Effects of Bevacizumab on the Tumor Vascularity Assessed with DCE-MRI in Recurrent Anaplastic Astrocytomas

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Introduction: High-grade primary brain tumors have poor prognosis with median survival of 14.6 months for grade IV (glioblastoma) and 19.2 months for grade III once diagnosed. The prognosis for recurrent ones is even worse. New antiangiogenic agents targeting the tumor vasculature have shown significant benefit in patients' survival, which spawned interests in mechanism investigation. MRI gives the opportunity to address this purpose. In this study dynamic contrast enhanced MRI (DCE-MRI) was used to monitor the effects of bevacizumab, an anti-VEGF antiboby, on physiologic measures of tumor vascularity, such as blood brain barrier (BBB) permeability, represented as the transfer constant K^{trans}, in patients with recurrent anaplastic astrocytomas (AA, Grade III).

Patients and methods: *Patients:* Thirty-one adult patients with recurrent AA were enrolled in a phase II clinical trial of bevacizumab alone (ClinicalTrials.gov identifier: NCT00290797). Each patient underwent MRI prior to, up to 96 hours, and approximately 4 weeks after the initiation of therapy (bevacizumab 10 mg/kg i.v.). Patients' steroid dose had to be stable for at least 1 week before the treatment. *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 $\sim 1\times1\times5$ 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 ($\sim 1\times1\times1$ mm^3) were also obtained. *DCE-MRI processing:* The DCE-MRI time series was motion corrected (3dvolreg, AFNI[1]); a vascular input function was generated from the venous sinuses; and parameteric maps of K^{trans} and *fpv* 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 other 3D T1 images and all parametric maps were rigidly coregistered (FLIRT). The enhancing tumor was roughly outlined by hand and refined using an expectation maximization algorithm [2] to generate volumes of interest, which could be applied to calculate the maximal values of each DCE-MRI parameter. *Statistical analysis:* VOIs were applied to the pre- and post-treatment parametric maps, and the maximal values were compared by repeated ANOVA with post-hoc paired tests. Each parameter was also correlated to the interval between the start of the treatment and off-study dates. P<0.05 was considered significant.

Results and discussion: Fig.1 shows typical changes of responding AA patients in enhancing tumor volume (ETV), K^{trans}, and fpv following bevacizumab. For the group, the ETV decreased by 23.5% at 4-day and 41.2% at 4-week (p<0.05, Fig.2). Similarly, significant reductions in K^{trans}, and *fpv* were also seen at 4-week (p<0.05, Fig. 2). Baseline enhancing tumor volume was related to the patients' outcome, patients with larger tumors at the baseline and after the treatment had worse prognosis. K^{trans} prior to therapy was weakly correlated to the patient's prognosis.

Conclusions: Bevacizumab reduces enhancing tumor volume, K^{trans}, and fpv in patients with recurrent anaplastic astrocytoma, which is consistent to its expected biological effect of acting on the tumor vasculature. Patients with larger enhancing tumor volume, hence, greater burden of disease at the onset of the trial, and greater baseline K^{trans}, possibly representing higher malignancy, both correlated with poorer prognosis. These results are in accordance to what we found in recurrent GBM patients.
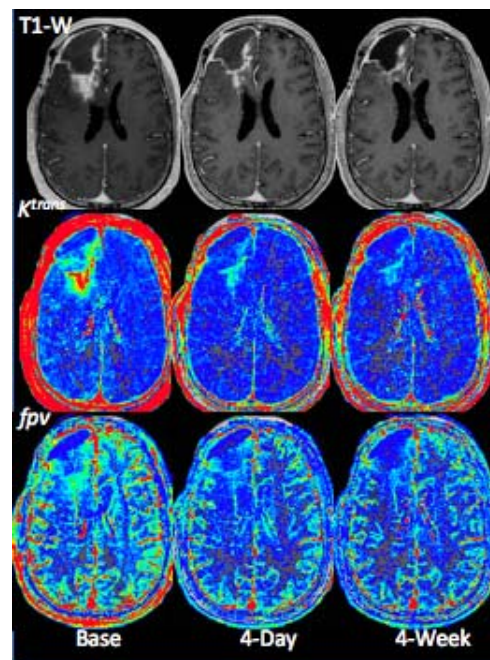

Fig. 1. representative images from one of the best responders showing the reduction of enhancing tumor volume, K^{trans}, and *fpv* after bevacizumab.
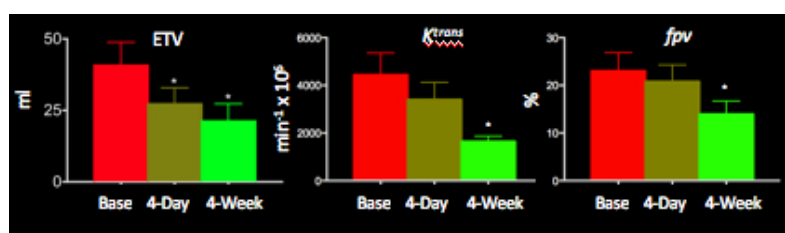

Fig. 2 Group results of enhancing tumor volume (ETV), K^{trans}, and *fpv* after bevacimumab.

References:
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