Hyperpolarized 13C MR Metabolic Imaging Provides an Early Biomarker of MGMT Activity and Response to Temozolomide Treatment


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Introduction: Although a number of studies have indicated that high levels of DNA repair protein O6-methylguanine-DNA methyltransferase (MGMT) predict response to Temozolomide (TMZ) therapy in gliomas [1], there is no non-invasive method for measuring MGMT activity in tumors in vivo. A recent study has shown that tumor metabolism can be examined in an orthotopic human glioblastoma xenograft model using DNP-hyperpolarized 13C MRSI [2]. The purpose of this study was to demonstrate that early TMZ-induced DNA damage modulates pyruvate metabolism in the absence, but not in the presence, of MGMT through a mechanism independent of apoptosis, and therefore to demonstrate that hyperpolarized 13C MR metabolic imaging using [1-13C]-pyruvate can provide an early biomarker of MGMT activity and response to TMZ treatment.

Methods: In order to assess the effect of MGMT on pyruvate metabolism in an orthotopic human glioblastoma xenograft model, MGMT-proficient U87-MG cells were produced from MGMT-deficient U87-MG cells through lentiviral infection encoding MGMT and subsequent sorting by flow cytometry (Figure 1) [3]. Twenty-three athymic rats with intracranial implantation of either MGMT-deficient U87-MG (MGMT−) or MGMT-proficient U87-MG (MGMT+) cells were divided into four groups: MGMT−-treated group (n=10) and MGMT+-treated group (n=4) received an oral administration of 100 mg/kg TMZ, and MGMT−-control group (n=10) and MGMT+ control group (n=3) received the vehicle only. All animals underwent 13C and 1H imaging study prior to treatment (D0), at D1 (days from treatment) and/or D2. All imaging studies were performed using a GE 3T scanner with a custom-designed 1H/13C rat coil. 13C 3D MRSI data was acquired following injection of 0.2 mmol/kg Gadolinium (Gd)-DTPA in order to estimate tumor volume. 13C data was caused

Results: TMZ treatment in MGMT−-tumors caused a rapid and significant drop in Lac/Pyr (Figure 2a), while Lac/Pyr increased in MGMT−-control tumors (Figure 2b). In contrast, both treated and control groups with MGMT+ tumors exhibited an increased Lac/Pyr level with findings comparable to MGMT−-tumor controls (Figure 2c and 2d). On D1, Lac/Pyr dropped by 21±22 % in MGMT−-treated rats, but increased 20±25, 16±11 and 23±18 % in MGMT−-control (p<0.004), MGMT+ treated (p<0.03) and MGMT+ control rats (p<0.02), respectively. Results from D2 showed similar findings (Figure 3a). In contrast, tumor volume increased over time for all groups (p<0.2) (Figure 3b). Tumor shrinkage was observed in MGMT−-treated group at later time points between D5 and D7 [6]. The results from biological assays and immunohistochemical analysis indicated that NAD+/NADH levels, LDH activity and the extent of apoptosis were not statistically different between the TMZ-treated and control tumors at day 2 following the initiation of treatment (Figure 4). These findings suggest that the early inhibition of hyperpolarized 13C pyruvate metabolism is specific to O6-methylguanine-DNA methyltransferase caused by TMZ in the absence of MGMT and occurs long before the delayed cell death typical of GBM treated with TMZ.

Conclusions: We have demonstrated that pyruvate metabolism monitored by hyperpolarized 13C MRSI can provide a very fast and reliable way to determine the status of MGMT and predict tumor response to TMZ treatment. The reduction of Lac/Pyr in MGMT-deficient tumors as early as one day after TMZ treatment implies that the altered pyruvate metabolism is independent of the typical delayed cell death induced by TMZ and specific to DNA damage caused in the absence of MGMT. The results from this study suggest that this technique may allow neuro-oncologists to quickly evaluate patient response to TMZ and enable them to tailor customized therapy for individual patients with brain tumors.


Acknowledgement: This research was supported by an academic-industry partnership grant from the UC Discovery program in conjunction with GE Healthcare.