10 Questions About the Use of Bevacizumab in the Management of Recurrent Malignant Gliomas

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1 What is bevacizumab?
Bevacizumab (Avastin; Genentech, South San Francisco, CA) is a monoclonal antibody that targets the vascular endothelial growth factor (VEGF), a predominant ligand for the VEGF receptors Flt-1 and KDR. The binding of VEGF to its receptors promotes endothelial cell proliferation as well as angiogenesis—a process required for tumor growth beyond 0.125 mm, which involves the formation of new blood vessels from existing vasculature. The rationale for targeting angiogenesis in brain tumors is based on the highly vascularized nature of malignant gliomas and the increased expression of angiogenic mediators, including VEGF, within brain tumors relative to nonmalignant tissue. Several mechanisms of action have been proposed for antiangiogenic therapies, including the inhibition of tumor-associated neoangiogenesis, a direct effect on VEGF-expressing tumor cells, potential injury to glioma stem cells by disruption of the microvascular stem cell niche, and the normalization of the tumor-associated vasculature, which leads to improved drug delivery.

2 What are the indications for the use of bevacizumab that are approved by the US Food and Drug Administration (FDA)?
After demonstrating significant improvements in progression-free survival (PFS) and overall survival (OS), bevacizumab, in combination with intravenous (IV) 5-fluorouracil–based chemotherapy, was initially approved by the FDA in 2004 for the first-line treatment of patients with metastatic colorectal cancer (mCRC). Bevacizumab was subsequently approved in combination with standard chemotherapy for the treatment of advanced non–small-cell lung cancer, metastatic breast cancer, and previously treated mCRC because of its ability to improve PFS and/or OS outcomes in these tumor types. In May 2009, the FDA-granted accelerated approval of bevacizumab as a single agent for the treatment of glioblastoma that has progressed following prior therapy. The accelerated approval was based on an improvement in objective response rate reported in 2 studies—an open-label, multicenter, randomized, noncomparative phase 2 trial, BRAIN, that evaluated bevacizumab with and without irinotecan (Camptosar; Pfizer, New York, NY), a topoisomerase I inhibitor, in 167 patients with glioblastoma at first or second relapse, and the single-arm, single-institution NCI 06-C-0064E trial that evaluated bevacizumab monotherapy in 56 patients with glioblastoma that had progressed following treatment with temozolomide and radiation therapy.

3 How is bevacizumab administered?
Consistent with the half-life of bevacizumab (approximately 20 days), as well as regimens used in other tumor types, most studies in patients with recurrent malignant gliomas have evaluated bevacizumab on a schedule of 10 mg/kg IV every 2 weeks or 15 mg/kg every 3 weeks in combination with irinotecan. Recent studies in the treatment of brain tumors have also evaluated bevacizumab as a single agent administered at 10 mg/kg every 2 weeks. Bevacizumab therapy is continued until disease progression, intolerable toxicity, or patient/physician decision to discontinue treatment. Dose modifications of bevacizumab are not required, even when administered to patients taking enzyme-inducing epileptic drugs.

At first administration, bevacizumab is given by IV infusion over 90 minutes, following the delivery of chemotherapy. In subsequent cycles, infusions can be shortened to 30 to 60 minutes, as tolerated. Bevacizumab is administered without premedication or prechemotherapy hydration.

4 What is the clinical efficacy of bevacizumab in recurrent glioblastoma and anaplastic glioma?
Malignant glioma is associated with a poor prognosis, with almost all cases recurring after initial therapy and with no clearly established standard of care for recurrent disease. Historical phase 2 trials of a variety of chemotherapeutics have reported response rates between 5% and 6% and 6-month PFS (PFS-6) rates between 9% and 28% in patients with previously treated glioblastomas. Patients with recurrent anaplastic gliomas have shown better outcomes in historical trials, with response rates of approximately 35% and PFS-6 rates of between 17% and 47%.

In the largest clinical trial to evaluate bevacizumab in patients with recurrent glioblastomas to date, 38% (31 of 82) of patients treated with bevacizumab and irinotecan responded to therapy, and the PFS-6 rate was 50% (Table 1). In retrospective analyses and additional phase 2 studies, response rates with combination therapy have ranged between 38% and 62%, and PFS-6 rates have ranged between 30% and 46% in patients with recurrent glioblastomas, representing a significant improvement compared with historical outcomes in this patient population. Similar data regarding response and survival are also observed in patients with recurrent glioblastoma treated with single-agent bevacizumab (Table 1). Bevacizumab-containing regimens in patients with recurrent anaplastic gliomas also appear to achieve favorable outcomes relative to those with historical regimens, with response rates ranging between 34% and 68% and PFS-6 rates ranging between 32% and 68% (see Table 1). The clinical benefits demonstrated in these studies, have established the use of bevacizumab-containing regimens as an active treatment option for recurrent malignant gliomas.
TABLE 1. Outcomes With Bevacizumab-Containing Therapy in Recurrent Glioblastoma and Anaplastic Glioma

<table>
<thead>
<tr>
<th>Author</th>
<th>Tumor Type</th>
<th>Regimen</th>
<th>Radiographic Response</th>
<th>Progression-Free Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Key studies in glioblastoma</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Stark-Vance16</td>
<td>Glioblastoma (n = 11), other HGG (n = 10)</td>
<td>BV + irinotecan</td>
<td>5%</td>
<td>42%</td>
</tr>
<tr>
<td>Pope et al17</td>
<td>Glioblastoma (n = 10), AG (n = 4)</td>
<td>BV + irinotecan or etoposide</td>
<td>0%</td>
<td>50%</td>
</tr>
<tr>
<td>Vredenburgh et al18</td>
<td>Glioblastoma (n = 23), AG (n = 9)</td>
<td>BV + irinotecan</td>
<td>3%</td>
<td>59%</td>
</tr>
<tr>
<td>Vredenburgh et al19</td>
<td>Glioblastoma (n = 35)</td>
<td>BV + irinotecan</td>
<td>57%</td>
<td>24%</td>
</tr>
<tr>
<td>Cloughesy et al9</td>
<td>Glioblastoma (n = 167)</td>
<td>BV alone (n = 85); BV + irinotecan</td>
<td>28%; 38%</td>
<td>NA</td>
</tr>
<tr>
<td>Kreisl et al10</td>
<td>Glioblastoma (n = 48)</td>
<td>BV; BV + irinotecan</td>
<td>71% by Levin criteria; 35% by MacDonald criteria</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Key studies in anaplastic glioma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norden et al20</td>
<td>Glioblastoma (n = 33)</td>
<td>BV + CT</td>
<td>34%</td>
<td>59%</td>
</tr>
<tr>
<td>Chamberlain and Johnston23</td>
<td>Glioblastoma (n = 50)</td>
<td>BV</td>
<td>42%</td>
<td>42%</td>
</tr>
<tr>
<td>Desjardins et al22</td>
<td>AG (n = 21)</td>
<td>BV + irinotecan</td>
<td>9%</td>
<td>52%</td>
</tr>
<tr>
<td>Chamberlain and Johnston23</td>
<td>AA (n = 25)</td>
<td>BV</td>
<td>0%</td>
<td>64%</td>
</tr>
<tr>
<td>Chamberlain and Johnston24</td>
<td>AO (n = 22)</td>
<td>BV</td>
<td>0%</td>
<td>68%</td>
</tr>
</tbody>
</table>

**Note:** CR, complete response; PR, partial response; SD, stable disease; Median; 6 mo, 12 mo.

**Abbreviations:** AA, anaplastic astrocytoma; AG, anaplastic glioma; AO, anaplastic oligodendroglioma; BV, bevacizumab; CT, chemotherapy; HGG, high-grade glioma; NA, not available; PR, partial response; SD, stable disease.

5 Which agents should be used with bevacizumab to maximize clinical benefit?

Bevacizumab was first evaluated in combination with irinotecan for the treatment of previously treated malignant gliomas on the basis of its activity with irinotecan-containing regimens in patients with mCRC.16 The encouraging response rate (43%) seen in this initial retrospective study in glioma prompted the use of bevacizumab with irinotecan in later phase 2 studies in patients with malignant gliomas.9,17–19,22 Several small studies have combined bevacizumab with other chemotherapeutic agents, including carboplatin, carmustine, etoposide, and temozolomide,17,20 and a recently published study demonstrated that bevacizumab with hypofractionated stereotactic irradiation is active in patients with recurrent malignant gliomas.26 Although it appears that bevacizumab-based therapy improves response and PFS-6 rates relative to historical outcomes in patients with recurrent glioma,27 the relative contribution of chemotherapeutic agents to the activity of bevacizumab has yet to be determined. In a recent phase 2 study that evaluated the efficacy of single-agent bevacizumab followed by combination therapy with bevacizumab and irinotecan upon tumor progression in recurrent glioblastoma, the authors concluded that it is “unclear whether irinotecan adds significant antiglioma activity to bevacizumab” when considering the results of their study and the results of the randomized, noncomparative phase 2 study evaluating the safety and efficacy of bevacizumab with and without irinotecan.16 The ideal partner for bevacizumab has yet to be defined, in part because of the inherent complexity of cross-trial assessments and the lack of trials directly comparing bevacizumab-containing regimens. This unanswered question highlights the need for prospective, randomized trials to establish the regimen that achieves maximum clinical benefit in patients with recurrent malignant gliomas.

6 Is bevacizumab effective as a monotherapy?

As mentioned previously, several recent studies have evaluated the safety and efficacy of single-agent bevacizumab in recurrent glioblastoma, and data from these studies have supported the accelerated approval by the FDA for single-agent bevacizumab in this setting.1 In the randomized, noncomparative phase 2 BRAIN study,9 bevacizumab monotherapy achieved a response rate of 28% (24 of 85), PFS-6 rate of 43%, and median OS of 9.2 months (Table 1). Responses, based on both World Health Organization radiographic criteria and stable or decreasing corticosteroid use, were seen in...
25.9% (95% confidence intervals, 17.0%–36.1%) of patients. Although the randomized design was not intended to compare outcomes between the treatment arms, the response and PFS-6 rates with single-agent bevacizumab were lower than those observed with bevacizumab plus irinotecan (38% and 50%, respectively, but with overlapping confidence intervals), and the median OS was similar (9.2 vs. 8.7 months) between the treatment arms.

In the single-arm NCI 06-C-0064E study,10 which evaluated the efficacy of single-agent bevacizumab in patients with previously treated glioblastoma, the response rate, PFS-6 rate, and median PFS with single-agent bevacizumab were 35%, 29%, and 16 weeks, respectively (Table 1). When the response assessment criteria in this study were restricted to include both World Health Organization radiographic criteria and stable disease (Table 1), the PFS durations were 28 to 29 weeks (Table 1). Mean corticosteroid dose reductions of 46% (n = 21) were documented in patients undergoing bevacizumab treatment, dehiscence at the site of the craniotomy or at the site of the vascular access device may also occur, and the exact incidence is not known. It is recommended that bevacizumab be discontinued in patients who develop specific severe adverse events (ie, intracranial hemorrhage, bowel perforation, wound dehiscence),33 and temporary suspension of bevacizumab is recommended in patients with severe hypertension that is not controllable with medication.35 Overall, clinical experience suggests that bevacizumab-containing therapy is associated with manageable, class-specific toxicity, and severe bevacizumab-related adverse events are observed in a minority of patients with malignant gliomas.

What is the side effect profile of bevacizumab in patients with malignant gliomas?

Bevacizumab-containing regimens are generally well tolerated in patients with malignant gliomas, with the most common side effects being low-grade bleeding, hypertension, impaired wound healing, and proteinuria1,9,19,18 similar to adverse events seen in other solid cancers treated with bevacizumab. Serious side effects, such as bleeding events, gastrointestinal perforation, reversible posterior leukoencephalopathy syndrome (RPLS), and more severe wound-healing complications, have been reported less frequently. Life-threatening intracranial hemorrhages have occurred in only a small percentage (≤3%) of patients treated with bevacizumab,16–20 and a confounding factor in interpreting these rates is that patients with recurrent glioblastomas are already at a significant risk of thromboembolic events—an epidemiologic analysis reported a 7.5% incidence of thromboembolism in 9489 patients with malignant gliomas.30 Occasional instances of gastrointestinal perforation and RPLS (each <1% incidence) have also been reported with bevacizumab.31,32 Following reoperation for recurrent glioblastoma and subsequent treatment with bevacizumab-containing treatment, dehiscence at the site of the craniotomy or at the site of the vascular access device may also occur, although the exact incidence is not known.

Can bevacizumab treatment alleviate the need for chronic corticosteroid use?

The use of bevacizumab has been shown to reduce both tumor and peritumoral edema in patients with malignant gliomas, thereby reducing the requirement for chronic corticosteroid use. Several studies have reported that corticosteroid reductions were feasible in 33% to 59% of patients with malignant gliomas following bevacizumab treatment,3,10,18,20 and 2 trials have reported average corticosteroid dose reductions of 72% and 59%,10,13,8 respectively. It appears that a considerable proportion of patients undergoing bevacizumab treatment are able to dramatically reduce their corticosteroid doses, and that this effect of bevacizumab can be rapid. In a study of patients with malignant brain tumors, the number of tumor and peritumoral edema events was reduced as early as 18 days after the start of bevacizumab-based therapy.17 The ability of bevacizumab-based therapy to reduce corticosteroid dosage may be an important benefit because chronic corticosteroid use in patients with malignant gliomas is associated with significant morbidity and numerous side effects, including a Cushingoid pattern of weight gain; induction of hyperglycemia, skin fragility, and bleeding; myopathy; lymphenia; infection; and thromboembolism.35–37

What are the appropriate treatment options for disease that progresses on antiangiogenic therapy?

Patients with malignant gliomas who experience tumor progression after antiangiogenic treatment have limited treatment options. In a retrospective analysis of 55 patients with malignant gliomas, those patients with disease that progressed after treatment with a bevacizumab-containing chemotherapeutic regimen responded poorly to a second bevacizumab and chemotherapy combination. In fact, no radiographic responses were observed after the regimen switch, and only 9% of patients (2 of 23) had prolonged PFS.20 In a prospective study of 48 patients with heavily pretreated recurrent glioblastomas treated with bevacizumab monotherapy, 19 patients went on to receive bevacizumab plus irinotecan upon disease progression. None of the 19 patients, however, had radiographic responses to postprogression therapy, and the median PFS was 30 days in this cohort.10 In a retrospective study of 50 patients with recurrent glioblastoma treated with single-agent bevacizumab (the majority at second relapse), response to an alternative cytotoxic therapy in the subset of patients with an initial response to bevacizumab (42%; n = 21) was similarly meager, with a median OS of 2.0 months and a survival range of 1.0 to 5.5 months.21

One explanation for the lack of response after bevacizumab treatment is that antiangiogenic therapy only treats 1 of several tumor compartments—the angiogenic-dependent contrast-enhancing component—and does not target the highly infiltrative angiogenic-independent compartments. Consequently, at the time of tumor progression, the tumor phenotype has been altered and may resemble gliomatosis cerebri. Although it is currently unclear what the appropriate options are for patients with disease that progresses following antiangiogenic treat-
mment, novel therapies that target glioma infiltration, migration, and interaction with the extracellular matrix may provide new strategies for treating the angiogenic-independent compartments and the emerging phenotype seen in patients failing bevacizumab after an initial response.

**Has the optimal role of bevacizumab therapy in the management of patients with brain tumors been defined?**

Although the accumulating evidence suggests that bevacizumab has a safe risk/benefit ratio in patients with recurrent disease, there are still a number of unanswered questions pertaining to the optimal use of bevacizumab in patients with malignant gliomas. First, no direct comparisons regarding the ideal treatment schedule or dosing of bevacizumab have been performed in this patient population. It is not apparent whether bevacizumab should be administered weekly, biweekly, or every 3 weeks, and dose–response studies of bevacizumab have not been conducted in patients with malignant gliomas to date. Second, there are no clear guidelines for evaluating neuroradiographic response or progression, and it is debatable as to what constitutes the best response criteria for bevacizumab-containing regimens for patients with newly diagnosed glioblastomas. A key consideration for the medical oncologist is whether bevacizumab, which is arguably the best salvage treatment for recurrent contrast-enhancing malignant glioma, should be used in the frontline setting or whether it should be reserved for use upon disease progression. These questions will need to be resolved by the results of ongoing and future studies to more clearly define the optimal use of bevacizumab in the management of malignant gliomas.

**REFERENCES**


AUTHOR PLEASE ANSWER ALL QUERIES

AQ1—Please provide pull quote for this manuscript, if necessary.

AQ2—Please note that the reference “Chamberlain and Johnston, In press” cited in Table 1 and in the text, has been listed in the reference list as Ref. 21 and the references have been renumbered accordingly.