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Antiangiogenic therapy for patients with glioblastoma: current challenges in imaging and future directions

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“Antiangiogenic agents such as bevacizumab and cediranib can rapidly decrease enhancement after initiation of treatment, producing an apparently high ‘response rate’ ... thus the term ‘pseudoresponse’ has been used to define such a situation.”

Glioblastoma (GBM) is the most common primary malignant brain tumor, and despite recent advances in therapy, the prognosis for patients with GBM remains dismal. The median survival of newly diagnosed GBM patients is 15 months when treated with the current standard of care, which is a multimodality approach that includes maximal surgical resection followed by concurrent chemoradiation and 6 months of adjuvant temozolomide [1]. GBM is one of the most vascular tumors known, and there has been great interest in developing antiangiogenic agents for the treatment of GBM [2]. One of the key regulators of angiogenesis is VEGF, which induces tumor vascularization and facilitates tumor growth [3]. Bevacizumab is a humanized monoclonal antibody that targets VEGF, and was recently awarded accelerated approval by the US FDA as a single agent for use in recurrent GBM based on results of two Phase II trials [4,5]. A number of other antiangiogenic agents that target VEGF, PDGF, integrins and FGF are being evaluated in the treatment of newly diagnosed and recurrent GBM.

Glioblastoma is characterized by abnormal vasculature and a blood–brain barrier (BBB) that is significantly more permeable than normal brain tissue [6]. This increased permeability results in contrast material leaking out of tumor capillaries and increasing enhancement on T1-weighted images. Antiangiogenic agents such as

bevacizumab and cediranib can rapidly decrease enhancement after initiation of treatment [7], producing an apparently high ‘response rate’. Some of the improvement observed on contrast-enhanced MRI scan results from a rapid normalization of abnormally permeable blood vessels that restores, at least in part, the integrity of the BBB. Hence, use of this class of drugs results in higher response rates compared with historical controls [4,5,7]. The use of antiangiogenic drugs likely alters the image characteristics of enhancing tumor more effectively than that of nonenhancing tumor. Hence, the extent of reduction in contrast enhancement may not reflect the true anti-tumor activity of the antiangiogenic agent. Not infrequently, the radiographic image observed after antiangiogenic therapy suggests a radiographic response that is more impressive than the clinical benefit derived from the therapy; thus the term ‘pseudoresponse’ has been used to define such a situation [8]. ‘Pseudoresponse’ highlights the limitation that contrast enhancement is only a surrogate marker of tumor burden, and may in part be a reflection of disruption of the BBB. Antiangiogenic agents have been shown to improve survival primarily by reducing tumor-associated edema in experimental animal models [9]. One of the mechanisms of tumor progression after the use of antiangiogenic agents is that of vascular co-option, in which

tumors adapt to the inhibition of angiogenesis by increased infiltration and co-option of native brain blood vessels [10]. This particular type of tumor progression is not associated with disruption of the BBB, and is better appreciated on T2-weighted or fluid attenuation inversion recovery (FLAIR) images as an area of increased hyperintensity.

“Recognizing the urgent need to address the limitations of the Macdonald criteria, particularly with the increased use of antiangiogenic therapies for patients with brain tumors, the Response Assessment in Neuro-Oncology working group has proposed new recommendations for evaluating response in patients with high-grade gliomas.”

Since 1990, the Macdonald criteria have been the most widely used method to determine response in clinical trials of patients with brain tumors, as well as routine clinical practice [11]. With this, criteria response is determined by 2D measurements of enhancing tumor (the product of the maximal cross-sectional enhancing diameters on the same plane) on CT or MRI scans, while taking into account the patient's steroid dose and neurologic status [11]. There are several limitations of the Macdonald criteria, as it is based on the WHO criteria and utilizes measurement of the largest cross-sectional area of tumor on contrast-enhanced CT or MRI scans. GBM can be irregular in shape, include large necrotic cavities, or be partially or completely nonenhancing, creating difficulty in accurately measuring the cross-sectional area. Thus, response evaluation based on finding a difference in the largest cross-sectional area of tumor on contrast-enhanced CT or MRI is even more difficult with antiangiogenic therapy.

Recognizing the urgent need to address the limitations of the Macdonald criteria, particularly with the increased use of antiangiogenic therapies for patients with brain tumors, the Response Assessment in Neuro-Oncology (RANO) working group has proposed new recommendations for evaluating response in patients with high-grade gliomas [8,12]. Similar to the Macdonald criteria, the RANO criteria utilize 2D measurements on MRI and clinical factors for response assessment. However, the recommendations try to address some of the limitations of the Macdonald criteria by suggesting precise definitions of measurable (>10-mm diameter) and nonmeasurable disease (<10-mm diameter). In case of multiple lesions, RANO recommends a minimum of two lesions (similar to Response Evaluation Criteria In Solid Tumors [RECIST] version 1.1) and a maximum of five lesions for measurement. Relevant to antiangiogenic drugs, the group recommends FLAIR or T2 hyperintensity as a surrogate for nonenhancing tumor to help determine progression, and thereby include nonenhancing disease as criteria for determining tumor response [12]. However, RANO does not quantify the degree of FLAIR or T2 change necessary to define progression. Tumor-related edema or ischemia, radiation effect, demyelination and infection can all result in increased FLAIR or T2 signal, and make it difficult to distinguish them

from nonenhancing tumor. Owing to these limitations of the RANO criteria, novel imaging techniques that will help discern nonenhancing tumor from gliosis hold the promise of improving the accuracy of measuring response.

There are several novel imaging techniques that appear promising and will likely become a part of the standard assessment of response in patients with GBM treated with antiangiogenic agents in the near future. At present, they are limited in their application owing to their availability at select centers only. These include dynamic susceptibility contrast (DSC) MRI, dynamic contrast-enhanced (DCE) MRI, diffusion MRI and positron-emission tomography (PET). DSC MRI measures cerebral blood volume (CBV), cerebral blood flow (CBF), and mean vessel density, DCE MRI measures vascular permeability, diffusion MRI measures tissue density, and PET measures different physiologic tumor processes.

“Dynamic contrast-enhanced magnetic resonance imaging consists of repeated imaging with a T1-weighted sequence and provides information about endothelial permeability.”

Dynamic susceptibility contrast MRI uses rapid echo-planar imaging measurement of T2-weighted signal changes after an injection of a bolus of a compound such as gadolinium. T2 signal drop caused by the passage of gadolinium-containing contrast agent through the tissues can be used to calculate the relative CBV (rCBV), relative CBF (rCBF), mean transit time and mean vessel density. Blood vessel diameter can be measured with MRI by comparing spin-echo planar DSC images and gradient-echo DSC images. Gradient-echo planar images are sensitive to vessels of all size, whereas spin-echo images are sensitive to smaller vessels [7].

Dynamic contrast-enhanced MRI consists of repeated imaging with a T1-weighted sequence and provides information about endothelial permeability. This technique can be used to measure K-trans (the rate at which contrast material moves from the vasculature to the extracellular space), dependent upon the leakiness of the capillaries and their surface area, and is often utilized as a marker for the permeability of tumor vasculature. DCE MRI has been combined with biomarkers to help predict clinical outcome. In a study, 31 patients with recurrent GBM were treated with cediranib, an inhibitor of the VEGF receptor tyrosine kinases, and the authors calculated a 'vascular normalization index' by combining values of K-trans, microvessel volume and circulating collagen IV. The new index, which was a combined value of these three parameters after 1 day of anti-VEGF therapy, was predictive of overall survival (OS) and progression-free survival [13].

Most MR-perfusion protocols currently employ gadolinium-based contrast agents. However, owing to its tendency to extravasate into the extracellular space, gadolinium may actually underestimate rCBV in some patients [14]. The use of an iron oxide nanoparticle, ferumoxytol with its large molecular size, exhibits significantly less extravasation from leaky vessels into the interstitium, and thus allow for a more accurate measurement of rCBV [14].

Diffusion MRI is based on the random (Brownian) motion of water, and the values generated from these sequences are reported as the apparent diffusion coefficient (ADC). The greater the density of structures impeding water mobility, the lower the ADC; therefore, ADC is considered a noninvasive indicator of cellularity or cell density. Water molecules are more restricted in their movement within cells and less restricted in the extracellular space. Edema increases interstitial fluid and thereby increases the ADC, while increased cellular density lowers the ADC by restricting diffusion. Quantification of diffusion changes by a voxel-by-voxel approach is termed the functional diffusion map. Recently, the rate of change of tissue showing abnormally low ADC (functional diffusion map-classified 'hypercellular' tissue) within regions of T2 signal abnormality was shown to be an early predictor of tumor progression, time to progression and OS following treatment with bevacizumab [15].

“Apparent diffusion coefficient values can potentially be used as a noninvasive surrogate for VEGF expression and response to bevacizumab...”

In a Phase II trial of cediranib (a small-molecule inhibitor of the VEGF receptor) for recurrent GBM, a patient-specific threshold was selected below which ADC values were determined to be abnormally low and suggestive of tumor [16]. The increase in the percentage of low ADC portion of FLAIR on MRI with treatment with cediranib was suggestive of increasing infiltrative tumor according to the authors of the study [16]. However, since no histopathologic confirmation was available, one is not sure that this is truly representative of infiltrative tumor cells or just caused by hypoxia from antiangiogenic agents. Potentially, the degree of diffusion restriction may help to distinguish between the two processes. If one is able to do so, then ADC maps can help visualize regions of tumor growth that are not visible on contrast-enhanced MRI and can be used to show regions of infiltrative tumor cells with antiangiogenic agents.

Apparent diffusion coefficient values can potentially be used as a noninvasive surrogate for VEGF expression and response to bevacizumab, since ADC is influenced by cellular density, necrosis and edema. Regions of enhancing tumor were segmented and mapped onto ADC images to generate an ADC histogram, and ADC histogram analysis was shown to be predictive of response to bevacizumab in patients with recurrent GBM [17]. Tumors with low ADC values prior to bevacizumab therapy were more likely to progress by 6 months compared with those with high ADC values. This histogram analysis was more accurate than the Macdonald criteria at first follow-up. Similar results were seen in patients with newly diagnosed GBM when treated with upfront bevacizumab [18]. Patients with lower ADC prior to therapy had a significantly longer progression-free survival compared with those with high ADC values (459 vs 315 days), and this was associated with a trend

towards longer OS that did not achieve statistical significance (581 vs 429 days) [18]. This retrospective study demonstrated the utility of ADC histogram analysis in predicting patients that may benefit from upfront bevacizumab treatment, and has the potential to be a useful predictive marker of clinical benefit to antiangiogenic agents. However, these findings need to be validated in a prospective study.

Positron-emission tomography scan with radioactively labeled glucose or amino acid tracers has been used to assess response in brain tumor patients, but its application has been limited mostly to research purposes and clinical trials thus far. One promising PET tracer is the thymidine analogue 3'-¹⁸F-fluoro-3'-deoxy-L-thymidine (FLT), which has been used as a marker for tumor cell proliferation. In a study of recurrent malignant glioma, 19 patients treated with irinotecan and bevacizumab underwent FLT-PET at baseline, 1–2 weeks and 6 weeks post-therapy [19]. Greater than 25% reduction in FLT uptake (defined as response) predicted for improved OS. Patients who showed a response lived three-times longer than those who did not show any change (10.8 vs 3.4 months) [19]. Another novel tracer is ¹⁸F-fluoromisonidazole (FMISO) PET, which can help predict areas of hypoxia within brain tumors [20]. Hypoxia is a driving force for angiogenesis, and increased FMISO uptake has been associated with greater tumor aggressiveness and decreased survival in patients [20]. FMISO PET can also potentially be used to demonstrate vascular normalization and improved CBF.

“One promising positron-emission tomography tracer is the thymidine analogue 3'-¹⁸F-fluoro-3'-deoxy-L-thymidine...”

Conclusion

Novel therapies including antiangiogenic drugs for GBM pose a unique challenge to our ability to accurately define treatment response in these patients. These imaging challenges in patients with brain tumors led to the formation of an international working group to propose the RANO criteria to address some of these challenges. The RANO criteria are increasingly being used to define response in most clinical trials. Prospective clinical studies are needed to further explore the utility of novel imaging modalities (perfusion and diffusion MRI and/or PET) for measuring treatment response in the era of antiangiogenic agents and define their role in the management of patients with GBM.

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