Abstract: Rapidly dividing glioma cells maintain adequate oxygen and nutrient delivery through co-opting existing host blood vessels or promoting the formation of new vessels, a process called angiogenesis. Vascular endothelial growth factor is a mediator of hypoxia-induced endothelial cell proliferation and migration and is highly expressed in gliomas, where it acts as a potent regulator of angiogenesis. The use of vascular endothelial growth factor receptor antagonists and vascular endothelial growth factor scavenging antibodies has generated excitement in neuro-oncology because of the rapid but reversible decrease in vascular permeability. This decrease in vascular permeability is marked by a decrease in cerebral edema and a decrease in contrast enhancement visualized on magnetic resonance imaging. These effects on the tumor vasculature are mistakenly referred to as tumor responses because the historical method of measuring tumor response and progression was based on tumor size assessed by contrast permeability through a leaky blood brain barrier. Despite the difficulties in accurately measuring the effect of antivascular endothelial growth factor therapy on tumor viability, several studies confirm that the antivascular endothelial growth factor human monoclonal antibody bevacizumab combined with irinotecan can significantly improve 6-month progression free survival of patients with malignant gliomas compared with historical controls. The impact of cytotoxic chemotherapy on the efficacy of bevacizumab and the effect of this therapy on overall survival are important questions that remain to be answered.

Key Words: bevacizumab, irinotecan, glioblastoma, VEGF, anaplastic glioma

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Malignant gliomas are the most common type of primary brain tumor in adults. It is estimated that over 12,000 new cases of glioblastoma and over 3000 new cases of anaplastic glioma are diagnosed in the United States every year.1 Despite advances in surgery, radiation therapy, and chemotherapy, the prognosis of patients with malignant gliomas remains poor, with a median survival of approximately 12 to 14 months for patients with glioblastoma2 and 2 to 3 years for patients with anaplastic glioma.3 Patients with recurrent malignant gliomas respond to therapy less than 15% of the time and have median progression-free survival (PFS) times of 9 and 13 weeks for glioblastoma and anaplastic astrocytoma, respectively.4

Angiogenesis, the process of new blood vessel formation, is a pathologic hallmark of glioblastoma and is critical for tumor development and maintenance. The initiation of tumor angiogenesis is a complex process whereby multiple molecules in normal and tumor tissues activate a series of signaling events leading to new vessel formation.5,6 Rapidly dividing glioma cells require nutrient and oxygen delivery, which can be maintained by means of co-opting existing host vessels or promoting the formation of new vessels. Glioblastomas display microvascular proliferation and a poorly organized vascular bed that leads to regions of inadequate blood flow and hypoxia.7 Vascular endothelial growth factor (VEGF) is a mediator of hypoxia-induced endothelial cell proliferation and migration and is highly expressed in gliomas, where it acts as a potent regulator of angiogenesis. Recruitment of tumor vessels from the surrounding tissues requires angiogenic growth factors, including VEGF, the related placental growth factor, and others. VEGF is secreted by tumor cells and acts in a paracrine manner on the VEGF receptors (VEGFRs) on endothelial cells to stimulate endothelial cell proliferation, migration, and survival.8 The importance of VEGF is highlighted by the fact that the degree of vascularization has been linked to prognosis in gliomas and other solid tumors, and VEGF levels in glioblastomas have been correlated with tumor blood vessel density, invasiveness, and patient prognosis.9

However, the importance of VEGF in anaplastic glioma biology is less well established. Anaplastic astrocytomas, by definition, do not have histologic evidence of vascular proliferation and thus do not show marked contrast enhancement on magnetic resonance imaging (MRI). In addition, anaplastic astrocytomas do not have areas of necrosis and thus would not be expected to have notable hypoxia-mediated VEGF expression. Ultimately, anaplastic astrocytomas undergo malignant transformation to higher-grade glioblastomas, with evidence of abundant angiogenesis and necrosis. A therapeutically attractive approach may be to use anti-VEGF therapy to retard or delay the “angiogenic switch,”10 that is, to delay the time at which the tumor begins to secrete VEGF or at which microenvironmental changes (ie, in the tissue stroma or infiltrated immune cells) occur that lead to higher VEGF levels; such an approach may be expected to delay or inter-
rupt the process of angiogenesis and higher grade tumor transformation. However, whether antiangiogenic therapy can affect this process in recurrent anaplastic astrocytomas is currently unknown, and several clinical trials are evaluating the effectiveness of anti-VEGF therapy in this patient population.

Antiangiogenic therapy in gliomas is attractive for multiple reasons, including the prominent role of angiogenesis in glioblastoma growth and proliferation and the lack of VEGF-mediated processes in adult human tissues. The accessibility of intravascular VEGFR localized to endothelial cells circumvents the challenge of delivering the drug to the tumor beyond the impermeable blood–brain barrier. In addition to the potential for direct anti-tumor effects, antiangiogenic therapy has been shown to prune abnormal vessels and “normalize” existing vasculature, which may paradoxically improve drug and oxygen delivery to the tumor for a period of time following drug administration. Interestingly, this window of normalization can lead to a temporary improvement in tumor oxygenation and blood flow, which may enhance the effectiveness of radiation therapy and chemotherapy. In addition, anti-VEGF therapy has been shown to reduce cerebral edema through elimination of VEGF, previously known as the vascular permeability factor, which may reduce the need for steroid use and have a beneficial impact on neurological function. This steroid-sparing effect could lead to a notable improvement in patients’ quality of life.

The most compelling rationale for using antiangiogenic therapy for patients with glioblastomas comes from clinical experience with bevacizumab (Avastin; Genentech, San Francisco, CA). Bevacizumab is a humanized monoclonal antibody that binds to circulating VEGF-A (the most common isoform of VEGF in gliomas) and possesses high antiangiogenic and anti-tumor activity. Bevacizumab was the first U.S. Federal Drug Administration–approved antiangiogenic therapy for solid tumors when it was shown that bevacizumab combined with irinotecan (CPT-11) improved response rates and overall survival (OS) for patients with metastatic colorectal cancer. Subsequently, bevacizumab has received approval for the treatment of several other solid tumor types, including localized colorectal, lung, and breast cancers. Although bevacizumab seems to have some activity as a single agent, no studies have shown that bevacizumab confers a survival advantage when used without cytotoxic chemotherapy, suggesting that sequestration of circulating VEGF is not sufficient to produce anti-tumor activity and that bevacizumab may be able to potentiate the effects of cytotoxic chemotherapy. The exact mechanism by which this may occur is still unknown, but it could be due to improved chemotherapy delivery. Bevacizumab’s dose-limiting toxicities are predominantly “on-target” side effects related to VEGF signaling blockade and include hypertension, arterial and venous thrombosis, proteinuria, hemorrhage, and fatigue.

Irinotecan is a topoisomerase I inhibitor that inhibits DNA synthesis by binding to the topoisomerase DNA complex and preventing reformation of single-strand DNA breaks. When used as a single agent for patients with recurrent malignant glioma, irinotecan has minimal activity, with a response rate of only 5.8% and a 6-month PFS rate of 15.7%. Given the modest activity of this agent in patients with recurrent glioblastoma, there is some debate about irinotecan’s contribution to the efficacy of a combination regimen with bevacizumab. However, recent data showed that the addition of chemotherapy to anti-VEGF therapy improved the therapeutic efficacy of this regimen in animal models not because of improved chemotherapy delivery but because of an enhanced antiendothelial effect, as suggested by the endothelial cell fibrosis observed in tumors receiving bevacizumab combined with cytotoxic chemotherapy. Certainly this regimen is convenient for patients who can receive sequential dosing of bevacizumab and irinotecan on the same day. Although there are limited overlapping toxicities between the 2 agents, irinotecan is associated with dose-limiting neutropenia and diarrhea, and bevacizumab combined with irinotecan seems to be more toxic than either agent alone. It is possible that other cytotoxic agents are as equally effective as irinotecan, and several ongoing studies are evaluating the effect of bevacizumab combined with temozolomide, carboplatin, topotecan, and etoposide in patients with recurrent malignant glioma.

CLINICAL STUDIES OF BEVACIZUMAB IN PATIENTS WITH MALIGNANT GLIOMAS

The first clinical studies using bevacizumab and irinotecan for patients with malignant gliomas were conducted by Dr. Stark-Vance and were based on the successful treatment of colorectal cancer with this regimen. Stark-Vance treated 21 patients with recurrent glioblastoma with bevacizumab plus irinotecan and observed an overall response rate of 43%, which included 1 patient who achieved a complete response, 8 who achieved a partial response, and 11 who had stable disease using MacDonald response criteria based on a decrease in tumor enhancement on T1-weighted postgadolinium contrast scans. There were 2 treatment-related deaths as a result of intracranial hemorrhage and intestinal perforation.

These exciting results led to the initiation of prospective clinical studies to test this combination in patients with recurrent malignant gliomas. Vredenburgh et al treated 32 patients with bevacizumab (10 mg/kg every 2 weeks) and 1 of 2 doses of irinotecan (125 mg/m² every 2 weeks for patients who did not receive enzyme-inducing antiepileptic drugs [EIAEDs] and 340 mg/m² every 2 weeks for those who did receive EIAEDs). They observed an overall response rate of 63%; the response rate was 61% for patients with glioblastoma and 67% for patients with anaplastic glioma based on the MacDonald criteria. Including patients who had completed radiation therapy within 4 weeks of the study’s initiation may have artificially elevated the radiographic response rate and 6-month PFS data. The 6-month PFS rate was 30% for patients with glioblastoma and 56% for patients with anaplastic glioma. These results compare favorably with data from The University of Texas M. D. Anderson Cancer Center database that included 8 negative trials, with 6-month PFS rates of 15% for patients with glioblastoma and 31% for patients with anaplastic glioma. These promising data demonstrated a significant improvement in PFS rates, far surpassing...
ing those of any other therapy recently reported in the literature. However, bevacizumab plus irinotecan was associated with a modest amount of toxicity, and 28% of the patients had to be removed from the Vredenburgh et al23 trial because of potential drug-related adverse events. That trial also had 2 treatment-related deaths, and 4 patients experienced thrombotic events, including 2 patients with pulmonary embolism, 1 with a deep venous thrombosis and 1 with an arterial ischemic event.

Expanding on their initial study, Vredenburgh et al24 treated an additional 12 patients with an alternate bevacizumab schedule of 15 mg/kg every 3 weeks combined with irinotecan and reported these findings with their earlier results. Although the small size of the second cohort precluded definitive analysis, it seems that the higher bevacizumab dose did not improve the rate of PFS. In addition, although this dosing schedule seemed to be safe, there was additional toxicity. Overall, 31% of the patients had to be removed from the study because of treatment-related toxicities, including thromboembolic events, proteinuria, and gastrointestinal toxicities. In addition, 4 patients (3 in the higher dose cohort) elected to stop treatment as a result of excessive fatigue, and 1 patient experienced a central nervous system (CNS) hemorrhage. Wagner et al25 presented an update on the long-term outcome of the patients on the Vredenburgh trials at the 2008 Annual Meeting of the American Society of Clinical Oncology. The 6-month PFS rate was 59% for patients with anaplastic glioma and 43% for patients with glioblastoma. The 2-year OS rate was 15% for patients with glioblastoma and 33% for patients with anaplastic glioma. Although long-term responses have been observed with bevacizumab plus irinotecan, the dramatic radiographic response rate and improvement in 6-month PFS rates have not translated into a notable increase in OS when compared with historical controls. This observation is troubling and raises questions about this regimen’s degree of anti-tumor activity in patients with recurrent malignant gliomas.

Further substantiating the potential effectiveness of bevacizumab plus irinotecan in patients with recurrent malignant gliomas, Norden et al26 recently published their sin-recurrent malignant gliomas. Several key issues were high-

sion. Second, the authors demonstrated that patients who required anticoagulation for venous thrombotic events were safely anticoagulated without an elevated risk of hemorrhage. In this series, 11 patients were treated with low-molecular-weight heparin, and there were no bleeding events, except epistaxis in 1 patient. The safety of anticoagulation in patients with gliomas treated with bevacizumab was recently confirmed.27 Although previous clinical trials have required the removal of patients receiving anticoagulants, future studies will most likely not make this exclusion.

The low response rates with irinotecan monotherapy and the suggestion that irinotecan increases toxicity have led to several studies designed to determine irinotecan’s relative contribution to the effectiveness of combination therapy with bevacizumab. Fine28 recently completed a phase II study at the National Institutes of Health in which patients were treated with bevacizumab alone. A preliminary analysis showed that patients with glioblastoma had a response rate of 60% and a 6-month PFS rate of 30%. On this regimen, only 4 of 79 patients (5%) had thrombotic events. These response and PFS rates are similar to the published data on bevacizumab plus irinotecan, but toxicity was markedly lower in the study by Fine,28 suggesting that most of the radiographic response and clinical benefit may be attributable to bevacizumab and that eliminating irinotecan may improve the therapy’s tolerability.

A Genentech-sponsored study further evaluated the use of bevacizumab alone for recurrent disease, for which only preliminary results are available.29 This was a randomized, open-label noncomparative study of bevacizumab alone (10 mg/kg every 2 weeks) versus bevacizumab combined with irinotecan (340 mg/m² if patients were receiving EIAEDs and 125 mg/m² if patients were not receiving EIAEDs) in patients with recurrent glioblastoma. Patients with a first or second recurrence were randomized to 1 of the 2 arms, but the design allowed patients who did not achieve a response with bevacizumab alone to cross over to the bevacizumab plus irinotecan arm. Over 80 patients were recruited to each arm, although the study was not adequately powered to detect statistical differences between the 2 groups. The primary objective was to determine the efficacy of each regimen in improving 6-month PFS rates compared with historical controls. Radiographic response data were assessed using MacDonald criteria. An update of the central review of the radiographic response data and 6-month PFS rates was presented at the 2008 American Society of Clinical Oncology meeting.29 Results showed response rates of 28.0% for patients receiving bevacizumab alone versus 37.8% for patients receiving bevacizumab plus irinotecan. The 6-month PFS rate was 42.6% for patients receiving bevacizumab alone and 50.3% for patients receiving bevacizumab plus irinotecan. Although there is a suggestion that the addition of irinotecan to bevacizumab increased the percentage of patients who were alive and progression free at 6 months, the study was not designed to statistically evaluate this difference. Data are not currently available for the patients who crossed over to the bevacizumab plus irinotecan arm after their tumors proved to be unresponsive to bevacizumab alone. The median
OS times were 9.2 months for the bevacizumab-alone arm and 8.7 months for the combination arm. Neither of these median OS times seem to be significantly different than the published median OS time for patients receiving temozolomide for recurrent glioblastoma.30 With this regimen, a short-term gain in PFS may not translate into a survival improvement, although larger studies are needed to confirm these observations.

As predicted from the studies described above, the toxicity associated with the combination arm was higher than that associated with the bevacizumab-alone arm.32 A total of 66.0% of the patients in the combination arm had grade 3 or higher toxicities, compared with 46.0% of the patients in the bevacizumab-alone arm. Additionally, 26.2% of the patients in the bevacizumab-alone arm had serious adverse events, compared with 43.0% in the combination arm. The grade 3 or higher toxicities were mostly arterial and venous thrombotic events and infection, although 2 CNS hemorrhages and 1 gastrointestinal perforation were observed in the combination arm. Therapy was discontinued in 4.8% of the patients in the bevacizumab-alone arm, compared with 17.7% in the combination arm, as a result of toxicities. Clearly, the addition of irinotecan led to more toxicity. Lowering the dose of bevacizumab may be another viable method for limiting patient toxicity. Bokstein et al31 treated 20 patients with recurrent glioblastoma who were not receiving EIAEDs with a lower dose of bevacizumab (5 mg/kg) combined with irinotecan (125 mg/kg) every 2 weeks. This regimen had radiographic response rates of 47% and a slightly lower 6-month PFS rate (25%) but dramatically lower toxicity, with only 10% of the patients having a greater than grade 2 toxicity and none having hemorrhage. Thus, some of the toxicities associated with the combination regimen can be reduced with lower doses of bevacizumab.

BIOMARKERS OF RESPONSE TO BEVACIZUMAB AND IRINOTECAN

Despite these encouraging results, only a subset of patients experience a radiographic response and an even smaller group has prolonged disease-free survival. Several groups are actively studying potential imaging and tissue biomarkers that might predict response and OS and thus be used to select those patients who would be most likely to benefit from the combination therapy. Noninvasive imaging techniques are being used to determine whether changes in vascular permeability are predictive of long-term response. Dramatic decreases in vascular permeability, as measured by dynamic contrast-enhanced-MRI, have been detected as early as 24 hours after treatment with bevacizumab plus irinotecan. In a recent study by Desjardins et al,32 changes in the permeability constant ($K_{trans}$) value were highly correlated with the percentage of decline in tumor volume from baseline to the end of the first cycle of bevacizumab and irinotecan treatment. However, no dynamic contrast-enhanced-MRI measures at either 24 hours or 6 weeks from the start of treatment were predictive of PFS or OS. Other MRI techniques, including MR perfusion, diffusion-weighted imaging, and MR spectroscopy, are being evaluated as potential biomarkers of long-term response.

More encouraging results were recently obtained using positron emission tomography (PET). The thymidine analog 3′-deoxy-3′,18F-fluorothymidine ($^{18}$F-FLT) has been developed as a PET tracer to image cellular proliferation in vivo which is retained in proliferating cells through the activity of thymidine kinase. In a small cohort of 20 patients, Chen et al33 showed that response demonstrated by FLT-PET at 6 weeks after the start of treatment was more predictive of OS than response determined by conventional MRI. These results are encouraging, but several questions remain. For example, the permeability of FLT is limited to a similar extent as that of gadolinium contrast agents. Bevacizumab induces a dramatic decrease in vascular permeability, which also limits FLT entry beyond the blood–brain barrier and thus would limit FLT’s utility for measuring proliferation within the tumor. Because both contrast agents and FLT are permeability limited, why FLT would be a more sensitive predictor of long-term survival than contrast agents is unknown. These provocative results need to be confirmed in a large multicenter trial, although the general applicability of this expensive and resource-intensive technique remains an important concern for smaller community hospitals.

Although few tissue biomarkers predict response or OS in patients with other solid tumors who are treated with bevacizumab, there is great interest in determining predictors of response to treatment. Given the prominent role that hypoxia plays in driving angiogenesis, invasion, and secretion of VEGF, Sathornsumetee et al34 evaluated the tissue levels of VEGF and immunohistochemical markers of hypoxia in patients with glioblastoma who were treated with bevacizumab. They showed that high tissue VEGF levels were correlated with radiographic response but not OS. They also showed that tissue expression of the hypoxia marker carbonic anhydrase IX (CA9) was associated with poor outcome. Hypoxia-inducible factor 2α ($\alpha$) expression was not independently associated with poor outcome, but patients with combined CA9 and hypoxia-inducible factor 2α tissue expression had the worst OS. These data may be useful in stratifying patients in future clinical trials, but more work needs to be done to validate these biomarkers to identify those patients most likely to benefit from anti-VEGF therapy.

UNANSWERED QUESTIONS AND CURRENT CHALLENGES

Clearly, bevacizumab plus irinotecan shows promising efficacy, with 6-month PFS results far exceeding those in any recent trial of other drug combinations in patients with recurrent glioblastoma. Before accepting this regimen as the new standard, however, multiple questions remain to be answered. First, the optimal dose and frequency of bevacizumab administration should continue to be explored. Although usually given every 2 weeks, alternative dosing schedules of bevacizumab are scientifically intriguing and have important implications for patient care. For example, the optimal dose of bevacizumab required to adequately sequester proangiogenic VEGF in patients with recurrent glioblas-
toma is currently unknown. Given the importance of VEGF in glioma biology, removal of circulating VEGF is of critical importance. However, higher doses of bevacizumab are unlikely to provide added benefit, because VEGF bound to bevacizumab is biologically inactive and excess bevacizumab will likely only increase toxicity. Measuring free VEGF levels in patients treated with different doses of bevacizumab will help identify the lowest biologically effective dose. As in other solid tumors, “tumor escape” from anti-VEGF therapy may involve other growth factors important for angiogenesis, including VEGF-C, VEGF-D, placental growth factor, platelet-derived growth factor, and basic fibroblast growth factor. New agents targeting these other factors are being developed, and determining the optimal biologic dose and dosing schedule of bevacizumab will be important for upcoming studies using combination therapy to target VEGF and escape pathways. Furthermore, bevacizumab’s biologic half-life of 3 weeks should theoretically allow for less frequent dosing without a decrease in therapeutic efficacy. Finally, because bevacizumab is administered intravenously, fewer trips to clinical infusion centers may also improve patients’ quality of life. Optimizing the dose and dosing schedule should be an important goal of future studies.

A second and critically important issue is to determine the mechanism by which anti-VEGF therapy, such as bevacizumab, has a clinical impact on malignant gliomas. Part of the difficulty in describing the effect of anti-VEGF therapy is that the brain tumor community’s definition of response is dependent on vascular permeability. We continue to use MacDonald response criteria, which use standard MRI to measure changes in tumor size based on T1-weighted postgadolinium images. Because anti-VEGF therapy reduces vascular permeability, it also decreases gadolinium enhancement, which is consistent with the previous standard definition of response. We and others have observed dramatic decreases in contrast enhancement as early as 24 hours following a single dose of anti-VEGF therapy. This would classify as a response, but it is unlikely that there has been a significant, if any, anti-tumor effect. These changes are best reclassified as a decrease in vascular permeability or vascular response rather than a true tumor “response.” New response criteria are currently being formulated to better define the effect of these treatments on MRI scans and to assist with endpoint definition for clinical trials that evaluate the efficacy of these agents.

One important question that has been raised is whether anti-VEGF agents are acting as supersteroids, because the clinical impact of these agents is through reduction of vasogenic edema and subsequent long-term control of tumor vascular permeability. Although this may be one beneficial impact of anti-VEGF treatment, this seems unlikely to be the only mechanism. Many patients have prolonged disease-free survival while receiving bevacizumab alone or in combination with irinotecan, suggesting that in selected patients, anti-VEGF therapy has a true anti-tumor effect. However, the potential steroid-sparing effect should not be disregarded. Long-term corticosteroid use has many side effects and is associated with significant patient morbidity. Current and future studies should include quality-of-life measures to determine whether there is an improvement in quality of life and whether the long-term side effects of these expensive agents, such as hypertension, thrombosis, and proteinuria, justify their long-term use.

There are several unanticipated consequences of prolonged antiangiogenic therapy that may negatively impact the long-term outcomes of patients with malignant glioma. Although initial improvements in tumor blood flow and oxygenation after antiangiogenic therapy have been eloquently described, the long-term impact of continuous antiangiogenic therapy may have an opposite effect. VEGFR inhibition has been shown to increase tumor hypoxia and, after prolonged inhibition, can lead to the release of other proangiogenic factors, such as fibroblast growth factor, and the re-establishment of a dense, abnormal vasculature. This abnormal vasculature may then restrict drug delivery. Several reports have shown conflicting results when evaluating the effect of antiangiogenic therapies on temozolomide delivery to glioma xenografts in vivo, with some experiments showing a decrease and others showing an increase in drug exposure. These differences may be related to the relative timing of administration of each drug and the dose of the antiangiogenic agent being used. In some cases, a lower dose of the antiangiogenic drug was more effective in increasing drug delivery. Without a better understanding of how to optimize the anti-tumor efficacy of any regimen, these preclinical studies should urge caution in the use of empirical combination therapies with antiangiogenic agents.

Another unanticipated effect is that the use of antiangiogenic therapy may enhance the infiltrative glioblastoma phenotype. Clinical experience and a recent report suggest that a subset of patients treated with bevacizumab and irinotecan may develop nonenhancing tumor progression without evidence of an increase in tumor vascularity. In 2000, Rubenstein et al described the unanticipated effect of antiangiogenic therapy on tumor invasion. Using an anti-VEGF antibody, they were able to slow bulk tumor growth; however, as a consequence, there was increased tumor infiltration and co-option of the host vasculature. Similarly, Kunkel et al demonstrated that intracranial glioma tumors treated with the anti-VEGFR-2 antibody DC-101 showed an increase in the number and total area of small satellite tumors. Tumor cells were found to have migrated along blood vessels over long distances to eventually reach the pial surface and spread in the subarachnoid space. In these orthotopic models, systemic antiangiogenic therapy prolonged animal survival but ultimately led to enhanced glioma invasiveness. We and others have observed an infiltrative, nonenhancing pattern of tumor progression in patients treated with bevacizumab who initially responded to therapy. This infiltrative pattern can spread throughout the brain, reaching a state similar to gliomatosis cerebri. Although there is no standard method to quantitate this pattern of progression radiographically, evidence of tumor infiltration on MRI frequently coincides with clinical evidence of progression. Although this may be limited to a subset of patients, a better understanding of the physical and molecular mechanisms responsible for this in-
vasive phenotype is needed to prolong the survival of patients with malignant gliomas who are treated with antiangiogenic therapy.

CONCLUSIONS AND FUTURE DIRECTIONS

Antiangiogenic therapy offers unparalleled opportunities for treating malignant gliomas. Bevacizumab combined with irinotecan is one of the most promising regimens to be introduced for the treatment of recurrent malignant gliomas. High radiographic response rates indicate the impact of this regimen on vascular permeability, which can occur rapidly on sequestration of free VEGF. Early clinical trials demonstrated a significant improvement in 6-month PFS rates compared with historical control data. Furthermore, bevacizumab plus irinotecan is well tolerated, with on-target side effects of hypertension, proteinuria, fatigue, and thrombosis and a low rate of CNS hemorrhage noted in multiple studies. Despite the dramatic decrease in vascular permeability and improvements in PFS, there may not be a significant improvement in OS, and multiple questions remain regarding the best way to use bevacizumab and other anti-VEGF agents for recurrent glioblastoma. Upcoming studies will evaluate the efficacy of bevacizumab in combination with radiation and temozolomide for newly diagnosed patients. One such study, the Radiation Therapy Oncology Group 0825 trial, is a randomized, placebo-controlled study that will allow patients to receive bevacizumab and irinotecan at the time of tumor progression. The findings from this study are expected to help us better understand the potential anti-tumor effects of combining anti-VEGF therapy with radiation and chemotherapy because one of the primary objectives of the study will be OS, which is less subject to bias than PFS based on imaging. Using bevacizumab upfront presents a challenge to the field of neuro-oncology to develop novel approaches to overcome resistance to anti-VEGF therapies and salvage patients in whom bevacizumab fails.

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