Bevacizumab: A Controversial Agent Against High-Grade Gliomas

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Introduction
Glioblastoma multiforme (GBM) is the most common primary malignant brain tumor in adults. Despite the current regimen of surgical resection with subsequent external beam radiotherapy and temozolomide, mean survival is 14.6 months and 2-year survival is 26%.1 GBM is a highly vascular tumor, a result of its increased expression of vascular endothelial growth factor (VEGF) compared to other brain tumors. VEGF promotes endothelial cell proliferation, and is thought to have a pivotal role during tumor progression. Multiple treatment modalities have targeted VEGF and VEGF receptors (VEGFRs) due to their essential roles in the regulation of angiogenic processes.2 Bevacizumab is a recombinant humanized monoclonal antibody that inhibits VEGF. Positive results from Phase II clinical trials with bevacizumab for recurrent GBM led to its U.S. Food and Drug Administration approval.3,4

Bevacizumab can produce significant decrease in contrast enhancement as early as 1 to 2 days after the beginning of treatment, and often results in radiologic response rates of 25% to 60%.5,6 However, it has been noted that rapid improvement in radiographic response is not directly correlated to decreased tumor burden or improved survival. Furthermore, there are significant adverse effects associated with this agent that must be considered when tailoring therapy. These topics and current studies evaluating the use of bevacizumab for high-grade gliomas are discussed.

Criteria for Radiographic Response
Macdonald, et al. published criteria in 1990 for assessment of response of high-grade gliomas to treatment. These criteria were developed in an effort to adopt more uniform and rigorous norms of treatment, and have become the standard for assessing response to therapy in high-grade gliomas. They are based on two-dimensional tumor measurements on contrast-enhanced computed tomographic (CT) or magnetic resonance imaging (MRI) scans, in conjunction with corticosteroid use and clinical assessment. Tumor size is measured as the largest cross-sectional area (largest cross-sectional diameter x largest diameter perpendicular to it). The Macdonald criteria define progression of disease as either a 25% or more increase in size of the contrast enhancing lesion on sequential MRI scans, or clinical deterioration that is unexplained (Table 1).6

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<th>Table 1. Macdonald Criteria: Current response criteria for malignant gliomas</th>
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<td><strong>Response</strong></td>
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<td>Complete response</td>
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The Macdonald criteria have a number of important limitations. Contrast enhancement is nonspecific and can represent treatment-related inflammation, seizure activity, postsurgical changes, ischemia, and radiation necrosis, among others. Multiple factors can influence enhancement such as steroid doses, changes in radiologic techniques, and anti-angiogenic agents such as bevacizumab. By normalizing the abnormally permeable tumor vessels, anti-VEGF therapy produces a rapid decrease in enhancement that does not correlate with a decrease in tumor size. Furthermore, a significant number of patients treated with bevacizumab who initially experience a decrease in tumor contrast enhancement subsequently develop progressive increase in non-enhancing T2 or FLAIR signals suggestive of infiltrative tumor (Figure 1).7

It has been shown that a non-enhancing tumor pattern of progression after treatment with bevacizumab is correlated with worse survival.8 These findings have triggered multiple studies examining the effect of bevacizumab on tumor cells and employing different imaging modalities to accurately assess tumor response.

Physiologic effect of bevacizumab and resulting imaging characteristics
There is a significant disparity between the unparalleled imaging response rates that bevacizumab produces in recurrent malignant gliomas and the modest survival benefits, if any, that have been reported.9 These apparent responses to anti-angiogenic therapy may be partly a result of normalization of abnormally permeable tumor vessels and have been demonstrated not to be representative of an anti-glioma effect. By decreasing contrast leakage, anti-VEGF therapy produces a rapid decrease in enhancement that does not always correlate with a decrease in tumor size. Therefore, caution needs to be exercised when evaluating imaging studies for response to anti-angiogenic agents.10

Iwamoto, et al. studied the effect of bevacizumab therapy on GBM growth by analyzing the imaging and histological characteristics of patients who discontinued bevacizumab therapy because of tumor progression. At the time bevacizumab was discontinued, the pattern
of progression was predominantly non-enhancing tumors in 13 of 37 patients (35%). These results differ greatly from the typically observed pattern of increased enhancement at the site of recurrent disease that occurs in 90-95% of patients who do not receive bevacizumab. Lower Karnofsky performance status (KPS) and a non-enhancing pattern of recurrence were associated with shorter overall survival after discontinuing bevacizumab (p values 0.001 and 0.05, respectively). Iwamoto, et al. stipulated that the apparent relationship between a non-enhancing pattern and shorter survival may reflect a change in tumor biology, particularly because non-enhancing tumor progression was a negative prognostic factor independent of performance status. Histological analysis before and after treatment demonstrated a significant increase of hypoxia markers after bevacizumab failure. It has been well established in the literature that hypoxia is a promoter of angiogenesis, tumor invasion, and resistance to therapy. These findings strongly suggest that the anti-angiogenic effect of bevacizumab resulted in an increase in tumor hypoxia, leading to more invasive tumor behavior.

Other studies contend that bevacizumab and other anti-VEGF therapies mediate temporary control of tumor growth but do not achieve a change in overall survival. Norden, et al. reported their analysis of 34 patients with recurrent malignant glioma that underwent treatment with either bevacizumab or cediranib (AZD2171, a pan-VEGF receptor inhibitor) and compared them to 18 patients that underwent cytotoxic chemotherapy (with either edotecarin or gimatecan). Median progression-free survival was 8 weeks in patients treated with cytotoxic therapy, compared to 22 weeks in patients treated with anti-angiogenic therapy (P=0.01). However, median overall survival was nearly identical in the two groups, with 39 weeks in the cytotoxic therapy group and 37 weeks in the anti-angiogenic therapy group. These results suggest that anti-angiogenic therapy does not prolong overall survival in patients with recurrent malignant glioma. The increased progression-free survival observed could reflect the initial impairment of tumor growth that is short-lived (and may be seen in the rapid decrease in enhancement that is observed after the beginning of treatment), with eventual onset of different forms of resistance that inevitably result in progressive disease.

An increasing number of studies investigating the mechanisms of tumor resistance to anti-angiogenic agents suggest that anti-VEGF therapy may result in the co-option of normal vasculature, producing an invasive non-enhancing phenotype. Rubenstein, et al. analyzed the histologic pattern of growth of human glioblastoma cells that were stereotactically implanted in the striatum of adult athymic rats that were then treated with systemic anti-VEGF antibody. Although anti-VEGF treatment resulted in prolongation of survival (median survival of control vs. treated animals was 18.5 vs. 34.5 days, respectively, P<0.0001), tumors adopted a more infiltrative and invasive pattern on histological evaluation (Figure 2). Comparison of sections of control and anti-VEGF treated tumors revealed that, instead of growing as a single confluent mass with a distinct border, anti-VEGF treated tumors were surrounded by multiple satellite tumors that appeared to extend from the margin of the original tumor. Immunohistochemistry analysis demonstrated that greater than 90% of the satellite tumors were associated with at least one blood vessel, suggesting
that these tumors infiltrated the brain to adopt or “co-opt” existing vessels in response to anti-angiogenic treatment (Figure 3). Paez-Ribes, et al. noted a similar pattern when analyzing the effects of anti-VEGF treatment on an orthotopic mouse model of glioblastoma. A highly invasive and qualitatively distinct tumor pattern was observed, with tumor cells found in close proximity to resident normal blood vessels. Further preclinical studies are necessary to elucidate the apparent ability of malignant gliomas to adapt to inhibition of angiogenesis by increased infiltration and cooption of host vessels.

**Diffusion weighted imaging as biomarker for bevacizumab treatment response**

Imaging criteria that include non-enhancing components of tumors are necessary to assess the response to bevacizumab treatment. However, evaluating FLAIR or T2 signal abnormality can lead to an inaccurate analysis of response to treatment, since infiltrating tumor is difficult to differentiate from edema, gliosis, or treatment related leukoencephalopathy (Figure 4). Jain, et al. addressed this issue by obtaining volumetric measurements of contrast enhancing lesions and non-enhancing lesions of patients treated with bevacizumab alone or concurrent chemotherapy for a follow-up period of 1 year. These regions of interest were co-registered with corresponding diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC) maps (lower ADC values are suggestive of high cellularity and higher grade of the tumor, whereas the opposite is true for higher ADC values). Imaging analysis demonstrated a progressive decrease in ADC values especially early on (6 weeks and 3 months after treatment) in non-enhancing lesions in patients that had progression of disease, even though...
they showed a progressive decrease in size of contrast enhancing lesions. This suggests that ADC and DWI measurements can be used to determine early treatment failure by demonstrating non-enhancing infiltrative tumor growth.\textsuperscript{16} Efforts are currently underway to identify more accurate radiographic means of evaluating the response of tumors to anti-angiogenic treatment. Studies suggest that advanced MRI techniques such as perfusion imaging (dynamic susceptibility MRI), permeability imaging (dynamic contrast-enhanced MRI), magnetic resonance spectroscopy, and [\textsuperscript{18}F]-fluorothymidine and amino acid positron emission tomography may demonstrate tumor response or differentiate non-enhancing tumor from other causes of increased FLAIR signal.\textsuperscript{10,17}

Adverse Effects

Studies have reported adverse effects such as brain hemorrhages, epistaxis, oral cavity bleeding, vaginal bleeding, proteinuria, spontaneous colon perforations, thromboembolic complications, hypertension, and impaired craniotomy wound healing, among others. Vredenburgh, et al. noted that 4 out of 32 patients (12.5%) undergoing treatment with bevacizumab for recurrent malignant glioma had thromboembolic complications, and 2 patients (6.25%) died – one from a pulmonary embolus and the other from an arterial ischemic stroke.\textsuperscript{4} Kreisl, et al. reported thromboembolic events occurring in 6 out of 48 patients (12.5%) receiving bevacizumab therapy after glioblastoma recurrence. Three of these events were pulmonary emboli, and one was a cerebral vascular event; all patients were removed from the study for drug-associated toxicity. One patient had a bowel perforation.\textsuperscript{3} Norden et al. also reported a colon perforation that necessitated emergent surgery on a patient undergoing bevacizumab therapy for malignant glioma. Nine out of 55 patients (16.4%) experienced hemorrhage, primarily epistaxis or other mucosal bleeding. Two patients had asymptomatic brain hemorrhages that were detected on routine imaging.\textsuperscript{7} Patients with malignant gliomas have been demonstrated to be at a high risk of thromboembolic events regardless of therapy due to a tumor-induced hypercoagulable state; procoagulant and anti-fibrinolytic substances are preferentially secreted by malignant gliomas compared to other brain tumors.\textsuperscript{18} Clearly, the role of anti-angiogenic agents in increasing the risk of thromboembolic and other adverse effects needs to be better defined.

Conclusion

New criteria for radiographic response, along with innovative imaging techniques, are necessary for future clinical trials employing anti-VEGF therapy. Further studies elucidating the molecular interaction between tumor cells and anti-angiogenic agents such as bevacizumab are warranted. The incidence of adverse effects when undergoing bevacizumab therapy is significant and should be appropriately considered when tailoring therapy to an individual patient.

References


Figure 4

This patient presented with a recurrent left frontal GBM with enhancing tumor and increased Flair signal of both frontal lobes. After 6 months of bevacizumab there was a dramatic resolution of the enhancing tumor. However, there has been progression of decreased ADC signal and increased DWI signal in the right frontal lobe that represented tumor progression.


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