Malignant gliomas are the most common and aggressive primary brain tumors in adults. Despite optimal treatment with surgery, radiotherapy, and temozolomide, tumor recurrences are frequent and patients with malignant gliomas continue to have poor prognoses. Malignant gliomas are often highly vascularized, and significant advances have been made in the last few decades in our understanding of the mechanisms of tumor angiogenesis. Recently, bevacizumab, an antibody against vascular endothelial growth factor, has demonstrated significant activity in recurrent glioblastomas, resulting in US Food and Drug Administration approval and raising the prospect for other antiangiogenic drugs now entering clinical trials.


Approximately 14,000 new cases of malignant gliomas are diagnosed each year in the United States; glioblastomas (GBMs) (grade 4 gliomas) account for approximately 70% of such cases, while anaplastic, or grade 3, gliomas represent the other 30% of cases. Although this incidence may seem relatively small compared with other cancers, malignant gliomas are associated with significant morbidity and mortality. Despite standard treatment with maximal safe resection, radiotherapy, and temozolomide chemotherapy, median survival of patients with GBM is less than 15 months. The median survival of patients with grade 3 glioma is only slightly better, ranging from 2 to 5 years.

Tumor growth is highly dependent on the acquisition of a new vascular supply, as demonstrated by studies published by Judah Folkman and colleagues beginning in the 1960s. They showed that a tumor may survive with preexisting blood vessel supply only until it reaches a size of a few millimeters. After that, angiogenesis, ie, growth of new blood vessels, is required for further tumor expansion. Glioma angiogenesis was demonstrated more than 30 years ago by showing that transplantation of human and experimental gliomas in rabbit corneas elicited intense neovascularization and tumor growth, while glioma transplantation into the avascular aqueous humor of the eye was incapable of growing beyond a very small size. Since then, our understanding of the multiple pathways involved in the angiogenesis process has grown significantly. More recently, multiple antiangiogenic drugs have entered clinical trials for malignant gliomas, and bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor (VEGF), received US Food and Drug Administration accelerated approval for recurrent or progressive GBM in May 2009.

VEGF AND GLIOMAS

The VEGF family of growth factors and their respective receptors are the best characterized proangiogenic proteins in human gliomas. Several groups have shown that glioma cells express and secrete VEGF, whose expression correlates with tumor vascularization and aggressiveness. Vascular endothelial growth factor production and secretion by tumor cells is stimulated mainly by hypoxia, and malignant gliomas are rapidly growing and innately
gliomas treated with bevacizumab and irinotecan showed no significant hemorrhage and an astounding radiographic response rate of 66%11 compared with historical rates of 9%.12 This led to more rigorous prospective clinical trials of bevacizumab in recurrent malignant gliomas (Table). The combination of bevacizumab and irinotecan was studied in single-arm phase 2 trials for recurrent anaplastic gliomas (n = 33) and GBM (n = 35), respectively, and showed response rates of 61% and 57% and progression-free survival (PFS) at 6 months of 55% and 46%,13,21 These results compared favorably with historical rates of PFS at 6 months of 9% to 15% for recurrent GBM and 17% to 31% for recurrent anaplastic gliomas.12,20 However, irinotecan had been previously tested as a single agent in phase 2 trials and showed radiographic response rates of only 2.5% to 6% and no improvement in PFS.22,23 These studies raised the question of irinotecan’s contribution to the bevacizumab combination regimen. We therefore conducted a phase 2 trial of single-agent bevacizumab for recurrent GBM. Forty-eight heavily pretreated patients were included and the radiographic response was 35% and the PFS at 6 months was 29%.10 A large phase 2 trial randomized 167 patients with recurrent GBM to either single-agent bevacizumab or bevacizumab with irinotecan. This noncomparative randomized study showed response rates of 28% and 38%, respectively, and a PFS at 6 months of 43% and 50%, respectively.9 In addition to the radiographic responses and prolongation of PFS, patients treated with bevacizumab often had less vasogenic edema and decreased corticosteroid dependence secondary to neutralization of VEGF, a known vascular permeability factor. Our data19 combined with those of the single-agent bevacizumab arm of the randomized phase 2 trial9 supported the accelerated approval of bevacizumab for recurrent or progressive GBM by the Food and Drug Administration.

TABLE 2. Prospective Studies of Bevacizumab for Recurrent Glioblastoma

<table>
<thead>
<tr>
<th>Source</th>
<th>Agent Studied</th>
<th>No. of Patients</th>
<th>Median Age, y</th>
<th>Median KPS Score</th>
<th>Median No. of Prior Recurrences</th>
<th>Radiographic Response Rate, %a</th>
<th>6-Month PFS, %b</th>
<th>Median PFS, mo</th>
<th>Median OS, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kreis et al,10 2009</td>
<td>Bevacizumab, single agent</td>
<td>48</td>
<td>53</td>
<td>90</td>
<td>2</td>
<td>35</td>
<td>29</td>
<td>3.7</td>
<td>7.2</td>
</tr>
<tr>
<td>Friedman et al,9 2009</td>
<td>Bevacizumab, single agent</td>
<td>85</td>
<td>54</td>
<td>80</td>
<td>1</td>
<td>28.2</td>
<td>42.6</td>
<td>4.2</td>
<td>9.2</td>
</tr>
<tr>
<td>Friedman et al,9 2009</td>
<td>Bevacizumab plus irinotecan</td>
<td>82</td>
<td>57</td>
<td>80</td>
<td>1</td>
<td>37.8</td>
<td>50.3</td>
<td>5.6</td>
<td>8.7</td>
</tr>
<tr>
<td>Vredenburgh et al,13 2007</td>
<td>Bevacizumab plus irinotecan</td>
<td>35</td>
<td>48</td>
<td>80</td>
<td>2</td>
<td>57</td>
<td>46</td>
<td>5.6</td>
<td>9.8</td>
</tr>
<tr>
<td>Gilbert et al,14 2009</td>
<td>Bevacizumab plus irinotecan</td>
<td>57</td>
<td>NA</td>
<td>80</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Gutin et al,15 2009</td>
<td>Bevacizumab plus repeated irradiation</td>
<td>20</td>
<td>56</td>
<td>80</td>
<td>1</td>
<td>50</td>
<td>65</td>
<td>7.3</td>
<td>12.5</td>
</tr>
<tr>
<td>Reardon et al,16 2009</td>
<td>Bevacizumab plus etoposide</td>
<td>27</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>4.4</td>
<td>10.7</td>
</tr>
<tr>
<td>Sathornsumetee et al,17 2009</td>
<td>Bevacizumab plus erlotinib</td>
<td>25</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>48</td>
<td>24</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Maron et al,18 2008</td>
<td>Bevacizumab plus temozolomide</td>
<td>32</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>37.5</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Soffietti et al,19 2009</td>
<td>Bevacizumab plus fotemustine</td>
<td>22</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>35</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: KPS, Karnofsky performance scale; NA, not available; OS, overall survival; PFS, progression-free survival.

aHistorical radiographic response rate was 9% in phase 2 trials of drugs considered ineffective.12
bHistorical 6-month PFS has varied from 9% to 15% in phase 2 trials of drugs considered ineffective.12,20
cStudies published only in abstract form.

hypoxic tumors. More specifically, VEGF-A binds to VEGF receptors-2 expressed in blood vessels, which promotes endothelial cell migration and proliferation and consequently new blood vessel formation. In addition, both hypoxia and VEGF recruit bone marrow–derived cells that also contribute to the angiogenesis process.

RATIONALE FOR ANTIANGIOGENIC THERAPIES IN MALIGNANT GLIOMAS

There are multiple reasons for believing that antiangiogenic drugs could play a significant role in the treatment of malignant gliomas. Malignant gliomas are often highly vascularized tumors, and vascular proliferation is one of the pathological hallmarks of GBM. One of the difficulties of developing effective treatments for gliomas has been poor drug penetration through the blood–brain barrier. By targeting the tumor vasculature, it is theoretically possible to bypass this dependence on drugs to cross the blood–brain barrier to reach their target. Finally, there is also both experimental and clinical evidence that antiangiogenic drugs can decrease vasogenic edema and patients’ requirement for corticosteroids, which is a significant cause of morbidity in this population.

BEVACIZUMAB IN MALIGNANT GLIOMAS

Bevacizumab, a humanized monoclonal antibody that targets VEGF, was first approved in combination with chemotherapy for colorectal, lung, and breast cancers. Despite initial reluctance to evaluate bevacizumab in patients with brain tumors owing to concerns of intracranial hemorrhage, a series of 29 patients with recurrent malignant gliomas treated with bevacizumab and irinotecan showed
Bevacizumab is usually well tolerated, with the most common adverse effects being hypertension and minor bleeding, such as epistaxis. Intracranial hemorrhage occurred in less than 4% of patients and was severe in only approximately 1% of patients. Other uncommon but serious adverse events with bevacizumab include wound-healing complications, thromboembolic events, proteinuria, bowel perforation, and posterior reversible encephalopathy syndrome.9

Given that irinotecan does not seem to improve efficacy of single-agent bevacizumab in recurrent malignant gliomas and has significant toxicity effects, such as diarrhea and myelosuppression, other agents and strategies have been tried in conjunction with bevacizumab in this patient population. Phase 2 studies with bevacizumab and daily low-dose temozolomide, oral etoposide, erlotinib, or nitrosourea did not seem to improve outcomes in recurrent GBM when compared with studies with single-agent bevacizumab. A pilot study of bevacizumab with repeated irradiation included 20 patients with recurrent GBM and found a response rate of 50% and a PFS at 6 months of 65%, but selection of patients with smaller tumors make comparisons with other studies difficult.23 Multiple trials combining bevacizumab with either cytotoxic agents or newer targeted drugs are ongoing for recurrent gliomas, and enrollment in these studies should be encouraged. Patients with recurrent malignant GBM who are not candidates for ongoing clinical trials should receive the Food and Drug Administration–approved single-agent bevacizumab regimen if medically appropriate.

Owing to these promising results of bevacizumab as a single agent in recurrent GBM, there is growing interest in evaluating the use of the drug as part of the initial treatment strategy for patients with newly diagnosed GBM. Early results from phase 2 trials showed that incorporation of bevacizumab into the standard upfront treatment for newly diagnosed GBM increased median PFS, but prolongation of overall survival is still unclear. To definitely address this question, 2 large phase 3 trials for newly diagnosed GBM are currently randomizing patients to standard radiotherapy and temozolomide with or without bevacizumab.

**POTENTIAL LIMITATIONS OF ANTIANGIOGENIC THERAPY IN GLIOMA**

Much of what we have learned regarding the biological basis for glioma angiogenesis is based on the standard animal model of human xenografts grown orthotopically in immunodeficient mice. These generally develop as encapsulated balls of tumor that because of their encapsulated nature require de novo vascular supply to grow.24 By contrast, human gliomas grow in situ as highly infiltrative individual tumor cells that may or may not have a central area of tumor bulk with associated vascular proliferation and high angiogenic activity. For many gliomas, particularly anaplastic gliomas, there is often little evidence for vascular proliferation, as the individual infiltrative tumor cells tend to grow along preestablished normal cerebral vasculature, and thus there is no need for tumor-associated angiogenesis. Indeed, there is at least a theoretical concern that inhibiting malignant glioma angiogenesis may prevent the establishment of tumor bulk but has little effect on the infiltrative component of the disease and therefore has little impact on the overall survival of the patient. Early clinical and radiographic observations of patients treated with bevacizumab suggest that this may be the case.25,26 Possibly more concerning is recent laboratory evidence that suggests that inhibition of VEGF may actually increase the invasive nature of tumor cells.27 These data are very disturbing, for it is the infiltrative tumor cells that are most often responsible for clinical relapse and ultimately the death of patients with gliomas. Clinical studies will need to be devised to either corroborate or negate these experimental observations. If true, the use of antiangiogenic agents may have to be restricted to patients with tumors that are clearly highly vascular rather than those that are mostly infiltrative.

**FUTURE DIRECTIONS**

The recent Food and Drug Administration approval of single-agent bevacizumab for recurrent GBM represents a significant therapeutic advance, considering the few therapeutic options available for this aggressive tumor. Two ongoing phase 3 clinical trials will provide essential data on the value of adding bevacizumab to standard treatment for newly diagnosed GBM. Because antiangiogenic agents can rapidly normalize leaky abnormal tumor vessels and decrease enhancement on scans after treatment initiation, additional studies are needed on how to best evaluate radiographic response in patients treated with anti-angiogenic drugs.28 Furthermore, mechanisms of resistance to antiangiogenic therapies should be investigated.25,26 Clinical,20 molecular,12 and/or radiographic markers32 to identify patients more likely to respond to antiangiogenic therapies need to be validated. Finally, because patients with malignant glioma continue to have a poor prognosis despite optimal treatment, enrollment in clinical trials involving rational drug combinations with newer drugs that are directed against validated molecular targets should be encouraged.

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**Author Contributions:** Both authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. **Study concept and design:** Fine. **Acquisition of data:** Iwamoto. **Analysis and interpretation of data:** Iwamoto and Fine. **Drafting of the manuscript:** Iwamoto and Fine. **Critical revision of the manuscript for important intellectual content:** Fine. **Administrative, technical, and material support:** Fine. **Study supervision:** Fine.

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