Quantitative DCE-MRI and Positron Emission Tomography (PET) for Assessment of Treatment Response in a Mouse Xenograft Model of Colorectal Cancer

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Introduction  The development of signal transduction modulators (STMs) and incorporation of such agents into existing treatment protocols; including surgery, chemotherapy and radiation therapy, has been a major focus of cancer research over the last decade. STMs interfere with signaling pathways involved in cancer progression: growth, angiogenesis, invasion and metastases. The establishment of quantitative physiologic endpoints of STMs responsiveness is critical due to alternative mode of action. Here we compare quantitative dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) and positron emission tomography (PET) endpoints used in two separate studies to assess: 1) anti-angiogenesis and 2) tumor metabolic activity, which can serve as molecular markers for cytotastic efficacy of STMs. A mouse xenograft model of human colorectal cancer was used to assess therapeutic efficacy (by tumor growth, gadolinium (Gd) kinetics in DCE-MRI and glucose uptake by 18FDG-PET) of one responsive (STM-R) and one non-responsive (STM-NR) agents.

Methods  HT29 tumor xenografts were established in athymic nude mice. Animals were treated with respective agents accordingly; both agents administered by 100 mg/kg oral gavage (STM-R once and STM-NR twice daily). DCE-MRI, to assess anti-angiogenic effects of therapeutics, was performed on animals at baseline (BL – before start of treatment), on day 7 (D7) of treatment, and at the end of the treatment cycle (D21 or D25). A catheter pre-loaded with gadolinium (Magnevist®) was placed in the lateral tail vein of anesthetized animals. Animals were placed into a 4.7 Tesla Bruker PharmaScan MRI scanner (with a 31mm-diameter Bruker volume coil) and a series of fast T1-weighted modified driven equilibrium Fourier transforms (MDEFT) pulses were applied for total acquisition time of 15 minutes. The scan parameters were as follows: FOV = 4.0 cm; slice thickness = 1.5mm; TE/TR = 9.3/116.6 ms; number of slices = 4; number of averages = 1; matrix size = 128 x 256; number of evolutions = 60; resolution time = 15 s. After 1 minute of image acquisition (pre-contrast), 0.2 mmol/kg Magnevist® was injected through the tail vein catheter and T1-weighted Gd-enhanced MRI scans were continuously taken for another 14 minutes. Images were analyzed with Bruker ParaVision software version 3.0.2. 18F-2-deoxyglucose-PET (18FDG-PET) was performed on animals at BL and at the end of treatment (D20 or D24). Fasted animals (4-16hrs) were injected in the lateral tail vein with approximately 250µCi /18FDG. Animals were placed on a heated pad (38°C) for one hour post injection to allow for conscious 18FDG uptake. Under isoflurane anesthesia, mice were placed on a heated pad and a 10 minute emission was acquired with a microPET scanner (Inveon, Siemens Medical). Slice by slice axial images were analyzed with AsPiProVM. All data presented is an average of 3-10 tumors. Statistical analysis was performed with GraphPad Prism 4.03. Model-free analysis was performed with Microsoft Excel and two-compartment modeling was performed with SAMII.

Results  Figure 1 (top panel; A & B) shows complete growth inhibition for the STM-R and modest growth inhibition for STM-NR. The area under the Gd uptake (T1 signal intensity) versus time curve (AUC) and the initial AUC (IAUC), taken over the first 60 seconds post Gd injection, were evaluated as model-independent measurements of tumor vascular perfusion (IAUC) or tumor perfusion and permeability (AUC). Tumors that responded to treatment with STM-R showed a significant decrease in the AUC and IAUC on D7 compared to control tumors (p<0.05, p=0.2 ; Figure 1C). Further compartmental analysis of tumors treated with the STM-R showed decreases in both ktrans and kep on D7 and D21 of treatment compared to control. The STM-NR did not significantly decrease AUC or IAUC compared to vehicle treatment (Figure 1D). Figure 2 shows contrast-enhanced MR images of tumors at baseline and at the end of treatment for both STMs used. The figure illustrates the rapid, early uptake of Gd in the tumor rim, indicative of higher tumor perfusion and increased vascularization in this region. Since we also observed a decrease in the IAUC and AUC in all non-treated tumors on D7 and D21/25 in both studies we wanted to determine if tumor size alone correlated to IAUC and AUC of the Gd-time curve. We determined by use of Spearman’s r test that in both studies, AUC and IAUC correlated negatively with tumor volume (evaluation of 25 and 28 xy pairs). The FDG-PET data agreed with the DCE-MRI analysis. A significant (p=0.01) reduction in tumor 18FDG uptake was observed in tumors treated with the STM-R (800% increase on D21 for vehicle-treated controls and 80% decrease in uptake for STM-R versus BL). Despite a 45% reduction in tumor volume for the STM-NR, no decrease in tumor 18FDG uptake was observed (960% increase on D21 for the vehicle group and 1135% increase in uptake for STM-NR versus baseline).

Conclusions  Our study demonstrates the utility of DCE-MRI and PET to evaluate the anti-angiogenic and metabolic activity of highly responsive tumors. Our data also shows that DCE-MRI and PET did not provide any indication of moderate therapeutic response, as our STM-NR did manage to reduce tumor volume by 45% compared to control. However, it is interesting and important to note that the STM-R is a drug designed to directly inhibit signaling processes critical in angiogenesis in addition to signaling processes responsible for tumor proliferation, while our STM-NR is a drug designed to indirectly inhibit angiogenesis by preventing upregulation of signals by the tumor and directly inhibit proliferation and death signaling in the tumor. This may explain the complete lack of response evaluated by DCE-MRI. Nevertheless, this does not adequately describe the complete lack of response evaluated by PET imaging and analysis. Finally, it is also important to notice that in xenograft model, the total tumor volume is directly negatively correlated with Gd-uptake kinetics.

Figure 1: Tumor volume and vascular perfusion assessment

Figure 2: Contrast-enhanced images of responsive and unresponsive tumors