Bevacizumab and other novel therapies for recurrent oligodendroglial tumors

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Practice points

- The treatment of recurrent, alkylator refractory oligodendroglioma/anaplastic oligodendroglioma and oligoastrocytoma/anaplastic oligoastrocytoma is challenging given the paucity of effective treatment options and lack of randomized controlled trials on which to base therapy.
- Bevacizumab is a humanized, anti-VEGF monoclonal antibody that was granted accelerated approval by the US FDA in March 2009 for single-agent treatment of recurrent glioblastoma based on the high radiologic response rate demonstrated in two Phase II clinical trials.
- Notwithstanding the lack of prospective, randomized data, treatment of oligodendroglial tumors with bevacizumab can be recommended tentatively recognizing that preliminary studies only suggest efficacy.
- Somatic mutations of the isocitrate dehydrogenase enzymes (IDH1 and IDH2) appear to play a critical role in the pathogenesis of most anaplastic oligodendroglioma/anaplastic oligoastrocytoma; agents that target these mutations are a potential therapeutic option that has yet to be investigated.
- A distinct subset of glioma with hypermethylation of CpG islands (CIMP⁺ or G-CIMP) has been identified and found to be associated with improved outcome.
- Reversal of CIMP status through inhibition of DNA methyltransferase with an inhibitor such as decitabine may provide a target for future studies.

Oligodendroglioma (WHO Grade 2) and anaplastic oligodendroglioma (WHO Grade 3) are glial tumors composed of neoplastic cellular elements that resemble oligodendrocytes. The treatment of recurrent, alkylator refractory oligodendroglial tumors is challenging given the paucity of effective treatment and lack of randomized controlled trials on which to base therapy. Notwithstanding the lack of prospective, randomized data, treatment of oligodendroglial tumors with bevacizumab can be recommended tentatively recognizing that preliminary studies suggest efficacy. Somatic mutations of the isocitrate dehydrogenase enzymes (IDH1 and IDH2) appear to play a critical role in the pathogenesis of most oligodendroglial tumors and agents that target these mutations are a potential therapeutic option. Additionally, reversal of CpG island hypermethylated phenotype status through inhibition of DNA methyltransferase with an inhibitor such as decitabine may provide a target for future studies.

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Oligodendroglioma (O: WHO grade 2), oligoastrocytoma (OA: WHO grade 2), anaplastic oligodendroglioma (AO: WHO grade 3) and anaplastic oligoastrocytoma (AOA: WHO grade 3) are glial tumors composed of neoplastic cellular elements that resemble oligodendrocytes or oligodendrocytes and astrocytes (in the case of OA and AOA). Generally, oligodendroglial tumors have a more favorable natural history, are more responsive to therapy and are slower growing than other glial tumors of similar grade. The treatment of recurrent, alkylator refractory oligodendroglial tumors is challenging given the paucity of effective treatment options and lack of randomized controlled trials on which to base therapy. This article focuses on the use of bevacizumab and other novel therapies for treatment of recurrent oligodendroglial tumors. The treatment of newly diagnosed AO/AOA and the use of chemotherapy are discussed in our preceding article regarding anaplastic oligodendroglial tumors.

Overview of oligodendroglioma classification & molecular pathology

Historically, oligodendroglial tumors have been classified according to histologic morphology although distinctions between astrocytoma and oligodendroglioma are incomplete leading to classes of glioma with mixed histology such as oligoastrocytoma (OA), anaplastic oligodendroglioma (AOA) and glioblastoma with oligodendroglial components. A large fraction of oligodendroglial tumors share a characteristic genetic profile consisting of codeletion of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q). This genetic alteration is strongly linked to a favorable clinical behavior and classic oligodendroglioma histology such that it is considered a defining feature [1]. Other favorable prognostic factors associated with oligodendroglial tumors include isocitrate dehydrogenase (IDH) mutation, methylated methylguanine-DNA methyltransferase (MGMT) promoter and CpG island hypermethylated phenotype (CIMP⁺). This constellation of positive prognostic molecular features is enriched in the transcriptionally defined proneural glioma subclass which characterize oligodendroglial tumors and appears to reflect a route of pathogenesis distinct from that taken by other high-grade gliomas [2].

VEGF pathway inhibition

Angiogenesis, the process by which new blood vessels form from existing vasculature through endothelial cell migration and proliferation, is believed to be required for the growth of all solid neoplasms [3]. Neovascularization of brain tumors, particularly gliomas, is thought to be driven mainly by VEGF signaling through its endothelial receptor VEGFR2 [4]. The physiologic and pathologic effects of the VEGF pathway include survival, proliferation, migration and permeability of endothelial cells. VEGF pathway inhibitors are the main anti-angiogenic agents that have been developed for brain tumor therapy. The humanized, anti-VEGF monoclonal antibody bevacizumab was granted accelerated approval by the US FDA in March 2009 for single agent treatment of recurrent glioblastoma. The approval was based on the high radiologic response rate (in an independent radiology review) demonstrated in two prospective Phase II clinical trials [5,6].

Clinical experience with VEGF pathway inhibition

Based on the bevacizumab experience for glioblastoma, investigators have investigated whether other recurrent malignant gliomas such as oligodendroglial tumors could be treated in a similar fashion. Notwithstanding modest data suggesting efficacy, there is a lack of prospective randomized data using bevacizumab in the treatment of oligodendroglial tumors and the use of bevacizumab is considered off-label use and investigational. A review of bevacizumab for recurrent oligodendroglial tumors is considered below and summarized in [Table 1](#). To date, there have been no prospective trials of bevacizumab exclusive to pure oligodendroglial tumors. Two investigators have retrospectively reviewed their experience with bevacizumab for recurrent anaplastic oligodendroglioma [7,8]. A retrospective review of 22 recurrent, alkylator-refractory AO patients that were treated with single agent bevacizumab reported a partial radiographic response in 68% of patients [7]. 6-month and 12-month progression-free survival (PFS) were 68 and 23%, respectively. A second retrospective review of 25 patients with recurrent oligodendroglial tumors that were treated with the combination of bevacizumab and irinotecan (CPT-11) reported similar results [8]. The radiographic response rate was 72% and 6-month PFS was 42%.

Table 1. Summary of studies utilizing bevacizumab-based therapy for the treatment of recurrent anaplastic oligodendroglioma and anaplastic oligoastrocytoma.

Study (year)	Design	Number of patients	Results	Ref.
Chamberlain <i>et al.</i> (2009)	Retrospective study of bev for recurrent AO	AO = 22	RR: 68% PR PFS6 = 68%, PFS12 = 23%	[7]
Tallibert <i>et al.</i> (2009)	Retrospective study of bev + CPT11 for recurrent AO and AOA	O = 7, AO = 12, OA = 1, AOA = 5	RR: 72% PFS6 = 42%	[8]
Desjardins <i>et al.</i> (2008)	Prospective study of bev + CPT11 for recurrent malignant glioma	AO = 8	RR: 1 CR, 6 PR PFS6 = 62%, mPFS28 wks, mOS61 wks	[9]
Reardon <i>et al.</i> (2009)	Prospective study of bev + daily etoposide for recurrent malignant glioma	AA = 13, AO = 13, PXA = 1	RR: 24% PFS-6 = 55%, mPFS 30 wks, mOS65 wks	[10]
Sathornsumetee <i>et al.</i> (2010)	Prospective study of bev + erlotinib for recurrent malignant glioma	AA = 24, AO = 7, PXA = 1	RR: 31% (1 CR, 9 PR) PFS6 = 44%, mPFS 23 wks, mOS 71 wks	[11]
Kreisl <i>et al.</i> (2011)	Prospective study of bev for recurrent anaplastic glioma	AA = 21, AO = 4 AOA = 6	RR 43% PFS6 = 20.9%, mPFS 2.9 m, mOS 12 m	[12]

AA: Anaplastic astrocytoma; AO: Anaplastic oligodendroglioma; AOA: Anaplastic oligoastrocytoma; Bev: Bevacizumab; CPT11: Irinotecan; CR: Complete response; m: Months; mOS: Median overall survival; mPfs: Median progression-free survival; O: World Health Organization grade II oligodendroglioma; PFS6: 6-month progression-free survival; PFS12: Twelve months progression-free survival; PR: Partial response; PXA: Pleomorphic xanthoastrocytoma; RR: Radiographic response; Wks: Weeks.

Oligodendroglial tumors were included along with other malignant gliomas in several nonrandomized, prospective Phase II studies. It is instructive to review these studies as mixed oligodendroglial tumors often emulate the clinical behavior of astrocytic tumors rather than pure oligodendroglial tumors, particularly for tumors lacking the 1p19q codeletion. In addition, a minority of these studies reported results for pure oligodendroglial tumors independently, although the numbers are small, limiting the generalizability of this information. In a prospective study of malignant glioma patients treated with bevacizumab plus irinotecan, the eight patients with recurrent AO had 6-month PFS of 62% (95% CI: 23–86%) and a median PFS of 28 weeks (95% CI: 17–60 weeks) [9]. One AO patient had a complete radiographic response and six had a partial radiographic response. 6-month and median overall survival (OS) were 88% and 61 weeks, respectively. Kreisl *et al.* conducted a prospective study of single agent bevacizumab for the treatment of recurrent anaplastic glioma [12]. In total, 32% of the patients in the study had an anaplastic oligodendroglial tumor. The reported results included patients with anaplastic astrocytoma and anaplastic oligodendroglial tumors. 6-month PFS, median PFS, median OS and radiographic response rate were 20.9%, 2.9 months, 12 months and 43%, respectively. Two other prospective studies investigated the use of bevacizumab in combination with erlotinib or etoposide for recurrent malignant gliomas [10,11]. These studies

reported 6-month PFS 24–31%, median PFS 23–30 weeks and median OS 65–71 weeks. Whether bevacizumab is most effective when administered as a single agent versus when combined with a cytotoxic chemotherapy partner as is done for essentially all other solid cancers is unclear. Currently, there is no compelling data to suggest chemosynergy with combined therapy notwithstanding the recently reported prospective randomized Phase II Dutch BELOB trial that purportedly showed improved outcome when bevacizumab was combined with lomustine (CCNU) as compared with single agent lomustine or bevacizumab in first recurrent glioblastoma [13].

Safety profile of bevacizumab

Experience has demonstrated that bevacizumab is generally well tolerated in primary brain tumor patients and toxicities observed are similar to those that have been described with other tumor types. Reported rates of grade 3 or higher adverse events with bevacizumab have ranged between 18 and 66% and the rate of serious treatment-related adverse events is lower when bevacizumab is used as a single agent [5,12,14]. In a randomized, noncomparative Phase II study of bevacizumab alone or in combination for patients with recurrent glioblastoma, the rate of grade 3 or greater adverse events was 46% with monotherapy versus 66% with combination therapy [5].

The most common bevacizumab associated adverse events in clinical trials for recurrent glioblastoma include low-grade

hemorrhage (intracranial or systemic), hypertension, impaired wound healing and proteinuria [5,12,15]. These toxicities are likely caused by on-target, class-specific actions of antiangiogenic agents that disrupt VEGF signaling in normal tissue. Serious adverse events such as ischemic stroke, myocardial infarction, gastrointestinal perforation, reversible posterior leukoencephalopathy and nephrotic syndrome were uncommon in glioblastoma studies (each $\leq 2\%$ incidence). The rate of grade 2 or greater bleeding events was reported in up to 5.3% although, life threatening intracranial hemorrhages were rare ($\leq 3\%$) [5,12,14,15]. The incidence of serious hemorrhage falls within the expected range in patients with high-grade gliomas. There may be an increased rate of venous thromboembolic events with bevacizumab for malignant glioma, although the magnitude of the increase is difficult to assess given the high rate of thromboembolic events that occur in patients with malignant glioma and further, at least in other solid cancers, no increase is seen. Also, thrombocytopenia may be increased if bevacizumab is combined with temozolomide or lomustine.

Practical issues surrounding bevacizumab administration

Several practical issues related to treatment administration, combination therapy, response evaluation and disease control need to be considered with the use of bevacizumab for malignant glioma. The recommended dose for malignant gliomas is 10 mg/kg intravenously every 2 weeks as a single agent. Of note, there are not any direct comparison studies of this regimen to other dosing and treatment schedules.

In the treatment of other solid tumor types, bevacizumab is usually combined with a cytotoxic chemotherapeutic agent. As mentioned above, there have not been any prospective randomized studies powered to compare bevacizumab monotherapy versus combination therapy in malignant gliomas (except for the above mentioned BELOB trial). The radiographic response rates and PFS-6 rates are similar when comparing studies of monotherapy with those that utilized combination therapy (predominantly irinotecan). In addition, Phase II studies of irinotecan suggest irinotecan is overwhelmingly ineffective as single agent therapy for recurrent malignant glioma. The identification of a potential combination

partner for bevacizumab remains an area of active research.

Bevacizumab is not contraindicated and dose modifications are not required for patients who are receiving other concomitant medications such as enzyme-inducing antiepileptic drugs or anticoagulation. Therapeutic anticoagulation does minimally increase the risk of systemic or intracranial hemorrhage when combined with bevacizumab from a baseline rate of 1–2% to 6% [16]. Nonetheless, the majority (80%) of intracranial hemorrhage is low grade not requiring medical intervention.

Rare but serious adverse events that require bevacizumab dose delay or discontinuation include grade 2 or greater intracranial hemorrhage, ischemic infarct (brain or cardiac), bowel perforation and wound dehiscence. Temporary suspension of bevacizumab is recommended 4 weeks before surgery and for patients who have evidence of moderate-to-severe proteinuria or severe hypertension that is not controllable with medication.

Bevacizumab may be particularly beneficial in patients with large enhancing tumors with significant peritumoral edema. Neutralization of VEGF results in stabilization of the blood–brain-barrier (BBB) with a resultant decrease in vascular permeability, leading to an improvement in edema reducing the requirement for chronic steroid use. The ability of bevacizumab-based therapy to reduce corticosteroid usage is an important benefit, because chronic corticosteroid use is associated with significant morbidity and side effects including a Cushingoid pattern of weight gain, hyperglycemia, skin fragility, myopathy, lymphopenia and thromboembolism.

Not all malignant glioma patients respond to bevacizumab-based therapy and no biomarkers have currently been identified which enable predictions as to which patient will respond to bevacizumab. A number of studies that assayed for angiogenic factors (serum or urinary VEGF, basic fibroblast growth factor, matrix metalloproteinase, urokinase plasminogen activator or circulating endothelial cells) have as yet to identify a predictive biomarker.

Controversy exists with bevacizumab therapy for malignant gliomas in regard to response assessment, duration and timing of treatment. First, it is unclear if the radiographic response reported with therapy is secondary to a true antitumor effect or merely restoration of the BBB with resulting improvement in contrast

enhancement. This issue is particularly challenging as some patients experience clear progression of nonenhancing tumor making assessment of disease response and progression particularly challenging. The Response Assessment in Neuro-Oncology (RANO) Working Groups was organized to address those issues and have made response assessment recommendations that include the use of T2-weighted MRI imaging to assess for worsening of nonenhancing disease [17]. Fluid Attenuating Inversion Recovery (FLAIR) MRI in conjunction with clinical symptoms appears to be the best indicator of progressive disease and an increase in FLAIR signal often precedes the reemergence of contrast-enhancing tumor [7,18–20].

The outcome of discontinuing therapy in bevacizumab responders has not been described in the literature, but many clinicians fear that abrupt cessation of anti-VEGF therapy would result in rebound edema, clinical deterioration and early tumor progression. Most clinicians continue bevacizumab therapy indefinitely until tumor progression. In preclinical experiments a rebound phenomenon leading to accelerated tumor growth and increased local invasion and distant metastases as well as rapid regrowth of blood vessels occurs when VEGF inhibition is suspended [21]. In a retrospective analysis of five placebo-controlled clinical trials in systemic tumors, cessation of therapy prior to disease progression did not support a decreased time to disease progression, increased mortality or altered disease progression [21]. Similarly, in several retrospective studies of bevacizumab cessation in recurrent glioblastoma after disease progression on bevacizumab, introducing a nonbevacizumab containing regimen did not compromise subsequent time to disease progression [22,23]. Whether continuing bevacizumab after disease progression on bevacizumab is of benefit is still uncertain and may be answered upon completion of the Australian CABARET and Dutch BELOB trials.

When to introduce bevacizumab in the treatment of malignant gliomas remains an area of controversy. There are reports both *in vitro* and in patients that bevacizumab promotes invasion and may result in a gliomatosis-like pattern of recurrence that is poorly responsive to subsequent therapy. The proposed mechanism is that by inhibiting VEGF, bevacizumab induces an

invasive phenotype that co-opts available cerebral vasculature rather than utilizing angiogenesis. Several retrospective clinical studies and the recent AVAglio prospective trial in newly diagnosed glioblastoma suggest; however, diffuse brain invasion is the natural history of glioblastoma when tumor mass effect and edema is not operant. The majority of clinical data suggests a diffuse disease pattern of recurrence is common over time regardless of treatment [18,20,24].

Future treatments

• Isocitrate dehydrogenase mutation

Somatic mutations of the isocitrate dehydrogenase enzymes (IDH1 and IDH2) appear to play a critical role in the pathogenesis of most AO/AOA [25–28]. The IDH enzymes catalyze the conversion of isocitrate to α -ketoglutarate [26]. The enzymes utilize NADP⁺ as a cofactor to generate α -ketoglutarate and NADPH in a reversible reaction. Over 90% of the IDH mutations in gliomas affect IDH1 [28]. The IDH1 mutations target specific arginine residues and are exclusively heterozygous raising the possibility of a novel gain-of-function phenotype whereby the mutant enzymes produce high levels of what is ordinarily a minor metabolic product, R(-)-2-hydroxyglutarate, with relative depletion of α -ketoglutarate and NADPH [25,27–30]. The role of 2-hydroxyglutarate in tumor development is not clear.

Agents that target the IDH mutations are a potential therapeutic option that has yet to be investigated. Studies have demonstrated that the IDH mutation is a positive prognostic factor independent of age, functional status, 1p/19q codeletion and MGMT promoter methylation status [31].

• G-CIMP phenotype

CpG islands are genomic regions that contain a high frequency of CpG (phosphodiester bond between cytosine and guanine) sites. In humans, most promoter genes contain unmethylated CpG islands and methylation of CpG islands results in silencing of gene transcription. Concerted hypermethylation at a large number of loci has been associated with various cancer types, presumably through inactivation of tumor suppressor genes. A distinct subset of gliomas with hypermethylation of CpG islands (CIMP⁺ or G-CIMP) has been identified and found to be associated with improved

outcome [32]. Better prognosis for oligodendroglial tumors with CIMP⁺ phenotype was verified in a study from van den Bent *et al.* [31]. Many genes involved in tumor initiation and or progression become methylated in CIMP⁺ tumors. Reversal of CIMP status through inhibition of DNA methyltransferase with an inhibitor such as decitabine may provide a potential method of treatment of CIMP⁺ gliomas.

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