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# Angiogenesis in Malignant Gliomas and Bevacizumab Resistance

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## Abstract

Standard therapy for malignant gliomas includes maximal resection followed by radiotherapy and temozolomide. The increase in neovascularization in high-grade gliomas serves the increased metabolic demands of these fast-growing tumors and the main pathway mediating this process involves vascular endothelial growth factor (VEGF) and its receptor. This pathway is targeted by bevacizumab (BEV), an anti-VEGF monoclonal antibody. Though preclinical trials with BEV were promising, clinical trials failed to show improvement in overall survival, and ultimately GBM become resistant to BEV. By better understanding the molecular mechanisms involved in angiogenesis, new targets may be identified and by elucidating the mechanism behind BEV resistance, new treatment modalities may be developed to treat these aggressive tumors.

**Keywords:** angiogenesis, bevacizumab, vascular endothelial growth factor, glioma, glioblastoma

## 1. Introduction

Glioblastoma multiforme (GBM) is the most common primary adult brain tumor with 9000 predicted new cases in the US each year [1]. Prognosis remains poor and standard therapy includes maximal safe resection followed by radiotherapy and temozolomide chemotherapy [2]. Because of their high metabolic demand, GBM tend to outgrow their blood supply, leading to a hypoxic, necrotic core [3]. One of the hallmarks of these aggressive tumors, therefore, is their ability to signal new blood vessels to grow into the tumor mass to counteract this effect. This chapter will examine the current state of our understanding of these pro-angiogenic pathways involving VEGF, integrins, angiopoietins, platelet-derived growth factor (PDGF), protein kinase C and mTOR [4–6]. The primary pathway involves VEGF [6] and is targeted by bevacizumab (BEV), a monoclonal antibody to VEGF [7]. BEV resistance, thought to be due, in part, to redundant angiogenic pathways, remains a serious concern, as few subsequent treatment options exist. Other mechanisms of BEV resistance will be discussed, including vessel co-option, vascular intussusception, vascular mimicry, and recruitment of bone-marrow-derived cells.

## **2. Angiogenesis**

Normal endothelial cells form a monolayer interconnected by tight and adherens junctions made up of molecules such as occludin, claudin, and junction adhesion molecule proteins. These structures form the basis of the blood brain barrier. Endothelial cells are surrounded by pericytes, which regulate cell proliferation and a vascular basement membrane is formed by the endothelial cells and pericytes [8].

Sprouting is the process by which new blood vessels are produced from existing blood vessels and this serves to supply the increased metabolic demands of rapidly growing tumors [10]. This is achieved by increasing the production of proangiogenic factors, of which, VEGF is one of the most important players [6]. Often, hypoxia is the trigger for signaling the expression of proangiogenic factors via the expression of hypoxia-induced factor (HIF1 $\alpha$ ) [11], although other hypoxia-independent pathways exist involving the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase PI3K pathways [4]. A balance of proangiogenic and antiangiogenic signals within the tumor microenvironment determine whether angiogenesis will occur, the so-called “angiogenic switch” [9]. When the proangiogenic signal predominates, pericytes secrete matrix metalloproteases and detach from the basement membrane. Endothelial cells loosen their tight and adherens junctions. Plasma proteins leak out of the blood vessel and supply a scaffold for the new blood vessel. Endothelial cells migrate into this extracellular matrix in response to integrin signaling. A single endothelial cell serves as the “tip cell” to direct the nascent blood vessel toward the proangiogenic signal. The trailing “stalk cells” form the lining of the new lumen. Signaling by Ang-2, VEGF, Notch, PDGF, neuropilins and others are involved in this process. These new blood vessels, however, tend to be tortuous and lack an intact blood-brain barrier, making them leaky, leading to vasogenic edema in the vicinity of the tumor [12]. Hypoxic tumors also tend to be more resistant to standard chemotherapy regimens. Agents targeting angiogenic pathways, therefore, could reduce peritumoral edema, reduce hypoxia, and improve the delivery of cytotoxic agents [13].

The VEGF family consists of VEGF-A, B, C, D and placental growth factors (PlGF1–4) and their receptors—VEGFR-1, 2, 3, neuropilin (NRP)-1, and NRP-2 [5, 14–17]. This family has been shown to be important in normal and pathologic angiogenesis, maintenance of blood vessels, migration of endothelial cells, and vascular permeability. The most important of these is VEGF-A (VEGF) [18] that forms disulfide-linked homodimers that then bind to VEGFR-1 and VEGFR-2. These are both receptor tyrosine kinases that in turn signal through the PI3K/MAPK pathway as well as the AKT1 signaling pathway [19]. Most of the proangiogenic signaling is effected by VEGF-A binding to VEGFR-2, which has strong tyrosine kinase activity [20]. VEGFR-1 binding is thought to modulate VEGFR-2 signaling by sequestering VEGF-A, which binds to VEGFR-1 with higher affinity than it does to VEGFR-2 [21].

## **3. Bevacizumab**

Standard of care for high-grade gliomas starts with maximal surgical resection [22] followed by Temozolomide chemotherapy [2]. Because of the FDA approval of BEV with Irinotecan (IRI) in colorectal cancer, two single-arm Phase II prospective studies for patients with recurrent malignant gliomas were undertaken in 2007.

The BRAIN trial started with two cohorts of 35 patients with GBM who progressed after standard therapy. Twenty-three patients received both BEV and IRI every 14 days and once this was deemed safe, a second cohort of 12 patients was treated with IRI for 4 doses in 6 weeks and BEV every 3 weeks. The results seemed

promising with a 6 month progression-free survival (PFS-6) of 46% (vs. 15% in historic controls) and median overall survival (OS) of 42 weeks, vs. 21 months in historic controls). However, complications included thromboembolism, grade 2–3 proteinuria, and intracranial hemorrhage [23]. A second trial involved 9 Grade III and 23 Grade IV glioma patients who had progressed on standard therapy treated with BEV and IRI every 2 weeks of a 6-week cycle. PFS-6 was 38% and the median overall survival was 40 weeks in Grade IV patients. Though no intracranial hemorrhages occurred, three patients developed deep venous thromboses or pulmonary emboli, and one patient had an arterial ischemic stroke [24]. As a result of these studies, BEV was FDA approved for use as a combination with IRI or alone in recurrent high-grade glioma in 2009. In 2014, the BELOB trial, a randomized Phase II trial randomized 148 patients to receive BEV 10 mg/kg every 2 weeks, lomustine 110 mg/m<sup>2</sup> every 6 weeks or combination of both. The primary endpoint was OS at 9 months and was found to be 38% in the BEV arm, 43% in the lomustine arm, and 59% in the BEV/lomustine arm [25]. The EORTC-2601 trial compared lomustine monotherapy to BEV plus lomustine combination therapy and though PFS was improved (4.2 vs. 1.5 months), no significant difference in OS (9.1 vs. 8.6 months) was noted [26].

Because BEV looked promising in the recurrent setting, three trials were commenced to determine its efficacy in newly diagnosed GBM. The first of these was a single-arm, multicenter Phase II trial of 70 patients with newly diagnosed GBM comparing combined RT, TMZ and BEV (concurrent administration of daily TMZ and biweekly BEV with RT followed by TMZ for 5 days every 4 weeks and continued biweekly BEV) with a control arm in which patients received RT/TMZ followed by TMZ for 5 days every 4 weeks and BEV at recurrence. Though addition of BEV improved PFS (13.6 vs. 7.6 months), no significant improvement in OS was seen (19.6 vs. 21.1 months). Importantly, the BEV cohort showed increased incidence of cerebrovascular ischemia, wound infections, GI perforations, GI bleeds, and CNS hemorrhage [27]. RTOG 0825 was a large randomized, placebo-controlled, double-blinded trial of 637 patients in which patients received Stupp protocol with either BEV or placebo from week 4 of RT continued for 12 weeks. Though there was an improvement in PFS was slightly improved (10.7 vs. 7.3 months) no significant survival benefit was seen in the BEV group (15.7 vs. 16.1 months). There was an increased incidence of hypertension, thromboembolism, wound dehiscence, visceral perforation, serious hemorrhage, and serious neutropenia in the BEV group [28]. Finally, in a similar design, the AVAglio study randomized 921 patients to receive Stupp protocol with BEV or placebo every 2 weeks starting during RT and continuing until the disease progressed or unacceptable toxic effects developed. The median PFS was improved (10.6 vs. 6.2 months) but no improvement in overall survival (16.8 vs. 16.7 months) was seen. BEV did, however, appear to decrease dependence on steroids and prolong cognitive function in this study, though the rate of adverse events was higher with bevacizumab than with placebo [29].

Other chemotherapy agents such as carboplatin, irinotecan, erlotinib, and etoposide have shown no improvement in survival when added to Bevacizumab [30–33]. Aflibercept (VEGF Trap), is a recombinant fusion protein of the

Extracellular domains of VEGF fused to the Fc portion of immunoglobulin G1; it binds with high affinity to both VEGF and placental growth factor (PlGF) and thus scavenges both VEGF and PlGF. A Phase II study of patients with recurrent high glioma demonstrated no survival benefit and moderate toxicities including hypertension, lymphopenia, and wound healing complications [34]. Other antiangiogenic agents such as sunitinib, cediranib, and vandetanib, which are tyrosine-kinase inhibitors that target VEGF, have likewise failed to show survival benefit [35–37].



#### **4. Pseudoprogression and pseudoresponse**

Pseudoprogression is an inflammatory treatment-related effect seen on MRI that can occur weeks to months after the end of therapy. Therefore, new gadolinium enhancement and T2 signal in the vicinity of the resection cavity may not necessarily represent recurrent tumor as pseudoprogression is thought to occur occurs in about 30% of cases [38]. Furthermore, only surgery can definitively distinguish between pseudoprogression and true progression, though spectroscopy, PET scan, functional MRI, and magnetic resonance perfusion have been employed, but with sensitivities of less than 80% [39]. Pseudoprogression has been treated with corticosteroids, hyperbaric oxygen, pentoxifylline, and vitamin E. Bevacizumab has also been used to treat pseudoprogression as it stabilizes the blood-brain barrier [40].

Confounding the picture further is the phenomenon of pseudoresponse. Because bevacizumab normalizes tumor vasculature, restoring the blood-brain barrier and reducing peritumoral edema [41, 42], MRI tend to show reduced T2 signal and gadolinium enhancement, making it difficult to visualize the underlying tumor. Bevacizumab may, however, increase perfusion, reduce hypoxia, and improve delivery of cytotoxic agents to the tumor [43, 44]. These tend to be a transient effect, however.

#### **5. Bevacizumab resistance**

Though it seems to improve PFS and reduce steroid dependence, bevacizumab does not confer a survival benefit. Ultimately, malignant gliomas overcome the antiangiogenic effect of BEV and tumor progression occurs. There are many mechanisms by which tumor cells can achieve resistance to bevacizumab [8]. In a process called vessel co-option, tumor cells migrate along and grow around existing blood vessels. Intussusception is the process by which existing blood vessels are enlarged and bifurcated. Tumor cells may incorporate into the endothelium of native blood vessels in a process called vascular mimicry that is associated with invasion, rapid tumor growth, and resistance to radiotherapy. Endothelial progenitor cells may be recruited, and cancer-like stem cells may differentiate into endothelial cells or pericytes to supply new blood vessels [45].

As antiangiogenic agents like BEV cause vessel regression and hypoxia, tumor cells switch from a proliferative to a migratory phenotype [42]. This type of migratory cell expresses mesenchymal markers and matrix metalloproteases used to degrade the extracellular matrix and allow for cell migration [46]. The c-MET tyrosine kinase and its ligand, hepatocyte growth factor (HGF) are both strongly up-regulated in hypoxic environments as well as in patients with BEV resistance. Its downstream targets are likewise phosphorylated, including focal adhesion kinase (FAK) and STAT3, which are involved in promoting cell migration [47]. Targeting members of this signaling pathway could lead to improvements in survival and may help to overcome BEV resistance [48] and rilotumumab, a monoclonal antibody to HGF is currently under investigation [49].

BEV-induced hypoxia may also alter the metabolism of tumor cells toward aerobic glycolysis to increase glucose uptake and promoting proliferation and migration. Hypoxic microenvironments cause increased levels of hexokinase-2 [50, 51] known to promote proliferation and drug resistance, and pyruvate dehydrogenase kinase-1 ultimately blocking pyruvate from entering the Krebs cycle [52]. The phosphoinositol-3-kinase (PI3K)/Akt pathway and Myc also are involved in this metabolic shift [53, 54].

Finally, BEV treatment may lead to the adoption of other proangiogenic pathways involving fibroblast growth factor, platelet-derived growth factor, transforming growth factor- $\alpha$ , Ang-2, and Tie-2 [55]. The integrin family of cell-adhesion molecules is attractive targets for antiangiogenic therapy as hypoxia induces overexpression of  $\alpha v \beta 3$  and  $\alpha v \beta 5$  in GBM and correlate with tumor aggressiveness [56, 57].  $\alpha 5$  integrin is upregulated and  $\beta 1$  and  $\alpha 5$  integrin were downregulated in tumor cells resistant to BEV.

## 6. Conclusion

GBM remains an incurable and difficult to treat malignancy. Due to its aggressive nature, the tendency for tumor cells to invade into normal brain along blood vessels and white matter tracks, and its ability to supply its metabolic needs via a number of complimentary proangiogenic mechanisms, new targets and therapies are needed. Targeting multiple angiogenic pathways simultaneously with monoclonal antibodies and receptor tyrosine kinase inhibitors may help mitigate the problem of targeting angiogenesis and bevacizumab resistance.

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## Conflict of interest

I have no conflicts of interest to declare.

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