

Increased Blood Flow during anti-VEGF Induced Vascular Normalization

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Purpose: Anti-angiogenic therapies can potentially normalize abnormal brain tumor vasculature and improve tumor microenvironment¹. Although the concept of vascular normalization continues to receive much attention and several potential pharmacodynamic biomarkers are being evaluated, the physiology behind the vascular normalization phenomenon is still not fully understood². Studies have shown that vascular parameters such as vessel size, micro-vessel blood volume and tissue surface permeability decrease during anti-angiogenic therapy³, whereas clinical experience also suggests that tumors remain vascularized during treatment, probably caused by the activation of alternative pro-angiogenic pathways². We have compared MR-derived flow characteristics in patients treated with an anti-angiogenic agent to that of a patient control group not receiving anti-angiogenic therapy.

Methods and Materials: 18 patients with newly diagnosed glioblastomas have so far been included. Of these, 10 patients were enrolled in a Phase II clinical trial of an oral pan-VEGF receptor tyrosine kinase inhibitor (cediranib, AstraZeneca Pharmaceuticals, UK), whereas the remaining 8 patients were enrolled in a companion study that did not include anti-VEGF treatment and acted as a control group. All 18 patients received the same MR imaging regimen over a period of two months (9 visits including 2 baseline scans). Also, all patients received radiation treatment and chemotherapy as part of the ongoing clinical treatment protocol. The MR imaging protocol included axial T1-weighted pre- and post-contrast (Gd-DTPA) images for outlining of the enhancing tumor region and a double-echo DSC-MRI sequence where the high signal-to-noise, short-echo (TE=31ms) gradient-echo signal was used to derive values of cerebral blood flow in both tumor and normal-appearing tissue^{3,4}. Tumor CBF values were normalized to normal-appearing white-matter tissue in order to account for any global systemic effects.

Results: Across patients, compared to the baseline MR examinations, quantitative (not normalized) tumor and normal-appearing tissue CBF values in the anti-VEGF treatment group increased during the study period. For the control patient group, tumor CBF values decreased over the same period whereas normal-appearing tissue remained relatively unchanged. Further, results of linear mixed model analysis showed that the normalized CBF values of the anti-VEGF group was significantly different over time compared to those of the control group ($P=0.047$). Figure 1 shows the mean normalized CBF values for the two groups normalized to the second baseline visit. Figure 2 shows an example of the normalization window with an increase in normalized tumor CBF and decrease in T1-weighted post contrast volume.

Discussion: Because of their structural and functional vessel abnormality, solid tumors exhibit impaired blood flow characteristics¹. It is hypothesized however, that anti-VEGF therapy in combination with radiation and chemotherapy can kill or suppress cancer cells thereby normalizing tumor vascularity and increase blood flow⁵. We have shown data supporting this hypothesis, where patients undergoing anti-VEGF treatment showed increased CBF during the vascular normalization window. This effect was not observed in the control patient group. Also, the increase in normal tissue CBF suggests that most of anti-VEGF patients also get hypertension with resulting high blood pressure. The findings in our study are encouraging, suggesting that available anti-angiogenic therapy regimes improve the efficiency of the tumor vasculature thereby potentiate the effects of radiation and chemotherapy.

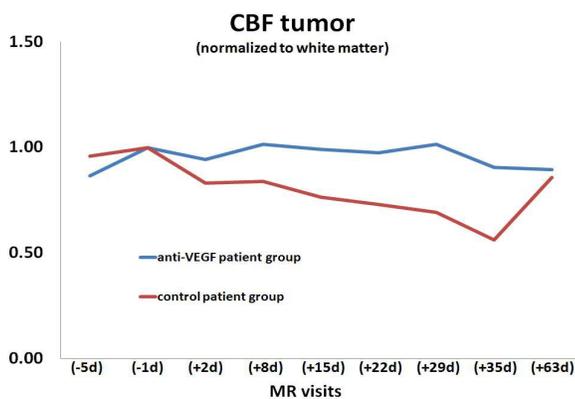


Figure 1: Mean normalized CBF values of the two patient groups relative to treatment start (d=0). Compared to the control group, the anti-VEGF treatment increases blood flow making the tumor vasculature more efficient.

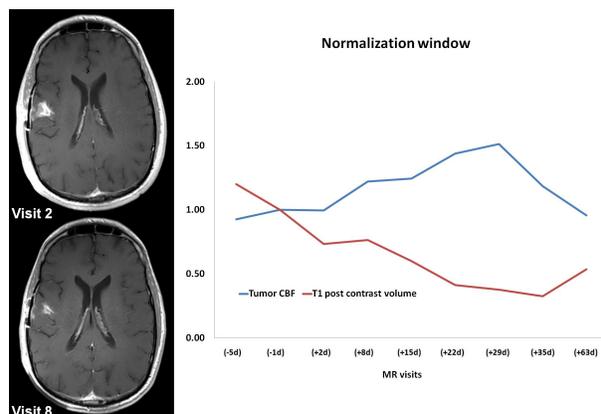


Figure 2: Example of the normalization window for one patient undergoing anti-VEGF therapy. The normalized CBF values increases over the two month period, whereas T1-weighted enhanced volume goes down.

[1] Jain RK, Nat Med 2001;7(9):987-89, [2] Jain RK, Nat Rev Clin Oncol 2009;6:327-38, [3] Batchelor TT et al, Cancer Cell 2007;11(1):83-95, [4] Bjornerud et al, JCBFM 2010;30(5):1066-78, [5] Griffon-Etienne G et al, Cancer Res 1999;5:3776-82