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Update on Antiangiogenic Therapy for Advanced Malignant Glioma

Edited by Timothy F. Cloughesy, M.D. and James J. Vredenburgh, M.D.

Gliomas are a broad category of primary brain tumors arising from glial stem/progenitor cells. They account for roughly 40% of all primary brain and central nervous system tumors, and 78% of malignant CNS tumors[1]. Of the different glioma subtypes, glioblastoma multiforme (GBM), a highly invasive and almost uniformly fatal tumor, is the most common. Standard treatment for GBM involves surgical debulking followed by combination treatment with radiotherapy (RT) and temozolomide (TMZ), an oral alkylating agent, followed by temozolomide alone. Despite such aggressive treatment, virtually all GBM patients relapse, and roughly 75% do not survive beyond 2 years[2].

GBM is among the most highly vascularized of all malignancies and relies upon angiogenesis for growth and histological progression[3]. Angiogenesis in GBM, like all solid tumors, is mediated primarily by vascular endothelial growth factor (VEGF), which stimulates capillary sprouting from pre-existing vessels toward VEGF-expressing tumor cells. Tumor VEGF expression and angiogenesis are hypoxia-driven, but can be activated independently by different tumor cell mutations[4]. Because VEGF is also the primary vascular permeability factor, excessive VEGF production in GBM disturbs the normal blood brain barrier—tumor capillaries leak fluid into the surrounding brain tissue, often causing extensive vasogenic edema with increased interstitial pressure and mass effect.

Besides VEGF, angiogenesis in malignant glioma is also induced by basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), angiopoietin-2 (Ang-2), stem cell factor, and hepatocyte growth factor/scatter factor through different signaling pathways[4, 5]. Brain tumor vasculature may also be formed by the recruitment and differentiation of bone marrow-derived progenitor cells to form new vessels (vasculogenesis); by formation of fluid-transporting channels within the tumor (intussusception); and by co-option of pre-existing vessels[5]. Co-option of normal host capillaries by infiltrating glioma cells is thought to be instrumental in GBM invasiveness, and a precursor to neovascularization[5, 6].

Antiangiogenic Therapy for Malignant Glioma

Bevacizumab (Avastin®; BV), a humanized anti-VEGF monoclonal antibody, showed initial, dramatic promise for advanced malignant glioma in combination with irinotecan (CPT-11) in a phase 2 trial of 68 patients with recurrent disease[7, 8]. Radiographic response rates were 61% and 57% for recurrent grade 3 tumors (anaplastic glioma) and GBM, respectively—markedly higher than historic responses observed with TMZ at first recurrence (35% for grade 3 tumors and 5% for GBM). Updated 2-year survival rates from this study were 33% for grade 3 patients and 15% for GBM patients[8]. In May 2009, the FDA granted accelerated approval for BV 10 mg/kg as a single agent for recurrent GBM, making it the first clinically validated antiangiogenic therapy for the disease. The approval followed preliminary data from a non-comparative, prospective phase 2 trial that demonstrated a 26% tumor response rate with a median duration of response of 4.2 months with single-agent BV[9]. Progression-free survival at 6 months (PFS6) for combination BV-irinotecan was 50.2%. Most recently, data were reported from a phase 2 trial of 48 heavily pretreated recurrent GBM patients treated with single-agent BV[10]. PFS6 was 29%, and overall survival (OS) at 6 months was 57%.

A number of studies are underway assessing BV in combination with various standard GBM treatments and newer small molecule therapies for both recurrent and newly diagnosed GBM. In the front-line setting, data from two phase 2 trials of BV in combination with TMZ/RT were recently presented. In the first study in 75 patients, 81% remained alive and progression free at 9 months, and 22 patients completed 6 cycles of BV plus TMZ/irinotecan, of whom 17 had a cold PET scan during treatment[11]. In the second study, researchers reported a PFS6 rate of 89.1% in 70 patients treated with BV plus TMZ/RT, which compares favorably to historical controls of TMZ/RT alone[12]. A randomized phase 3 trial of TMZ/RT plus either BV or placebo in newly diagnosed GBM or gliosarcoma is underway, but results are not expected for several years.

Another potentially promising antiangiogenic agent for GBM is cilengitide (EMD121974), a selective inhibitor of the $\alpha_V\beta_3$ and $\alpha_V\beta_5$ integrins, cell surface adhesion molecules that facilitate endothelial proliferation and migration through the extracellular matrix, and which are highly expressed in malignant gliomas. In a phase 2 study, 81 patients with recurrent glioma (93% GBM) received single-agent cilengitide at doses of either 500 mg or 2000 mg 2x/week[13]. The PFS6, median OS, and proportion of radiographic responders in this trial were 9.9%, 7.2 mo., and 8.6%, respectively, all favoring the 2000 mg dose. Most recently, data was presented from a phase 2 trial (NABTT 0306) in 94 patients with newly diagnosed GBM who were randomized to receive TMZ/RT plus either cilengitide 500 mg or 2000 mg[14]. The median overall survival was 18.9 months, which compared favorably to a median OS of 14.6 months reported from a phase 3 trial (EORTC) of

From the Editor-in-Chief

The Angiogenesis Foundation is pleased to present this issue of *Targeting Tumor Angiogenesis: Update on Antiangiogenic Therapy for Advanced Malignant Glioma.* Two preeminent experts, Dr. Timothy Cloughesy and Dr. James Vredenburgh, discuss the latest evidence on antiangiogenic treatments for glioma and what the future holds for new therapeutic targets under investigation.

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front-line TMZ/RT. A third agent, XL184, an oral small molecule tyrosine kinase inhibitor (TKI) of VEGFR-2, hepatocyte growth factor receptor (MET), and stem cell growth factor receptor (c-Kit), was evaluated in a phase 2 study in 42 recurrent GBM patients[15]. In data recently reported, 38% of patients had a best radiologic response of 50% from baseline (including a 100% reduction in one patient), and 35% had tumor reductions of > 24% to < 49%.

Control of cerebral edema with antiangiogenic therapy

Cerebral edema is a major cause of morbidity and mortality in a number of CNS disorders, including brain tumors[16]. Overproduction of VEGF by tumor cells and host stroma degrades the capillary basement membrane, which makes tumor vessels hyperpermeable and causes leakage of plasma fluid and proteins from the intravascular compartment into the brain parenchyma, often resulting in significant vasogenic edema and increased interstitial fluid pressure[16]. A major cause of death in GBM patients is cerebral herniation (seen in more than 60% of patients), which results primarily from cerebral edema and intracranial hypertension[17]. Corticosteroids are used to temporarily alleviate brain edema and reduce mass effect, but cause a number of serious dose-limiting adverse effects.

There is now compelling evidence that anti-VEGF therapy induces a significant anti-edema effect by transiently 'normalizing' tumor vasculature and restoring integrity of the blood brain barrier. In the previously mentioned phase 2 study of BV in 48 heavily pretreated GBM patients, cerebral edema decreased in 24 patients (50%), and 15 of 26 (58%) patients receiving corticosteroids were able to decrease their corticosteroid dose by an average of 59%[10]. The vascular effects of anti-VEGF therapy for GBM have been most elegantly demonstrated using cediranib (AZD2171; Recentin®), a small molecule oral TKI of VEGFR-2, PDGFR-α and -β and c-Kit. In a phase 2 trial of 30 patients with recurrent GBM treated with single-agent cediranib, researchers documented by MRI rapid and dramatic improvement in both tumor vessel structure (pruning and remodeling of abnormal vessels) and function (decreased vessel permeability and diameter) in 16 patients beginning as soon as 1 day after therapy initiation[18, 19]. The vascular changes corresponded with significant abatement of edema and decreased steroid requirement in 11/16 patients (3 were able to discontinue steroids altogether). Median PFS and OS for all 30 patients were 17 weeks and 32 weeks, respectively, and 16/30 patients (56%) had a radiographic response[18].

To determine the extent to which alleviation of edema may have contributed to increased survival, researchers treated mice bearing 3 different orthotopic models of GBM with either cediranib or dexamethasone control, and then used intravitrial microscopy, molecular techniques, and MRI to measure changes in tumor vasculature and edema during therapy[17]. As observed in the clinical study, cediranib therapy transiently induced vascular normalization, which decreased cerebral edema and significantly prolonged survival compared to untreated mice. Dexamethasone produced similar, but less pronounced effects. Of interest, the increased survival in the mice occurred despite persistent tumor growth, which suggests that alleviation of edema was the primary underlying mechanism. Two ongoing trials should provide important data on cediranib as part of combination therapy—a phase 1b/3 study in combination with lomustine (CCNU) in recurrent GBM, and a phase 1b/2 trial with TMZ/RT following surgery in newly diagnosed GBM.

Markers of antiangiogenic therapy response

An emerging challenge is how to best measure clinical response to antiangiogenic therapy in GBM patients. Tumor response using standard MRI has traditionally been measured as decreased contrast enhancement. Contrast enhancement, however, indicates disruption of the blood brain barrier, and there is concern that reduction in contrast enhancement observed during anti-VEGF therapy may reflect a normalization of vascular integrity—indicated by reduced leakage of contrast agent across the blood brain barrier—rather than a true anti-tumor effect. PET imaging with specific tracers that measure tumor metabolism, hypoxia, and perfusion may offer a more accurate picture of tumor response to angiogenesis inhibitors. This technique was recently evaluated in 21 patients with high-grade gliomas treated with combination BV 10 mg/kg and irinotecan[20]. Tumor metabolism, as measured by PET using fluorothymidine (FLT), was strongly predictive of overall survival as early as 1-2 weeks after therapy initiation and was more predictive of response than MRI in the study[20].

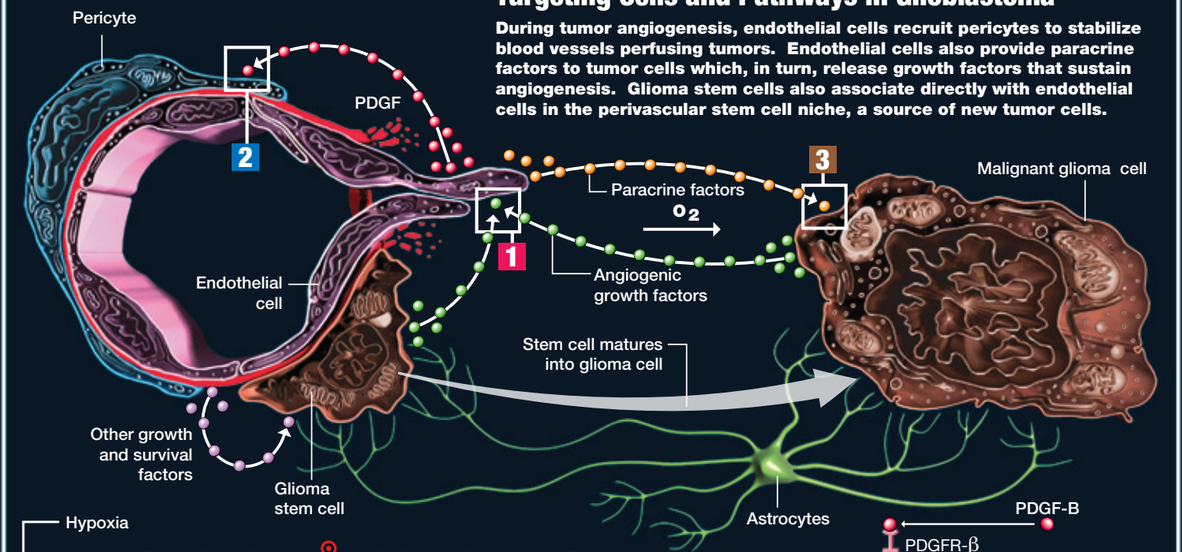
Vascular normalization, while apparently important for reducing edema, is also being evaluated as a potential biomarker for response to anti-VEGF therapy. In the phase 2 cediranib study, the extent of decrease in vascular permeability (volume transfer constant; K^{trans}), a functional marker of vascular normalization, after a single dose of cediranib was significantly associated with both prolonged PFS and OS (P=0.0015 and P=0.0039, respectively), as measured by vascular MRI[21]. In addition, prolonged OS also correlated with increased cerebral blood volume (CBV) of tumor microvessels after 1 cediranib dose in GBM patients (P=0.0056). Finally, a transient increase in plasma collagen IV during anti-VEGF therapy, which may represent thinning of the abnormally thickened basement membrane of tumor capillaries, was also associated with increased PFS (P=0.0010). Based on these findings, the study authors proposed creating a "vascular normalization index" from the composite parameters of K^{trans}, CBV and plasma collagen IV as a collective biomarker of response to cediranib therapy[21]. While only hypothesis generating at this stage, these results should be explored in larger prospective, randomized trials of antiangiogenic therapies for GBM.

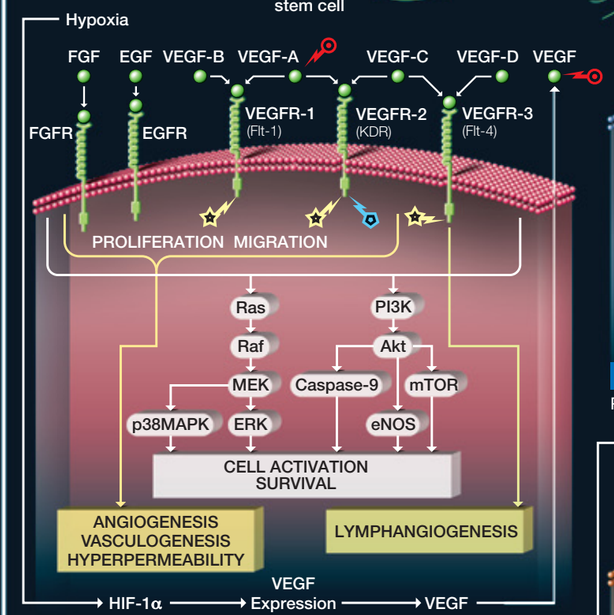
Researchers are also evaluating the use of apparent diffusion co-efficient (ADC) histogram as a means of predicting response to BV therapy[22]. ADC is generally higher in areas of lower cell density, such as necrotic regions where cellular integrity has been degraded following treatment or during tumor growth, and lower in areas of dense (non-enhancing) tumor. Because GBM patients with necrotic tumors tend to have better responses to BV, researchers speculated that ADC prior to initiation of BV therapy could help stratify patients based on their likelihood to respond to this agent. Forty-one patients with recurrent GBM treated with BV were retrospectively assessed and compared against a control group of 41 recurrent GBM patients not treated with BV. In the analysis, BV-treated patients with a low ADC_L at baseline had a 2.75-fold reduction in median time-to-progression compared to those with a high baseline ADC_L (hazard ratio, 4.1; 95% CI: 1.6, 10.4), while no difference was seen in control patients. The difference in BV effect on PFS, however, did not reach statistical significance between the two groups (P=0.33). Pretreatment ADC was more accurate at stratifying PFS6 among BV-treated patients than was determining response using Macdonald criteria (73% vs. 58% accuracy, P=0.034). These data suggest that baseline ADC may have utility for assisting in early treatment decisions, but validation in larger, prospective trials is required[22].

Another intriguing biomarker candidate in glioma is circulating endothelial progenitor (precurser) cells (EPCs)—bone marrow derived cells that are integrated into the tumor vasculature by tumor expression of angiogenic growth factors, notably VEGF and stromal cell-derived factor-1 (SDF-1). A recent study of 56 patients with various grade gliomas found a significant increase in levels of VEGFR-2/CD133-expressing EPCs in the peripheral blood of patients with high-grade tumors compared to patients with lower grade tumors or controls[23]. Both the absolute EPC count and the percentage of these cells in the peripheral blood correlated with survival post-surgery, with higher numbers significantly associated with shorter survival, presumably due to greater tumor angiogenesis. Separately, the researchers devised an angiogenic scale based on the degree of angiogenesis activity—migration, alignment, sprouting, tube formation—of human umbilical vein endothelial (HUVEC) cells cultured from blood samples. Not surprisingly, higher-grade tumors correlated with increased angiogenic

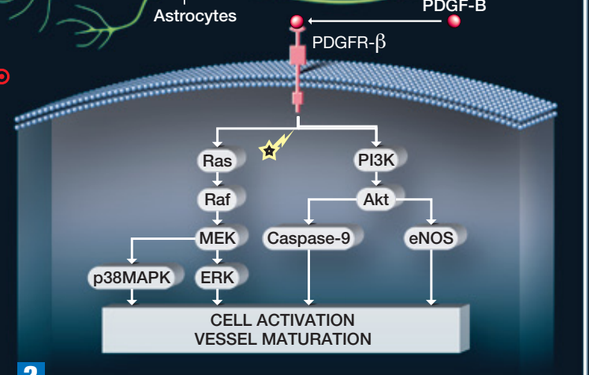
Targeting Cells and Pathways in Glioblastoma

During tumor angiogenesis, endothelial cells recruit pericytes to stabilize blood vessels perfusing tumors. Endothelial cells also provide paracrine factors to tumor cells which, in turn, release growth factors that sustain angiogenesis. Glioma stem cells also associate directly with endothelial cells in the perivascular stem cell niche, a source of new tumor cells.

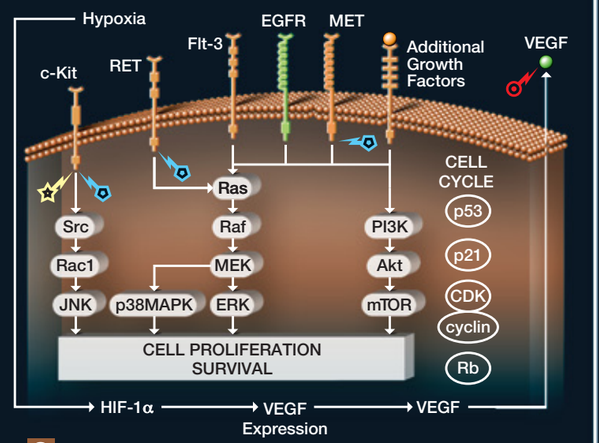




1 ENDOTHELIAL CELL The vascular endothelial growth factor (VEGF) family (A-D) binds to receptors VEGFR-1, VEGFR-2, VEGFR-3, activating signal transduction to promote angiogenesis,vasculogenesis, and lymphangiogenesis.



2 PERICYTE Platelet-derived growth factor (PDGF) and its receptor PDGFR-β mediate vessel maturation.



3 TUMOR CELL Multiple growth factors and receptors activate signal transduction and cell cycle pathways to stimulate tumor cell growth.

Targeted Agents

(Targets shown in diagram above and to the right)

- **Bevacizumab** (Avastin®)
- **Cediranib** (AZD2171, Recentin®)
- **Cilengitide** (EMD121974)
- **XL184**

Targeting Tumor Angiogenesis

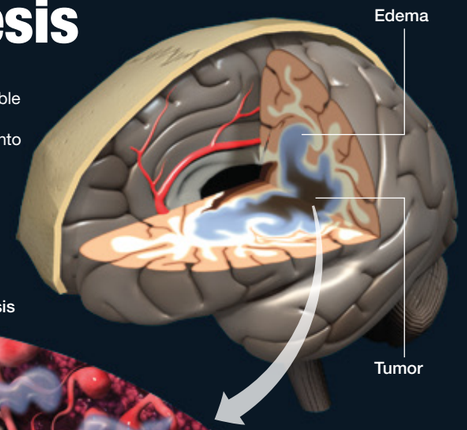
1 Cancer cells release growth factors that activate endothelial cells during the switch to the angiogenic phenotype. This occurs in response to gene mutations and hypoxia.

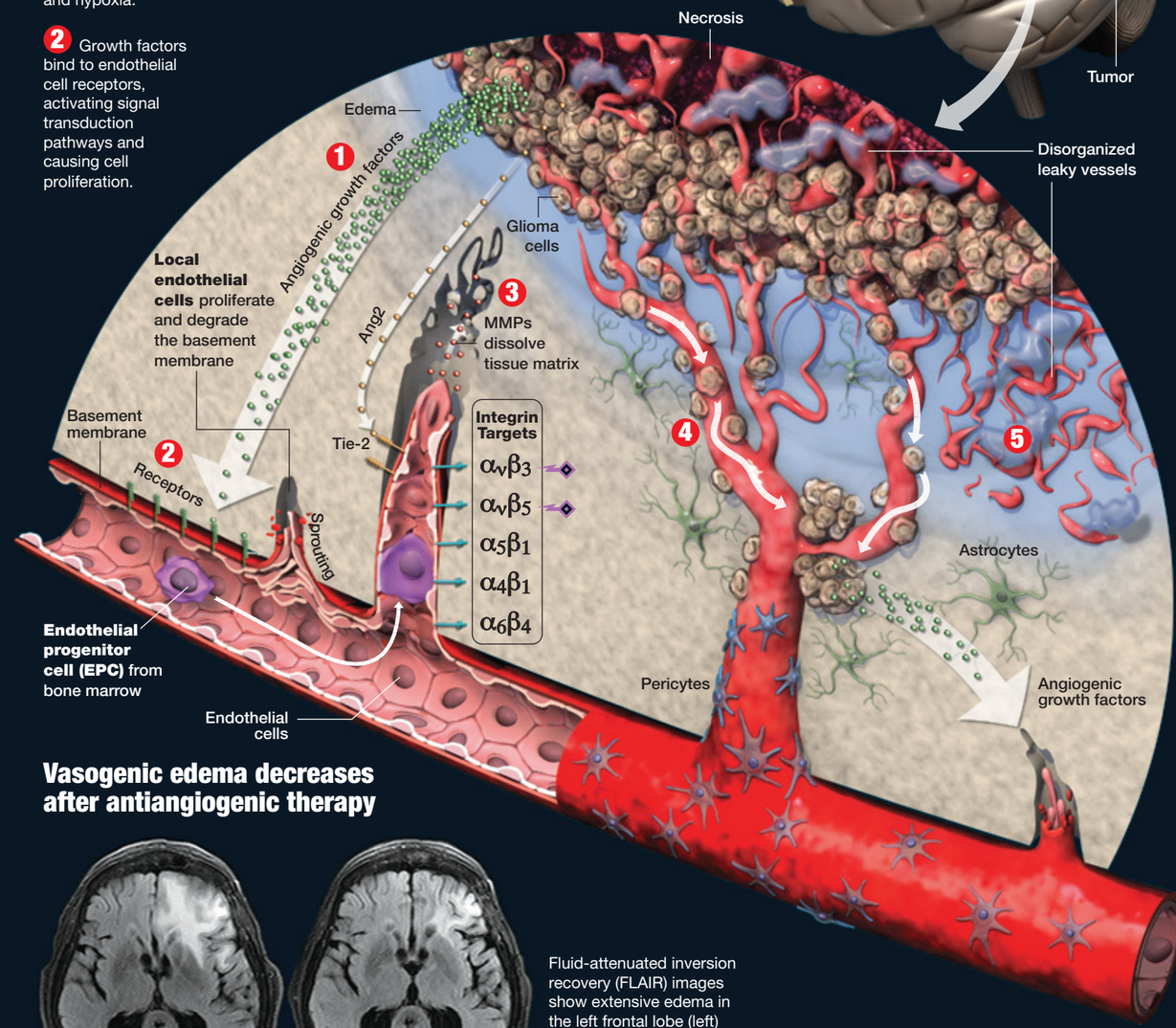
2 Growth factors bind to endothelial cell receptors, activating signal transduction pathways and causing cell proliferation.

3 Sprouting vessels secrete matrix metalloproteinases (MMPs) and migrate towards the tumor using specific αβ integrins.

4 Glioma cells migrate away from the primary tumor along the outside of host vessels. Proliferating tumor cells surround and 'co-opt' host vasculature.

5 Hyperpermeable tumor vessels leak fluid and proteins into surrounding brain tissue, causing vasogenic edema and increased interstitial fluid pressure.





Vasogenic edema decreases after antiangiogenic therapy

Before treatment | After treatment

Fluid-attenuated inversion recovery (FLAIR) images show extensive edema in the left frontal lobe (left) that decreases after treatment with cediranib (AZD2171, Recentin) (right)

Images courtesy of Massachusetts General Hospital, Department of Radiology

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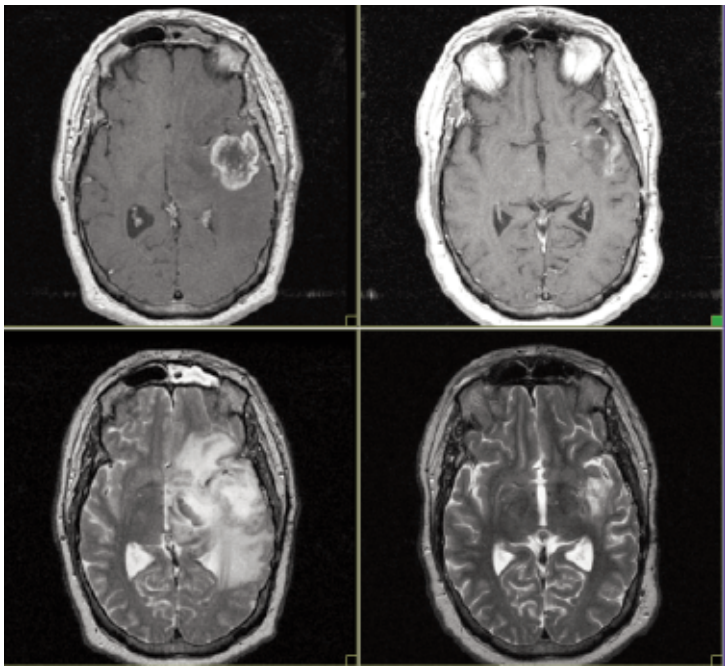

Post-gadolinium T1 (upper left) and T2 weighted (lower left) images of GBM before treatment with bevacizumab. After 12 weeks of bevacizumab 10mg/kg every 2 weeks there is dramatic reduction in contrast enhancement corresponding with PR for 9 months.

activity *in vitro*, as well as increased levels of plasma SDF-1. These results, while intriguing, require validation in larger randomized trials. Also of interest, a recent retrospective analysis of 44 patients with recurrent GBM treated with single-agent BV, showed that higher age (≥ 55 years) and poor performance status (KPS < 80) corresponded with significant improvement in PFS in BV-treated patients versus controls[24]. OS was also significantly improved in older patients. An analysis of VEGF expression from tumor samples showed that patients > age 55 had a 1.4-fold higher genetic expression of VEGF than those < age 55. These findings are consistent with other reports showing that older GBM patients and those with advanced disease have higher VEGF expression and tend to have better and longer responses to BV than younger patients. Future prospective studies of BV for advanced glioma may need to include more extensive molecular profiling of gene expression of angiogenic factors in both recurrent and front-line settings[24].

Antiangiogenic tumor escape

Tumor escape from antiangiogenic therapy is an important issue in GBM treatment. Although an incompletely understood process, mechanisms of antiangiogenic escape may include compensatory upregulation by the tumor of alternate growth factors and signaling pathways, contribution of angiogenic growth factors by host stroma, and co-option of normal vasculature by infiltrating tumor cells. There is also evidence that anti-VEGF therapy may convert some advanced gliomas to a more invasive, less angiogenesis-dependent phenotype, since a small subset of GBM patients appears to develop invasive, non-enhancing tumor progression during treatment. Whether this reflects an effect of angiogenesis inhibition, a natural progression of the disease, or simply the presence of tumors with a pre-existing invasive genotype is unclear at this time.

While not yet validated, it may be possible to limit antiangiogenic escape by targeting different angiogenic pathways simultaneously or by using chronic low-dose antiangiogenic therapy. It may also be necessary in GBM to identify therapies that simultaneously target both angiogenesis and perivascular invasion[25]. In a recent preclinical GBM study, exposure to BV was associated with significant upregulation of matrix metalloproteinases (MMP)-2, -9 and -12-molecules that facilitate tumor invasion and angiogenesis-as well as numerous non-VEGF proangiogenic factors, which corresponded with greater tumor invasiveness compared to non-treated controls[26]. Mice that were treated concurrently with broad-spectrum MMP inhibitors and BV had prolonged survival, although the combination did not affect tumor invasion.

Tumor escape from radiotherapy presents another serious treatment dilemma in GBM. Ionizing radiation induces a VEGF 'surge' in tumors, increases VEGFR-2 and $\alpha_V\beta_3$ integrin expression on endothelial cells, and mobilizes bone marrow-derived endothelial progenitor cells. These effects may explain the rapid tumor rebound sometimes observed in GBM patients undergoing RT[25, 27, 28]. Clinical studies in patients with GBM or rectal cancer treated concurrently with RT and BV have demonstrated synergistic antiangiogenic and anti-tumor effects[27]. Similar results have been produced with co-administration of RT and an antagonist of the $\alpha_V\beta_3$ integrin in experimental models of human GBM[28]. These data add to a growing body of clinical evidence supporting the addition of antiangiogenic therapy to counter RT-induced tumor escape.

New research also provides compelling evidence that gliomas and some other cancers are perpetuated by a small fraction of self-renewing cancer stem cells (CSCs) that occupy a treatment-resistant vascular CSC niche[29]. In preclinical GBM models, tumor cells preferentially associate with endothelial cells within the vascular niche and exchange growth and survival factors[30]. When antiangiogenic therapy was used in combination with low dose metronomic chemotherapy in a glioma xenograft model, the treatment eliminated the population of tumor-forming CSCs and curtailed tumor growth[31]. The researchers suggested that antiangiogenic therapy may sensitize CSCs to chemotherapy, and that combination therapy could be used to selectively target the CSC population[31]. Whether disruption of the CSC reservoir by antiangiogenic therapy represents a viable treatment strategy in GBM requires further study.

Toxicities and Safety Concerns

Hypertension, proteinuria, thrombotic events and, less frequently, bowel perforations, delayed wound healing, and heart failure have been associated with anti-VEGF therapy and necessitate careful clinical monitoring. Despite early concerns about cerebral bleeding, relatively few reports of this complication have surfaced in GBM patients on VEGF inhibitors, even though CNS hemorrhage can occur spontaneously in GBM patients. In the recent phase 2 trial of 48 recurrent GBM patients treated with single-agent BV, 6 patients (12.5%) were removed from the study for drug-associated toxicities (5 thromboembolic events and 1 bowel perforation)[10]. Because malignant gliomas release large amounts of tissue factor, GBM patients are inherently susceptible to venous thromboembolic events, and this susceptibility may be exacerbated during antiangiogenic therapy. For this reason, patients are advised to be physically active, to the extent possible, to lessen the risk for this complication.

Conclusions

Antiangiogenic therapy has dramatically altered the treatment landscape for patients with advanced malignant gliomas. Many patients with recurrent GBM who previously had few or no treatment options are benefiting from treatments that are alleviating symptoms, improving function, and, in some cases, dramatically prolonging survival compared with standard therapies. Despite these advances, there remain many significant treatment challenges. Clinicians are encouraged to refer appropriate patients to clinical trials, which provide the best opportunities to take advantage of new treatment approaches that incorporate antiangiogenic therapy.

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CME REQUIREMENTS

ACCREDITATION STATEMENT
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Release date is July 31, 2009. Expiration is July 31, 2010.

INTENDED AUDIENCE
Practicing oncologists in the U.S.

EDUCATIONAL OBJECTIVES
At the conclusion of this educational activity, clinicians will be able to:
- Describe angiogenesis pathways and molecular targets in advanced malignant glioma.
- Describe the rationale for antiangiogenic therapy for advanced glioma.
- Review the clinical data regarding the safety and efficacy of antiangiogenic agents for advanced glioma.

METHOD OF PARTICIPATION
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