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A Review of VEGF/VEGFR-Targeted Therapeutics for Recurrent Glioblastoma

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Abstract

Glioblastoma, the most common primary malignant brain tumor among adults, is a highly angiogenic and deadly tumor. Angiogenesis in glioblastoma, driven by hypoxia-dependent and independent mechanisms, is primarily mediated by vascular endothelial growth factor (VEGF), and generates blood vessels with distinctive features. The outcome for patients with recurrent glioblastoma is poor because of ineffective therapies. However, recent encouraging rates of radiographic response and progression-free survival, and adequate safety, led the FDA to grant accelerated approval of bevacizumab, a humanized monoclonal antibody against VEGF, for the treatment of recurrent glioblastoma in May 2009. These results have triggered significant interest in additional antiangiogenic agents and therapeutic strategies for patients with both recurrent and newly diagnosed glioblastoma. Given the potent antipermeability effect of VEGF inhibitors, the Radiologic Assessment in Neuro- Oncology (RANO) criteria were recently implemented to better assess response among patients with glioblastoma. Although bevacizumab improves survival and quality of life, eventual tumor progression is the norm. Better understanding of resistance

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mechanisms to VEGF inhibitors and identification of effective therapy after bevacizumab progression are currently a critical need for patients with glioblastoma.

Keywords

Glioblastoma; angiogenesis; vascular endothelial growth factor; malignant glioma

Malignant gliomas, including the most common subtype of glioblastoma, are rapidly growing destructive tumors that extensively invade locally but rarely metastasize. The current standard of care, including maximum safe resection followed by radiation therapy and temozolomide chemotherapy, achieves median progression-free and overall survivals of only 6.9 and 14.7 months, respectively.¹ After progression, salvage therapies have historically achieved radiographic response and 6-month progression-free survival rates of 5% to 15%, respectively.^{2–4} Several factors contribute to poor treatment response, including frequent de novo and acquired resistance, heterogeneity across and within tumors, complex and redundant intracellular pathways regulating proliferation and survival, and restricted central nervous system (CNS) delivery because of the blood–brain barrier and high interstitial peritumoral pressures.^{5,6}

Given this background, recent clinical studies have shown substantive radiographic responses and improved progression-free survival with bevacizumab, a humanized monoclonal antibody targeting vascular endothelial growth factor (VEGF),⁷ among patients with recurrent malignant glioma.^{8–11} However, initial enthusiasm has been tempered by relatively modest improvements in overall survival, difficulties in assessing response after anti-VEGF therapeutics, and an inability to identify effective therapy after bevacizumab failure. Nonetheless, initial results have sparked a flurry of studies attempting to more effectively exploit this therapeutic strategy. This article reviews the development, current status, and future challenges of VEGF-targeting therapeutics for patients with recurrent glioblastoma.

Angiogenesis in Malignant Glioma

Glioblastoma is among the most angiogenic of malignancies.¹² Angiogenic tumor vessels differ markedly from normal vessels. The dense network of angiogenic vessels in glioblastoma typically display structural, functional, and biochemical abnormalities, including large endothelial cell fenestrae, deficient basement membrane, decreased pericytes and smooth muscle cells, haphazard interconnections with saccular blind-ended extensions, complex tortuosity, and dysregulated transport pathways.^{13–18} These changes culminate in leaky and unstable blood flow, despite increased vessel density, which generates hypoxia, acidosis, and increased interstitial pressure within the tumor microenvironment.^{19,20}

Angiogenesis in glioblastoma is driven by both hypoxia-dependent and -independent mechanisms. Hypoxia, a prevalent feature in malignant glioma, inactivates prolyl hydroxylases, leading to hypoxia-inducible factor-1 α (HIF-1 α) accumulation. HIF-1 α dimerizes with constitutively expressed HIF-1 β , translocates to the nucleus, and activates several hypoxia-associated genes, including VEGF.²¹ Independent of hypoxia, glioblastomas commonly exhibit dysregulated activation of mitogenic and survival pathways, including the Ras/mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)/akt cascades that upregulate VEGF and other proangiogenic factors.^{22,23}

Although VEGF is the prominent angiogenic factor, glioblastoma tumors frequently express other proangiogenic factors, such as platelet-derived growth factor (PDGF), fibroblast

growth factor (FGF),²⁴ integrins, hepatocyte growth factor/scatter factor,²⁵ angiopoietins,²⁶ ephrins,²⁷ and interleukin-8.²⁸ The VEGF gene family includes 6 secreted glycoproteins (VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placenta growth factor [PlGF]). VEGF-A, the best characterized family member, typically localizes adjacent to perinecrotic regions within glioma pseudopalisades,²⁹ increases with higher glioma grade,^{24,30} and is associated with poor outcome among patients with glioblastoma.^{30,31} VEGF-A isoforms generated by alternative splicing can also originate from host sources, such as invading macrophages and platelets, whereas tumor stroma can sequester larger isoforms that are enzymatically cleaved and released.^{32,33} The VEGF receptor (VEGFR) family includes VEGFR-1 (Flt-1), VEGFR-2 (KDR), VEGFR-3, neuropilin-1 (NRP-1), and NRP-2, which exhibit different binding affinities of the VEGF homologs. VEGFR-1 and VEGFR-2 regulate angiogenesis, whereas VEGFR-3 regulates lymphangiogenesis. The NRPs, originally defined as mediators of axonal guidance in the CNS, also function as VEGFR tyrosine kinase coreceptors.³⁴ VEGF binding to VEGFRs on tumor blood vessels markedly enhances permeability and activates endothelial cell proliferation, survival, and migration.³⁵ Although primarily expressed by tumor endothelium, several solid tumors, including glioblastoma, express VEGFRs, which may function in an autocrine manner to promote tumor growth.³⁶

Tumor angiogenesis recruits several bone marrow–derived proangiogenic cells, including endothelial progenitor cells (EPCs) and pericyte progenitor cells, which support tumor vessels, and CD45+ “vascular modulatory” myeloid cells. The latter include tumor-associated macrophages and monocyte precursors expressing CD11b+, Tie-2, or VEGFR-1.^{37–40} Several cytokines chemoattract these cells from the bone marrow to the tumor, including VEGF, granulocyte-macrophage colony-stimulating factor, and stromal-derived factor-1 α (SDF-1 α).^{41–44} Bone marrow–derived progenitors significantly increase with hypoxia⁴⁵ or after either radiation therapy or cytotoxic chemotherapy.^{46,47} Furthermore, these cells can “home” to intracranial gliomas,⁴⁸ and their levels are increased in patients with malignant glioma.^{42,49} Antiangiogenic therapy can decrease circulating EPC levels in C6 murine glioma subcutaneous xenografts,⁵⁰ whereas SDF-1 α inhibition can diminish recruitment and infiltration of monocyte precursors.^{45,51}

Growing evidence links tumor angiogenesis with cancer stem cell biology. Tumors derived from glioma stem cells are more angiogenic and have higher vessel densities than those derived from nonglioma stem cells.⁵² Furthermore, conditioned media from glioma stem cells contain higher VEGF levels and can stimulate greater endothelial cell migration, proliferation, and tube formation than nonglioma stem cell media.⁵² Glioma stem cells preferentially localize to the perivascular niche, within which secreted angiogenic factors facilitate maintenance of the stem cell state.⁵³ Recent studies using the C6 murine glioma cell line show that stem cell–derived tumors exhibit increased microvessel density, perfusion, recruitment of EPCs, and levels of VEGF and SDF-1 compared with tumors derived from a low fraction of stem cells.⁵⁴ Furthermore, VEGF inhibition can suppress growth of glioma stem cell–derived tumors.^{52,54} Two groups have recently shown that glioblastoma stem cells can also contribute to tumor vessel formation.^{55,56}

Angiogenesis is a complex and critical feature of tumor biology, and offers several potential strategies for therapeutic exploitation. The following sections highlight some advanced treatment strategies focused on angiogenic targets for patients with glioblastoma.

VEGF-Targeting Therapies

Bevacizumab

Direct suppression of VEGFR activation can be achieved using strategies that target either the ligand or the receptor of the VEGF/VEGFR signaling axis. Ligand inactivation, by sequestering VEGF to either antibodies or soluble decoy receptor, prevents effective receptor binding. Bevacizumab, a recombinant humanized monoclonal antibody composed of human immunoglobulin G1 (IgG1; 93%) and murine VEGF-binding complementarity-determining regions (7%), binds all isoforms of VEGF with high affinity and specificity.⁷ In preclinical models, maximal tumor growth inhibition was achieved with trough serum concentrations of 10 to 30 $\mu\text{g/mL}$ (data on file, Genentech Inc.). Bevacizumab exhibits linear pharmacokinetics with a half-life of approximately 20 days (range, 11–50 days).⁵⁷ Phase I studies in patients with recurrent solid tumors did not identify dose-limiting toxicities or a maximum tolerated dose, and doses greater than 1 mg/kg produced serum levels over the target range of 10 $\mu\text{g/mL}$ for at least 14 days.⁵⁸ In preclinical studies, anti-VEGF antibody treatment inhibits angiogenesis and human glioblastoma growth in flank and intracranial xenograft models,^{59,60} whereas subsequent studies confirm that anti-VEGF treatment augments the cytotoxicity of either radiation therapy or chemotherapy.^{61–63} After the initial FDA approval of bevacizumab with irinotecan-based chemotherapy for colorectal cancer (CRC),⁶⁴ a retrospective series was reported of 21 heavily pretreated patients with recurrent malignant glioma who received bevacizumab (5 mg/kg every 2 weeks) plus irinotecan, as adopted from the CRC experience.⁶⁵ The regimen was associated with acceptable safety and unprecedented activity that included 9 patients with radiographic response (43%) and 11 with stable disease (52%).

These dramatic results prompted 2 single-arm, prospective phase II studies.^{10,11} The first study enrolled 35 heavily pretreated patients with recurrent glioblastoma, whereas the second study enrolled 23 patients with glioblastoma and 9 with recurrent grade III tumors. The first major finding of these studies was that the safety profile of bevacizumab among patients with recurrent malignant glioma is similar to that observed in other populations of patients with cancer. Specifically, the frequency and severity of fatigue, hypertension, proteinuria, thrombosis, hemorrhage, intestinal perforation, and wound-healing complications were similar between patients with a brain tumor and patients with other cancers. Furthermore, only 1 of 67 patients (1.5%) experienced CNS bleeding (grade 1 at week 60 of therapy).

The second major finding of these studies was confirmation of the marked antitumor benefit achieved with bevacizumab and irinotecan (Table 1). Radiographic response based on Macdonald criteria⁶⁶ was observed in 40 patients (60%), the 6-month progression-free survival rates were 38% to 46%, and the median overall survival was 40 to 42 weeks. In contrast, meta-analyses of salvage therapy for patients with recurrent glioblastoma, including 2 from the modern era, reported radiographic response rates of 5% to 10%, 6-month progression-free survival rates of 9% to 15%, and an overall survival of 22 to 26 weeks.^{2–4}

Two follow-up phase II studies became the basis of accelerated approval of single-agent bevacizumab for recurrent glioblastoma granted by the FDA in May 2009. The first study was a single-arm evaluation of single-agent bevacizumab among 48 recurrent patients at any progression with a Karnofsky performance score (KPS) of at least 60.⁹ The second study randomized 167 patients at first or second recurrence with a KPS of at least 70 to either single agent bevacizumab or bevacizumab plus irinotecan.⁸ The primary end point of both studies was 6-month progression-free survival relative to historical benchmarks. Notably, the randomized study was not designed to detect superiority between the arms and included

a crossover to bevacizumab plus irinotecan for patients who experienced progression on bevacizumab monotherapy. Assessments were performed by blinded, independent reviewers using Macdonald criteria⁶⁶ for the single-arm study and WHO Response Evaluation Criteria⁶⁷ for the randomized study. The toxicity profile reported in both studies confirmed the findings previously reported,^{10,11} although patients treated with irinotecan had more frequent adverse events, primarily attributed to irinotecan. Five patients (2.3%) in these studies developed intracranial hemorrhage (grade 1 in 3 patients, grade 2 in 1 patient, and grade 4 in 1 patient). Both studies showed significantly better outcomes than were previously reported with salvage therapy (Table 1). The outcome for patients treated with bevacizumab plus irinotecan seemed comparable to that for patients treated with single-agent bevacizumab. The basis for the FDA accelerated approval was a clinically meaningful and durable objective tumor response rate determined through independent radiographic review. Notably, the European Medicines Agency did not approve bevacizumab primarily because of the lack of a nonbevacizumab control arm in these studies.⁶⁸

Subsequent studies have focused on evaluating a variety of bevacizumab regimens for recurrent malignant glioma (Table 2). Four published series report activity of single-agent bevacizumab.^{8,9,69,70} Activity observed on a single study evaluating 15 mg/kg every 3 weeks does not seem substantially different from other studies incorporating 10 mg/kg every 2 weeks.⁶⁹ Thirteen reports, including 8 retrospective series and 5 prospective phase II studies, have evaluated bevacizumab plus chemotherapy involving irinotecan, carboplatin/cetuximab, or oral etoposide.^{8,10,11,71–80} Single studies also evaluated bevacizumab with either stereotactic radiation therapy⁸¹ or an EGFR tyrosine kinase inhibitor.⁸² Although comparison across these series is limited by the small number of patients per study and variations in study enrollment and treatment criteria, outcome of bevacizumab combinatorial regimens seems comparable to that achieved with single-agent bevacizumab. More than 50 clinical trials are evaluating bevacizumab with and without other therapeutics for patients with recurrent glioblastoma (www.clinicaltrials.gov).

Other VEGF-Targeting Drugs

VEGF Trap (aflibercept) sequesters all isoforms of VEGF-A and PlGF as a soluble, recombinant, decoy receptor, composed of the second Ig domain of VEGFR-1 and the third Ig domain of VEGFR-2 bound to the hinge region of the Fc portion of human IgG1.⁸³ VEGF Trap has greater affinity for VEGF (dissociation constant < 1 pMol/L) than anti-VEGF monoclonal antibodies (dissociation constant, 0.1–10 nMol/L).⁸⁴ In preclinical studies, VEGF Trap improved survival in an orthotopic glioblastoma model,⁸⁵ and enhanced the activity of radiation therapy.⁸⁶ In a phase I study among patients with advanced solid tumors, VEGF Trap was administered at doses ranging from 0.3 to 7.0 mg/kg intravenously every 2 weeks.⁸⁷ Dose-limiting toxicities were grade 3 and included transaminase elevation (1 mg/kg; n = 1), dyspnea and arthralgia (2 mg/kg; n = 1), hypertension (4 mg/kg; n = 1), proteinuria (7 mg/kg; n = 1), and rectal fissure (7 mg/kg; n = 1). Other common toxicities included dysphonia (47%), hypertension (38%), and proteinuria (11%). The frequency of grade 3 hypertension increased significantly at doses of 4 mg/kg or greater.

Maximal VEGF-bound VEGF Trap complex levels were reached at doses of 2 mg/kg or greater and free VEGF Trap levels remained greater than VEGF-bound VEGF Trap complex levels after administration of doses of 2 mg/kg or greater. Radiographic responses were observed among patients treated at doses of 3 mg/kg or greater. The half-life after doses of 4 mg/kg or greater was 5.1 to 7.4 days. The recommended phase II dose level was 4 mg/kg. The most common adverse events reported in a phase II study among patients with recurrent malignant glioma (glioblastoma, n = 32; grade III malignant glioma, n = 16) treated with 4 mg/kg every 2 weeks included grade 3 hypertension, fatigue, hand–foot

syndrome, thrombosis, and proteinuria.⁸⁸ Two patients experienced grade 4 events, including CNS ischemia and a systemic hemorrhage. Notably, 25% of patients discontinued therapy because of toxicity. Among patients with glioblastoma, 18% experienced a radiographic response and a 6-month progression-free survival rate of 7.7%. In this study, decreased permeability on dynamic contrast-enhanced MRI (DCE-MRI) and sustained suppression of free VEGF and PlGF levels were observed. A phase I study evaluating VEGF Trap with radiation therapy and temozolomide for patients with newly diagnosed malignant glioma is ongoing (<http://www.clinicaltrials.gov/ct2/results?term=NCT00650923>).

VEGFR-Targeted Therapies

Receptor Tyrosine Kinase Inhibitors

In addition to strategies that target VEGF ligand, suppression of VEGFR signaling can also be achieved by inhibiting VEGFR activation. Two strategies to achieve this goal include blocking the ligand binding site of VEGFR with either monoclonal antibodies or genetically engineered peptides, or blocking the tyrosine kinase activation site of VEGFR with small molecule inhibitors (tyrosine kinase inhibitors). Table 3 lists some VEGFR tyrosine kinase inhibitors currently under evaluation for glioblastoma. Although these molecules principally target VEGFR, they do so with varying potency and also inhibit other relevant receptors. This multitarget capability offers additional potential mechanisms of antitumor activity but may also increase toxicity.

Several VEGFR tyrosine kinase inhibitors have shown significant antiangiogenic and antitumor activity in preclinical glioblastoma models,^{89–94} which may also enhance cytotoxic therapy.^{95–97} In addition, several of these agents are undergoing evaluation in phase I/II clinical trials, but only cediranib has advanced to phase III investigation. In an initial phase II study of single-agent cediranib (45 mg/d), 27% of patients with recurrent malignant glioma experienced a radiographic response and a 6-month progression-free survival rate of 26%. “Class” type adverse events were observed, including hypertension and fatigue, but nearly half of the patients required a dose reduction or interruption of therapy because of toxicity.⁹⁸ In addition, cediranib induced rapid normalization of tumor vasculature, including a decrease in microvessel diameter and diminished permeability, which reversed after cediranib interruption.⁹⁹

Based on the encouraging findings shown in this study, a pivotal, randomized phase III study compared cediranib monotherapy (30 mg/d; n = 120), cediranib (20 mg/d; n = 120) plus lomustine, or lomustine alone (n = 60) among patients experiencing first recurrence of glioblastoma.¹⁰⁰ Median progression-free survival, which was the primary end point, was 92 days, 125 days, and 82 days on each arm, respectively. Although the hazard ratio for the combination arm was 0.7, statistical significance was not achieved and the overall study results were assessed as negative. Notably, cediranib dosing on both arms of the randomized study was less than that used in the prior single-arm phase II study, and this may have contributed to lower activity.

Results of a phase II study evaluating single-agent pazopanib among patients with recurrent glioblastoma were recently reported.¹⁰¹ Daily administration (800 mg) was associated with typical adverse events of VEGF/VEGFR inhibitors. Radiographic responses were noted in only 6% of patients and the 6-month progression-free survival was 3%. Limited activity of single-agent sunitinib was also recently reported in a phase II study of 25 patients with recurrent malignant glioma treated with 37.5 mg daily. Although 4 of 14 patients (29%) showed decreased tumor cerebral blood volume and cerebral blood flow, none experienced an objective radiographic response and median progression-free survival was only 1.6 months.¹⁰²

A phase I study evaluating vatalanib with imatinib and hydroxyurea among patients with recurrent malignant glioma noted that these agents could be safely combined at full-dose levels and that this regimen had modest evidence of antitumor activity.¹⁰³ XL-184, an oral VEGFR-2 inhibitor, is of particular appeal based on additional inhibitory activity against MET,⁹⁴ a tyrosine kinase inhibitor implicated in glioblastoma growth, invasion, and angiogenesis.²⁵ Several additional clinical trials evaluating VEGFR-2 tyrosine kinase inhibitors are ongoing for patients with glioblastoma, and results are expected soon. Preliminary results evaluating VEGFR tyrosine kinase inhibitors combined with standard radiation therapy and temozolomide for patients with newly diagnosed glioblastoma are also emerging.^{104–106}

Other VEGFR Inhibitors

In addition to direct suppression of VEGFR tyrosine kinase activity, other therapeutics can suppress VEGFR activation through directly blocking ligand binding. Ramucirumab (IMC-1121B) and IMC-18F1 are examples of monoclonal antibodies that competitively bind the VEGFR ligand binding site.¹⁰⁷ A phase II trial of ramucirumab is underway for recurrent glioblastoma (<http://www.clinicaltrials.gov/ct2/results?term=NCT00895180>).

CT-322 (Angiocept) is a novel, recombinant, pegylated, 94-amino acid peptide based on a human fibronectin domain that binds to and inhibits VEGFR-2 activation. This agent has shown antiangiogenic and antitumor activity when administered as a single agent and in combination with chemotherapy against xenograft models of pancreatic cancer.¹⁰⁸ Phase I and II clinical trials evaluating this agent are underway for both recurrent (<http://www.clinicaltrials.gov/ct2/results?term=NCT00562419>) and newly diagnosed glioblastoma patients (<http://www.clinicaltrials.gov/ct2/results?term=NCT00768911>).

Miscellaneous Antiangiogenic Agents

AMG 386

Angiopoietins (Ang1 and Ang2) and their respective tyrosine kinase receptors (TIE1 and TIE2) are key mediators of tumor angiogenesis.¹⁰⁹ Angiopoietins are upregulated in many cancers, including malignant glioma.^{110–113} Inhibiting angiopoietins in preclinical glioblastoma models exhibit significant antitumor activity.¹¹⁴ AMG 386 is an engineered peptibody composed of a truncated human IgG1 Fc domain covalently linked to 2 copies of a synthetic anti-angiopoietin peptide. AMG 386 suppresses angiogenesis through binding to and sequestering Ang1 and Ang2.¹¹⁵ In a recently reported phase I study of AMG 386 among patients with advanced solid tumors, the maximum tolerated dose was not reached and evidence of antitumor benefit was noted. In addition, the volume transfer constant (K^{trans}), a measure of tumor vessel permeability assessed by DCEMRI, was reduced,¹¹⁶ suggesting an antiangiogenic effect.¹¹⁷ A phase II study of AMG 386 was recently initiated for patients with recurrent glioblastoma, in which the first cohort of enrolled patients will be treated with single-agent AMG 386. After demonstration of adequate safety in this cohort, a second cohort will be treated with AMG 386 in combination with bevacizumab (<http://www.clinicaltrials.gov/ct2/results?term=NCT01290263>).

Cilengitide

Cilengitide (EMD 121974) is a cyclized RGD-containing pentapeptide that selectively and potently blocks activation of $\alpha v \beta 3$ and $\alpha v \beta 5$ integrins,¹¹⁸ which are upregulated in several cancers, including glioblastoma.^{119,120} Multiple integrin ligands are abundantly expressed in the glioblastoma microenvironment.^{121,122} Integrin activation through ligand binding is associated with several critical aspects of tumor biology, including growth factor signaling, survival, angiogenesis, invasion, and host response to tumors.^{123,124} Cilengitide

monotherapy has antitumor activity in orthotopic glioblastoma xenograft models that can also augment the activity of radiation and temozolomide chemotherapy.^{125–128} Cilengitide has shown consistent antitumor activity and a highly favorable safety profile across a spectrum of phase I and II clinical trials for patients with recurrent and newly diagnosed glioblastoma.^{129–133} Evidence that cilengitide may exert an antiangiogenic effect in patients with glioblastoma was obtained in a phase I study, in which changes in relative cerebral blood flow after 16 weeks of therapy correlated with pharmacokinetic exposures.¹³⁰ Cilengitide is being evaluated in a multinational, randomized, pivotal phase III study for patients with newly diagnosed glioblastoma.

Efficacy Assessment of VEGF/VEGFR Therapy

VEGF/VEGFR suppression can decrease tumor vessel permeability, which complicates the radiographic assessment of response in patients with malignant glioma as measured with contrast uptake.^{134,135} Although rapid and marked improvement in contrast enhancement has been noted as early as 1 to 2 days after anti-VEGF therapy,⁹⁹ these changes unlikely reflect a true antitumor effect. In some patients, progressive nonenhancing tumor infiltration assessed with T2/fluid-attenuated inversion recovery sequence (FLAIR) sequences has been noted despite improved enhancement.⁷⁹ The recently defined Response Assessment in Neuro-Oncology (RANO) criteria provide more accurate guidelines to assess response, including changes in T2/FLAIR signal abnormality and contrast enhancement, after treatment with antiangiogenic agents.¹³⁶

Potential biomarkers to predict benefit with VEGF/VEGFR therapy include imaging parameters, circulating factors, or factors expressed by tumor samples. Radiographic response, assessed early (96 hours after treatment initiation)⁹ or overall,⁷⁹ has been linked with improved progression-free survival after bevacizumab therapy. Diffusion-weighted imaging, including calculation of the apparent diffusion coefficient (ADC), reflects tumor cellularity based on assessment of water diffusivity. Change in ADC assessed for both enhancing and nonenhancing tumor regions distinguished bevacizumab progressors from nonprogressors in a retrospective review of 20 patients with recurrent malignant glioma.¹³⁷ In another study, pretreatment ADC values correlated with 6-month progression-free survival.¹³⁸ Changes in tumor vessel diameter and permeability, measured using K^{trans} , have also been shown to decrease rapidly after VEGFR tyrosine kinase inhibitor therapy and predict outcome.¹³⁹ Decreased uptake on F-18 fluorothymidine (FLT) PET correlated with overall survival among patients with recurrent glioblastoma treated with bevacizumab.¹⁴⁰ Although FLT can represent a surrogate of tumor cell proliferation, its uptake is also affected by vascular permeability; thus, whether diminished FLT uptake after bevacizumab therapy reflects decreased proliferation or permeability is unclear.^{141,142}

Circulating factors may also predict outcome to antiangiogenic therapy. Anti-VEGF agents typically induce increases in VEGF and PlGF levels and decreases in soluble VEGFR-2.^{99,143,144} Furthermore, plasma levels of soluble VEGFR-2, bFGF, and SDF-1 α can increase, whereas PlGF decreases among patients with glioblastoma who experience progression after VEGFR-2 tyrosine kinase inhibitor therapy.⁹⁹ In addition, circulating endothelial precursors are elevated in patients with glioblastoma,⁴² and their levels may be associated with response.^{99,145}

Markers from archival tumor material have also been assessed to predict response to bevacizumab. In one study, high VEGF expression correlated with radiographic response but not survival; instead, an inverse correlation between overall survival and markers of hypoxia, including HIF-2 α and carbonic anhydrase 9 (CA9), was observed.¹⁴⁶ However,

another study failed to correlate HIF-1 α , HIF-2 α , CA9, or GLUT-1 expression and bevacizumab response.¹⁴⁷

A novel approach integrating imaging and circulating factors with clinical benefit to VEGF/VEGFR therapy has recently been proposed. Although changes in tumor vessel permeability (K^{trans}), microvessel diameter, and circulating collagen IV correlated with progression-free and overall survival among patients with recurrent glioblastoma treated with the VEGFR tyrosine kinase inhibitor cediranib, combining these 3 factors into a “vascular normalization index” provided a more robust predictor of progression-free and overall survival.¹³⁹

Resistance to Antiangiogenic Therapy

Although antiangiogenic therapy benefits most patients with recurrent glioblastoma, progression is inevitable, with most patients dying of refractory disease soon thereafter. Although limited prospective data are available, cumulative experience has failed to identify effective therapy for patients experiencing progression after antiangiogenic therapy.^{9,148–150} Given the growing use of bevacizumab for recurrent glioblastoma, and its evaluation in large phase III studies for patients with newly diagnosed glioblastoma, the identification of active agents after bevacizumab progression is a critical need in neuro-oncology clinics today.

Two major types of resistance to antiangiogenic therapy have been proposed.^{151,152} Patients with recurrent glioblastoma uncommonly exhibit primary resistance. In contrast, most new diagnoses either respond or stabilize initially but later develop acquired resistance. Several mechanisms of acquired resistance have been described, including upregulation of proangiogenic growth factors, mobilization/recruitment of pericytes or bone marrow–derived endothelial precursor cells, and tumor adaptations to increase invasion/migration or allow survival in a relatively hypoxic/acidotic environment.^{151,152} Mechanisms underlying resistance to bevacizumab and other antiangiogenic agents among patients with glioblastoma remain poorly defined. In preclinical orthotopic glioblastoma models, VEGF/VEGFR-targeting therapeutics can be associated with an increase in circulating proangiogenic factors.^{46,153} Similar findings have been documented in patients with recurrent glioblastoma undergoing therapy with cediranib.⁹⁹ Thus one potential strategy for patients who experience progression on bevacizumab is to target additional angiogenic mediators.

Increased tumor cell invasion has also been documented in preclinical studies with VEGF/VEGFR inhibitors in orthotopic glioblastoma xenograft tumors,^{60,154–156} whereas a recent preclinical study showed that single-agent VEGFR tyrosine kinase inhibitor therapy did not affect tumor growth but diminished tumor-associated edema and improved overall survival.¹⁵⁷ Concern has been raised regarding the emergence of an infiltrative phenotype after anti-VEGF/VEGFR therapy among some patients with glioblastoma.^{74,79,150,158–160} Therefore, another potential therapeutic strategy to augment antiangiogenic agents that may also benefit patients with resistance to VEGF/VEGFR-targeting agents includes administration of inhibitors of tumor cell invasion. Clearly, better understanding of factors responsible for resistance to VEGF/VEGFR therapies is critically needed to further optimize the potential benefit of these agents.

Conclusions

Angiogenesis is a complex and distinctive process in glioblastoma, driven primarily by VEGFR signaling. The ability to therapeutically target multiple aspects of VEGFR activation has been developed and many strategies are under clinical evaluation. Initial studies with bevacizumab show that VEGF/VEGFR-targeting agents can be safely used in

patients with glioblastoma, including showing a low rate of intracranial hemorrhage. These studies also note highly encouraging rates of radiographic response and progression-free survival, although benefits in overall survival are more modest. Studies evaluating bevacizumab in combination with other agents have not shown superior outcome over single-agent bevacizumab, although multiple combinatorial regimens are currently under evaluation. Studies evaluating single-agent VEGFR tyrosine kinase inhibitors have yielded limited evidence of meaningful antitumor benefit; however, several agents are currently undergoing further evaluation. Several additional aspects of antiangiogenic therapy require further insight. Validated biomarkers are strongly needed for predicting which patients are more likely to benefit and for monitoring response. In addition, a better understanding of mechanisms of resistance to VEGF/VEGFR therapeutics is paramount so that effective strategies can be implemented to further improve outcome.

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Table 1

Outcome on Bevacizumab Studies for Recurrent Glioblastoma

<i>Parameter</i>	Vredenburgh et al. ¹¹ (BV + CPT-11, n = 23)	Vredenburgh et al. ¹⁰ (BV + CPT-11, n = 35)	Kreisl et al. ⁹ (BV alone, n = 48)	Friedman et al. ⁸ (BV alone, n = 85)	Friedman et al. ⁸ (BV + CPT-11, n = 82)	Historical Controls ⁴ (n = 225)
Radiographic response						
Complete	1 (4%)		1 (2%)	1 (1%)	2 (2%)	14 (6%)
Partial	(57%)	> 20 (57%)	16 (33%)	23 (27%)	29 (35%)	
PFS						
Median (wk)	20	24	16	17	22	9
6 mo	30%	46%	29%	43%	50%	15%
OS						
Median (wk)	40	42	31	37	35	25
6 mo	NR	77%	57%	NR	NR	NR

Abbreviations: BV, bevacizumab; CPT-11, irinotecan; n, number; NR, not reported; OS, overall survival; PFS, progression-free survival.

Table 2
Published Series of Bevacizumab as a Single-Agent and in Combination Therapy for Adults With Recurrent Glioblastoma

Single-Agent Bevacizumab							
Dose (mg/kg)	Dose Interval (wk)	Study Design	Number of Patients	CR/PR (%)	PFS, Median (wk)	PFS-6 (%)	OS, Median (wk)
10	2	Phase II	85	28	17	42	37
10	2	Phase II	48	35	16	29	31
15	3	Phase II	50	25	11	25	26
10	2	Retrospective series	50	58	40	42	34
Bevacizumab Plus Chemotherapy							
BV Dose (mg/kg)	Chemotherapy	Study Design	Number of Patients	CR/PR (%)	PFS, Median (wk)	PFS-6 (%)	OS, Median (wk)
10	Carboplatin + cetuximab	Retrospective series	6	83	19	22	30
10	Etoposide	Phase II	27	23	18	45	46
10	Irinotecan	Phase II	23	61	20	30	40
10	Irinotecan	Phase II	35	57	24	46	42
10	Irinotecan	Phase II	82	38	22	50	35
10	Irinotecan	Retrospective series	37	68	30	64	46
10	Irinotecan	Retrospective series	27	44	20	46	50
5	Irinotecan	Retrospective series	20	47	19	25	28
5 or 10	Irinotecan	Retrospective series	13	77	24	NR	27
5 or 10	Irinotecan + cetuximab	Phase II	43	26	16	30	29
5	Irinotecan or carboplatin or lomustine or etoposide	Retrospective series	44	NR	17	41	36
10	Irinotecan or carboplatin or carmustine or temozolomide	Retrospective series	33	NR	NR	42	NR
10	Irinotecan or carboplatin or etoposide	Retrospective series	10	40	NR	NR	NR
Bevacizumab Plus Biologic Agent							
Agent	Class	Study Design	Number of Patients	CR/PR (%)	PFS, Median (wk)	PFS-6 (%)	OS, Median (wk)
Erlotinib	EGFR tyrosine kinase inhibitor	Phase II	25	50	18	29	45
Bevacizumab Plus Stereotactic Radiosurgery							

Single-Agent Bevacizumab									
Dose (mg/kg)	Dose Interval (wk)	Study Design	Number of Patients	CR/PR (%)	PFS, Median (wk)	PFS-6 (%)	OS, Median (wk)	Reference	
Total Irradiation Dose (Gy)	Number of Fractions	Study Design	Number of Patients	CR/PR (%)	PFS, Median (wk)	PFS-6 (%)	OS, Median (wk)	Reference	
30	5	Phase II	20	50	29	65	50	Gutin et al. ⁸¹	

Abbreviations: BV, bevacizumab; CR, complete response; EGFR, epidermal growth factor receptor; NR, not reported; OS, overall survival; PFS, progression-free survival; PFS-6, 6-month progression-free survival; PR, partial response.

Table 3

Multikinase VEGFR Inhibitors for Glioblastoma

	VEGFR	KIT	PDGFR	FGF	RET	MET	RAF	EGFR
Cediranib	*	*	*					
Sunitinib	*	*	*					
Pazopanib	*	*	*					
Intedanib	*		*	*				
Brivanib	*			*				
E7080	*		*	*				
Vandetanib	*				*			*
Sorafenib	*	*	*				*	
XL-184	*	*			*	*		

Abbreviations: EGFR, epidermal growth factor receptor; FGF, fibroblast growth factor; KIT, c-kit proto-oncogene; MET, MNNG HOS transforming gene; PDGFR, platelet-derived growth factor receptor; RAF, c-raf proto-oncogene; RET, ret proto-oncogene; VEGFR, vascular endothelial growth factor receptor.