Detection of Early Response to Temozolomide Treatment in Brain Tumors Using Hyperpolarized ^{13}C MR Metabolic Imaging

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Introduction: Dynamic Nuclear Polarization (DNP) and the development of a dissolution process have enabled the real time investigation of in vivo metabolism with a huge gain in signal sensitivity [1]. A recent study has shown that metabolism can be examined in brain tumor model systems using these techniques [2]. The purpose of this study was to demonstrate the feasibility of using DNP hyperpolarized $^{13}C_1$-pyruvate to measure early response to therapy using an orthotopic human glioblastoma xenograft model. Temozolomide (TMZ), which is a standard chemotherapeutic drug for brain tumor patients, was used for treatment. Our emphasis was to detect early response to treatment with ^{13}C imaging parameters and compare them with changes in tumor volume over time.

Methods: Three athymic rats with intracranial implantation of human glioblastoma cells (U-87 MG) have been studied to date. One of the rats (Treated 1) received oral administration of 100 mg/kg TMZ on the 15th day after tumor implantation, and the second rat (Treated 2) received administration of 100 mg/kg TMZ on the 15th day, and 50 mg/kg TMZ on the 16th and 17th days after tumor implantation. The third rat was not treated (Untreated). All animals underwent ^{13}C and ^{1}H imaging study at D-1 (days from TMZ treatment initiation) or D0 for pre-treatment scan, D1, and several time points after treatment. The untreated rat was euthanized when it exhibited neurologic symptoms indicative of deteriorating body condition. All imaging studies were performed using a GE 3T scanner with a custom-designed $^{1}H/^{13}C$ rat coil. ^{13}C 3D MRSI data (TE/TR=140/215 ms, 4x4x5.4 mm resolution) were acquired using a double spin echo sequence with a centric k-space encoding, variable flip angle scheme and echo-planar readout [3] at 20 sec after the injection of approximately 2 ml (100 mM) hyperpolarized $^{13}C_1$-pyruvate through the tail vein. T1-weighted spin-echo images (TE/TR=10/700 ms, 8 cm fov, 320x192 matrix, 1.2 mm slice thickness) were acquired in axial plane after the injection of 0.3 mmol/kg Gadolinium (Gd)-DTPA, except for Treated 1 and Untreated who missed T1 post-Gd imaging at their pre-treatment scan. The carbon magnitude spectra were voxel-shifted in order to minimize partial volume effects. The ratio of lactate over pyruvate (Lac/Pyr) was calculated from the voxel centered at tumor in the ^{13}C data for the assessment of change in tumor metabolism. Tumor volume was estimated from the post-Gd images using software that was developed in our laboratory.

Results: The tumor metabolism measured by ^{13}C metabolic ratio was altered one day after TMZ treatment in the treated rats (Fig 1), while the tumor volume assessed from T1 post-Gd images started to show reduction at the 8th day after the initiation of treatment (Fig 2). Before treatment, the rats exhibited an elevated level of Lac/Pyr (Fig 1 and 3). The Lac/Pyr was reduced from 1.0 at D-1 to 0.4 at D1 for Treated 1 and from 2.7 at D0 to 1.7 at D1 for Treated 2, showing 39 % reduction shortly after the initiation of TMZ treatment (Fig 1). The level of Lac/Pyr of the untreated rat was 0.8 at D1 and continued to increase. The tumor volume of both treated rats showed a constant increase in their first few time points (from 0.013 cc at D1 to 0.023 cc at D6 for Treated 1, and from 0.26 cc at D0 to 0.36 cc at D4 for Treated 2), and started to decrease at the 8th day after the initiation of treatment (Fig 2). In contrast, the tumor volume for the untreated rat continued to increase over time.

Conclusions: We have demonstrated the feasibility of using DNP hyperpolarized $^{13}C_1$-pyruvate to detect early response to Temozolomide treatment in an orthotopic human glioblastoma xenograft model in rat brain. The ^{13}C data from the treated rats showed the ability to detect altered tumor metabolism as early as one day after TMZ treatment initiation, while the tumor volume from T1 post-Gd imaging showed the first sign of reduction at the 8th day after the initiation of treatment. The results from this study suggest that metabolic imaging with hyperpolarized $^{13}C_1$-pyruvate may provide a new tool for clinical neuro-oncologists to use in monitoring tumor response to therapy for patients with brain tumors.

References: [1] Golman et al. PNAS, 2006. [2] Park et al., *Proc. ISMRM, 17th Annual Meeting,* 2009. p 53. [3] Cunningham et al. J Magn Reson, 2007.

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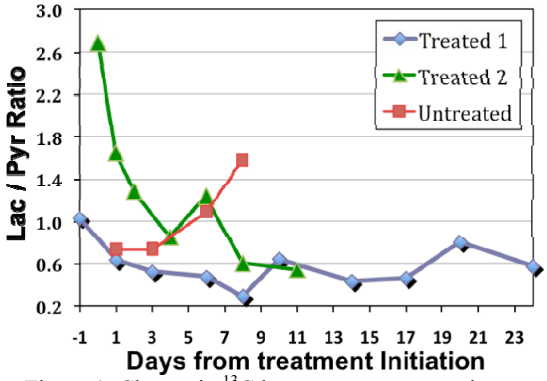

Figure 1: Change in ^{13}C lactate to pyruvate ratio (Lac/Pyr) over time in treated and untreated rats. The Lac/Pyr of the treated rats was reduced drastically one day after the initiation of treatment.

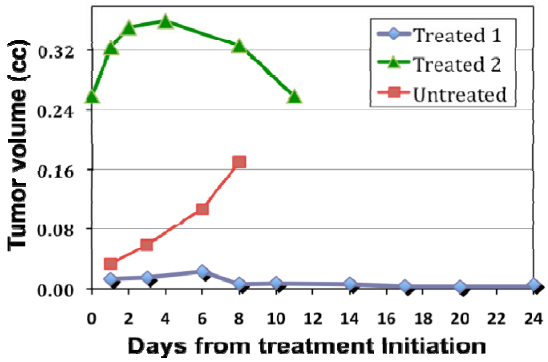

Figure 2: Evolution of tumor volume over time in treated and untreated rats. The tumor volume of treated rats started to decrease at D8.

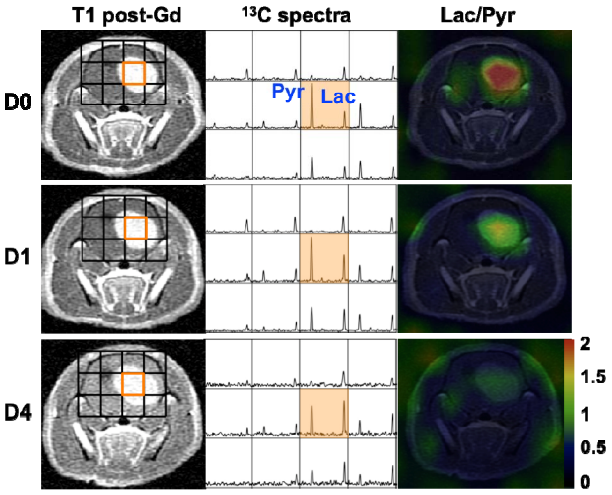

Figure 3: An example of T1 post-Gd images, ^{13}C spectra and Lac/Pyr overlay map from Treated 2 at D0 (pre-treatment), D1 (one day after treatment initiation) and D4 scan.