Assessment of chemotherapy in a mouse model of non-Hodgkin’s lymphoma using Dynamic contrast-enhanced (DCE) and diffusion weighted (DW) MRI

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Introduction: Non-Hodgkin’s lymphomas (NHLs) comprise a heterogeneous group of closely related B-cell and T-cell malignancies of the lymphatic system1. In MR physiological studies, dynamic contrast-enhanced (DCE) and diffusion weighted imaging (DWI) can serve as biomarkers of early prediction and detection of therapeutic response in cancer2. DCE-MRI utilizes a paramagnetic contrast agent (CA) for assessing tumor vascular properties. DW-MRI uses diffusion properties of water molecules to provide information on both vascular changes as well as cellular integrity. In DCE-MRI experiments, to track the interaction of water protons with CA, the Standard Model (SM) and Shutter Speed Model (SSM) are utilized for pharmacokinetic modeling. The SM model assumes a linear dependence between the change in longitudinal relaxation rate constant R1 (dR1/dΔT1) and the tissue concentration of CA3. Landis et al.4 has demonstrated transient departures from the fast exchange limit (FXL) as CA passes through the Region of Interest (ROI) or voxel. In our study, we assess the changes in kinetic model parameters obtained from the SSM and water apparent diffusion coefficient (ADC) values in the DLCL2 mouse xenograft model of diffuse large B-cell NHL treated with R-CHOP, where R refers to rituximab and CHOP is the standard chemotherapy combination of cyclophosphamide, hydroxydoxorubicin, Oncovin and prednisone.

Material and Methods: The DLCL2 cell line was implanted subcutaneously into flanks of 3-4 week old female nude mice (n =4). MR imaging was performed at 4.7 T after 4 weeks of tumor implantation using 35 mm inner diameter transmit-receive volume coil. DW-MRI was performed using the following b-values: 0, 200, 600, and 1000 s/mm2. A precontrast longitudinal relaxation time constant, T1, was acquired from the TR by using the Multiple Read Out Pulses (TMROP) sequence5, with the following imaging parameters TR/TE/FOV/matrix/NEX/slice/thickness=6ms/22 ms/1024x128x64/35 mm²/2/1 with TI (inversion time) = 4 heartbeats (480 ms), number of TI intervals = 60, and thickness 1 mm) as described elsewhere6. The DCE-MRI protocol used a T1-weighted ECG-gated saturation-recovery GRE sequence with the following imaging parameters: TR/TE/FOV/matrix/NEX/slice/thickness=7ms/2.75ms/90°/128x32/35 mm²/2/1 with TR = 1 heartbeat (120 ms) to obtain serial images (i.e., 150) from the same slice with a temporal resolution of about 5 s/image6. The dose of 0.1mmole/ kg of body weight Gd-DTPA was administered to mice by tail vein injection. DCE and DWI were again performed 5 days after treatment completion. The image processing and data analysis were performed using in house software written in Matlab. An arterial input function (AIF) was obtained from the left ventricular lumen using a baseline blood R1=1.7 s−1 and hematocrit (Hct= 0.5). The longitudinal relaxivity of CA for blood and interstitial space was set to R1 = 4.0 mM−1 s−1. The mean R1.0 value for the ROI was 1.6 s. The SM and SSM were used to calculate the vascular transfer constant Ktrans for a CA and extracellular volume fraction, ve and Ktrans, ve and the intracellular water proton lifetime, τi, respectively. All image reconstruction and data analysis were performed with an in-house software package written in Matlab (v. R2011b; Math-Works, Natick, MA). In the present work, a non- linear least square fitting method was used, and the sum of squares served as a measure of the goodness of fit. The kinetic model parameters and apparent diffusion coefficient (ADC) values were calculated before and after the RCHOP treatment. The significance of changes of these parameters was tested using a paired t-test, and significance was inferred at p ≤ 0.05.

Results and Discussions: A typical T1-weighted scout image with ROIs is shown in Fig.1. In ROIs analysis, pre-RCHOP SM Ktrans (mean Ktrans = 0.19 ± 0.12; [min−1]) and post-RCHOP SM Ktrans (mean Ktrans = 0.087 ± 0.04; [min−1]) were not significantly different (p > 0.05). The pre-RCHOP SM ve (mean ve = 0.34 ± 0.13) differed by about 45% from the post-RCHOP SM ve (mean ve = 0.18 ± 0.08). A significant difference (p = 0.04) was obtained between pre-RCHOP SSM Ktrans (mean Ktrans = 0.33 ± 0.16; [min−1]) and post-RCHOP SSM Ktrans (mean Ktrans = 0.13 ± 0.08; [min−1]). The pre-RCHOP SSM ve (mean ve = 0.6 ± 0.058) differed by about 46% from the post-RCHOP SSM ve (mean ve = 0.32 ± 0.048). Estimates of τs between pre-RCHOP (mean τs = 1.31 ± 0.20) and post-RCHOP treated (mean τs = 0.57 ± 0.17) were significantly different (p = 0.02). In our study, administration of RCHOP resulted in a significant increase (τs = 3.13, p = 0.015) in the mean ADC (pre mean ADC = (6.7 ± 0.5)×10−3 mm²/s and post mean ADC (7.80 ± 0.47)×10−3 mm²/s. The results showed no correlation between CA and ADC (p > 0.2). Significant (p <0.5) changes or decreasing trends were seen in all kinetic model parameters and ADC values after RCHOP treatment completion. In Fig. 1, we can see an inverse relationship between Ktrans and τc. Our preliminary results show that the SSM Ktrans and τc and ADC are most sensitive to these changes after the administration of RCHOP. The results demonstrated that DCE-MRI and DW-MRI measure different characters of tumors over the course of therapy. Therefore, a combination of DCE-MRI and DWI would be useful technique for the assessment of response to therapy in NHL cancer.

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References: