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Abstract: Glioblastoma is characterized by high expression levels of proangiogenic cytokines and microvascular proliferation, highlighting the potential value of treatments targeting angiogenesis. Antiangiogenic treatment likely achieves a beneficial impact through multiple mechanisms of action. Ultimately, however, alternative proangiogenic signal transduction pathways are activated, leading to the development of resistance, even in tumors that initially respond. The identification of biomarkers or imaging parameters to predict response and to herald resistance is of high priority. Despite promising phase II clinical trial results and patient benefit in terms of clinical improvement and longer progression-free survival, an overall survival benefit has not been demonstrated in four randomized phase III trials of bevacizumab or cilengitide in newly diagnosed glioblastoma or cediranib or enzastaurin in recurrent glioblastoma. However, future studies are warranted. Predictive markers may allow appropriate patient enrichment, combination with chemotherapy may ultimately prove successful in improving overall survival, and novel agents targeting multiple proangiogenic pathways may prove effective. See all articles in this CCR Focus section, "Discoveries, Challenges, and Progress in Primary Brain Tumors." Clin Cancer Res; 20(22); 5612-9. ©2014 AACR.

DOI: <https://doi.org/10.1158/1078-0432.CCR-14-0834>

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ZORA URL: <https://doi.org/10.5167/uzh-100856>

Journal Article

Accepted Version

Originally published at:

Batchelor, T T; Reardon, D A; de Groot, J F; Wick, W; Weller, M (2014). Antiangiogenic therapy for glioblastoma: current status and future prospects. Clinical Cancer Research, 20(22):5612-5619.

DOI: <https://doi.org/10.1158/1078-0432.CCR-14-0834>

Antiangiogenic Therapy for Glioblastoma: Current Status and Future Prospects

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Running Title: Angiogenesis Inhibition in Glioblastoma

Disclosure of Potential Conflicts of Interest

T.T. Batchelor reports receiving commercial research grants from AstraZeneca, Millenium and Pfizer; speakers bureau honoraria from Research To Practice; and is a consultant/advisory board member for Agenus, Kirin, Merck, Oakstone, Proximagen, and UpToDate. D.A. Reardon reports receiving speakers bureau honoraria from Merck/Schering and Roche/Genentech. J.F. de Groot reports receiving a commercial research grant from AstraZeneca and is a consultant/advisory board member for Roche/Genentech. W. Wick is a consultant/advisory board member for Apogenix and Roche. M. Weller reports receiving commercial research support from Merck Serono and Roche. No other potential conflicts of interest were disclosed.

Abstract

Glioblastoma is characterized by high expression levels of pro-angiogenic cytokines and microvascular proliferation, highlighting the potential value of treatments targeting angiogenesis. Antiangiogenic treatment likely achieves a beneficial impact through multiple mechanisms of action. Ultimately, however, alternative pro-angiogenic signal transduction pathways are activated leading to the development of resistance, even in tumors that initially respond. The identification of biomarkers or imaging parameters to predict response and to herald resistance is of high priority. Despite promising phase 2 clinical trial results and patient benefit in terms of clinical improvement and longer progression-free survival, an overall survival benefit has not been demonstrated in 4 randomized phase 3 trials of bevacizumab or cilengitide in newly diagnosed glioblastoma or cediranib or enzastaurin in recurrent glioblastoma. However, future studies are warranted: predictive markers may allow appropriate patient enrichment, combination with chemotherapy may ultimately prove successful in improving overall survival, and novel agents targeting multiple pro-angiogenic pathways may prove effective.

Introduction

Glioblastoma, the most common primary malignant brain tumor, affects more than 3/100,000 individuals each year. Median survival is below one year in population-based studies. Older age and lower performance status are associated with less aggressive care and shorter survival. The current standard of care includes maximal safe resection followed by radiotherapy plus concomitant and adjuvant chemotherapy with temozolomide. Elderly patients, i.e. patients > 65-70 years, not considered candidates for combined chemotherapy and radiation, mainly on the basis of comorbidities or impaired performance status, may be treated with radiation or temozolomide alone based on the promoter methylation status of O⁶-methylguanine DNA methyltransferase (*MGMT*), a mediator of resistance to alkylating chemotherapy drugs: : in patients with tumors lacking *MGMT* promoter methylation radiotherapy alone is acceptable whereas in patients with *MGMT* promoter methylation temozolomide with or without radiation is acceptable (1).

Angiogenesis has emerged as a primary target of drug development for glioblastoma over the last decade. This development was triggered by the disappointing outcomes with cytotoxic drugs and the recognition that the extensive pathological vascularization should make this disease potentially susceptible to antiangiogenic therapy. Bevacizumab, a humanized antibody to vascular endothelial growth factor (VEGF), received accelerated approval for recurrent glioblastoma in the United States (US) and many other countries based on radiographic response rates(2, 3). In contrast, because of the lack of a controlled trial bevacizumab did not receive approval in the European Union (EU), resulting in different standards of care between the US and the

EU. Although randomized trials in newly diagnosed glioblastoma patient have not demonstrated an overall survival benefit, the final status of bevacizumab in this setting has yet to be fully determined, as well be discussed subsequently. Other VEGF-targeting agents either have been or will continue to be explored in glioblastoma(4).

Mechanisms of Action and Resistance

The mechanisms of action of antiangiogenic therapies for solid tumors are multiple and may act in concert to delay tumor progression and ultimately prolong survival in several cancers. Folkman originally hypothesized that antiangiogenic agents confer an antitumor effect through induction of endothelial cell apoptosis, inhibition of new blood vessel growth, obliteration of small vessels, and decreased tumor perfusion, culminating in decreased delivery of oxygen and nutrients (“tumor starvation”) (5). However, during the initial stages of treatment, antiangiogenic agents may transiently “normalize” abnormal tumor vasculature by reducing blood vessel diameter and permeability which paradoxically improves tumor perfusion, reduces interstitial pressure, and improves tumor oxygenation(6-8), potentially sensitizing for radiotherapy and increasing tumor exposure to cytotoxic chemotherapy (Fig. 1)(7). Antiangiogenic therapy may also prevent VEGF-mediated vascular regrowth following endothelial cell injury after genotoxic therapies(9-11). Antiangiogenic agents may exhibit intrinsic antitumor activity, e.g., against glioblastoma stem-like cells (GSC) residing in the perivascular niche(12, 13). Antiangiogenic agents may interfere with VEGF-mediated recruitment of tumor-infiltrating VEGFR1 expressing monocytes(14). There is a potential role for antiangiogenic therapy in augmenting host immunity by reducing VEGF-mediated immune suppression(15) thereby improving the efficacy of immunotherapy(16). The

relative importance of these multiple mechanisms of action regarding the therapeutic benefit of antiangiogenic therapy is unknown and different mechanisms may be operative in distinct subsets of patients as well as at different stages of the disease.

The realization that antiangiogenic therapies provide transient clinical benefit and delay tumor progression prior to inevitable tumor progression has prompted an effort to better understand mechanisms of resistance to this class of therapeutic agent, as discussed subsequently. High rates of radiographic response rates and decrease in cerebral edema indicate a reduction in vascular permeability due to interruption of VEGF-A (originally termed vascular permeability factor) signaling(3, 6, 17). However, a lack of antitumor effect observed in some orthotopic rodent xenograft models of glioblastoma(18) suggests that angiogenesis inhibitors, e.g., cediranib, have limited intrinsic antitumor activity and that their main benefit may be limited to reductions in permeability and vasogenic cerebral edema(3, 6, 17). Notwithstanding a better understanding of the potential benefits of utilizing an optimal dose, schedule and drug combination, data from phase 3 clinical trials(19, 20) of bevacizumab suggest that some glioblastomas may be intrinsically resistant to antiangiogenic therapy. Inherent vessel insensitivity to the effect of VEGF inhibition could partially mediate this intrinsic resistance(21). Several adaptive resistance mechanisms may counteract any potential, initial benefit afforded by antiangiogenic therapy (Fig. 2). In the setting of VEGF signaling inhibition the tumor and its microenvironment release alternative pro-angiogenic growth factors to promote VEGF-independent angiogenesis(22-24) which may be further augmented by the recruitment of pro-angiogenic myeloid cells such as monocytes, M2-skewed macrophages, granulocytes and myeloid-derived suppressor

cells(14, 25, 26). Additionally, functional vessels are characteristically covered with pericytes which may protect endothelial cells from apoptosis in the face of VEGF blockade. Finally, adaptive resistance has been characterized by a transition to a mesenchymal and more invasive tumor phenotype(27-29). In the setting of antiangiogenic therapy, glioblastoma cells co-opt normal blood vessels(30) as a route of invasion into the surrounding brain. Although initial reports implied that anti-VEGF therapies were associated with non-enhancing radiographic tumor progression(31) originally interpreted as an increase in tumor invasion, subsequent reports did not support this observation(19, 20, 32, 33).

Clinical Trials

Clinical trials evaluating antiangiogenic agents for glioblastoma initially lagged behind other cancer indications due to concern of potentially serious adverse events in brain tumor patients, notably intracranial hemorrhage or stroke. However, early clinical experience confirmed the rarity of such events and that the toxicity profile of antiangiogenic agents for glioblastoma was not significantly different from that in other cancer indications; thereafter, clinical study of antiangiogenic agents for glioblastoma accelerated. A multitude of antiangiogenic agents have been evaluated for glioblastoma including tyrosine kinase inhibitors(34-49), monoclonal antibodies against VEGFR, and a soluble decoy receptor(50) (Table 1). Since clinical development is most advanced for bevacizumab, we focus herein on the design, results and conclusions of the major bevacizumab trials for glioblastoma.

Bevacizumab for recurrent glioblastoma

Dramatic overall radiographic response (ORR) rates and reassuring safety data led to two phase II studies which subsequently became the basis of the US Food and Drug Administration accelerated approval of bevacizumab as monotherapy for recurrent glioblastoma in 2009 (Table 2)(51). Of note, both studies compared outcome to historical benchmarks and included independent radiologic review. The BRAIN study randomized patients to bevacizumab (n=85) or bevacizumab plus irinotecan (n=82) but was not designed to detect differences between the two treatment arms(3). Outcomes for the bevacizumab and bevacizumab plus irinotecan arms included ORR rates of 28.2% and 37.8%, PFS-6 rates of 42.6% and 50.3% and median overall survival (OS) of 9.2 and 8.7 months, respectively. A single-arm study of bevacizumab among 48 patients treated at the US National Cancer Institute (NCI) noted ORR and PFS-6 rates of 35% and 29%, respectively, and a median OS of 7.75 months(2). Although the BRAIN and NCI trials generated unprecedented ORR and PFS-6 rates the European Medicines Agency declined to approve bevacizumab for recurrent glioblastoma due to the absence of a non-bevacizumab control arm, a modest OS increment versus historical controls, inadequate elucidation of true antitumor effect, and challenges with radiographic response assessment(52).

Thereafter, attempts to augment the benefit of single-agent bevacizumab included studies evaluating bevacizumab combined with chemotherapeutics(31, 53-62), targeted therapies(63-65) and re-irradiation(66-68). Unfortunately all of these combinatorial regimens failed to improve outcome beyond that of bevacizumab monotherapy could be due to a decrease of drug delivery to the tumor(8). A single exception is a phase II study in which 148 recurrent GBM patients randomized to

lomustine, bevacizumab or lomustine plus bevacizumab (Table 2)(69). Outcome was notably improved for the combination arm including PFS-6 of 41%, compared to 11% and 18% for lomustine and bevacizumab alone, respectively. The combination arm was also associated with improved overall survival at 9 months (OS9), the primary endpoint of this trial. The OS9 was 59% for the combination arm and 43% and 38% for lomustine and bevacizumab alone, respectively. Two aspects of this study warrant special comment. First this is the only study to date that incorporates a comparative, randomized statistical design with a non-bevacizumab control arm with minimal crossover to bevacizumab. Second, it is the first study to report a bevacizumab combination with improved outcome compared to bevacizumab monotherapy. Yet, the bevacizumab alone arm underperformed in this trial, and the differences between PFS and OS in all arms suggest that further interventions had a great impact on outcome in this trial. An ongoing phase III study to further evaluate these findings (EORTC 26101, NCT01290939) randomizes recurrent glioblastoma patients to lomustine or lomustine plus bevacizumab with a primary endpoint of OS.

Resistance to bevacizumab inevitably develops and such patients typically die rapidly due to ineffective therapies(2, 31, 54, 70-73). Retrospective data suggests that bevacizumab continuation beyond initial progression may modestly improve outcome(74). Prospective evaluation of this approach is forthcoming via an ongoing trial (TAMIGA). Nonetheless, effective therapies for bevacizumab refractory glioblastomas are desperately needed.

Bevacizumab for newly diagnosed glioblastoma

Initial single arm, phase II studies of bevacizumab in combination with temozolomide and radiation for newly diagnosed glioblastoma patients noted a near doubling of median PFS to 13-14 months compared to historical benchmarks and a nominal median OS increment to 20 months(75-77). Two randomized, placebo-controlled phase III studies, RTOG 0825 and AVAglio, reported extension of PFS but no difference in OS (Table 2)(78, 79). Specifically, median PFS was 47-71% longer for bevacizumab recipients compared to controls, but OS was not significantly different in the two treatment arms. Since 30-40% of controls on each study received bevacizumab at progression, crossover is a potential confounder in terms of the impact on OS, although this remains a matter of speculation. Importantly, both studies assessed pre-defined clinical and molecular prognostic factors for association with outcome but failed to identify any of these patient subgroups more or less likely to benefit from bevacizumab; however, there is ongoing investigation in both trials to determine whether more complex genetic signatures may define subgroups more likely to benefit from bevacizumab in combination with chemoradiation, as discussed below and elsewhere.

Both RTOG 0825 and AVAglio assessed other measures of clinical benefit. AVAglio noted preserved Karnofsky performance status and lower corticosteroid requirement among bevacizumab recipients. Unexpectedly, results from validated measures of quality of life (QOL) including the EORTC QLQ-C30 and BN20 questionnaires that were incorporated by both studies yielded conflicting results. Among bevacizumab recipients, consistently improved QOL scores were reported across five prospectively defined domains on AVAglio, while lower scores were noted for several domains on RTOG 0825. Moreover, in RTOG 0825 symptom burden was increased in

the bevacizumab arm versus the control arm using the MDASI-BT. The explanation for these discordant results remains unclear. Investigators in RTOG 0825 assessed radiographic response solely by enhancing tumor (Macdonald criteria(80)) and may have failed to identify early progression among bevacizumab recipients. In contrast, AVAglio assessed both enhancing and non-enhancing tumor (RANO criteria)(81). RTOG 0825, but not AVAglio, incorporated formal neurocognitive testing and noted diminished processing speed and executive function among bevacizumab recipients compared to controls. These notable findings warrant follow-up investigation. In summary, clinical trial data to date support improved PFS but lack of significant OS benefit with bevacizumab among recurrent and newly diagnosed glioblastoma patients.

Biological and Imaging Markers

The increased understanding of the molecular profile of glioblastoma suggests that subgroups of these patients may respond differentially to distinct classes of antiangiogenic agents. There are a number of tumor tissue and circulating candidate biomarkers for predicting the efficacy of antiangiogenic agents. Tumor tissue biomarkers that have been assessed, but not confirmed(79, 82) include a 9-gene signature representative of the mesenchymal subtype of glioblastoma(83, 84), VEGF expression(85, 86), *O6-methylguanine methyltransferase* promoter methylation status(79), epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor a (PDGFR-a) and c-KIT for VEGFR2 inhibition(6, 87). Negative predictive markers for the use of bevacizumab in newly diagnosed glioblastoma include an expanded set of mesenchymal genes(82), whereas the proneural molecular (tumors with *IDH* mutations excluded) subtype of glioblastoma specifically benefitted from

bevacizumab(86) versus the other three cancer genome atlas (TCGA) glioblastoma molecular subtypes. Independent, e.g. cross-trial confirmation of these putative predictive markers is needed, and their use in current clinical practice should be discouraged.

Circulating cytokines are attractive candidate biomarkers. However, in the AVAglio trial pretreatment plasma VEGF and sVEGFR2 levels were not associated with PFS or OS(20, 86, 88). Matrix metalloproteinase (MMP)-2 is a plasma candidate biomarker for efficacy of bevacizumab(89). Elevated soluble VEGFR1, a negative regulator of the VEGF signaling cascade, has been proposed as a resistance biomarker in other solid tumor types(90).

Radiographic response as defined by a reduction in tumor contrast-enhancement on brain CT or MRI scans may not reflect intrinsic antitumor activity since antiangiogenic treatment notably targeting VEGF signaling may rapidly reduce vessel permeability and contrast extravasation. This rapid and usually transient radiographic change is sometimes termed “pseudoresponse.” Consequently, antiangiogenic treatments have compelled a focus on brain tumor imaging leading to the introduction of novel, candidate techniques to accurately define tumor response and tumor progression. Some of these MRI methods include apparent diffusion coefficient (ADC)(91), dynamic contrast-enhanced (DCE) and dynamic susceptibility-contrast (DSC) techniques to assess baseline and dynamic features of glioblastoma vasculature(92, 93), as well as vessel architectural imaging (VAI) that exploits a temporal shift in the magnetic resonance signal, forming the basis for vessel caliber estimation(94). VAI techniques demonstrate vessel-normalizing microcirculation during

VEGF inhibition with cediranib, a pan-VEGF receptor tyrosine kinase inhibitor(94). The T₁-derived parameter K^{Trans} may reflect not only vessel normalization but also efficacy with VEGF inhibition. Cerebral blood flow may increase early after initiation of anti-VEGF therapy, identify responders, and is associated with improved tumor oxygenation status(87). Dopamine and amino acid positron emission tomography (PET) has been evaluated as an early imaging parameter of response to anti-VEGF therapy(95, 96). Further assessment of these imaging techniques and implementation of uniform imaging protocols in prospective, randomized trials is essential to determine their ultimate predictive value.

Future Directions

Significant effort and investment have been dedicated to the development of antiangiogenic therapies for glioblastoma. Consequently, new criteria for the assessment of disease by neuroimaging have been defined(81), new concepts of clinical trial design have been developed(97) and the quality of clinical trial design, conduct and analysis have been improved(20, 79, 98). Nevertheless, an overall survival benefit has yet to be identified after five randomized phase 3 trials in the newly diagnosed and recurrent glioblastoma setting. Where do we go from here?

First, future, pivotal, phase 3 trials of antiangiogenic agents should be conducted on the basis of data from well-designed, placebo-controlled, randomized, phase 2 trials when feasible(97). Second, it is highly likely that a future survival advantage is likely to come from the combination of antiangiogenic and cytotoxic treatments, similar to other solid tumor types. As noted, the only positive OS data from a randomized (phase 2) trial was observed for recurrent glioblastoma with chemotherapy plus bevacizumab. Third,

although striking differences in patient response to and duration of benefit from VEGF inhibitors among patients with glioblastoma have been observed, none of the promising neuroimaging, histological and circulating markers associated with radiographic or clinical benefit have yet been validated. This until now missed opportunity of drug development is equally unfortunate for the field of neuro-oncology and for the pharmaceutical industry and even more for patients who may derive benefit from this treatment approach. Thus, intensive effort should focus on the identification and validation of such predictive markers. Fourth, with improved cellular and rodent glioma models including patient-derived and stem-like cell models and feasible animal imaging techniques available, more preclinical studies focusing on predictive biomarkers and mechanisms of escape are feasible and should supplement the ongoing efforts of moving antiangiogenic agents forward.

Grant Support

T.T. Batchelor was supported by the NCI of the NIH under award numbers P50CA165962, R01CA129371, K24CA125440, K12CA090354, R13 CA124293.

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Table 1. Representative clinical trials of VEGF/VEGFR targeting therapeutics among recurrent glioblastoma patients

Agent	Mechanism	Dose	# Patients	ORR (%)	PFS-6 (%)	OS (median, months)	Reference
Aflibercept	Soluble decoy VEGFR	4 mg/kg biweekly	42	18	7.7	9.8	50
Cediranib	VEGFR TKI	30 mg daily	118	15.3	16	8.0	98
Nintedanib	VEGFR TKI	200 mg twice a day	13	0	4	8.1	48
Pazopanib	VEGFR TKI	800 mg daily	35	5.7	3	8.8	34
Pazopanib (+ lapatinib)	VEGFR TKI	400 mg daily	41	5	7.5	NR	47
Sorafenib (+ daily TMZ)	VEGFR TKI	400 mg daily	32	3	9.4	10.4	35
Sunitinib	VEGFR TKI	37.5 mg daily	32	10	10.4	9.4	42
Vandetanib	VEGFR TKI	300 mg daily	32	12.5	6.5	6.3	41
Bevacizumab	Humanized	10mg/kg	85	28	43	9.3	3

	anti-VEGF mAb	biweekly					
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Abbreviations: kg, kilogram; mAb, monoclonal antibody; mg, milligram; ORR, overall radiographic response; OS, overall survival; PFS-6, progression-free survival at six months; TKI, tyrosine kinase inhibitor; TMZ, temozolomide; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Table 2. Landmark clinical trials of bevacizumab for glioblastoma (GBM)

Trial	Regimen	# Patients	Median PFS (months)	PFS-6 (%)	Median OS (months)	Reference
RECURRENT GBM						
BRAIN	BEV	85	4.2	42.6	9.2	3
BRAIN	BEV + irinotecan	82	5.6	50.3	8.7	3
NCI	BEV	48	4.0	29	7.8	2
BELOB	BEV	50	3	18	8	69
BELOB	Lomustine	46	2	11	8	69
BELOB	BEV + lomustine	44	11	41	11	69
NEWLY DIAGNOSED GBM						
RTOG 0825	BEV + TMZ/XRT	312	10.7 (HR: 0.79; p=0.007)	NR	15.7	79
RTOG 0825	TMZ/XRT	309	7.3	NR	16.1	79
AVAGlio	BEV + TMZ/XRT	458	10.6 (HR:0.64, p<0.0001)	NR	16.9	78
AVAGlio	TMZ/XRT	463	6.2	NR	16.8	78

Abbreviations: BEV, bevacizumab; HR, hazard ratio; NCI, National Cancer Institute, USA; NR, not reported; OS, overall survival; PFS-6, progression-free survival at six months; TMZ, temozolomide; XRT, radiation therapy.

Figure 1. Normalization of tumor vasculature. (A) Tumor vasculature is structurally and functionally abnormal. One potential mechanism of action for antiangiogenic therapies is transient improvement in both the structure and the function of tumor vessels. However, sustained antiangiogenic treatment may eventually result in a vasculature that is both resistant to further treatment and inadequate for the delivery of drugs or oxygen. (B) Vessel structural patterns before, during and with sustained VEGFR2 blockade. (C) Diagram depicting the concomitant changes in pericyte coverage (green) and basement membrane thickness (blue) before, during and with sustained VEGFR2 blockage. (D) Changes in the balance of pro- and antiangiogenic factors leading to the phenotypic changes noted above. Reprinted from Jain (99).

Figure 2. Intrinsic and evasive tumor resistance to antiangiogenic agents. Some GBM patients do not respond to antiangiogenic therapies (intrinsic resistance). However, in patients who initially benefit, the treatment induces evasive resistance pathways, which bypass the angiogenic blockade. Pro-angiogenic and non-enhancing/infiltrative tumor growth patterns predominate following initial antiangiogenic response in GBM. Pro-angiogenic evasion results from activation of alternate pro-angiogenic factors or recruitment of BMDCs to promote VEGF-independent neovascularization. A more infiltrative growth pattern is observed in pro-invasive evasion. GBM stem-like cells may survive or be enriched by antiangiogenic therapy. BMDC: Bone marrow-derived cell; EPC: Endothelial progenitor cell; FLAIR: Fluid-attenuated inversion recovery; GBM: Glioblastoma; GSC: Glioblastoma stem cell; MMP: Matrix metalloproteinase; PPC:

Pericyte progenitor cell; SDF-1 α : Stromal-derived factor-1 α . Reprinted from Lu and Bergers (24).