Update on the Use of Angiogenesis Inhibitors in Adult Patients With Brain Tumors

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Abstract: The outcome following conventional therapy for patients with primary and metastatic brain tumors remains poor. Most primary brain cancers are angiogenic, and much research has targeted angiogenesis therapeutically. Vascular endothelial growth factor drives angiogenesis in brain tumors, although other factors contribute. Aggregate data confirm that the safety profile of antiangiogenic agents is acceptable among patients with brain cancer; the risks for serious adverse events, such as stroke, hemorrhage, and thrombosis, are low and similar to those observed in other cancers. Evidence of antitumor activity includes encouraging rates of radiographic response and progression-free survival. In addition, the potent antipermeability effects of these agents can substantially reduce cerebral edema and corticosteroid requirement. Importantly, most data demonstrate that antiangiogenic agents preserve neurologic function and improve quality of life. Unfortunately, the impact of angiogenesis inhibition on overall survival appears to be modest at best in patients with brain cancer. In addition, mechanisms of resistance, including selection favoring invasion, remain poorly understood.

Introduction

Brain cancers in adults include diverse primary malignancies that originate from tissues of the central nervous system (CNS), as well as secondary metastatic tumors. Among the former, glial neoplasms predominate, whereas neuronal-derived tumors are less common. Glial tumors are classified into grades 1 through 4. Grade 1 and 2 tumors, also known as low-grade gliomas and sometimes referred to by the misnomer "benign tumors," are characterized by relatively low rates of cellular density, pleomorphism, and proliferation. In contrast, grade 3 and 4 tumors, also referred to as high-grade gliomas, exhibit increased rates of these features; in addition, grade 4 tumors, including glioblastomas, are distinguished by the presence of necrosis and neovascular proliferation.

Treatment for most CNS tumors has historically included maximal safe resection followed by radiation therapy; chemotherapy, such as temozolomide, has been added for some tumor types more

recently. Nonetheless, the outcome for most patients remains poor, and better treatment strategies remain desperately needed.

Angiogenesis, or the formation of new blood vessels from preexisting vasculature, is a common feature of many primary CNS tumors. In glial tumors, markers of angiogenesis—including vessel density and expression of vascular endothelial growth factor (VEGF), the primary mediator of tumor angiogenesis—increase progressively as grade increases and are linked with prognosis.[1,2] Expression of several additional proangiogenic growth factors is also increased in some primary CNS tumors, including malignant gliomas, whereas the levels of endogenous angiogenesis inhibitors are often low.[3-6] In addition, targeting angiogenesis therapeutically in preclinical studies carried out in orthotopic brain tumor models has demonstrated evidence of antitumor activity.[7-9]

Based on these factors, clinical research efforts in neuro-oncology focusing on antiangiogenic therapies have increased dramatically over the past several years. Initial enthusiasm was somewhat tempered by potential safety concerns, which fortunately have not materialized. Extensive cumulative experience provides reassurance that antiangiogenic agents are associated with low rates of significant acute toxicities, including hemorrhage, stroke, thrombosis, and wound dehiscence, in patients with brain cancer.

Evaluation of potential longer-term toxicities, including effects on cognition, has been challenging because of several factors, including the following: (1) the confounding inherently invasive and destructive nature of these tumors; (2) collateral damage associated with established treatment modalities; and (3) limited survival of most patients. Nonetheless, therapeutic benefit associated with inhibition of angiogenesis is substantial for at least some primary CNS tumors, particularly glioblastoma. Specifically, unprecedented rates of radiographic response and progression-free survival (PFS) in patients with either recurrent or newly diagnosed glioblastoma have been achieved with bevacizumab (Avastin, Genentech), a humanized monoclonal antibody against VEGF. Furthermore, response is typically accompanied by preservation or improvement of neurologic function, as well as tapering or avoidance of chronic corticosteroid dependence.

Based on these results, bevacizumab received accelerated approval from the US Food and Drug Administration (FDA) for recurrent glioblastoma in 2009. Unfortunately, the overall survival (OS) benefit associated with bevacizumab as well as other antiangiogenic agents for patients with glioblastoma and other brain cancers appears to be minimal. Several issues remain unresolved and controversial regarding the role of antiangiogenic agents—bevacizumab in particular—in the treatment of glioblastoma, including interpretation of imaging response, optimal timing and dosing, the role of combinatorial agents, and mechanisms of resistance. In this review, we highlight the rationale for and clinical experience in targeting angiogenesis in selected primary brain tumors as well as metastatic CNS tumors.

Glioblastoma and Angiogenesis

Background

Glioblastoma, the second most common primary brain tumor, is diagnosed in approximately 11,000 patients each year in the United States.[10] The biology of glioblastoma is highly complex, in part because of the existence of distinct subtypes. Historically, glioblastomas have been classified as primary if they arise de novo. In contrast, secondary glioblastomas, which account for only 5% to 10%, arise from preexisting low-grade gliomas.[11] More recently, 3 to 4 subtypes of glioblastoma have been defined based on distinct patterns of gene expression.[12,13]

Despite standard therapy, including maximal safe resection followed by radiation therapy, daily temozolomide, and monthly cycles of adjuvant temozolomide, median survival is only 14.6 months, and fewer than 10% of patients are alive 5 years after diagnosis.[14]

Glioblastomas are often classified based on methylguanine methyltransferase (MGMT) status because this classification is highly predictive of response to current therapy. MGMT is a ubiquitous DNA repair enzyme that is capable of repairing damage from alkylating agents simply by removing the alkyl or methyl groups that such agents insert into DNA.[15] Approximately two-thirds of glioblastomas exhibit an unmethylated MGMT gene promoter, which leads to gene expression.[16] In such patients, the addition of temozolomide minimally improves median survival from 11.8 to 12.6 months compared with radiation therapy alone. In contrast, the addition of temozolomide to radiotherapy is associated with a median OS of 23.4 months among the one-third of patients who have newly diagnosed glioblastoma with a methylated MGMT gene promoter.[14] A recent phase 3 study demonstrated that intensification of the dose of adjuvant temozolomide as a strategy to overcome MGMT failed to improve outcome, regardless of MGMT status.[17] Thus, better therapies are desperately needed for all patients with glioblastoma multiforme (GBM), but especially for those with unmethylated MGMT tumors.

Glioblastoma is one of the most angiogenic of cancers, with VEGF levels that are significantly greater than those of other glial tumors and normal brain tissue.[2,5,18-20] Additional proangiogenic growth factors are upregulated in glioblastomas, including platelet-derived growth factor (PDGF), placental growth factor, neuropilins, fibroblast

growth factor, angiopoietins, integrins, interleukin 8, and DLL4-Notch signaling.[3-6] Elevated VEGF levels are likely linked to a "perfect storm" of hypoxia that is both endogenous and treatment-induced,[21-23] as well as hypoxia-independent dysregulated signaling through the phosphoinositide 3-kinase (PI3K)/Akt and Ras/MAPK pathways.[24-28] Characteristic pseudopalisades of tumor cells emanating from necrotic regions are associated with significant hypoxia and the secretion of proangiogenic cytokines.[29] In addition, glioma stem cells, which localize to an angiogenic niche within GBM tumors,[30] express significant levels of proangiogenic factors, including VEGF.[31-33] Nonetheless, angiogenesis may contribute differentially to tumor pathophysiology among different subtypes of glioblastoma. Specifically, angiogenic cytokine profiles have been shown to differ between primary and secondary glioblastoma tumors,[34] and angiogenic factors are particularly associated with the mesenchymal glioblastoma subtype based on gene expression analyses.[35]

Most preclinical studies demonstrate that VEGF suppression improves survival in orthotopic GBM models. Decreased tumorigenicity has been observed in some of these studies,[7-9] whereas one study demonstrated no effect on tumor growth despite enhanced survival.[36] In addition, some preclinical studies have demonstrated that VEGF-targeted therapy may enhance invasion and host vessel co-option.[8,37]

Clinical Experience

The clinical benefit of bevacizumab among patients with glioblastoma was first reported in a series of heavily pretreated patients with recurrent disease[38] and was quickly confirmed in single-arm, phase 2 studies.[39-41] In contrast to historical data derived from meta-analyses of patients with recurrent glioblastoma treated in cooperative group clinical trials before the introduction of bevacizumab, which showed radiographic response and 6-month PFS (PFS-6) rates of 5% and 10% to 15%, respectively,[42-44] initial studies of bevacizumab demonstrated radiographic response and PFS-6 rates of approximately 50% and 40%, respectively. Importantly, these initial studies also allayed safety concerns, including documentation of rare hemorrhages and strokes, and rates of thrombosis, fatigue, hypertension, proteinuria, wound dehiscence, and intestinal perforation were low and similar to those observed among other cancer populations treated with bevacizumab.[45] Accelerated approval of bevacizumab by the FDA for recurrent glioblastoma was granted in May of 2009 based on durable radiographic responses noted in 2 parallel, phase 2 studies that included independent radiologic review.[46] In BRAIN (A Study to Evaluate Bevacizumab Alone or in Combination With Irinotecan for Treatment of Glioblastoma Multiforme), 167 adult patients with glioblastoma at first or second recurrence and a KPS of at least 70 were randomized to receive either bevacizumab or bevacizumab plus irinotecan.[47] Dual primary endpoints for this study were rates of objective response rate (ORR) and PFS-6 relative to historical benchmarks. Importantly, the study was not statistically powered to detect superiority of either of the treatment arms. In this study, a trend toward improved outcome was noted for the combination arm. Specifically, the ORRs for bevacizumab monotherapy and for bevacizumab plus irinotecan were 28.2% and 37.8%, respectively, while the PFS-6 rates were 42.6% and 50.3%, respectively. Nonetheless, median OS was 9.2 months for the monotherapy arm and 8.7 months for the combination arm, and patients in the combination arm experienced higher rates of adverse events, attributable primarily to irinotecan.

The second study that contributed to accelerated FDA approval enrolled a more challenging group of patients with glioblastoma in that the eligibility criteria did not restrict based on number of prior progressions, and patients were allowed a Karnofsky performance status (KPS) of as low as 60.[48] The primary endpoint for this single-arm, phase 2 study conducted at the National Cancer Institute (NCI) was PFS-6 and was compared with historical data. The outcome of this study was lower compared with the outcome of BRAIN, likely reflecting the more challenging patient population; nonetheless, the ORR and PFS-6 rates were 35% and 29%, respectively. Median OS in this study was 7.75 months.

The unprecedented rates of ORR and PFS observed in BRAIN and the NCI study led to accelerated approval for bevacizumab monotherapy in the United States in May 2009.[46] Of note, an OS benefit was also noted in these studies relative to historical benchmarks, although the increment was less robust. Specifically, OS in the BRAIN and NCI bevacizumab studies was 7.8 to 9.2 months, compared with 5.0 to 6.3 months in large series of patients with recurrent GBM treated in the recent era before bevacizumab.[42,43,49] Very similar survival data were also noted in a retrospective series of contemporaneous patients with recurrent GBM treated at a single institution. In this study, OS was 9.0 months for those who received salvage bevacizumab therapy, compared with only 6.1 months for those treated with non-bevacizumab regimens (P=.04).[50] Nonetheless, the European Medicines Agency rejected approval of bevacizumab for recurrent glioblastoma in November 2009 because of the lack of a non-bevacizumab control arm, a modest observed survival benefit, poor elucidation of the underlying mechanism of antitumor activity, and challenges to classifying the radiographic response and progression with VEGF-targeting agents.[51]

Limitations of the traditional criteria for radiographic response in neuro-oncology, which rely historically on

measurement of the bidimensional product of enhancing tumors as described by the Macdonald criteria,[52] were recognized by many clinicians early in the development of bevacizumab and other VEGF/VEGF receptor (VEGFR)–targeting therapeutics for CNS cancers. Specifically, VEGF/VEGFR blockade potently decreases the permeability of tumor vasculature, which can markedly diminish contrast uptake within hours of dosing.[53] Although the antipermeability effect of these agents often benefits patients by reducing neurologic deficits and the need for long-term dependence on high-dose corticosteroids,[54,55] such rapid changes in contrast uptake unlikely reflect direct antitumor activity and can therefore be misinterpreted as a "pseudoresponse." Furthermore, reports of progressive T2/fluid attenuation inversion recovery (FLAIR) changes with or without clinical decline were increasingly described among patients with recurrent glioblastoma following VEGF/VEGFR inhibitor therapy.[56-58] These observations contributed to the development of the Response Assessment in Neuro-Oncology (RANO) criteria, which modified the response assessment in patients with glioblastoma undergoing antiangiogenic therapy to require assessment of both the enhancing and nonenhancing tumor components, with the latter measured by T2/FLAIR changes.[59]

In an attempt to build on the clinical benefit associated with single-agent bevacizumab, several subsequent reports evaluated a multitude of agents administered in combination with bevacizumab to patients with recurrent glioblastoma, including chemotherapeutics,[41,50,58,60-68] targeted therapies,[69-71] and reirradiation.[72-74] None of these combinations generated outcome data significantly superior to those achieved with bevacizumab monotherapy, although it is unclear whether this finding reflects a lack of true complementary antitumor activity for the evaluated combinations or simply the limited inherent antitumor activity of each of these agents against recurrent glioblastoma. Of note, recently reported data demonstrated that patients randomized to receive bevacizumab plus lomustine had a substantially better outcome than those treated with either bevacizumab or lomustine alone.[75]

Following the encouraging activity noted with bevacizumab among patients with recurrent glioblastoma, several additional agents targeting VEGF or VEGFR were evaluated. In particular, several tyrosine kinase inhibitors (TKIs) targeting VEGFR have been studied, including pazopanib (Votrient, GlaxoSmithKline),[76,77] AEE788,[78] sunitinib (Sutent, Pfizer),[79-81] vatalanib,[82-84] sorafenib (Nexavar, Bayer/Onyx),[85-87] and vandetanib (Caprelsa, AstraZeneca).[88,89] Although most of these agents target additional growth factor receptors beyond VEGFR2 that are potentially relevant to glioblastoma physiology, evidence of therapeutic benefit has been disappointing, and benefit appears in general to be inferior to that achieved with bevacizumab. Among VEGFR TKIs, cediranib, an oral inhibitor of KIT and the PDGF receptor in addition to VEGFR2, has been the most extensively studied, including in an initial single-arm, phase 2 study followed by a randomized, phase 2 study. Although encouraging evidence of single-agent activity was initially reported,[90] the randomized study reported that the outcomes achieved with cediranib monotherapy, as well as with cediranib plus lomustine, failed to surpass that of lomustine monotherapy.[91] Interestingly, it has been reported that a subset of patients who fail VEGFR TKI therapy may still benefit from bevacizumab.[92,93]

Aflibercept (Zaltrap, Sanofi/Regeneron) is a recombinant fusion protein linking the extracellular domains of VEGF to the Fc portion of immunoglobulin G1 that exhibits high VEGF-binding potency. It is currently FDA-approved for macular degeneration and metastatic colorectal cancer and has also been evaluated in patients with malignant glioma. Despite promising preclinical data in GBM models,[94,95] aflibercept was ineffective and associated with moderate toxicity among patients with recurrent malignant glioma in a recent phase 2 study.[96]

Given the therapeutic benefit observed in the recurrent setting, bevacizumab has been further evaluated in patients with newly diagnosed glioblastoma. Three single-arm, phase 2 studies were initially reported in which bevacizumab was added to standard radiation with temozolomide followed by adjuvant temozolomide.[97-99] Each of these studies affirmed that the addition of bevacizumab did not lead to unexpected or increased adverse events. PFS in these studies was 13 to 14 months and essentially doubled that of historical data without bevacizumab.[100] OS was encouraging, at approximately 20 months.

Two registration studies, RTOG (Radiation Therapy Oncology Group) 0825 and AVAglio (Phase 3 Trial of Bevacizumab Plus Temozolomide and Radiotherapy in Newly Diagnosed Glioblastoma Multiforme), which evaluated the addition of bevacizumab to standard radiation and temozolomide for patients with newly diagnosed glioblastoma, have been recently reported.[101,102] The 2 studies had several similarities, including a randomized, placebo-controlled, phase 3 study design and statistical power to evaluate dual endpoints of median PFS and OS. Importantly, there were also significant differences between the 2 studies. First, AVAglio enrolled patients regardless of degree of resection. In contrast, RTOG 0825 mandated submission of tumor tissue for correlative genetic studies and thus excluded patients who underwent diagnostic biopsy only. Because of this difference, RTOG 0825 enrolled a higher percentage of patients (60%) with a gross total resection, a known positive prognostic factor, while excluding patients with multifocal disease, a known negative prognostic factor.[103] Another important difference between the 2 studies was that RTOG 0825, which was conducted primarily in

North America, unblinded patients at the time of progression and allowed control patients to cross over and receive bevacizumab. Of note, approximately 30% of control patients in AVAglio also crossed over and received bevacizumab following progression, although this crossover was not formally incorporated into the study design. The impact of such crossover on OS remains to be determined. Another important difference between the studies was the method used to assess response. RTOG 0825 used the Macdonald criteria,[52] which did not include assessment of nonenhancing changes on magnetic resonance imaging. In contrast, a modified version of the RANO criteria[59] was used for response assessment in AVAglio, which included evaluation of both enhancing and nonenhancing disease. Other differences between the 2 studies included the duration of adjuvant temozolomide (6 cycles in AVAglio vs 12 in RTOG 0825), continuation of single-agent bevacizumab until progression following completion of planned adjuvant temozolomide (AVAglio only), and starting point of bevacizumab dosing during radiation (day 1 in AVAglio vs after day 21 in RTOG 0825).

Other than a higher rate of gross total resection in RTOG 0825, patient characteristics between the 2 studies were comparable and equally distributed between the study arms (Table 1). Importantly, both studies confirmed the overall safety of bevacizumab administered to patients with newly diagnosed glioblastoma. Of note, efficacy measures in both studies were also remarkably similar (Table 2). PFS was more than 4 months longer for patients in the bevacizumab arm of each of the studies compared with those in the control arm. Furthermore, a PFS benefit was consistently observed regardless of clinical prognostic factors or MGMT status. Unfortunately, no difference in OS was observed between the treatment arms of both studies, and neither study identified a subset of patients in whom the addition of bevacizumab provided a survival benefit. It remains unclear how the lack of survival improvement yet PFS benefit, noted consistently between RTOG 0825 and AVAglio, will be interpreted by regulatory agencies, particularly given ongoing controversies regarding response assessment in the setting of agents that alter vascular permeability.

Both RTOG 0825 and AVAglio importantly included assessments of other measures of potential clinical benefit. AVAglio reported significantly higher rates of preservation of a KPS of at least 70, as well as markedly lower rates of corticosteroid requirement, among recipients of bevacizumab. Both of these factors would be expected to translate into significantly improved quality of life (QOL) for patients with glioblastoma. Unfortunately, RTOG 0825 has not reported outcome on either of these important endpoints. Formal QOL assessment was incorporated into both studies, as a secondary objective for AVAglio and as an exploratory objective for RTOG 0825. Despite the use of similar, validated QOL questionnaires, discordant results were unexpectedly noted. Specifically, among bevacizumab recipients, AVAglio noted consistently superior scores, whereas RTOG 0825 reported poorer scores for some domains. The explanation for these discordant results is unclear, but they may reflect lower rates of adherence in RTOG 0825 and/or differences in data analysis between the 2 studies. An independent review of the QOL data from both studies should be performed before firm conclusions are drawn regarding the impact of bevacizumab on this important endpoint among patients with glioblastoma. An important strength of RTOG 0825 was the incorporation of formal neurocognitive testing. Of note, although bevacizumab was shown to be associated with stable or improved neurocognitive function among patients with recurrent glioblastoma,[104] processing speed and executive function were noted to be poorer in the patients with newly diagnosed glioblastoma treated with bevacizumab in RTOG 0825. These data indicate that neurocognitive function in bevacizumab recipients should be further evaluated in a consistent manner.

Although a subset of patients with glioblastoma appears to derive long-term antitumor control with bevacizumab therapy, resistance inevitably emerges, as has been observed with every other treatment approach evaluated in patients with glioblastoma. Currently, one

Table 1. Patient Characteristics: AVAglio and RTOG 0825

Category	AVAglio		RTOG 0825	
	Placebo	BEV	Placebo	BEV
Number of patients	463	458	309	312
Age				
Median, y	56	57	—	—
<50 y	—	—	21	18
Male	64	62	63	56
KPS ≥90	70	67	61	60
Surgery				
Biopsy	10	13	0	0
Subtotal	48	46	38	34
Complete	42	41	59	63
Methylated MGMT	26	26	28	29
RPA class				
3	16	17	15	11
4	60	57	64	71
5	23	26	18	16

AVAglio, Phase 3 Trial of Bevacizumab Plus Temozolomide and Radiotherapy in Newly Diagnosed Glioblastoma Multiforme; BEV, bevacizumab; KPS, Karnofsky performance status; MGMT, methylguanine methyltransferase; RPA, recursive partitioning analysis; RTOG, Radiation Therapy Oncology Group.

Table 2. Outcome for Patients With Newly Diagnosed Glioblastoma Treated in AVAglio and RTOG 0825

Category	AVAglio		RTOG 0825	
	Placebo[a]	BEV	Placebo[a]	BEV
Number of patients	463	458	309	312
Median PFS, mo	6.2	10.6 (HR, 0.64; *P*<.0001)	7.3	10.7 (HR, 0.79; *P*=.007)[b]
Median OS, mo	16.8	16.9	16.7	15.7

AVAglio, Phase 3 Trial of Bevacizumab Plus Temozolomide and Radiotherapy in Newly Diagnosed Glioblastoma Multiforme; BEV, bevacizumab; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RTOG, Radiation Therapy Oncology Group.

[a] Controls for AVAglio and RTOG 0825 were differentially "contaminated" by BEV crossover at progression of disease.

[b] RTOG 0825 PFS did not reach predefined 30% reduction in HR.

of the greatest challenges in neuro-oncology clinics is the treatment of patients with glioblastoma following bevacizumab progression, as no effective salvage therapy has been identified to date. Most patients succumb to tumor progression within a few months of bevacizumab failure,[48,61,67,105-108] although a modest survival benefit was reported in a retrospective series of patients who underwent reirradiation.[109] A recent retrospective analysis demonstrated that bevacizumab continuation beyond initial progression was associated with a modest improvement compared with non-bevacizumab salvage therapy, although all patients fared quite poorly.[110] A randomized, prospective study to evaluate bevacizumab continuation beyond initial progression among patients with recurrent glioblastoma is expected to initiate accrual in the near future.

Extensive efforts have been made to define biomarker predictors of response to antiangiogenic agents among patients with malignant glioma. A wide array of potential biomarkers—including tumor tissue proteins, imaging parameters, and circulating markers—have been assessed, but none has been validated.[111] Ongoing and future efforts are critically needed to address this elusive challenge.

Grade 3 Malignant Glioma and Angiogenesis

Grade 3 malignant gliomas account for approximately 4% of all primary CNS tumors. The most common subtypes of grade 3 malignant glioma are anaplastic astrocytoma, anaplastic oligoastrocytoma, and anaplastic oligodendroglioma.[10,112] These tumors occur in younger people than do grade 4 glial tumors, and are usually diagnosed early in the fourth decade of life. A better outcome is linked with oligodendroglioma histology, chromosome arms 1p and 19q deletion, MGMT methylation, and mutation of the isocitrate dehydrogenase 1 gene.[113-120] Following maximal safe resection, patients with grade 3 malignant gliomas have historically been treated with radiation or chemotherapy,[116] although more recent studies have confirmed a significant survival benefit associated with radiation and adjuvant chemotherapy.[121,122] Ongoing studies are evaluating temozolomide chemoradiotherapy, as is routinely used for patients with glioblastoma, as well as the different components of this approach among patients with newly diagnosed grade 3 malignant glioma based on the status of chromosome arms 1p and 19q (NCT00887146 and NCT00626990). Although survival is in general better than in patients who have grade 4 tumors, nearly all patients who have grade 3 malignant gliomas ultimately develop progressive disease, and median survival times are approximately 20, 61, and 56 months among patients with anaplastic astrocytoma, anaplastic oligoastrocytoma, and anaplastic oligodendroglioma, respectively.[117,121] Of note, patients with anaplastic oligodendroglioma that exhibits 1p and 19q codeletion have recently been shown to have a 2-fold improvement in OS following combined chemoradiotherapy.[121]

Grade 3 gliomas are angiogenic, but typically exhibit lower levels of VEGF expression and microvessel density than glioblastomas.[2,20,123-126] Several reports have confirmed adequate safety of bevacizumab therapy among patients with recurrent anaplastic gliomas in addition to encouraging evidence of therapeutic benefit, including relatively high rates of radiographic response, PFS, and OS.[54,58,62,69,127-133] Importantly, several of these reports confirm additional measures of therapeutic benefit, such as preservation or improvement of neurologic function, performance status, and QOL, as well as a diminished requirement for prolonged corticosteroid treatment. Nonetheless, no registration studies are under way to extend regulatory approval for the use of bevacizumab to patients with grade 3 malignant glioma.

Other Primary CNS Tumors and Angiogenesis

In addition to its activity among patients with malignant glioma, the activity of bevacizumab in small series of patients with other primary malignant brain tumors has been reported.

Bilateral Vestibular Schwannomas

Bilateral vestibular schwannomas, a hallmark of neurofibromatosis type 2 (NF2), typically cause deafness by middle

age.[134,135] Treatment options have historically been limited to surgery or radiation therapy, but these interventions can also contribute to hearing loss.[136,137] Increased expression of VEGF and its receptors has been demonstrated in a high percentage of vestibular schwannomas.[138,139] In a recently reported retrospective series of patients with NF2 and progressive bilateral vestibular schwannomas, bevacizumab therapy was associated with a high rate of radiographic response. Remarkably, this was accompanied by a durable hearing response in most patients.[139]

Meningioma

Meningiomas, which arise from arachnoid cap cells of the dura, are the most common primary CNS malignancy and account for 34% of all primary brain tumors.[10] Approximately 80% of meningiomas are grade 1, and are often effectively treated with surgery and/or radiotherapy. In contrast, grade 2 and 3 meningiomas, which account for 15% and 3% of all meningiomas, respectively, typically recur following surgery and radiotherapy. A variety of medical therapies, including several different chemotherapeutic agents, various targeted and biologically based therapies, and antihormonal agents, have been evaluated, with limited antitumor benefit shown for most patients.[140-142] Measures of angiogenesis, including increased levels of vessel density and VEGF expression, are detectable in many meningiomas,[143-147] and some series have linked these factors with meningioma grade and prognosis.[148-150] Three retrospective series have evaluated the use of bevacizumab among heavily pretreated patients with recurrent/progressive meningioma,[151,152] including a subset with NF2.[153] In general, bevacizumab was well tolerated by these patients, although isolated episodes of CNS hemorrhage and intestinal perforation were reported. Evidence of antitumor activity, including radiographic responses and prolonged PFS, was noted in these studies, and a phase 2 study of single-agent bevacizumab is ongoing for patients with recurrent/progressive meningioma (NCT01125046).

Ependymoma

Ependymomas account for 2% of all primary brain tumors among adults and can arise throughout the CNS axis.[10,154,155] Maximal safe resection and radiation therapy are considered standard therapeutic approaches.[156] Effective therapy for patients with recurrent tumors remains poorly defined.[157-159] Some ependymomas have been noted to be angiogenic, with increased VEGF expression and vessel density.[126,160] A small retrospective series recently reported a high rate of radiographic response, as well as encouraging PFS and OS, following bevacizumab therapy among adults with anaplastic ependymoma that had recurred despite surgery and radiotherapy.[161] A phase 2 study evaluating carboplatin and bevacizumab for adults with recurrent ependymoma has recently opened (NCT01295944) through the Collaborative Ependymoma Research Network.

Hemangioblastoma

Hemangioblastomas are rare vascular tumors that can arise within the CNS, either spontaneously or in association with von Hippel-Lindau disease.[162] Antitumor benefit associated with antiangiogenic agents, including bevacizumab, has been reported in some patients with recurrent and/or progressive, unresectable hemangioblastomas.[163-165]

Brain Metastases and Angiogenesis

Brain metastases are roughly 10 times more common than primary brain tumors among adults, with approximately 170,000 cases diagnosed annually in the United States.[166] The most common systemic cancers linked to CNS metastases are lung cancer, breast cancer, and melanoma.[167] Treatment typically includes surgery and radiotherapy. The outcome for most patients is poor. Effective systemic therapies have not been defined.

Unlike malignant gliomas, in which vigorous angiogenesis is a consistent and noteworthy feature, brain metastases exhibit angiogenesis that varies with the subtype of the underlying tumor.[168-172] Of note, diminished angiogenesis has been observed in some experimental models of metastatic brain tumors.[173]

Antiangiogenic therapies, including bevacizumab, have not been extensively evaluated in prospective studies of patients with metastatic brain tumors. Nonetheless, adequate safety, including a low rate of brain hemorrhage, has been noted in large meta-analyses of patients who had CNS metastases treated with bevacizumab.[174,175] In addition, encouraging preliminary clinical benefit for some indications has recently been reported.[176-180] Prospective trials evaluating the therapeutic benefit of and adverse events associated with antiangiogenic agents for patients with brain metastases are ongoing.[181]

Conclusion

Patients with primary and metastatic brain cancers represent a substantial proportion of the cumulative cancer population. Benefit from conventional therapies is limited to a subset of patients and is typically not durable. More effective therapeutic strategies are critically needed.

Angiogenesis, a common feature of many brain tumors, is particularly noted in high-grade gliomas. A wide spectrum of antiangiogenic agents has been investigated for brain cancer, with bevacizumab being the most commonly evaluated. Studies have confirmed acceptable safety profiles for these agents, including rates of both potentially

life-threatening and less serious adverse events comparable with those in other cancer indications.

Bevacizumab has widespread regulatory approval for recurrent glioblastoma based on durable radiographic responses noted in uncontrolled clinical trials. Full FDA approval of bevacizumab for glioblastoma is contingent on subsequent demonstration of unequivocal clinical benefit and currently depends on the results of 2 recent placebo-controlled, randomized, phase 3 studies for patients with newly diagnosed disease. These studies demonstrated substantial increments in PFS with bevacizumab, although an OS benefit was not observed in either study. Discordant results regarding the impact of bevacizumab on QOL and evidence of neurocognitive decrement observed in one of the studies indicate that deeper study of these relevant endpoints is required. Nonetheless, consistent data supporting preservation of neurologic function and reduction in corticosteroid dependence associated with bevacizumab are noteworthy. The role of antiangiogenic agents, including bevacizumab, in other, less common CNS cancers is under evaluation, but encouraging preliminary data support further investigation of antiangiogenic agents in patients with grade 3 malignant glioma, vestibular schwannoma, progressive meningioma, ependymoma, hemangioblastoma, and some types of CNS metastases.

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