Optimization of Combined Anti-VEGF Plus Radiation Therapy in Brain Tumor Xenograft Models

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Introduction: The anti-angiogenic drug bevacizumab is approved for the treatment of recurrent glioblastoma multiforme, the most common and most aggressive primary brain tumor. No systematic studies have been performed to determine if and how bevacizumab and radiation should be combined for optimal therapeutic response. Furthermore, it is becoming increasingly clear that standard MRI measures of response, which entail measuring contrast-enhanced tumor volume, have proven unreliable for the evaluation of anti-angiogenic drugs since these drugs also decrease contrast extravasation. Consequently, the goal of this study was to evaluate and optimize the combination of anti-VEGF and radiation therapy in the treatment of a U87 xenograft brain tumor model by evaluating changes in tumor blood volume and enhancing volume.

Methods: *Animal Model:* U87 human grade IV astrocytoma cells were cultured, harvested, and 200,000 cells were injected into athymic rats (n=34) using intracranial, stereotaxic approach. B20 (Genentech, South San Francisco, CA) was given at day 10 and 14 (5 mg/kg) post-tumor cell inoculation and combined with 3 daily radiation (7 Gy) treatments (RT) beginning at days 8, 12 and 14 or alone at day 10. Imaging was performed on days 8, 10, 12, 14, 16, 21, and 28. *MRI:* Images were obtained on a Bruker 9.4 T scanner fitted with a linear transmit coil, and surface receive coil. A loading dose of contrast agent (0.1 mmol/kg Omniscan, Nycomed Amersham) was administered to minimize leakage effects that confound rCBV measurements derived from DSC-MRI. DSC images were acquired using an EPI sequence (TE/TR=18ms/1s, FOV=3.5cm, matrix=96). Post contrast T1 weighted images were acquired using a spin-echo T1-weighted RARE sequence (TE/TR = 12.6ms/1500ms, FOV =3.5cm, matrix =256).

Figure 1: Tumor Volume

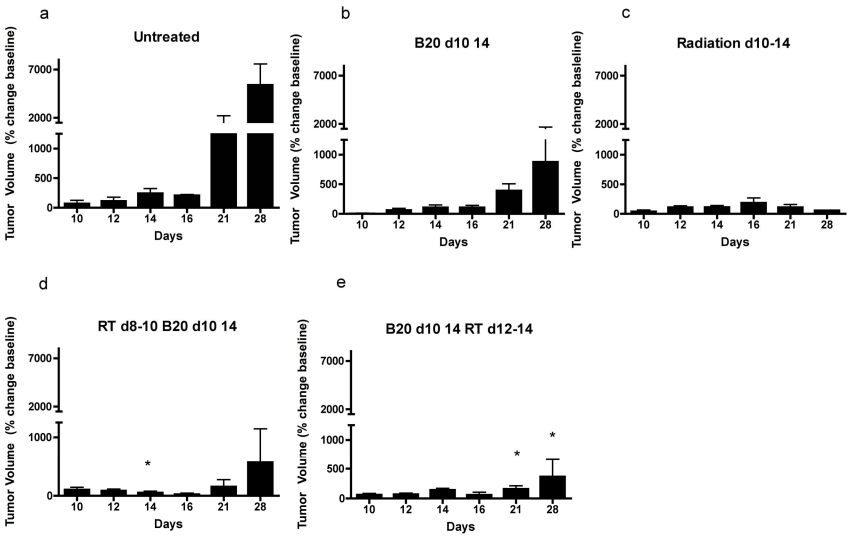
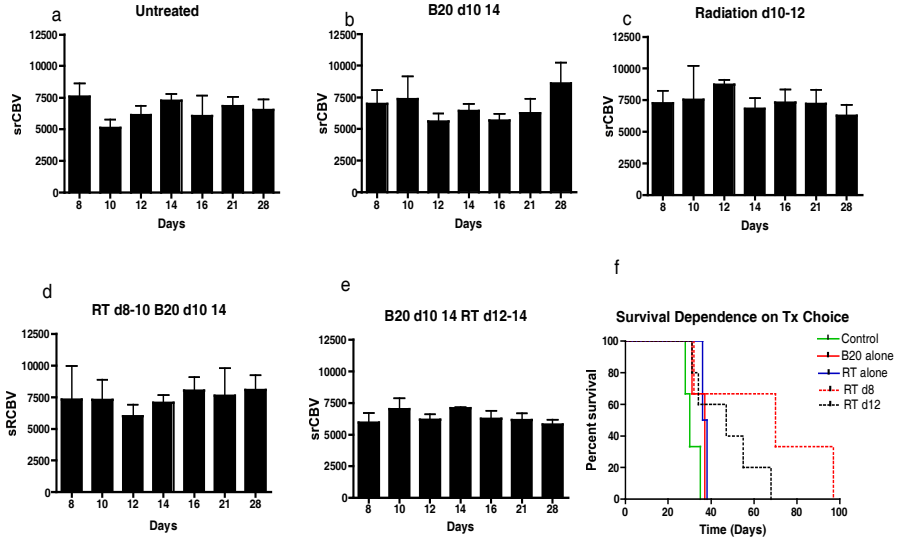


Figure 2:rCBV



Analysis: The DSC data was processed to create rCBV maps, corrected for any leakage effects[1]. Enhancing tumor volumes (reported in mm^3) 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 α=0.05 level of significance was used.

Results: Figure 1 shows enhancing tumor volume as a function of four treatment days for each treatment paradigm. Pre-B20 RT starting at Day 8 (Fig 1d) inhibited tumor growth on day 14 compared to untreated controls (Fig 1a). When RT and B20 were given concurrently, (Fig 1e) tumor growth was inhibited on days 21 and 28. Figure 2 shows the median rCBV as a function of seven treatment days for the different treatment paradigms, with little treatment-induced changes observed. All treatments increased the survival (Fig 2f) with radiation treatment before anti-VEGF providing the most benefit.

Discussion: The degree of tumor vascularity in the U87MG xenograft model depends on the timing of the radiation and anti-VEGF therapies. Interestingly, RT before anti-VEGF provided a significant increase in survival and decrease in tumor volume. For the imaging studies included here tissue markers of proliferation (Ki67), hypoxia (HIF1α), and vascular density (vWF) are being analyzed to provide additional insight. **Conclusion:** In general these results demonstrate that the temporal combinations of drugs do influence treatment efficacy and that radiation may improve the circulation and/or permeability to improve the delivery of anti-VEGF therapies. With larger study cohorts, currently underway, these questions can be more fully addressed. **Acknowledgements:** NIH/NCI RO1 CA082500, Advancing Healthier Wisconsin / MCW Translational Brain Tumor Program **References** (1) Schmainda KM et al. Am J Neurorad 2004; 25:1524-1532.