REVERSAL OF ADC CHANGES IN TUMORS AFTER TREATMENT AT SHORT DIFFUSION TIMES

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Introduction

Diffusion-weighted magnetic resonance imaging (DWI) has been suggested as a biomarker to detect tumor early response to treatment. The conventional DWI uses the pulsed gradient spin echo (PGSE) sequence, which uses relatively long diffusion times (e.g. >20ms) and has been shown to be sensitive to variations in cell density (1). Following treatment, the measured apparent diffusion coefficient (ADC) of tumors usually increases as cells die. Shorter diffusion times (e.g. <5ms) provide the ability to probe structure at subcellular length scales and provides a means to detect intracellular changes, including those caused by treatments, which may precede cellular variations (2). One approach to achieve short diffusion times is the oscillating gradient spin echo (OGSE) sequence (3). In the current study, both PGSE and OGSE methods have been used to study a colon cancer model (SW620) treated by Barasertib (AZD1152), a selective inhibitor of Aurora B Kinase (4). The preliminary results indicate that the change in ADC varies with diffusion time following treatment, implying tumor pathophysiological information at different length scales can be probed at different diffusion times.

Methods

Animal Preparation: Six nude mice were injected with 1×10^5 SW620 cancer cells into the right hind limb. Two weeks after the injection, they received daily treatments of 25mg/kg Barasertib dissolved in 0.2ml of drug vehicle (DMSO). Each treatment was administered by a single intraperitoneal injection. Mice were scanned at 3- and 4-day post-treatment (3 for each time point) and were then sacrificed. Tumor tissues were collected and fixed, and histological images were obtained with H&E staining.

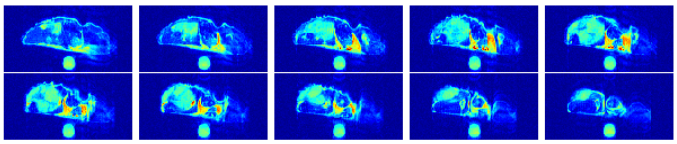

Fig.1. Representative diffusion-weighted OGSE images of ten axial slices of a mouse at frequency 250Hz. A tumor is at the right hind limb and a water phantom is beneath the mouse.

MRI Experiments: Both OGSE and PGSE sequences were implemented using a fast spin echo (FSE) acquisition on a Varian horizontal 4.7T magnet with a gradient strength up to 40G/cm. The parameters are: gradient duration δ=20ms, separation Δ=26.2ms, echo train length =8, echo spacing =9.2ms. Two b values were used: 0, 1000s/mm^2 for the PGSE method and 0, 400s/mm^2 for OGSE. Gradients with 50-250Hz were used in the OGSE method, corresponding to diffusion times approximately from 10 to 2ms. Matrix size 128×64 and FOV=40×20mm yielded an isotropic in-plane resolution 312.5μm. A twin-echo navigation method was performed to correct the motion artifacts (5).

Results

Fig. 1 shows representative diffusion-weighted OGSE images of different slices at 250Hz. The ADCs in tumors before the treatment were compared with those after 3 and 4 days of treatment. Fig.2 shows the measured ADCs of the same mouse. Tumor ADCs obtained by the PGSE method increase continuously after the treatment, presumably indicating decreasing cell density caused by cell apoptosis in response to the treatment of AZD1152 (4). By contrast, the tumor ADCs obtained by the OGSE method show a different behavior. At each time point, the ADCs measured using OGSE increased with gradient frequency, implying reduced restriction at the shorter diffusion lengths probed with higher frequencies. Post-treatment, the ADCs at low frequency (50Hz) increase slightly compared to those pretreatment, similar to the PGSE results. However, when gradient frequency is >100Hz (diffusion times <~5ms), the tumor ADCs by the OGSE method decrease after treatment, indicating an increase in the degree of hindrance to free diffusion at short length scales, consistent with increased restricting structures within the intracellular space. Both the decreased cell density and increased nuclear size at 4-day post-treatment have been confirmed with the histological analysis (images not shown).

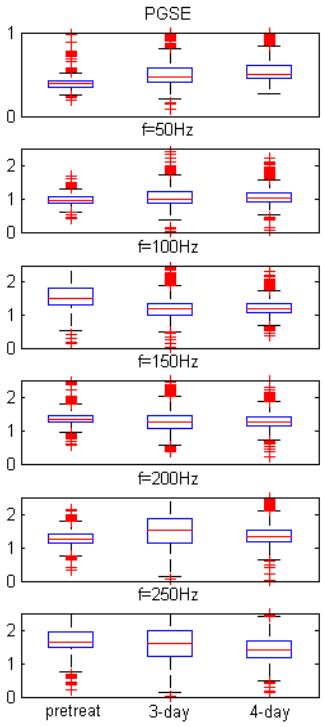

Fig.2. Comparison of ADCs at pretreatment, 3- and 4-day post-treatment. Vertical axes are ADC [μm^2/ms].

Discussion

Barasertib (AZD1152) causes DNA ploidy which significantly changes the average structural contents within affected cells (4), and hence may cause increases in intracellular restriction effects after treatment. The PGSE method with long diffusion times is not able to probe such variations, but detected increased ADCs post-treatment as cell density decreased. In contrast, the OGSE method with relatively high frequencies detected decreased ADCs. Such a change may correspond to increased DNA and other intracellular changes inside tumor cells (4). The current work demonstrates that temporal diffusion spectroscopy using OGSE spectra (6) provide novel insights into tissue microstructure, and may reveal changes within cells not detectable by conventional methods. DWI using specific gradient frequencies provides a different contrast to PGSE methods, and may provide a more sensitive means to monitor tumor early response to chemotherapy.

References: (1) Xu et al. MRM 2009. (2) Colvin et al. ISMRM 2010. (3) Parson et al. MRM 2006 (4) Wilkinson et al. Clin Caner Res 2007 (5) Mori et al. MRM 1998. (6) Gore et al. NMR Biomed 2010.

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