with low cardiovascular risk, the treatment goal is 140/90 mm Hg; in high-risk patients, it is 130/80 mm Hg.[38]

The management of hypertension associated with bevacizumab and other anti-VEGFR agents follows the principles of hypertension management in general. Other risk factors for developing hypertension should be addressed, including reduction of salt intake and avoidance of excessive alcohol, nonsteroidal anti-inflammatory drugs, sympathomimetics, oral contraceptives, and corticosteroids when possible.[38,39] A single antihypertensive agent is typically sufficient to control blood pressure. There are no controlled studies to support use of a specific agent or class of agents. Nonetheless, some considerations are pertinent. For example, among calcium channel blockers, diltiazam and verapamil inhibit CYP 3A4 and nifedipine induces VEGF. Because amlodipine and felodipine do not share the potential for major drug interactions, these newer agents are preferred.[39] Angiotensin-converting enzyme (ACE) inhibitors work more quickly than calcium channel blockers and should be considered when rapid treatment is desirable; in addition, they are the preferred treatment in the context of proteinuria. Table 1 summarizes some other considerations in choice of class of anti-hypertensive agent. Monitoring blood pressure weekly during the first bevacizumab cycle and then with each subsequent infusion is advisable. Patients with essential hypertension are encouraged to monitor blood pressure at home.[29]

Proteinuria

The kidneys normally prevent significant loss of plasma proteins in the urine. Glomeruli act as molecular sieves, retaining high–molecular weight proteins, and low–molecular weight proteins filtered into the tubular lumen are reabsorbed in the proximal tubule. Several studies have noted that hypertension is a strong risk factor for bevacizumab-associated proteinuria,[33,40] leading to the hypothesis that bevacizumab-induced hypertension produces proteinuria by increasing intraglomerular pressure.[33]

Although hypertension likely contributes to proteinuria, the role of VEGF in maintaining glomerular integrity represents another important mechanism. Podocytes, a key constituent of the glomerular filtration mechanism, constitutively express VEGF; moreover, VEGF receptors are present on glomerular capillary endothelial cells.[41] In mice, targeted heterozygous deletion or pharmacologic inhibition of VEGF in podocytes produces renal injury, including loss of endothelial fenestrations and proteinuria.[42] The thrombotic microangiopathy that these animals develop precedes the onset of hypertension. Similarly, renal biopsy specimens from several patients who developed proteinuria while receiving bevacizumab revealed a consistent pattern of thrombotic microangiopathy.[42] Renal thrombotic microangiopathy with proteinuria has also been reported with the VEGFR TKIs sunitinib[43] and sorafenib.[44]

Normal urine protein excretion is 40–80 mg daily, and levels >150 mg daily are considered to be abnormal. There are several ways to measure urinary protein excretion. Historically, a 24-hour timed urine collection for assessment of total albumin or protein was traditional. However, in addition to their inconvenience, such measurements have a surprisingly high coefficient of variation (up to 20%).[45] Single-voided specimens are far more convenient but vary substantially in terms of urine protein concentration. Because urinary creatinine is a marker of urine concentration, the ratio of urine protein to urine creatinine (UPC) provides an estimate of urine protein that controls for concentration. Fortuitously, because daily urine creatinine production for an average-sized adult is ~1000 mg, a spot UPC ratio assessment approximates 24 h urine protein excretion in grams. A normal UPC ratio is <0.2. Finally, urine dipsticks detect albuminuria; however, their dependence on urine concentration, relative insensitivity for nonalbumin proteins, and lack of specificity make them a better screening tool than means of quantifying and following proteinuria. However, dipstick-determined proteinuria is not a substitute for the more quantitative UPC ratio.

The National Cancer Institute CTCAE, version 4.0, grades proteinuria in adults from 1 to 3. Grade 1 proteinuria corresponds to a 1+ urine dipstick with 24-hour urine protein level <1.0 g. A 2+ urine dipstick or 24-hour protein level of 1.0–3.4 g qualifies as grade 2, and 24-hour urine protein level ≥3.5 g constitutes grade 3 proteinuria. A recent meta-analysis of several randomized trials with and without bevacizumab has quantified the risk of proteinuria.[46] Thirteen percent of patients receiving bevacizumab had at least grade 1 proteinuria, and 2.2% had grade 3+ proteinuria (a 5-fold increase, compared with patients receiving chemotherapy without bevacizumab). High-grade proteinuria is a dose-limiting toxicity for another VEGF-sequestering agent, aflibercept (VEGF Trap).[47] Corresponding data for VEGFR-targeting TKIs are more elusive, although

Table 1. Consideration in choice of antihypertensive agents

Class of Drug	Cancer-specific cautions or reasons to avoid	Basis for preferred selection	General cautions and contraindications
Angiotensin-converting enzyme inhibitors	Coadministration/titration with renal clearance-dependent agents (e.g. cisplatin and pemetrexed); hyperkalemia	Left ventricular systolic dysfunction; diabetic nephropathy	Renovascular disease; peripheral vascular disease; renal impairment
Angiotensin II receptor blockers	Coadministration/titration with renal clearance-dependent agents (e.g., cisplatin and pemetrexed); hyperkalemia	Intolerance of other agents, especially ACE inhibitors; left ventricular systolic dysfunction; diabetic nephropathy	Renovascular disease; peripheral vascular disease; renal impairment
Beta blockers	Asthenia; malaise; fatigue; QT interval prolonging drugs	Angina; history of myocardial infarction; anxiety	Bradycardia/heart clock; diabetes (risk for hypoglycemia); asthma/ chronic obstructive pulmonary disease (wheezing)' decompensated heart failure
Calcium channel blockers (e.g., dihydropyridines)	Lower extremity swelling	Elderly patients; isolated systolic hypertension	Preexisting edema; slow onset of action
Thiazide diuretics	Gout; hypercalcemia; hypokalemia; young patients (age $\leq$45 yr); QT interval prolonging drugs	Elderly patients; isolated systolic hypertension secondary stroke prevention; typically least expensive	Gout; documented sulfa allergy

Reprinted from open access: Maitland and colleagues.[47]

phase II axitinib trials reported all-grade proteinuria rates of 18%–36% and grade 3+ rates of 0%–5%.[41] Similarly, 30% of women in a phase II study of cediranib for ovarian cancer developed grade 1 or 2 proteinuria at a median of 2 weeks after starting therapy;[48] median time to development of proteinuria with bevacizumab in glioblastoma has not been reported.

The incidence of bevacizumab-related proteinuria appears to be lower in patients with glioblastoma than other cancers. The BRAIN study found grade 1 proteinuria in only 4% and grade 3 proteinuria in just 1 of 167 patients.[20] None of the 48 patients treated in the National Institutes of Health bevacizumab study were reported to develop proteinuria.[21] Why proteinuria is less common in brain tumor patients has not been examined, although a shorter median duration of therapy may play a role.

Patients receiving bevacizumab require periodic monitoring for development of proteinuria. The package insert recommends dipstick of serial urinalyses, and because of the relative infrequence of clinically significant proteinuria in glioblastoma (particularly in the context of recurrent tumor), monitoring every other infusion seems to be reasonable.[41] According to the manufacturer, a urine dipstick $\geq$2+ warrants further assessment with a 24-hour urine collection for protein (http://www.gene.com/gene/products/information/pdf/avastin-prescribing.pdf); permanent discontinuation of bevacizumab is recommended for nephrotic syndrome and temporary suspension for 24 h urine protein totaling $>$2 g, with resumption when $<$2 g. Our practice has been to follow the UPC ratio after the urine dipstick shows 2+ proteinuria. There are no suggested bevacizumab dose modifications for patients with renal dysfunction.

Beyond holding or discontinuing drug, management of bevacizumab-associated proteinuria remains uncertain. For proteinuria in general, ACE inhibitors and angiotensin II receptor blocks (ARBs) reduce the severity of the proteinuria and the risk of end-stage renal disease beyond their impact when controlling hypertension. Despite the relative frequency of anti-VEGF agent-induced proteinuria, no interventional studies have been conducted, thus precluding evidence-based treatment recommendations.[41] Nonetheless, ACE inhibitors or ARBs have been shown to reduce proteinuria in patients treated with mTOR inhibitors, and their renoprotective effects might be useful in patients with mild proteinuria. In patients with both hypertension and proteinuria, agents from these classes represent a rational first choice.

Reversible Posterior Leukoencephalopathy Syndrome

Reversible posterior leukoencephalopathy syndrome (RPLS), also known as posterior reversible encephalopathy syndrome, represents a neurological condition associated both with VEGF-sequestering agents and with TKIs targeting VEGFR. The clinical syndrome typically consists of the relatively acute onset of headaches, seizures, confusion, and often, cortical blindness. Most patients are markedly hypertensive. MRI typically reveals T2/FLAIR hyperintensities predominating in the white matter (Fig. 1). The lesions are typically more prominent in the posterior cerebral hemispheres but may involve anterior regions and posterior fossa structures. Contrast enhancement is variable but usually absent. The 2 principal theories relating to pathogenesis implicate failure of cerebral vasomotor autoregulation because of hypertension or primary endothelial damage (akin to pre-eclampsia).

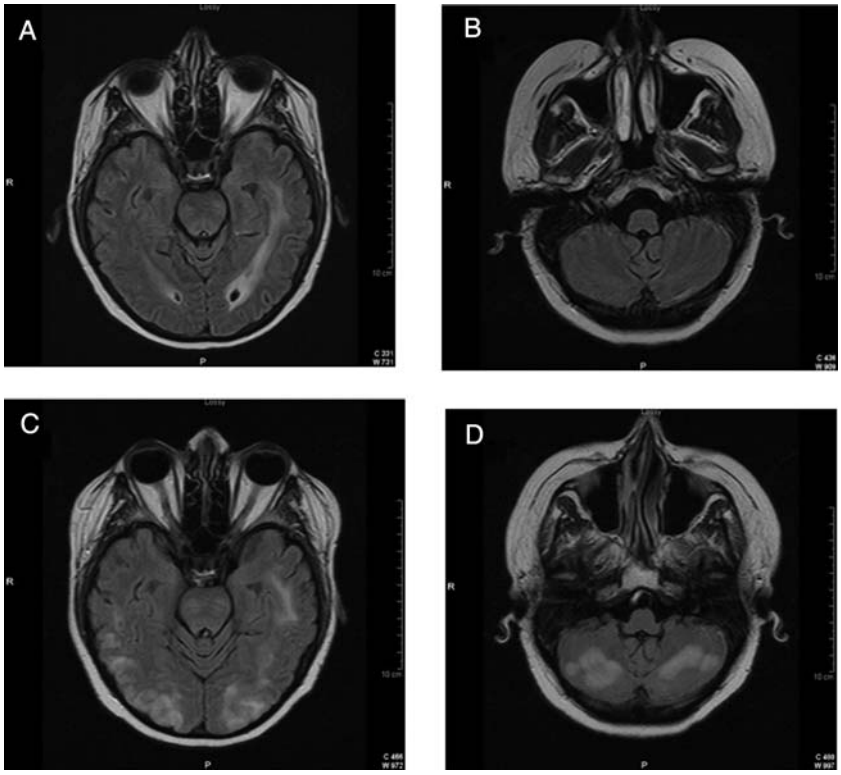

Fig. 1. Reversible posterior leukoencephalopathy syndrome (RPLS): This 47-year-old woman had an 18-month history of a corpus callosum glioblastoma that progressed despite radiation with temozolomide, temsirolimus with sorafenib, and then BCNU (Carmustine). She presented 3 weeks after starting bevacizumab with headache, seizures, unresponsiveness, and blood pressure of 160/100 mm Hg. FLAIR-weighted MRI sequences 2 weeks before (A and B) and 3 weeks after her first dose of bevacizumab (C and D).

Table 2. Incidence of thrombotic events and CNS hemorrhage from anti-VEGF therapies in patients with malignant gliomas

Study	Agent(s)	Number of patients	Number with DVT/PE	Number with CNS or Systemic Bleed	Number with stroke
Vredenburgh, JCO 2007[24]	Bev/CPT	35	4 (11%)	1 (0.03%)	0
Vredenburgh, Clin Cancer Res[59]	Bev/CPT	32	3 (9%)	0	1 (3%)
Friedman[20]	Bev & Bev/CPT	167	11 (7%)	5 (3%)	9 (5%)
Sathornsumetee[73]	Bev/Erlotinib	57	3 (5%)	1 (2%)	1 (2%)
Kreisl[85]	Bev & Bev/CPT	48	6 (8%)	0	0
Gilbert[55]	Bev/CPT, Bev/TMZ	117	14 (12%)	9 (8%) 8 grade 1 or 2	1 (1%)
Lai et al.[17]	Bev	70	13 (19%)	2 (3%)CNS, 2(3%) GI	6 (9%)
Batchelor[58]	Cediranib	31	1 (1%)	0	0
Wen[57]	XL184	153	15 (10%)	7 (5%)	0

Anti-VEGF agents are capable of producing both of these mechanisms, and this may help explain why both bevacizumab and VEGFR TKIs have been implicated in RPLS.[49,50] RPLS usually resolves quickly with treatment of hypertension and removal of the offending agent; subsequent reintroduction of an anti-VEGF agent is generally discouraged, although a recent case report noted successful resumption of bevacizumab post-RPLS (PMID 21900098).[51]

Hemorrhage

Anti-angiogenic agents are associated with an increased risk of both systemic and intracerebral hemorrhage (Table 2). Although an early meta-analysis of randomized controlled studies of bevacizumab failed to demonstrate a significant increase in the risk of hemorrhage,[52] a more recent meta-analysis involving 12 617 patients from 20 randomized trials suggested

that bevacizumab was associated with an increased risk of bleeding.[53] Overall, high-grade hemorrhages (grades 3–5) occurred in 3.5% of patients. Bevacizumab was associated with an increased the risk of bleeding with an RR of 2.48 (95% confidence interval [CI], 1.93–3.18), compared with the controls. This risk was greater for patients treated with higher doses of bevacizumab (5 mg/kg/week; RR, 3.02; 95% CI, 2.42–3.78), compared with those receiving lower doses of bevacizumab (2.5 mg/kg/week; RR, 2.01; 95% CI, 1.43–2.83). Most hemorrhages occurred within the first 5 months of treatment. The most common type of hemorrhage is epistaxis, but more serious forms of bleeding, such as hemoptysis, gastrointestinal bleeding, intracerebral hemorrhage, and intratumoral hemorrhage, may also occur.

VEGFR inhibitors are also associated with an increased risk of hemorrhage. One meta-analysis examining the use of sorafenib and sunitinib in 6799 patients with a variety of cancers found an incidence of high-grade bleeding of 2.4% (95% CI, 1.6–3.9) and an RR of 2.0 (95% CI, 1.14–3.49).[54]

The underlying mechanisms for the increased bleeding risk are complex and include damage of vascular integrity by the inhibition of endothelial survival and proliferation, particularly in tissues with a high VEGF dependence such as injured mucosal membrane of the airway; dysregulation of the coagulation cascade; damage to the tumor infiltrated vascular wall as a consequence of an antitumor effect; decreased matrix deposition in the supporting layers of vessels; and occasionally, treatment-induced thrombocytopenia.[53]

Low-grade systemic hemorrhages, such as epistaxis, are relatively common in patients with glioblastoma treated with bevacizumab. In the BRAIN trial, 27.4% of patients in the bevacizumab-alone arm, and 40.5% in the bevacizumab and irinotecan arm experienced grade 1 or 2 systemic hemorrhages.[20] However, grade 3/4 hemorrhages were uncommon, occurring in $<2\%$ of patients in this study, and in 0%–4% of other trials of bevacizumab in patients with glioblastomas.[22,24,55,56] Similarly, the rate of grade 3/4 hemorrhages in patients with glioblastoma treated with VEGFR inhibitors is low: 3% with cabozantinib (XL184)[57] and $<1\%$ with cediranib.[58] In summary, although for years, bevacizumab was not available for treating patients with glioblastoma because of concerns about the potential risk of intracerebral hemorrhage, all the studies to date have shown that the risk of intracerebral hemorrhage is low, ranging from 1% to 3.8%.[20,21,59,60]

There is also increasing evidence that patients with brain metastases treated with bevacizumab have a low risk of intracerebral hemorrhage. None of the 115 patients in the AVF3752g (PASSPORT) trial in which patients with non small-cell lung cancer and brain metastases treated with bevacizumab had grade ≥ 2 intracerebral hemorrhage.[61] In a retrospective analysis from 13 randomized controlled trials of bevacizumab, compiling 187 patients with occult brain metastases, 3.3% of patients with brain metastases had grade 4 cerebral hemorrhage, compared with 1 grade 5 hemorrhage (1%) in control patients. In the same report, 3 (0.9%) of 321 patients with occult metastases in single-arm studies who received bevacizumab developed cerebral hemorrhage, and 1 (0.8%) of 131 patients with brain metastases treated without bevacizumab developed a grade 2 cerebral hemorrhage.[62]

These data suggest that the risk of intracerebral hemorrhage in patients with brain tumor treated with anti-VEGF/VEGFR therapy is low. In the absence of overt intratumoral hemorrhage, treatment of primary and secondary brain tumors with anti-VEGF/VEGFR therapies is relatively safe. Exceptions may include those metastases with a higher propensity to hemorrhage, such as melanoma and choriocarcinoma.

Thrombosis and Other Vascular Events

Venous thromboembolic events (VTE) are common in patients with malignant gliomas. A review of published studies examining the risk of VTE in patients with malignant glioma reported that the 6-week peri-operative period had the highest rate of VTE.[63] However, after this initial period, the overall risk of VTE (17 months of follow up) is 24%. More recently, a retrospective review of the incidence of VTE in patients with malignant glioma compiled data on 9489 patients.[52] This large study revealed an overall incidence of VTE of 7.5%, with more than half of the events occurring within 2 months of a neurosurgical procedure. This study also identified risk factors for developing VTE, including age >65 years, diagnosis of glioblastoma, and recent neurosurgical procedures. A comparable increase in the risk of arterial thrombosis has not been reported for patients with malignant gliomas.

Vascular events, including venous and arterial thrombosis, have been reported as a frequent complication of anti-angiogenic therapies. However, the variable, often high reported rate of VTE in patients with malignant gliomas makes it difficult to determine whether the reported incidence of VTE exceeds the anticipated rate associated with the disease. Conversely, because arterial thromboses are uncommon in patients with malignant gliomas, arterial events are more likely to be considered directly related to anti-angiogenic therapy.

Early anti-angiogenic agents, notably thalidomide, were associated with a marked increase in the incidence of both venous and arterial thromboses.[65,66] For many of the systemic cancers treated with chemotherapy combinations with thalidomide, the increase in the incidence of thromboembolic events was dramatic. In a study of multiple myeloma, venous thrombotic events were noted in 34%, and in a separate study, a chemotherapy combination regimen including thalidomide for renal cell cancer had a VTE rate of 43%.[67] In addition, arterial thrombosis was reported in 7% of patients with prostate cancer treated with thalidomide.[68] These findings have led to the recommendation that thalidomide be administered in conjunction with low-dose warfarin, although the protective impact of a low-dose anticoagulant has not been fully established. Thalidomide has been used as a treatment for patients with malignant

gliomas. In reported studies that did not include warfarin prophylaxis, the rate of VTE was ~20%.[69,70] Similar rates of VTE have been reported with other immunomodulatory agents, such as lenalidomide, that are currently under investigation for a variety of primary brain tumors, including glioblastoma and pediatric infiltrative brainstem gliomas.[71] These findings underscore the potential for anti-angiogenic therapies to augment already high rates of VTE in patients with brain tumor.

The introduction of more-targeted anti-angiogenic agents, such as bevacizumab, generated concerns regarding treatment-induced arterial and venous thrombosis. Early phase II studies of bevacizumab in a wide variety of cancers reported rates of venous and arterial thrombosis ranging from 3% to 19% but did not include patients with glioma because of concerns about tumor and brain hemorrhage. An initial analysis that compiled data from 5 randomized (non-CNS tumor) trials of chemotherapy with or without bevacizumab that comprised 1745 patients determined that there was no increased risk of VTE with the addition of bevacizumab ($P = .44$).[52] However, a subsequent meta-analysis compiling the results of 15 randomized controlled trials reported a significantly increased risk of VTE in patients treated with bevacizumab.[72] In this study evaluating a total of 7956 patients, the RR of developing VTE was 1.33 with use of bevacizumab ($P < .001$). Furthermore, the risk was unchanged with the use of low-dose bevacizumab (2.5 mg/kg/week), compared with high dose (5.0 mg/kg/week).

All studies, to date, of bevacizumab in recurrent malignant gliomas have been relatively small, and none has included a treatment arm without bevacizumab to allow comparison of the RR of VTE with and without the drug. The incidence of VTE in these studies has ranged from 5% to 10% (Table 2). The combination of signal transduction modulator erlotinib with bevacizumab did not signficiantly increase the risk of VTE.[73] In addition, cediranib, an oral TKI that directly targets the VEGF receptor, was tested in patients with recurrent glioblastoma and produced only a low incidence of VTE.[58]

We obtained unpublished data from Genentech from the Avastin Adverse Event database[74] for both venous (VTE) and arterial (ATE) thrombotic events in patients undergoing treatment with a bevacizumab-containing regimen to provide a foundation to compare incidence in other solid tumors with high-grade gliomas. The database defined a VTE as a deep venous thrombosis, pulmonary embolus, mesenteric venous occlusion, retinal vein thrombosis, upper extremity thrombosis, or phlebitis. A small percentage of the patients in this database were in studies in glioblastoma, and these data reveal that the overall incidence of VTE (on study) was 7%. However, patients receiving bevacizumab alone had an incidence of 3.6%, compared with 8.9% with the combination of bevacizumab and irinotecan. For colorectal cancer, the rate of grade 3 or 4 VTE was 15% among patients treated with bevacizumab with chemotherapy, compared with 13.6% when treatment was chemotherapy alone. Similarly, in non small-cell lung cancer, the incidence of VTE was 5.6% with bevacizumab, compared with 3.2% with chemotherapy alone. Of interest, in breast cancer, the incidence of VTE was 3% with bevacizumab and paclitaxel and 4.3% with placebo and paclitaxel. Overall, the only risk factor for developing VTE was the addition of bevacizumab to chemotherapy.

The database defined an ATE as angina, stroke, myocardial infarction, transient ischemic attack, atrial fibrillation, or peripheral vascular disease. Overall, an evaluation of randomized controlled trials revealed that the incidence of grade 3 or higher ATEs was 2.4% with bevacizumab-containing regimens, compared with 0.7% with chemotherapy regimens without bevacizumab (data obtained from the Genentech Adverse Event Database). Similarly, pooling data from 5 studies in non small-cell lung cancer, breast, and colorectal cancer that evaluated bevacizumab-containing regimens (1745 patients) revealed an incidence of ATE of 3.8%. Risk factors for developing ATE from the entire database included age >75 years, history of arterial disease, baseline hypertension, an Eastern Cooperative Oncology Group (ECOG) performance status >2, and nonreceipt of anticoagulation therapy while undergoing treatment with bevacizumab. The BRAIN study, which treated 163 patients with recurrent glioblastoma with either bevacizumab alone or in combination with irinotecan, reported grade 3–5 ATEs in 3% of patients, consistent with other solid tumor studies.[20]

Assessment and management of thrombotic complications is complex and requires assessment of the impact of the anti-angiogenic agent on the event and the risk of treating the thrombosis. Most clinical trials that incorporate anti-angiogenic treatments permit continuing the therapy when there is evidence that the VTE is resolving. The recommended treatment for the VTE includes the use of standard anticoagulants and the continuation of bevacizumab in the absence of hemorrhage. Although there are no direct comparisons of the use of low–molecular weight heparin with oral warfarin in this context, there is a trend toward the use of low–molecular weight heparin because of reports of improved efficacy and no issues of drug-drug interactions or impact of diet on efficacy that are prominent with warfarin.[75]

The risk of anticoagulation in patients with glioma treated with bevacizumab has been investigated. A small series with 21 patients looked at concomitant anticoagulation with bevacizumab treatment, both given for a mean of 72 days.[76] There were no lobar hemorrhages; 3 small parenchymal hemorrhages were detected, with 1 being symptomatic and the others petechial. A larger study retrospectively reviewed 282 patients with high-grade glioma treated with bevacizumab, with 64 patients also receiving a systemic anticoagulant. Overall, the hemorrhage rate in the group receiving anticoagulation was 20%, with intracerebral hemorrhage accounting for half of the events, 2 (3%) of which were grade 4. Most of the intracerebral hemorrhages reported were asymptomatic and detected as

punctuate changes on MRI. Two patients (1%) who were treated with bevacizumab but not anticoagulation had serious intracerebral hemorrhage.

Patients who develop ATE should have the anti-angiogenic treatment stopped. Treatment of an ATE should be guided by the disease process, recognizing that the optimal management of stroke, myocardial infarction, and peripheral vascular occlusion may be quite different. No guidelines currently exist for the non-classic events, such as the chronic diffusion restriction and/or apparent diffusion coefficient (ADC) decrease changes that have been reported with bevacizumab, as described above. The pathogenesis and clinical importance of these findings have not yet been well defined, although ongoing research may soon provide some guidance.

The identification of stroke in patients undergoing anti-angiogenic therapy may be challenging. MRI, particularly diffusion-weighted imaging (DWI) and ADC mapping are well established as diagnostic tools for conventional strokes. Typically, changes on DWI and ADC occur acutely with the event and resolve within a few weeks. However, vascular events that develop with anti-angiogenic agents may not follow this pattern (see Fig. 2). A recent study reported on 18 consecutive patients who were undergoing treatment with bevacizumab and were prospectively evaluated with DWI and ADC imaging.[77] Thirteen of the 18 patients developed stroke-like lesions, defined as diffusion restriction on DWI with an accompanying decrease in ADC. Most of these changes were not associated with clinical findings. Of interest, these imaging abnormalities lasted up to 80 weeks.

Wound Healing

Angiogenesis is a necessary step in wound healing. Anti-angiogenic agents potentially interfere with wound healing by impairing neovascularization, disturbing platelet-endothelial cell interaction, and reducing VEGF-induced tissue factor on endothelial cells.[78] The long half-life of bevacizumab of 20 days (range, 11–50 days) results in a more extended risk of wound healing, compared with VEGFR inhibitors, which have a shorter half-life and usually less wound healing issues. In one study of patients with colorectal cancer who underwent surgery, 10 (13%) of 75 patients who had surgery within 60 days of bevacizumab treatment had complications, compared with complications in only 1 (3.4%) of 29 patients who had surgery after chemotherapy alone.[78]

The frequency of wound breakdown of all grades in patients with glioblastoma treated with bevacizumab ranges from 0% to 6%.[20,22,24,55,79] Similarly low rates have been reported with VEGFR inhibitors, such as cabozantinib (XL184; 2%).[57]

The impact of prior bevacizumab chemotherapy on craniotomy wound healing was recently evaluated in a retrospective review [74]. Two hundred nine patients underwent a repeat craniotomy, of whom 23 received preoperative bevacizumab and 18 received postoperative bevacizumab. Significantly more patients receiving preoperative bevacizumab developed healing complications (35%) than nonbevacizumab-treated patients (10.0%; $P = .004$). Postoperative bevacizumab was associated with 6% impaired healing, which was not significantly different from nonbevacizumab-treated control subjects ($P > .99$). The wound healing complications were more striking for the third craniotomy than for the second craniotomy and for a shorter delay between bevacizumab and surgery. On the basis of these results, the authors recommended performing repeated craniotomy after a minimum of 28 days after last administered dose of bevacizumab whenever possible.[80]

Because many patients receiving bevacizumab require placement of venous access ports, the effect of the agent on wound dehiscence or impaired wound healing is a common clinical issue. In one study involving 195 ports placed in 189 patients, the incidence of wound dehiscence was significantly higher in those patients receiving bevacizumab within 10 days of port placement.[81] A more recent retrospective review evaluated wound healing in 1108 port placements in patients who were treated with bevacizumab.[78] Patients treated with bevacizumab within 1 day of port placement had an absolute risk of wound dehiscence requiring chest wall port explant of 2.4%. The risk of wound dehiscence was inversely proportional to the interval between bevacizumab administration and port placement, with significantly higher risk seen when the interval was <14 days.[82]

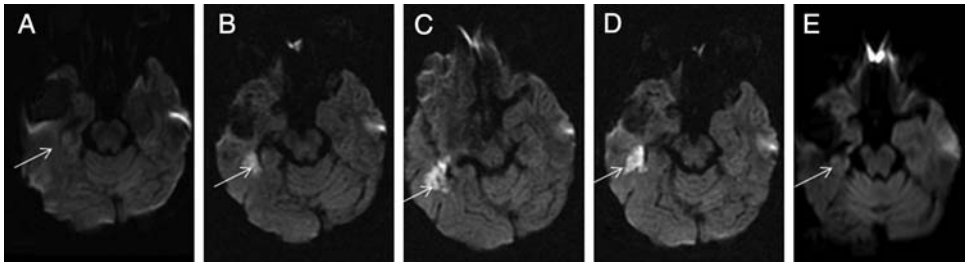

Fig. 2. Imaging changes associated with a vascular event in a patient treated with bevacizumab. A, Pretreatment. B, Ten months later. Rapid onset of weakness. Bevacizumab stopped. C,Twelve months later, 2 months after stopping bevacizumab. D, Fifteen months, 5 months after stopping bevacizumab. E, Twenty-one months after stopping bevacizumab.

Although studies are limited, ideally, bevacizumab should be avoided 4 weeks before and after surgery. For smaller surgeries, bevacizumab should be avoided for at least 2 weeks, whenever possible. Surgery can usually be performed sooner with VEGFR inhibitors because of their shorter half-life, but a washout of at least 1 week is recommended.

Bowel Perforation

Anti-angiogenic agents can contribute to bowel perforation by several mechanisms, including tumor necrosis, exacerbation of existing gastric ulcers or diverticulitis, obstruction, chemotherapy-associated colitis, ischemic perforation of normal bowel or anastomosis, arterial thromboembolic events, and exacerbation of steroid effects.[53] The risk factors most relevant to patients with brain tumor include underlying diverticular disease and peptic ulceration, constipation, and the concomitant use of corticosteroids.

In a meta-analysis compiling 12 294 patients with a variety of solid tumors from 17 randomized controlled trials, the incidence of gastrointestinal perforation was 0.9% (95% CI, 0.7%–1.2%). The RR was 2.14 (95% CI, 1.19–3.85; $P = .011$), and mortality was 21.7% (95% CI, 11.5%–37.0%). Most of the cases of gastrointestinal perforation occurred within the first 6 months of treatment.[83] The RR was higher for those receiving 5 mg/kg of bevacizumab (2.67; 95% CI, 1.14–6.26) than for those receiving 2.5 mg/kg (1.61; 95% CI, 0.76–3.38). Higher risks were also observed among patients with colorectal carcinoma (RR, 3.10) and renal cell cancer (RR, 5.67).[53]

There are only a limited number of studies addressing the risk of bowel perforation in patients with brain tumor. In one retrospective review of 244 patients with high-grade glioma treated with anti-angiogenic agents, predominantly bevacizumab, 6 developed bowel perforation (2.5%); 2 of these patients died, and 4 eventually recovered.[20] All of these patients had received concomitant corticosteroids.[84] The incidence of bowel perforation in clinical trials of bevacizumab in patients with glioblastomas range from 0% to 2.9%.[21,22,24,59,85] Fewer data are available for patients with glioblastomas treated with VEGFR inhibitors. In a trial involving 153 patients treated with cabozantinib (XL184), the incidence of bowel perforation was 2%.[57]

Bowel perforation is generally associated with a high mortality and requires prompt surgical assessment.[86] A nonoperative approach involving bowel rest, intravenous fluids, and broad-spectrum antibiotics is usually preferred, although surgical intervention is sometimes necessary. However, this latter treatment is often complicated by problems with wound healing.

Conclusions

Bevacizumab is now routinely used in the treatment of patients with malignant glioma Other anti-angiogenic agents are being evaluated and may also be used in the treatment of malignant gliomas because of the importance of angiogenesis in tumor growth. Although angiogenesis is an enticing target for therapy, these agents have well-recognized complications. Common and significant toxicities include hypertension, proteinuria and risk for renal failure, posterior leukoencephalopathy syndrome, venous and arterial thromboembolic disease, bowel perforation, and poor wound healing. Diligent evaluation for these toxicities is important, because early intervention may decrease morbidity and mortality risk. Prompt recognition of an anti-angiogenic agent–related toxicity may also mandate treatment cessation to avoid exacerbation of the adverse event(s). Currently, the data on the occurrence and optimal management of these treatment-related complications in patients with gliomas are limited. Therefore, much of the available knowledge and management guidelines are based on data from the experiences in a variety of systemic cancers. Future studies that systematically evaluate potential clinical and genetic risk factors for toxicities, to determine the true incidence of these toxicities in the brain tumor population, leading to the establishment of both screening and treatment guidelines, are needed.

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