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 system[1]. 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 cancer[2]. 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 R_1 ($\Delta R_1 = 1/\Delta T_1$) and the tissue concentration of CA[3]. 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 this 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 chemotherapeutic combination of cyclophosphamide, hydorxydoxorubicin, 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/mm^2. A precontrast longitudinal relaxation time constant, T_{10}, was acquired from the T_1 by using the Multiple Read Out Pulses (TOMROP) sequence[6] with the following imaging parameters TR/TE/θ/FOV/matrix/NEX/slice/thickness=6ms/2.2 ms/10^0/128x64/35 mm^2/2/1 with TI (inversion time) = 4 heartbeats (480 ms), number of TI intervals = 60, and thickness 1 mm) as descried elsewhere[5]. The DCE- MRI protocol used a T_1- weighted an ECG-gated saturation-recovery GRE sequence with the following imaging parameters: TR/TE/θ/FOV/matrix/NEX/slice/thickness=7ms/2.75ms/90^0/128x32/35 mm^2/2/1 with t_s = 1heartbeat (120 ms to obtain serial images (*i.e.,* 150) from the same slice with a temporal resolution of about 5 s/image[6]. 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 R_1 = 1.7 s and hematocrit (Hct= 0.5). The longitudinal relaxivity of a CA for blood and interstitial space was set to R_1 = 4.0 mM^{-1}s^{-1}. The mean R_{10} value for the ROI was 1.6 s. The SM and SSM were used to calculate the vascular transfer constant K^{trans} for a CA and extracellular volume fraction, v_e and K^{trans}, v_e, and the intracellular water proton lifetime τ_i, 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 $p \leq 0.05$.

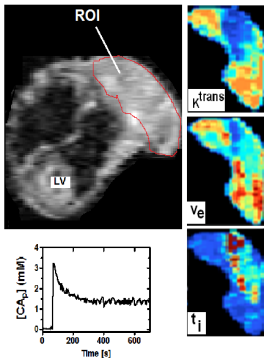

Fig.1.Top left: Precontrast T_1-weighted scout image with ROIs drawn. Bottom left: A typical AIF obtained from LV. Right: SSM parameter maps for K^{trans}, v_e and τ_i (top to bottom). The range for the scale bar for each parameter are K^{trans}: 0-0.6 min^{-1}; v_e: 0-0.6; τ_i =0-2 [s].

Results and Discussions: A typical T_1 -weighted scout image with ROIs is shown in Fig.1. In ROIs analysis, pre-RCHOP SM K^{trans} (mean K^{trans} = 0.19 ± 0.12: [min^{-1}]) and post-RCHOP SM K^{trans} (mean K^{trans} = (0.087 ± 0.04: [min-1]) were not significantly different ($p > 0.05$). The pre-RCHOP SM v_e (mean ve = 0.34 ± 0.13) differed by about 45% from the post-RCHOP SM v_e (mean v_e = 0.18 ± 0.08). A significant difference ($p = 0.04$) was obtained between pre-RCHOP SSM K^{trans} (mean K^{trans} = (0.33 ± 0.16: [min^{-1}]) and post-RCHOP SSM K^{trans} (mean K^{trans} = 0.13 ± 0.08: [min-1]). The pre-RCHOP SSM v_e (mean ve = 0.6 ± 0.058) differed by about 46% from the post-RCHOP SSM v_e (mean v_e = 0.32 ± 0.048). Estimates of τ_i s between pre-RCHOP (mean τ_i = 1.31 ± 0.20) and post-RCHOP treated (mean τ_i = 0.57 ± 0.17) were significantly different ($p = 0.02$). In our study, administration of RCHOP resulted in a significant increase ($t = 3.13$, $p = 0.015$) in the mean ADC (pre mean ADC = (6.7 ± 0.5)× 10^{-4} mm^2/s and post mean ADC (7.80 ± 0.47)× 10^{-4} mm^2/s. The results showed no correlation between ADC and v_e ($p > 0.2$).
Significant ($p < .05$) 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 K^{trans} and τ_i. Our preliminary results show that the SSM K^{trans} and τ_i and ADC are most sensitive to these changes after the administration of RCHOP. The results demonstrated that DCE-MRI and DW-MRI measure different characteristics 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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