

Optimization of Bevacizumab Dosing in Brain Tumors Using MRI Measures of Enhancing Tumor Volume and Relative Cerebral Blood Volume

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Introduction: Promising results have been obtained with the anti-angiogenic agent, bevacizumab, for the treatment of brain tumor patients.¹ Despite these early promising results, the optimal dose and drug combinations have not yet been defined.² Traditionally optimal dose has been based on maximal tumor-cell kill, which for chemotherapeutic agents, is set by using the maximum tolerated dose (MTD).³ However, the relationship between MTD and the optimally biologically active dose (OBD) for anti-angiogenic agents is unclear. Efficacy seems to range with tumor type studied and is not necessarily achieved at the maximum dose.³ Consequently, the goal of this study was to characterize the bevacizumab dose-response relationship for brain tumors by measuring the contrast-agent enhanced tumor volumes and relative cerebral blood volume (rCBV) using dynamic susceptibility contrast (DSC) imaging. The studies were performed in the U87 brain tumor model for a range of bevacizumab doses over an 8-day period.

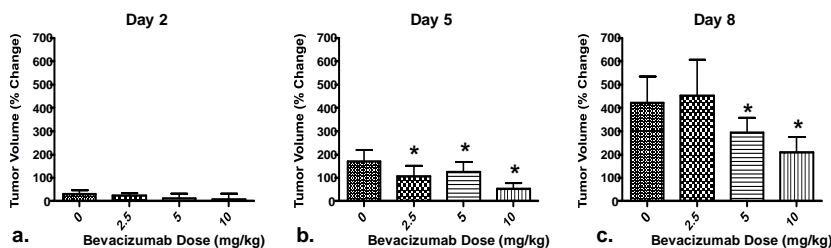
Methods: *Animal Model:* U87 human grade III astrocytoma cells were cultured in vitro, using 20% FBS. After reaching confluency, cells were harvested and 200,000 cells were inoculated into athymic rats using intracranial, stereotaxic approach. At day 16 post tumor-cell inoculation animals were randomized, imaged, and received a single IV injection of bevacizumab (Avastin, Genentech, South San Francisco, CA) at a dose of 0 (n=6), 2.5mg/kg (n=5), 5mg/kg (n=5) or 10mg/kg (n=6). Imaging was performed on days 18, 21, and 24 post tumor cell-inoculation (days 2, 5 and 8 post-treatment).

MRI: Images were obtained with Bruker 9.4 T scanner fitted with a linear transmit coil, and surface receive coil. DSC images were acquired using an EPI sequence (TE/TR=18ms/500ms, FOV=3.5cm, matrix=94). Post contrast T1 weighted images were acquired using a spin-echo T1-weighted RARE sequence (TE/TR = 9ms/1500ms, FOV =3.5cm, matrix =256).

Analysis: The DSC data was processed to create rCBV maps, corrected for any leakage effects⁴. Enhancing tumor volumes (reported in mm³) were determined from the post-contrast T1w images, in all slices showing enhancing tumor. A two-tailed Mann-Whitney test was used to determine if significant differences existed between the untreated group and each of the treated groups at each post-treatment day. An $\alpha=0.05$ level of significance was used.

Results: Figure 1 shows the enhancing tumor volume as a function of bevacizumab dose for three different treatment days (Fig 1a-c).

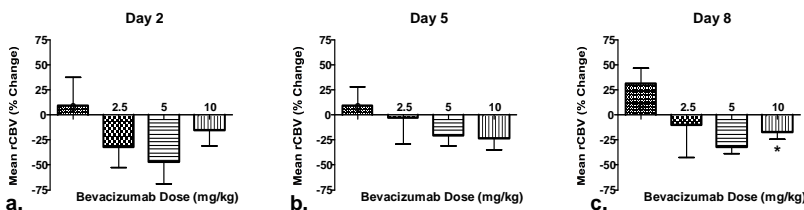
Figure 1 T1+C Volume



On day 2 post-treatment, there are no significant differences in tumor volume between the treated and untreated groups. On day 5, all dosages show a significant decrease in tumor volume, while on day 8 post-treatment only the two highest doses (5, 10mg/kg) show a significant inhibition of tumor volumes.

Figure 2 shows the rCBV as a function of bevacizumab dose for three different treatment days. In treated animals, rCBV is decreased compared to baseline values at each time point. Independent of dose, the rCBV continued to decrease despite large increases in tumor volume over time. However, only for the 10mg/kg does, at day 8, is the mean rCBV significantly different than that for the untreated rats.

Figure 2 rCBV



Discussion: Significant inhibition of U87MG tumor volume and the degree of vascularity depended on dose and day post-treatment. The lack of complete inhibition may be explained by the presence of additional angiogenic factors not targeted by bevacizumab. While in this study enhancing tumor volume proved to be a good indicator of treatment response, it is not consistently so in the clinical

population. This discrepancy may be due to the effect of steroid administration which may decrease or even preclude contrast agent enhancement. Furthermore, since most clinical studies incorporate bevacizumab in combination with chemotherapy, combination therapies will be studied in subsequent rCBV studies using our xenograft model. Our results demonstrate that in a pre clinical model, rCBV estimates of tumor perfusion may provide useful information that could aid in the optimization of antiangiogenic treatments. Future studies of combination treatments using rCBV maps may additionally assist effective design of dosing and temporal treatment paradigms for malignant gliomas. **Acknowledgements:** NIH/NCI RO1 CA082500, Advancing Healthier Wisconsin / MCW Translational Brain Tumor Program **References** (1) Mirimanoff RO et al. JCO 2006; 24:2563-2569. (2) Tuma R. JNCI 2005; 97:950-951. (3) Bergsland E et al. Oncologist 2004; 9:36-42. (4) Schmainda KM et al. Am J Neuroradiol 2004; 25:1524-1532.