Taming Glioblastoma: Targeting Angiogenesis

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More than 30 years ago, Judah Folkman hypothesized that tumor angiogenesis could be a target of anticancer therapy. Some of the initial studies were actually performed in patients with glioblastomas, which had the greatest extent of tumor angiogenesis among a variety of human malignancies. The identification of vascular endothelial growth factor (VEGF) also provided a firm foundation for the development of antiangiogenic drugs. Fast forward to 2007: We now have multiple agents that specifically block tumor angiogenesis in various malignancies. In this issue of the Journal of Clinical Oncology, two groups independently describe phase II clinical trials of bevacizumab plus irinotecan for recurrent glioblastomas. Vredenburgh et al noted an objective response rate of 57% and a 6-month progression-free survival of 46% with this regimen. These results are remarkable indeed when compared with a benchmark response rate of 6% and 6-month progression-free survival of 15% from salvage cytotoxic chemotherapies. Although the radiographic responses were impressive, resolution of gadolinium enhancement could also be caused by bevacizumab-induced changes in vascular permeability, impairing our ability to visualize these tumors on magnetic resonance imaging (MRI). To demonstrate that bevacizumab plus irinotecan had an impact on the underlying tumor, Chen et al went one step further by using 18F-fluorothymidine positron emission tomography (FLT-PET) as an adjunctive measure of tumor response. They reported a 47% response rate by FLT-PET and a 65% 6-month survival, whereas metabolic responders lived three times longer than did nonresponders. These results are consistent with earlier findings that response to cytotoxic chemotherapies was associated with a significantly lower treatment failure rate and a hazard ratio of 0.5. Taken together, both studies establish a role for combining antiangiogenic drug and cytotoxic chemotherapy to treat recurrent glioblastomas. However, these results should be interpreted within the context of glioblastoma behaviors and our ability to measure treatment efficacy.

The rationale for combining an antiangiogenic agent with cytotoxic chemotherapy is based on the phenomenon of vascular normalization, which leads to increased tissue oxygenation, decreased interstitial hypertension, and improved drug delivery to tumors. This was demonstrated experimentally with DTC101, a monoclonal antibody specific for VEGF receptor 2. As hyperpermeable vasculatures were pruned away by DTC101, increased tissue oxygenation acted synergistically with external-beam radiation in controlling U87 glioblastomas implanted in mouse brains. Interestingly, this normalization window peaked at day 5 of DTC101 treatment. For combination bevacizumab and cytotoxic chemotherapy, precise scheduling does not appear to be important, possibly because of immediate permeability changes and the prolonged half-life of bevacizumab. In patients treated with AZD2171, a pan-VEGF receptor tyrosine kinase inhibitor, Batchelor et al observed improvement in glioblastoma perfusion and permeability as measured by dynamic susceptibility contrast MRI within the first 24 hours. This is in contradiction to vascular damaging agents, which shut down well-developed tumor blood vessels and are highly schedule dependent when combined with cytotoxic chemotherapies. For example, ZD6126 induced hypoxia in U87 glioblastomas and interfered with radiation efficacy when administered 1 hour before radiation, but it was synergistic with radiation when administered 24 hours after radiation. Similarly, 5,6-dimethyl-oxanthenone-4-acetic acid and combretastatin A-4 disodium phosphate had the greatest tumor cell kill when administered 1 to 3 hours after cisplatin.

The current response criteria, or Macdonald’s criteria, may not be adequate for assessing glioblastoma response to antiangiogenic drugs. This is because tumor size is “estimated” on the basis of gadolinium leakage from hyperpermeable vasculatures. When antiangiogenic drugs change vascular permeability, they may alter the apparent size of glioblastomas on contrast-enhanced MRI or computed tomography, without affecting the underlying tumor mass. Therefore, it is critically important to incorporate adjunctive measures of tumor response, such as dynamic susceptibility contrast MRI for vascular perfusion and permeability, and FLT or 11C-methylmethionine PET for tumor metabolism. Chen et al used FLT-PET and noted that metabolic response correlated with MRI response and patient survival. Unlike [18F]fluorodeoxyglucose PET, FLT-PET has higher signal-to-noise ratio and is not confounded by a high rate of glucose utilization in the brain. But in order for FLT and 11C-methylmethionine PET to become accepted methods of assessing response in glioblastomas, more data are needed to evaluate their positive and negative predictive values.

It is equally notable that not all patients responded to bevacizumab plus irinotecan. Heterogeneity in vascular response to bevacizumab may explain some of these failures. In the AZD2171 trial, some patients had worsening or unchanged perfusion and permeability, whereas others responded favorably. There may be secondary pathways for tumor angiogenesis to occur in nonresponders when either VEGF or the VEGF receptor is blocked. In Chen et al’s cohort, metabolic heterogeneity was also noted, as seen...
in baseline standardized uptake volume (SUV) as well as post-treatment SUV at 1 to 2 weeks and 6 weeks. Using an SUV cutoff value of 1.33,17 one could separate the cohort at baseline into a high-metabolism group with a median survival of 260 days and a low-metabolism group with a median survival of 196 days. Although it did not reach statistical significance, this difference raises a question of baseline SUV as a predictive marker of intrinsic glioblastoma biology. Clearly, a larger sample size is needed to answer this question.

The spectrum of neurologic complications from antiangiogenic agents is poorly characterized. It is reassuring that Vredenburgh and Chen reported no spontaneous hemorrhage, and only four participants (11%) in Vredenburgh’s cohort developed thromboembolism requiring treatment discontinuation. Although this compares favorably with reported rates of thromboembolism of approximately 30%,20,21 a larger sample size would be needed to estimate the rates of hemorrhage and thromboembolism in patients treated with bevacizumab plus irinotecan. Whether anticoagulation in this setting would increase the risk of hemorrhage into glioblastomas is also unanswered. Furthermore, rebound cerebral edema is not well characterized in these reports. In the AZD2171 trial,13 tumor enhancement volume and permeability increased substantially during a 14-day drug holiday. Because bevacizumab’s half-life is long, approximately 20 days, there may be delayed rebound cerebral edema 3 to 4 weeks after stopping this drug. Prophylactic dexamethasone to treat this rebound edema may be necessary. Lastly, there have been cases of bevacizumab-associated reversible posterior leukoencephalopathy syndrome.22,23 This peculiar syndrome is probably caused by a drop in circulating VEGF leading to endothelial dysfunction and subsequent vasogenic edema in the occipital brain. Why certain individuals develop this syndrome, and why it occurs exclusively in the posterior cerebral circulation, is unclear.

Finally, future medical treatment of glioblastomas will require combining drugs directed at multiple targets. Angiogenesis is just one of six major hallmarks of cancer: self-sufficiency in growth signals, evading apoptosis, insensitivity to antigrowth signals, sustained angiogenesis, limitless replicative potential, and tissue invasion and metastasis.24 But most of these hallmarks are based on cellular and molecular mechanisms, making them less applicable in the clinical setting. One can, however, readily identify clinically-observable hallmarks of glioblastoma behavior such as tumor growth, angiogenesis, and invasion.25 Recent experiments demonstrated that stem-like glioblastoma cells have angiogenesis-independent but highly invasive phenotype, suggesting that blocking angiogenesis may not be enough to control glioblastomas.26 Now, the race is on to find a drug that blocks invasion and add it to the combined modality treatment; and to develop robust response criteria that separately measure drug efficacy against tumor growth, angiogenesis, and invasion in glioblastomas.

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
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REFERENCES