

High-Dose Antiangiogenic Therapy for Glioblastoma: Less May Be More?

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Targeting angiogenesis in glioblastoma rapidly reduces vascular permeability and contrast enhancement on MRI and prolongs progression-free survival. The long-term efficacy of bevacizumab and other antiangiogenic agents is limited, however, because of the rapid development of resistance. Alternative dosing approaches may be one mechanism of prolonging therapeutic efficacy. *Clin Cancer Res*; 17(19); 6109–11. ©2011 AACR.

In this issue of *Clinical Cancer Research*, von Baumgarten and colleagues (1) report on an orthotopic murine model of glioma that permits direct visualization of vascular kinetics in real time. In their model, they observed that both low and high doses of the VEGF inhibitor bevacizumab induced vascular normalization (as defined by morphologic changes and reduced permeability), whereas only the highest dose tested resulted in an increase in blood flow velocity. In addition, microregional tumor cell regression occurred only at the highest dose. The authors suggest these results may provide a rationale for using higher doses of antiangiogenic therapy to treat patients with glioblastoma.

Antiangiogenic therapy is one of the most exciting recent developments in the treatment of glioblastoma. The marked reduction in contrast enhancement of glioblastoma on MRI following VEGF inhibition sparked excitement in the field and spurred the development of antiangiogenic therapies for this disease. Multiple agents targeting endothelial cell growth factor ligands and receptors, including those of VEGF, placental growth factor, fibroblast growth factor, and the angiopoietins, are currently in development. Bevacizumab, the most extensively tested of the antiangiogenic agents, recently received accelerated approval in the United States as monotherapy for the treatment of recurrent glioblastoma on the basis of a significant improvement in progression-free survival compared with historical controls (2).

However, the benefits and mechanisms of action of antiangiogenic therapy remain under intense study. For instance, it is unclear whether outcomes differ depending on whether the VEGF pathway is disrupted by targeting the ligand itself (e.g., using bevacizumab) or by targeting the

VEGF receptor (e.g., using cediranib). Multiple clinical trials with bevacizumab have demonstrated impressive improvements in progression-free survival in both recurrent and newly diagnosed glioblastoma, but these studies have not identified an overall survival benefit compared with historical controls (2, 3). Ongoing randomized phase III trials [RTOG 0825 (NCT00884741) and AVAGLIO [NCT00943826]] will attempt to definitively answer whether bevacizumab improves overall survival when combined with both radiation and temozolomide.

Hope persists that antiangiogenic drugs will be able to improve overall survival despite the absence of data demonstrating that these agents have direct antitumor effects. Clinical observations have confirmed that antiangiogenic therapy can rapidly reduce vascular permeability and cerebral edema and improve patients' symptoms. Although vascular regression leading to tumor starvation is one potential explanation for the effectiveness of antiangiogenic therapy, Jain (4) proposed that its benefits are largely due to vascular normalization, that is, tumor vessel pruning and reduction in vascular permeability (and edema) lead to transient improvements in blood flow and oxygenation. Although these vascular effects could potentiate the antitumor effects of radiation and/or chemotherapy, it remains unclear how vascular normalization itself could contribute to improvements in outcome, yet evidence points in that direction. In mouse models, vascular normalization with a concomitant reduction in cerebral edema prolonged animal survival despite continued tumor growth (5). Of interest, the authors showed that the higher doses of bevacizumab prolonged animal survival compared with lower doses, although there was no statistical superiority to the highest dose (1). These findings seem to be consistent with a greater or prolonged reduction in cerebral edema in the higher-dose groups, thus leading to an improvement in animal survival in the higher-dose groups.

Alternatively, antiangiogenic therapy may exert its effects by initiating other modulatory changes within the tumor microenvironment that indirectly affect tumor cell viability. For instance, antiangiogenic therapy-mediated effects on

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tumor-associated myeloid cells may be one mechanism for indirect influence on tumor growth. Recent studies by Kamoun and colleagues (5) and our group (6) showed that both bevacizumab and cediranib reduce the number of infiltrating myeloid cells, such as proangiogenic macrophages, *in vitro*. In a recent clinical trial, we also showed that an early reduction in CD14⁺/VEGFR1⁺ monocytes was associated with response to the VEGF inhibitor aflibercept in patients with recurrent glioblastoma (7), making such a reduction a potential biomarker of efficacy. Because it is known that tumor-associated myeloid cells can promote tumor proliferation, invasion, and resistance to therapy, early reduction in macrophage infiltration may be an important mechanism of action of antiangiogenic therapy.

Of concern, however, the current study by von Baumgarten and colleagues (1) points to a potentially undesirable indirect effect of high-dose antiangiogenic therapy. It is known that through rapid and sustained vascular pruning, high-dose and prolonged antiangiogenic therapy can induce tumor hypoxia and necrosis in glioblastoma (8, 9). Although the benefits of regional hypoxia and necrosis are unknown, their detriments have been well documented. In animal models of glioblastoma, central necrosis is surrounded by a rim of viable tumor adjacent to highly vascularized normal brain tissue, allowing for continued tumor cell survival, proliferation, and infiltration. Furthermore, hypoxia is an important mediator of glioma stem cell survival (10) and glioblastoma resistance (8), and it enhances radiotherapy and chemotherapy resistance. Thus, reassurances are needed that high-dose antiangiogenic therapy does not promote tumor hypoxia and accelerate tumor resistance (Fig. 1).

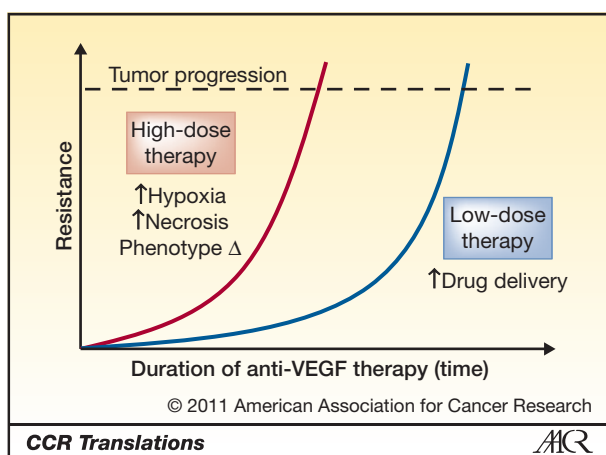


Figure 1. A model for the potential therapeutic benefits of low-dose antiangiogenic therapy. High-dose antiangiogenic therapy may induce a more rapid reduction in vascular permeability, leading to vascular normalization and reduction in cerebral edema. Potential consequences of higher doses include the promotion of tumor hypoxia, a well-known mediator of tumor treatment resistance, and promotion of an aggressive phenotype. An alternative approach is to use lower doses, which may delay the onset or extent of hypoxia, simultaneously improve oxygenation and drug delivery, and ultimately translate into improved patient survival.

In addition, unexpected relationships between the dose of antiangiogenic agents and coadministered drugs indicate that high doses of antiangiogenic agents may actually have more negative consequences than lower doses. Multiple clinical trials of combination treatments for recurrent glioblastoma have shown that chemotherapeutic or molecularly targeted agents in conjunction with bevacizumab confer little or no benefit over bevacizumab alone. Given the impact of antiangiogenic therapy on vascular permeability, it may be that antiangiogenic therapy negatively affects delivery of the coadministered drug to the tumor. Recent studies in an orthotopic glioma model showed that lower doses of antiangiogenic therapy actually improved concomitant drug delivery compared with control treatment and high-dose antiangiogenic treatment (11). Furthermore, we recently demonstrated that patients whose tumors progressed during bevacizumab therapy developed perivascular fibrosis, which may further limit drug delivery despite the persistence of "supervessels" and vascular normalization (9).

The discrepancies in the evidence regarding the VEGF pathway inhibitors suggest a complex and potentially paradoxical relationship between dose or vascular-inhibiting potency and overall benefit in glioma. High-dose antiangiogenic therapy may in the short term produce rapid tumor response due to changes in vascular permeability and the tumor microenvironment. Over time, however, negative effects due to tumor hypoxia and necrosis may contribute to the development of a phenotype that is resistant not only to antiangiogenic agents but to all treatments, thereby negating any early benefits.

In most patients, the clinical benefits of antiangiogenic therapy, regardless of their etiology, are transient. The average time to tumor progression for patients with recurrent glioblastoma receiving standard doses of bevacizumab is ~4 months, and it seems to be even shorter for patients treated with highly potent VEGF inhibitors (12, 13). Once bevacizumab resistance develops, there are no known effective salvage regimens. Although many mechanisms of resistance have been proposed, VEGF-independent angiogenesis-driven tumor growth, nonenhancing tumor progression, and transformation into a highly treatment-resistant mesenchymal phenotype are potential resistance mechanisms observed in both the clinic and animal models. If antiangiogenic agents promote rapid and aggressive tumor resistance, then new approaches to integrating antiangiogenic therapy, such as using lower doses or intermittent dosing schedules to delay the onset of hypoxia and simultaneously improve oxygenation and the efficacy of coadministered drugs, are desperately needed. A greater emphasis on understanding the mechanisms of action of and development of resistance to antiangiogenic therapies is therefore critical for their successful integration into glioblastoma treatment.

Disclosure of Potential Conflicts of Interest

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