Acute Effects of Bevacizumab on Glioblastoma Vascularity Assessed with DCE-MRI and Relation to Patient Survival

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Introduction: Glioblastoma multiforme (GBM) is characterized by rapid growth and abnormally tortuous and leaky tumor vasculature, providing a potential therapeutic target for anti-angiogenic agents such as Bevacizumab. The anti-VEGF antibody Bevacizumab (Genentech) alone has recently been shown to have a therapeutic benefit in GBM patients [1]. In this trial, dynamic contrast enhanced MRI (DCE-MRI) was used to monitor the acute effects of Bevacizumab on physiologic measures of tumor vascularity, such as blood brain barrier (BBB) permeability, represented as the transfer constant K^{trans}. In addition, we relate these to progression free survival (PFS) and to overall survival (OS).

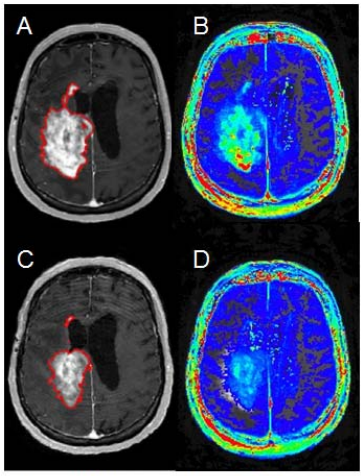

Fig. 1. GBM prior to *(A,B)* and 3 days after *(C,D)* Bevacizumab show reduction in enhancing tumor volume (3d T1 post contrast *A, C)* and BBB permeability (K^{trans} map – *B, D).*

Patients and methods: *Patients:* Forty-five patients (mean 54 y, range 38-85 y) with recurrent GBM were enrolled in a phase II clinical trial of Bevacizumab alone (ClinicalTrials.gov identifier: NCT00290797). Each patient underwent MRI prior to and up to 96 hours after the initiation of therapy (Bevacizumab 10 mg/kg i.v.) during which time their steroid dose was stable for at least 1 week. *MRI methods:* For DCE-MRI, 30 sequential 3D T1-SPGR (1.5 T GE Signa) or T1-FFE (3 T Philips Acheiva) slabs covering the tumor were obtained every 20 sec for 10 minutes, with resolution ~1×1×5 mm^3. Infusion of contrast (0.1 mmol/kg Gd-DTPA or gadoteridol at 0.3 ml/s) began after the 5th scan. Whole brain post contrast 3D T1 volumes (~1×1×1 mm^3) were also obtained. *DCE-MRI processing:* The DCE-MRI time series was motion corrected (3dvolreg, AFNI[2]); a vascular input function was generated from the venous sinuses; and parameteric maps of K^{trans}, k_{ep}, and f_{pv} were computed by a nonlinear least squares fit of the signal intensity curves to the generalized kinetic model (DEMRI3 model, 3dNLfim, AFNI). *Image Analysis:* The baseline 3D T1 was used as a reference to which the second visit 3D T1 and both sets of parametric maps were rigidly coregistered (FLIRT). The enhancing tumor was roughly outlined by hand and refined using an expectation maximization algorithm [3] to generate volumes of interest, which could be applied across all datasets. (Fig.1). *Statistical analysis:* Both VOIs were applied to the pre and post treatment parametric maps, and the mean values were compared by paired *t*-test. Each parameter was also divided into two groups according to the median and Kaplan-Meier survival curves were compared. P<0.05 was considered significant.

Results and discussion: Fig.1 shows typical changes in enhancing tumor volume and K^{trans} following a single dose of Bevacizumab. For the group, the enhancing tumor volume decreased by 39% (p<0.0001, Fig.2). Similarly, significant changes in K^{trans}, k_{ep} and f_{pv} were also seen, regardless of whether the pretreatment or the post-treatment VOI was used for measurement (Fig. 2). Enhancing tumor volume was predictive of both PFS and OS, larger tumors had a worse prognosis. K^{trans} prior to therapy was the only kinetic parameter found to predict OS (p=0.0298, Fig. 3). However, the percentage reduction in K^{trans} resulting from Bevacizumab did not predict PFS or OS.

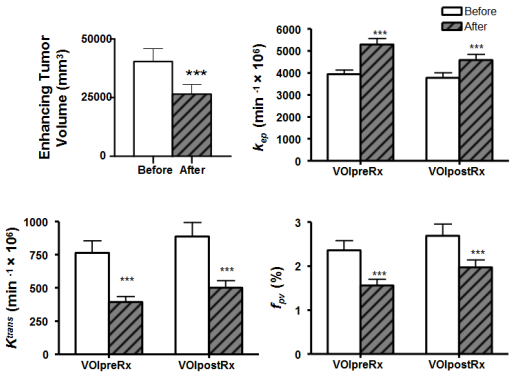

Fig. 2. Effects of Bevacizumab on MRI parameters measured with VOIs from pre and post treatment MRIs.

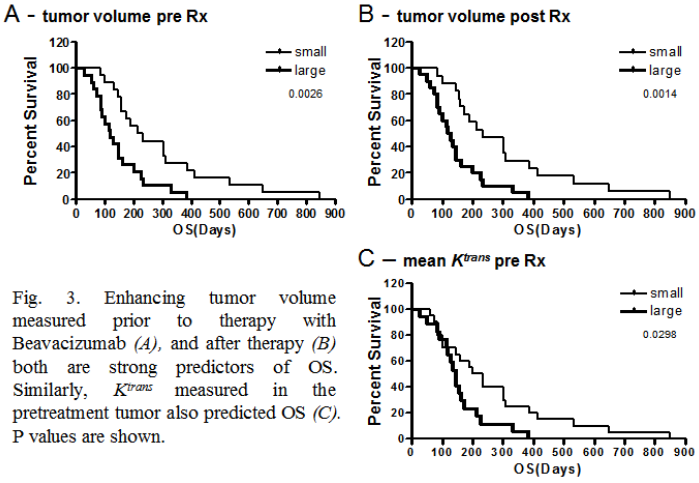

Fig. 3. Enhancing tumor volume measured prior to therapy with Beavacizumab *(A),* and after therapy *(B)* both are strong predictors of OS. Similarly, K^{trans} measured in the pretreatment tumor also predicted OS *(C).* P values are shown.

Conclusions: Bevacizumab dramatically reduces K^{trans} (46%) and enhancing tumor volume (39%) in recurrent GBMs within 96 h of a single dose, presumably due to alterations of the tumor vasculature. The decrease in permeability (K^{trans}) is not an artifact of reduced enhancing volume, as this reduction is seen in the "core" tissue which persistently enhances. However, tumors in which Bevacizumab resulted in larger decreases in K^{trans} did not demonstrate an improved survival over those with smaller reductions in K^{trans}. GBMs with larger enhancing tumor volume, hence, greater burden of disease at the onset of the trial, and greater baseline K^{trans}, possibly representing higher grade, both predicted poorer PFS and OS.

References:

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