Reductions in blood volume in normal white matter are found in glioma patients treated with bevacizumab

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Introduction: Bevacizumab (Avastin, Genentech, San Francisco, CA) is the first FDA approved anti-angiogenic agent and has shown efficacy in a number of different tumors including glioma when used in combination with conventional cytotoxic agents[1,2]. DSC MRI measurements of relative cerebral blood volume (rCBV), referenced to normal appearing white matter (NAWM), are frequently used in assessing glioma[3], including in monitoring treatment response. However, during the course of one such study we made the incidental finding that blood volumes appeared reduced in glioma patients treated with bevacizumab. In this study we investigated whether this observation could be confirmed and whether it was associated specifically with bevacizumab treatment.

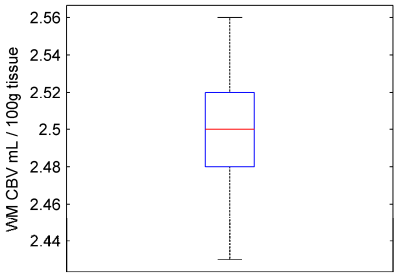

Figure 1. Box and whisker plot of NAWM CBV measurements in patients not treated with bevacizumab.

Methods: This retrospective study was approved by the Institutional Review Board of this institution. A total of 102 DSC MRI scans (B_0 1.5T; T_R 1s; T_E 47ms; FA 40°; matrix 128×128; FOV 228×228 mm; 10×5mm slices) were acquired using a gradient echo EPI sequence during injection of 0.1mmol/kg Gd-DTPA from three groups of patients. Six patients (4 male and 2 females, age: 50 ± 14) had only received surgery, radio- and chemotherapy after initial diagnosis. Thirteen patients (8 males and 5 females, age: 52 ± 12) had received bevacizumab and temozolomide after surgery and chemotherapy following initial diagnosis. A further 13 (8 males and 5 females, age: 52 ± 13) received bevacizumab and irinotecan after tumor reoccurrence, having previously received surgery, radio- and chemotherapy at initial diagnosis. Patients who were not treated with bevacizumab were scanned once after initial treatment. Newly diagnosed patients were scanned before treatment (i) and approximately, 3, 6 and 12 months afterwards. Recurrent glioma patients were scanned at 6 and 3 months before and immediately before bevacizumab treatment (r) and at 3 and 6 months afterwards. Signals were measured in regions of interest of approximately 10 pixels in NAWM contralateral to the tumor. Arterial input functions were obtained from 10 arterial pixels selected using an automated method[4]. Signal measurements were converted to concentration-time curves (CTCs) and deconvolved by standard methods[5]. Absolute CBV was calculated as the ratio of area under the deconvolved tissue CTC to the area under the AIF CTC.

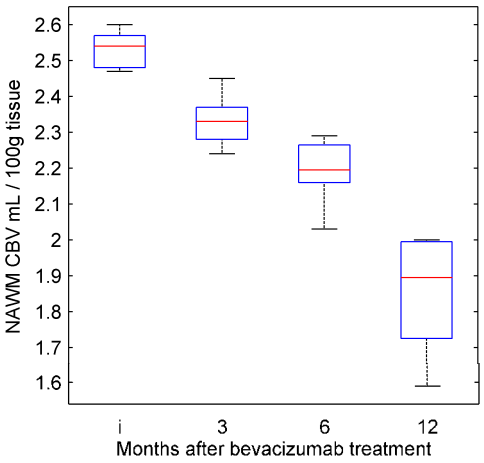

Figure 2. Box and whisker plot of NAWM CBV measurements in patients treated with bevacizumab after initial (i) diagnosis.

Results: Figs. 1-3 give box and whisker plots of NAWM CBV measurements in patients not treated with bevacizumab, treated with bevacizumab at initial diagnosis and at recurrence respectively. Fig. 2 demonstrates a substantial drop in CBV at 3 months post-treatment that increases to 26% (median) at 12 months. Fig. 3 demonstrates normal CBV measurements compared to Fig. 1 (approximately 2.5 mL/100g) before recurrence and bevacizumab treatment, and decreases after treatment that is similar to those seen in the newly diagnosed patients. Again, differences after bevacizumab relative to pre-treatment values were statistically significant in all instances ($p < 0.001$, t-test).

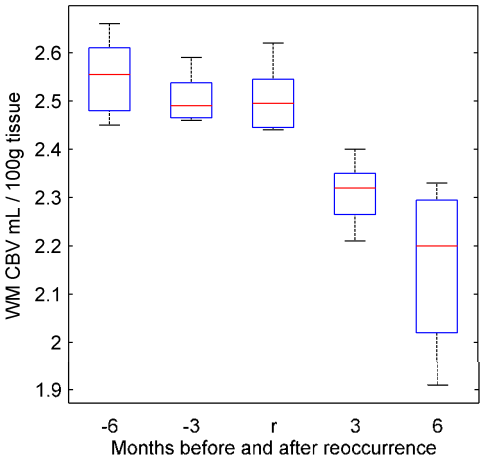

Figure 3. Box and whisker plot of NAWM CBV measurements in patients treated with bevacizumab after recurrence (r).

Discussion: It is clear from Figs. 2 and 3 that glioma treatment is associated with substantial reductions in CBV. Normal values found in the recurrent glioma patients before bevacizumab treatment strongly suggest that standard treatments – surgery, cytotoxic chemotherapy and radiation – received by these patients at initial diagnosis are not sufficient to cause this reduction. It therefore appears that these reductions are associated with treatment with bevacizumab. The cause of this is unclear. Turnover of endothelial cells in the brain is thought to be very slow so interference in this process is unlikely. It is possible that low levels of VEGF are necessary for the maintenance of normal function as in the kidney[6] and that bevacizumab disrupts this process.

Radiologically, this study suggests that care need be exercised in the use of rCBV measurements to monitor treatment with bevacizumab and possibly other antiangiogenic agents. Tumor rCBV measurements are likely to underestimate initial reductions in blood volume after bevacizumab treatment. Furthermore the continued reduction in CBV in NAWM may suggest an apparent increase in blood volume in stable tumors.

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