Commentary

Identification of the hidden survival advantage for anti-angiogenic therapy in glioblastoma

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Glioblastoma (GBM) remains one of the most aggressive of malignancies associated with significant morbidity and mortality for patients. Treatment has relied on surgery, radiation, and chemotherapy with emerging biologically based therapies under active investigation. A hallmark of GBM clinically and pathologically has been the intense tumor-associated angiogenesis that occurs with the disease. GBM associated angiogenesis promotes not only tumor progression but has a marked impact on a patient's neurological function due to abnormalities of the blood-brain-barrier and dysregulation of cerebral autoregulation of blood flow, a phenomena required for neurological function.

The development of anti-angiogenic therapy in the form of VEGF neutralizing antibodies and VEGF receptor tyrosine kinase inhibitors has offered an opportunity to intervene against this GBM phenotype. While some benefit for patients is seen in the setting of recurrent disease, large scale randomized studies combining bevacizumab (VEGF neutralizing antibody) with standard chemotherapy and radiation in newly diagnosed GBM failed to demonstrate a survival advantage (1,2). Given the importance of angiogenesis to GBM this was highly disappointing. In order to better understand the mechanism behind this general failure and search out windows where VEGF inhibition would provide a clinical benefit Batchelor and colleagues examined GBM patients with advanced imaging modalities in the setting of standard therapy combined with anti-angiogenic therapy (3). The investigators posit that a "vascular normalization index" composed of factors derived from imaging to include perfusion, vessel diameter and permeability, circulating biomarkers, changes in tumor interstitial pressure, and measures of tumor oxygenation may be utilized to identify patients likely to benefit from anti-angiogenic therapy.

In this study of 40 patients newly diagnosed with GBM undergoing standard chemoradiation with the addition of the oral pan-VEGF receptor tyrosine kinase inhibitor, cediranib, the investigators observed that patients experiencing a durable increase in tumor perfusion had improved survival compared to those having a decreased tumor perfusion or those in the standard treatment cohort. Importantly, this survival advantage was independent of the known prognostic factors of performance status and O6-methyl guanine methyl transferase (*MGMT*) gene promoter methylation status. In addition, it was this same subset of patients with increased tumor perfusion associated with cediranib therapy that demonstrated a decrease in the differential of arteriole and venule oxygen saturation levels suggesting enhanced delivery of oxygen to the brain and tumor tissue with cediranib. The end result of these observations the investigators state is a normalization of the tumor vasculature generating a hypothesis that this phenomena results in improved tumor oxygenation promoting enhanced cytotoxicity from therapy and/or improved drug delivery to the tumor. It was noted that the majority of patients had reductions in tumor enhancement with contrast on magnetic resonance imaging (MRI) and improvements in tumor-associated vasogenic edema; however, only the subset with

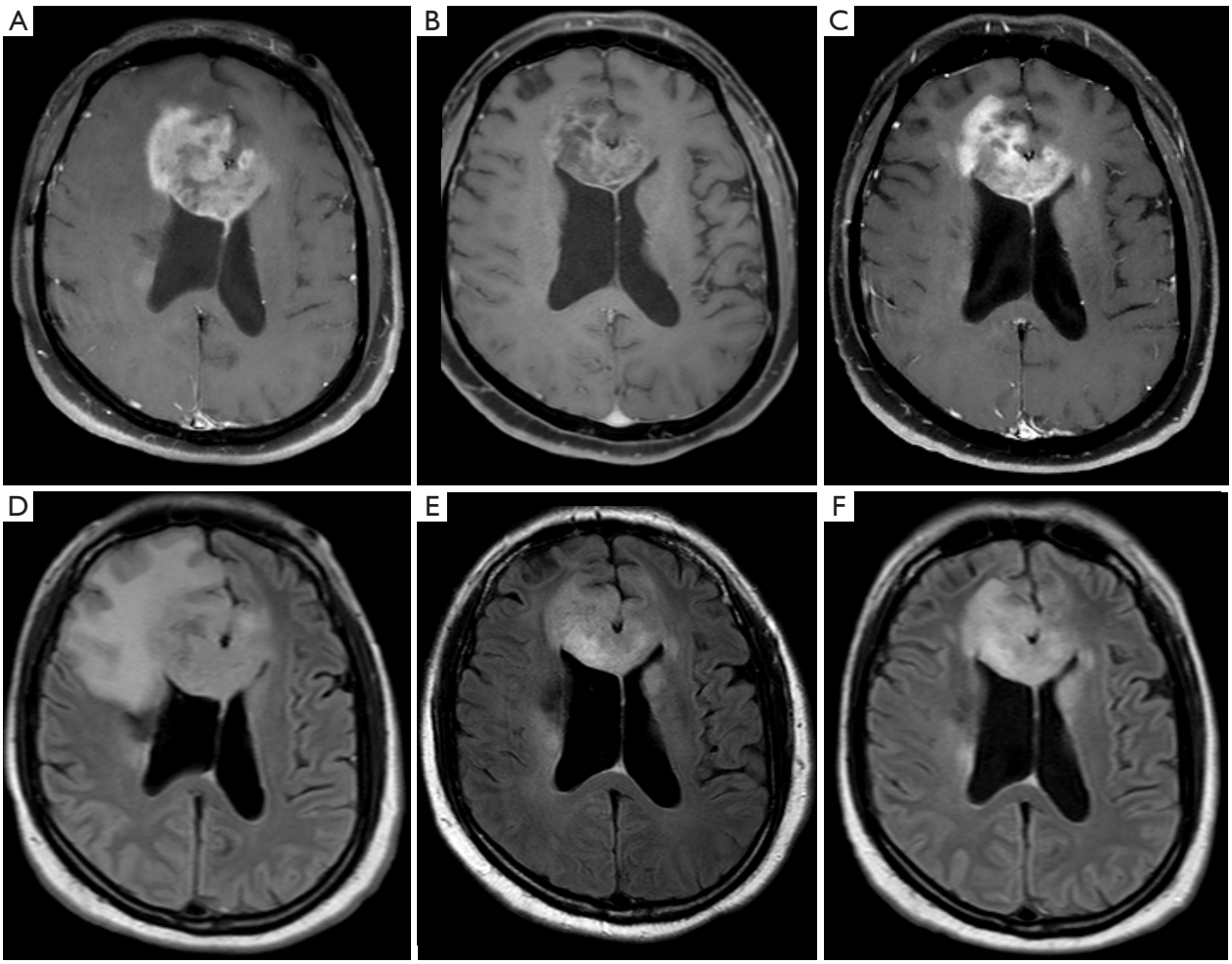

Figure 1 The montage of MRIs for a patient with frontal GBM demonstrates the characteristic changes seen with the initiation of anti-angiogenic therapy, in this case with bevacizumab. The top row (A-C) are the post-contrast T1 weighted sequences demonstrating an initial (A) robustly enhancing mass lesion in the right frontal lobe extending into the corpus callosum that briskly shows a response to bevacizumab after 8 weeks of therapy (B), but proves to be of poor duration as enhancement returns by 16 weeks (C). The bottom row (D-F) follows the same time sequence on the T2-weighted FLAIR sequences where significant tumor edema is seen at baseline (D) but responds well to bevacizumab (E). GBM, glioblastoma; MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery.

increased tumor perfusion realized a survival advantage. In *Figure 1*, an example of a patient with a frontal GBM shows a reduction in contrast enhancement following treatment with bevacizumab and a marked improvement in vasogenic edema; however, this effect is not durable. The development of markers such as tumor perfusion quantification to select patients for which durable responses may exist is essential to the improvement of care for this population. It is important to recognize that the imaging measurement used to determine tumor perfusion was dynamic susceptibility contrast (DSC) and the values were compared to a baseline obtained prior to the initiation of therapy. This form of tumor perfusion analysis is in routine use particularly in brain cancer with findings of elevated or increased perfusion often interpreted as an imaging correlative for disease progression and activity. The findings of this study indicate an awareness of biological therapy use, such as anti-angiogenic therapy, is essential to the correct interpretation of treatment response and provide support for the use of rigorous assessment criteria such as the Response Assessment in Neuro-Oncology (RANO) (4).

The deployment of anti-angiogenic therapy in patients with GBM has been associated with a steep learning curve for clinicians and scientist. The initial euphoria caused by dramatic radiographic responses was followed by confusion when controlled trials did not demonstrate a survival advantage for patients. The initial hypothesis that inhibition of tumor-associated angiogenesis in GBM would lead to improved patient outcomes has been modified by the realization that the clinical benefit related to survival is limited to a subset of patients. The ability to identify this subset of patients and more strategically deploy anti-angiogenic therapy is highlighted by the study of Batchelor and colleagues. By using advanced but readily available imaging platform, physiological metrics of tumor perfusion could be measured and normalized to uninvolved brain generating a usable measure for *in vivo* activity of cediranib. Importantly, the phenotypic measure of perfusion change was not associated with convincing changes in serum biomarkers or with tumor genotype. This suggest that GBM associated behaviors exist that are the summation of potentially multiple genetic alterations and thus may serve as an endpoint measure from which clinical decisions may be made.

In summary, Batchelor and colleagues illustrate the importance of a detailed evaluation of a tumor phenotype. In this case, the behavior of tumor-associated angiogenesis and the validation of measurements reflective of the biological process resulted in the identification of a patient subset responsive to this biologically targeted therapy.

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Footnote

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Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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