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

I. Park1,2, M. Chaumeil1,2, T. Ozawa1, S. M. Ronen1,2, D. B. Vigneron1,2, C. James1, and S. J. Nelson1,2
1Joint Graduate group in Bioengineering, University of California San Francisco/Berkeley, San Francisco, CA, United States, 2Surbeck Laboratory of Advanced Imaging, Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, CA, United States, 3Brain Tumor Research Center, Department of Neurological Surgery, University of California San Francisco, San Francisco, CA, United States

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 13C1-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 13C 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 and 17th days after tumor implantation. The third rat was not treated (Untreated). All animals underwent 13C and 1H 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 1H/13C rat coil. 13C 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 13C1-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 TMZ treatment 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 13C imaging parameters and compare them with changes in tumor volume over time.

Results: The tumor metabolism measured by 13C 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 drastically (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.

Conclusions: We have demonstrated the feasibility of using DNP hyperpolarized 13C1-pyruvate to detect early response to Temozolomide treatment in an orthotopic human glioblastoma xenograft model in rat brain. The 13C 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 13C1-pyruvate may provide a new tool for clinical neuro-oncologists to use in monitoring tumor response to therapy for patients with brain tumors.


Acknowledgement: This research was supported by GE Healthcare and the UC Discovery program, grant ITLB004-10148, and by NIH RO1 EB007588.