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Journal
Current Treatment Options in Neurology, 15(3)

ISSN
1092-8480

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Publication Date
2013-06-01

DOI
10.1007/s11940-013-0224-y

Peer reviewed

Published in final edited form as:
Curr Treat Options Neurol. 2013 June ; 15(3): 328–337. doi:10.1007/s11940-013-0224-y.

Anti-angiogenic Therapy in High-Grade Glioma (Treatment and Toxicity)

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Opinion Statement

Malignant gliomas continue to have a very poor prognosis and treatment responses at recurrence are very limited. Though anti-angiogenic therapy has not yet been shown to extend overall survival in this patient population, there is likely substantial benefit to reducing vasogenic edema, allowing for temporary improvement in neurologic function and minimizing the side effects of prolonged corticosteroid use. A trial of bevacizumab should be considered in those with worsening vasogenic cerebral edema such as seen in recurrent malignant gliomas, radiation necrosis, or progressive brain metastases. However, not all patients respond to anti-angiogenic treatment and if no radiographic or clinical responses are seen, then patients are not likely to benefit from further infusions. Though it is commonly well tolerated, some side effects, while rare, may be life threatening, and should be discussed with patients and their families. These discussions should also outline the goals of initiating therapy and when treatment should be stopped.

Keywords

Glioma; High-grade glioma; Anti-angiogenic; Treatment; VEGF; Vasogenic edema; Targeted therapy; Bevacizumab

Introduction

Glioblastoma (GBM) (World Health Organization [WHO] grade IV gliomas) are the most common type of malignant primary brain tumor in adults. The current standard of care for GBM, based on work by Stupp et al from 2005, is adjuvant focal fractionated radiation to 60 Gray over 6 weeks with concurrent temozolomide (an oral alkylating agent) followed by 6-12 cycles of temozolomide monotherapy. Despite advances in our understanding about how these tumors develop and proliferate, they remain a therapeutic challenge with median overall survival of 15 months and 5% 5-year survival rate [1]. Anaplastic gliomas (WHO grade III) are less common and prognosis is varied and heavily dependent on molecular characteristics such as 1p19q co-deletion and IDH mutation status. Emerging data shows a prolonged overall survival when chemotherapy is added to radiation in those patients with 1p19q co-deletion [2, 3], and while further studies are pending, the data demonstrates that long-term survival is achievable for some of these patients. However, malignant gliomas are not curable and the aim of treatment is to delay time to recurrence.

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Disclosure Jennie Taylor declares that she has no conflict of interest. Elizabeth R. Gerstner declares that she has no conflict of interest.

Angiogenesis and anti-angiogenic therapy in high grade glioma

GBM have marked vascular proliferation as a histologic signature. Several growth factors, namely vascular endothelial growth factors (VEGF), and placental growth factor (PlGF), are ligands for VEGF receptor-2 (VEGFR-2) located on endothelial cells [4]. Secretion of these growth factors correlates with tumor grade with higher-grade tumors expressing higher levels of growth factors and their corresponding receptors. Binding to VEGFR2 leads to dimerization and activation of several intracellular pathways, phosphatidylinositol 3′-kinase (PI3K), Akt, and mitogen-activated protein kinase (MAPK), culminating in endothelial cell proliferation, increased vascular permeability, and migration [5]. However, as the tumor bulk outgrows its blood supply, hypoxic conditions drive vascular co-option and new blood vessels are generated, allowing for further tumor growth. The cycle continues, producing invasion and increased production of dysfunctional blood vessels [6, 7]. Because of this dependency on generating vasculature for tumor growth and migration, angiogenesis has been a desirable target for the treatment of malignant gliomas.

Anti-angiogenic drugs are approved for use in a number of solid tumors. Drugs directed against circulating VEGF and tyrosine kinase inhibitors (TKIs) directed against angiogenic receptors have been developed. The mechanism by which these agents have an anti-tumor effect remains controversial. One proposed hypothesis is that of vascular normalization, as opposed to preventing new blood vessel formation and starving the tumor of the necessary nutrients and oxygen – the original hypothesis [8]. Tumor associated blood vessels are poorly formed, large in size, and leaky from inadequate pericyte coverage. Normalization leads to stabilization of these blood vessels and improved, more uniform perfusion, allowing for marked improvements in cerebral edema and better drug delivery [8, 9]. Targeting angiogenesis also likely disrupts the fragile cancer-stem-cell vascular niche, possibly making these cells more vulnerable to environmental changes [10]. It is likely that some combination of these possible mechanisms may be occurring in tumors.

Measuring Tumor Response

Magnetic resonance imaging (MRI) is the best tool to visualize malignant gliomas. Tumor-induced vascular permeability and dysfunction of the blood brain barrier (BBB), leads to extravasation of intravenously administered contrast as seen on post contrast T-1 weighted images, and a centrally necrotic, ring-enhancing lesion is appreciated (Figure 1 A). The extent of tumor infiltration is best seen on the T-2 weighted or fluid-attenuated inversion recovery (FLAIR) sequences, though it is difficult to distinguish from vasogenic edema (Figure 1 B). Because anti-angiogenic therapy targets the vasculature, the permeability of the blood-bran-barrier (BBB) is altered and there is often a dramatic and rapid radiographic response with reduction in contrast enhancement and vasogenic edema (Figure 1 C and D). Initially interpreted as a decrease in tumor burden, the correlation between decreased enhancement and the presence of tumor is likely more complex with tumor progressing behind the less permeable BBB (Figure 1 E and F). Regardless, improvement in neurologic function initially correlates with the decreased vasogenic edema and mass effect, often allowing a taper of corticosteroids.

Interpretations of continued radiographic response and defining progression, is now more challenging in the anti-angiogenic era. Increase in post-contrast T1-weighted sequences is no longer sufficient to detect progression, and other sequences such as diffusion weighted images (DWI) are being investigated [11, 12]. The revised Response Assessment in Neuro-Oncology Working Group (RANO) criteria incorporates changes on FLAIR sequence, neurologic function, and corticosteroid use, although these criteria still need to be validated [13] (•).

Resistance to anti-angiogenic treatment

Despite many patients experiencing an initial response, the use of anti-angiogenic agents have not translated to longer overall survival in malignant glioma patients and some patients do not respond at all. This has left clinicians frustrated and researchers looking for modes of anti-angiogenic escape/resistance. Those patients that do initially respond, likely acquire mechanisms of escape by up-regulating other non-VEGF dependent pro-angiogenic pathways, recruiting bone marrow-derived progenitor cells that promote tumor growth and blood vessel formation, and/or increasing pericyte coverage that leads to neovascular protection. Alternatively tumor cells may invade normal brain parenchyma by co-opting existing blood vessels [14]. VEGF and VEGFR-2 are not the only molecules involved in angiogenesis. Interactions between angiopoietin-1 (Ang-1), -2 (Ang-2) and their VEGFR-2-like tyrosine kinase receptor Tie-2, also play a role in angiogenesis and possible resistance. Ang-2 and Tie-2 inhibition are being evaluated as new anti-angiogenic targets in patients with malignant gliomas [5].

A subset of GBM may be less dependent on angiogenesis for growth, and therefore inherently resistant to drugs targeting angiogenesis [15]. Efforts are underway to identify potential biomarkers and predictors of response to targeting angiogenesis. Changes in plasma placental growth factor (PlGF), basic fibroblast growth factor (bFGF), matrix metalloproteinase-2 (MMP2), soluble VEGFR-1, stromal cell-derived factor-1alpha (SDF1α), and soluble Tek/Tie2 receptor correlated with survival in studies of cediranib in recurrent GBM, and are currently being studied in prospective trials [9].

In a few small retrospective studies of patients with progression on a VEGFR-TKI targeted agents, bevacizumab still provided response rates of 21-29%, median PFS6 12.5-29%, and median OS 5.2-7.8 months. Significant variation was noted depending on which VEGFR-TKI was used, with better responses following sunitinib than cediranib. This suggests that a subpopulation of patients who are treated with anti-VEGFR directed therapy might still benefit from anti-VEGF treatment, though others may not [16, 17].

Treatment

Pharmacologic treatment

Bevacizumab—Bevacizumab (Avastin®, Genentech/Roche) is a recombinant humanized IgG1 monoclonal antibody that binds to VEGF-A, and prevents it from interacting with VEGFR and downstream signal activation, with a long half-life of ~20 days. In early studies, when combined with irinotecan, radiographic response rates of 28- 40% and 6-month progression free survival (PFS6) rates of 40-50% were very encouraging [18-20]. It gained accelerated approval by the US Food and Drug Administration in 2009 as monotherapy for treatment of recurrent GBM based on a randomized non-comparative phase II trial of bevacizumab alone or in combination with irinotecan [21]. The PFS6 was 50.2% in the combination arm, compared to 35% with bevacizumab alone. The median overall survival (OS) was 8.9 months in the combination arm and 9.7 months for bevacizumab monotherapy arm. Though PFS6 was higher with the combination, the added toxicity and equivalency in median OS left in question the added benefit of irinotecan, leading bevacizumab to be approved as monotherapy for recurrent GBM in the US [14, 21] (Class II).

Based on these promising results, the ongoing AVAglio trial, a randomized phase III study of bevacizumab in newly diagnosed GBM, was launched. Patients were randomized to standard radiation and temozolomide with placebo or bevacizumab until progression or unacceptable toxicities. The study was designed with dual primary endpoints of PFS and OS, with preliminary results revealing an improved PFS in the bevacizumab arm, while the

OS data is still pending. Interim analysis of several secondary endpoints – including quality of life, steroid use, and radiographic response – all favor bevacizumab with an acceptable toxicity profile [22]. Final results are pending and will hopefully shed light on the role of anti-angiogenic therapy in newly diagnosed GBM patients.

Standard dosage: 10 mg/kg intravenously every 14 days. First infusion should be over 90 minutes, second at 60 minutes, and all subsequent infusions at 30 minutes if well tolerated. Decreased doses of 5 or 1.5 mg/kg or decreased dose frequency of every 3 or 4 weeks are also used if toxicity develops, but are not approved.

Contraindications: Patients with poorly controlled coagulopathies, bowel perforation, or significant hemorrhage may be at risk of worsening hemorrhage or thrombosis and should be treated cautiously. Bevacizumab should not be administered within 28 days of a major surgical procedure or 14 days of a minor procedure for concerns of poor wound healing.

Main drug interactions: There are no significant drug interactions with bevacizumab, though caution should be used in patients who are anti-coagulated and may be at higher risk for hemorrhagic events.

Main side effects: Many of the toxicities related to ant-angiogenic therapy are related to drug effects on normal vasculature and endothelial cells. Table 1 outlines the major side effects in detail, which are similar in glioma patients as compared to patients with other malignancies. In particular, GBM patients are at increased risk for venous thromboembolic events (VTE), and that risk increases further with anti-angiogenic therapy [19, 20, 23](•). Increased risk of intracranial hemorrhage is also of particular note in this patient population and treatment should be discontinued if there is significant hemorrhage [19, 24]. Occasionally patients report fatigue and hoarseness.

Emerging therapies

Several other drugs, many of which are approved for other malignancies and target anti-angiogenic pathways, are under investigation for malignant gliomas (Table 2). Many tyrosine kinase inhibitors (TKIs) – such as cediranib, sorafenib, sunitinib, and vandetanib – have been studied in phase II trials in gliomas. A few other monoclonal antibodies – such as ramucirumab targeting VEGFR2 and IMC-3G3 PDGFR-α – are under investigation. To date, no other targets of angiogenesis have demonstrated improvement in PFS or OS, or gained approval in glioma therapy.

Other roles for anti-angiogenic therapy

The anti-permeability effect of bevacizumab and anti-VEGFR TKI, leads to improvement in vasogenic edema, allowing patients to wean off corticosteroids and minimize the debilitating side effects of steroid myopathy, diabetes, hypertension, weight gain, insomnia, and mood disorders [25, 26]. Vasogenic edema from progressive radiation necrosis results from increased vascular permeability secondary to cytokine release from the radiation-targeted tissue. Over time, the tissue becomes hypoxic and necrotic, perpetuating the cycle of angiogenic factor (such as VEGF) release and further edema. Blocking VEGF disrupts this cycle, stabilizes vasculature, and allows a decrease in corticosteroid dependence. A few small series demonstrated efficacy and safety in using anti-angiogenic treatment in radiation necrosis [27, 28] (•). Bevacizumab's anti-permeability effect also improves vasogenic edema and decreases steroid dependence in patients with brain metastases [29-31].

Surgery

Effects on wound healing, by disrupting neovascularization is a well-known complication of anti-angiogenic therapy. In a recent large retrospective study of patients undergoing repeat surgery, eleven percent of the population received preoperative bevacizumab with a significant higher rate of post-operative complications (35% versus 10%, P=0.004) and perioperative morbidity rates of 44% compared to 21% in those who had not received bevacizumab. The authors recommended postponing elective surgery for at least 28 days after last bevacizumab infusion to minimize complications [32]. Recommendation for smaller surgeries, such as port placement, is to avoid bevacizumab for at least 2 weeks prior to the procedure.

Physical/speech therapy and exercise

Because glioma patients are at increased risk for thromboembolic events, which increases further with anti-angiogenic therapy, patients should remain physically active to minimize venous stasis and steroid myopathy.

Pediatric considerations

Studies evaluating the efficacy of bevacizumab in children with progressive or refractory low-grade gliomas have demonstrated objective radiographic and clinical responses and tolerable toxicities. Bevacizumab is often combined with chemotherapy in this population, potentially worsening some of the toxicities, though most are manageable and reversible with discontinuation of the drug or prolonging the interval between doses. This strategy may prove to be most useful in scenarios of unresectable symptomatic lesions – such as those near the optic nerve – where rapid treatment response may prolong nervous system function [33, 34].

For treatment of high-grade gliomas, though, only small studies are available and results have been disappointing when targeting angiogenesis, suggesting an alternative mechanism driving tumor growth that is independent of VEGF [35, 36]. Many pediatric brain tumors are diffuse infiltrating pontine gliomas, for which anti-angiogenic targets have not been successful in treating the tumor. However, there may be a role in treating radiation necrosis in this sensitive area [37, 38].

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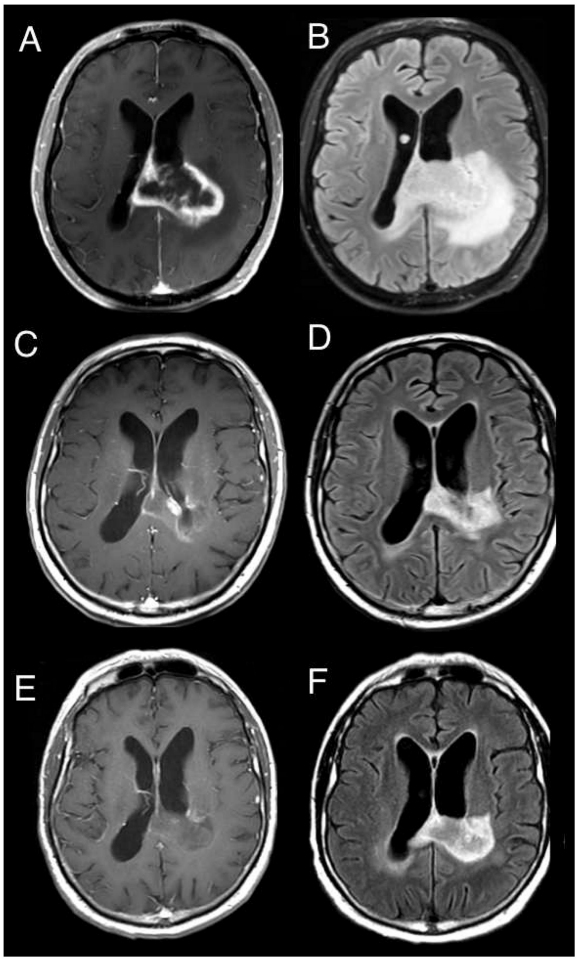

Figure 1.
Magnetic resonance imaging of 58-year-old man with recurrent glioblastoma prior and after receiving bevacizumab therapy. A and B: T-1 weighted post-contrast image (A) and T2/FLAIR (B) image prior to starting bevacizumab, demonstrating large area of central necrosis and infiltrative tumor with surrounding edema. C and D: T-1 weight post-contrast image (C) and T2/FLAIR (D) image 2 months after starting bevacizumab with significant reduction in contrast enhancement and edema. E and F: T1-weighted post-contrast (E) and T2/FLAIR (F) image 4 months after starting bevacizumab with continued minimal enhancement but progressive infiltrative tumor.

Table 1

Toxicities

Toxicity	Incidence with bevacizumab	Mechanism	Alteration to bevacizumab administration	Treatment
Hypertension	30% [52] (••)	Vasoconstriction secondary to decreased nitric oxide production and endothelial exposure to reactive oxygen species [52] (••)	Stop for uncontrolled BP [53]	ACE inhibitor or calcium channel blocker [53]
Proteinuria	5× increased risk in cancer patients [19, 20, 54]	Hypertension-induced increased intraglomerular pressure, and thrombotic microangiopathy [55, 56]	Stop for nephrotic syndrome. Hold for 24hr urine protein >2g [52] (••)	ACE inhibitor [52] (••)
Hemorrhage	Systemic: 68% [19] ICH: 2-5% [9, 19, 24, 48]	Endothelial cell apoptosis [57]	Stop treatment	Dependent on disease process
VTE	1.33× increased risk in cancer patients [58]	Endothelial cell apoptosis [57]	Continue if no indication of hemorrhage	Anticoagulation with LWMH if no contraindication
ATE	3% in glioma patients [19]	Endothelial cell apoptosis [57]	Stop treatment [52] (••)	Dependent on disease process
GI perforation	0 – 3% [19, 59]	Exacerbation of ulcers, diverticulitis, chemo-induced colitis, steroid effects, ATE, and endothelial cell dysfunction	Stop treatment	GI perforation management

BP (blood pressure); ACE (angiotensin converting enzyme); ICH (intracranial hemorrhage); VTE (venous thromboembolic event); ATE (arterial thromboembolic event); LMWH (low molecular weight heparin)

Table 2
Investigational anti-angiogenic treatment

Drug	Target	Most Advanced Phase Trial	Results
Antibodies			
IMC-3G3	PDGFR- α	Phase II recurrent GBM	Ongoing (clinicaltrials.gov)
Ramucirumab	VEGFR2	Phase II recurrent GBM	Ongoing (clinicaltrials.gov)
Tyrosine Kinase Inhibitor			
AEE788 [39]	VEGFR-1/2 EGFR	Phase I recurrent GBM	Significant toxicity in 17% and no responses
Cediranib [9, 26, 40]	VEGFR-1/2/3 c-kit PDGFR-α/β	Phase III in recurrent GBM Phase II in newly diagnosed GBM	No improvement over lomustine alone Ongoing (clinicaltrials.gov)
E7080	VEGFR-2/3 FGFR1 PDGFR-β	Phase II recurrent GBM Phase III advanced solid tumors (including GBM)	Ongoing (clinicaltrials.gov) Combined with E7050 (c-MET, VEGFR-2) ongoing
Enzastaurin [41]	PKC PI3K/AKT	Phase III in recurrent GBM	Stopped prematurely with no improvement over lomustine alone
Pazopanib [42]	VEGR-1/2/3 PDGFR- α/β c-kit	Phase II recurrent GBM Phase II recurrent GBM	PFS6 3%, median OS 8 months Combined with lapatinib (HER2/neu, EGFR) ongoing
Sorafenib [43, 44]	VEGFR-2/3 PDGFR- β FLT3 Raf kinase	Phase I/II in newly diagnosed GBM	Ongoing (clinicaltrials.gov)
Sunitinib [45, 46]	VEGFR-2 PDGFR-α/β c-kit	Phase II in recurrent GBM	PFS6 21.5% and median OS 12.6 months. Combination with irinotecan did not improve results
Tandutinib [47]	PDGFR FLT3 c-kit	Phase I/II recurrent GBM	Stopped because of toxicity
XL184 [48]	VEGFR-2 REF FLT3 c-kit	Phase II newly diagnosed GBM	Interim analysis PFS6 21%. Ongoing
Vatalanib [49]	VEGFR-1/2/3 PDGFR- β c-kit	Phase I/II newly diagnosed GBM	Well tolerated, but limited efficacy
Vandetanib [50]	VEGFR-1/2 EGFR RET	Phase I/II recurrent malignant glioma Phase II recurrent GBM with or without carboplatin	PFS6 6.5%, median OS 6.3 months Ongoing (clinicaltrials.gov)
Other			
Afibercept (VEGF-Trap) [51]	VEGF-A/B PlGF VEGFR-2	Phase II recurrent malignant glioma	<8% PFS6, median OS 12 weeks, 25% radiographic response
AMG 386	Ang-1/2 peptide-Fc fusion protein	Phase II recurrent GBM	Ongoing (clinicaltrials.gov)
PF-04856884	Ang-2 inhibitor	Phase II recurrent GBM	Ongoing (clinicaltrials.gov)

PDGFR (platelet derived growth factor receptor); GBM (glioblastoma multiforme); VEGFR (vascular endothelial growth factor receptor); PKC (protein kinase C); PI3K (phosphatidylinositol 3′-kinase); FLT3 (Fms-like tyrosine kinase); EGFR (epidermal growth factor receptor); PlGF (placental derived growth factor); Ang2 (angiopoietin-2)