The anti-angiogenic drug, SU11657, decreases brain tumor size and normalizes perfusion as indicated by DSC-MRI perfusion parameters

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INTRODUCTION Many studies have indicated the need for the functional evaluation of antiangiogenic therapies to properly assess their effectiveness (1-3). In this regard, we have obtained dynamic susceptibility contrast (DSC) data using a simultaneous GE/SE EPI imaging method from which we can derive perfusion parameters (CBF, CBV, MTT), which are sensitive to both the total vasculature (from the GE data) and the microvasculature (from the SE data) as well as providing a measure of the mean vessel diameter (mVD) from $\Delta R2^*/\Delta R2$. In addition, we demonstrate the feasibility and usefulness of computing tumor transit time distributions (TTDs) for the evaluation of brain tumors and their response to therapy. In this study these perfusion parameters are used to assess the treatment effects of an antiangiogenic drug, SU11657 (Sugen Inc., S. San Francisco, CA), which targets class III and V receptor tyrosine kinases (PDGFR, VEGFR, KIT, FLT3, CSF-1R).

METHODS Eighteen Fisher rats were inoculated with 9L brain tumors. Of these, six were treated with 20 mg/kg and 7 with 40 mg/kg of SU11657, administered via oral gavage. MR experiments were performed on a 3T Bruker system 14 days post-inoculation. A 2 min simultaneous GE/SE EPI pulse sequence (64x64, TR = 1s, GE[TE] = 10.3ms, SE[TE] = 76.6ms, 3 slices, slice = 2mm, 3.5cm FOV) was used for the DSC perfusion scan. At 1 min, a 0.25 mg/kg bolus of iron oxide contrast agent (MION; MGH Contrast Media Laboratory, Charlestown, MA) was administered i.v. To determine the enhancing tumor volume T1-weighted SE images (256x256, TR = 450ms, TE = 15 ms, slice = 2mm, 3 slices, 3.5cm FOV) were acquired following the administration of 0.2 mmol/kg dose of Omniscan (Nycomed). GE and SE CBF, CBV, and MTT maps were created using the SVD approach (3). The mVD maps were determined from the average of four $\Delta R2^*/\Delta R2$ images centered around the peak $\Delta R2^*$. Intravoxel transit time distributions (TTDs) were calculated from the negative derivative of the residue function (4). The maximum difference between a voxel's cumulative TTD and a normal cumulative TTD (averaged over a normal ROI) were also computed. Unpaired two-tailed *t*-tests were used to compare the effects of SU11657 treatment levels to untreated rats, with α=0.05 level of significance.

RESULTS Figure 1 demonstrates a decrease in tumor volume for each treatment dose, with a significant decrease occurring with 40 mg/kg SU11657 only. Figure 2 shows the normalized (to contralateral brain) GE, mVD and SE perfusion results. At 20mg/kg only the mVD decreased significantly. At 40 mg/kg GE and SE nCBF increased, the SE nCBV decreased, and both the GE and SE nMTT decreased, all significantly. Figures 3 and 4 are the mean untreated and treated TTDs for GE and SE, respectively. The 20 mg/kg dose does not influence the TTD while the 40 mg/kg dose produced a TTD more like normal brain tissue. As Figure 5 shows, there is a significant change between the maximum difference for normal and tumor cumulative TTD for the 40 mg /kg dose but not the 20 mg/kg dose.

Figure 1: Enhancement Area

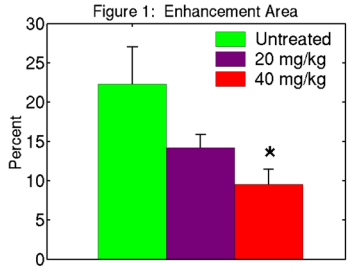


Figure 2: GE and SE Perfusion Parameters

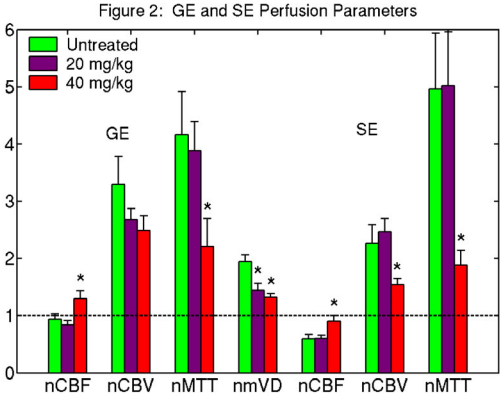


Figure 3: GE TTD

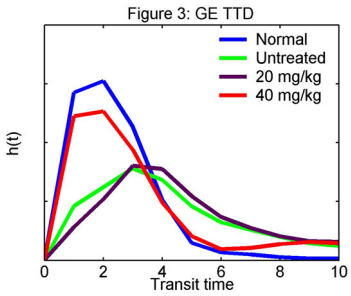


Figure 4: SE TTD

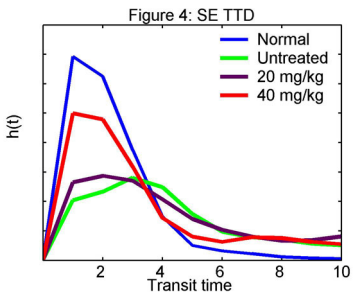
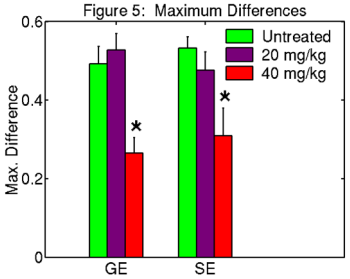


Figure 5: Maximum Differences



DISCUSSION Using a combined GE/SE DSC perfusion method we were able to evaluate functional and morphologic changes in the tumor vasculature following SU11657 antiangiogenic therapy, with the most significant changes occurring at the higher dose. Measurement of the tissue transit time distribution also demonstrated a normalization of tumor circulation, such that it was more like that of normal brain tissue. This normalization is consistent with the idea that pre-treatment with antiangiogenic drugs may significantly improve the response of tumors to conventional therapies such as radiation therapy and chemotherapy. Questions such as these warrant further study and demonstrate the potential of this method to play a key role in the evaluation and optimization of treatment strategies.

REFERENCES:

1. Eberhard, A., et al., Cancer Research, 60: 1388-1393, Mar. 1, 2000.
2. McDonald, D., et al., Cancer Research, 62: 5381-5385, Sept. 15, 2002.
3. Ostergaard, L., et al., MRM 36: 715-725, 1996.
4. Ostergaard L., et al., J. Cereb Blood Flow Metab, 1999: 690-699, 1999.

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