

Longitudinal patterns of diffusion measures in children treated for B-cell Lymphoma

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PURPOSE: Approximately 80% of children treated for mature B-cell lymphoma survive, but no prospective study of early therapy-induced, subclinical alterations in white matter (WM) has been reported. These children receive a very similar chemotherapy regimen as acute lymphoblastic leukemia (ALL) patients, who show both WM structural abnormalities¹ and neurocognitive deficits² after therapy. It is hypothesized that the lymphoma patients will show WM structural abnormalities even if those are not associated with clinical signs and symptoms of myelinotoxicity. The purpose of this study is to examine early changes of cerebral white matter integrity of pediatric mature B-cell lymphoma patients during treatment using diffusion tensor imaging (DTI).

PATIENTS AND METHODS: This study included 19 patients (12 males, 7 females), ranging in age from 4.7 to 20.7 years at beginning of treatment (median=15.2 years), enrolled on an IRB approved risk adapted treatment protocol for mature B-cell lymphoma using high-dose chemotherapy without radiation therapy. Patients were scheduled to receive five magnetic resonance imaging studies: at baseline or Day 7 of therapy if unable to schedule earlier, at Day 15 of therapy, after chemotherapy course 3 or course 4 based upon risk stratification, at the end of therapy, and at 12 months post-diagnosis.

MR imaging was performed on either a 1.5T or 3T whole-body system (Siemens Medical Systems, Iselin, NJ). Conventional T1, T2, and FLAIR imaging was collected on all subjects. These images were registered to the ICBM average 152 T2 atlas aligned in Talairach space found in SPM, and resampled to a 1mm isotropic resolution using nonlinear registration tools from the FMRIB Software Library (FSL) (<http://fsl.fmrib.ox.ac.uk/fsl/>). Diffusion tensor imaging was acquired with 12 diffusion gradient directions and voxel-wise tensor calculations were performed with the DTI toolkit under SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>) to generate maps of fractional anisotropy (FA) and radial diffusion (RD). The calculated output maps were also registered to the atlas space using FSL. A previous voxel-based analysis identified bilateral continuous regions involving predominantly the anterior, superior, and posterior corona radiata and superior longitudinal fasciculus as the most common location for T2 weighted hyperintensities in ALL patients who developed treatment induced WM abnormalities³. This cluster was used as a region of interest (ROI) for the present study, and mean values for the ROI were extracted. FA was plotted as a function of time on study for each patient, and through empirical observation, two distinct groups were identified. Statistical test were performed using paired t-tests to evaluate the differences between baseline and each time point as well as between end of therapy and the 12 month follow-up for the two groups independently for both FA and RD.

RESULTS: There were a total of 71 patient examinations completed. Eleven patients were assigned to group 1 which showed a decrease in FA followed by a slow return toward baseline, and 8 patients formed group 2, demonstrating an immediate spike in FA followed by a return to normal appearing development. **Figure 1** shows the average FA and RD values for group 1 (top) and group 2 (bottom). Statistically significant differences in FA and RD between baseline and post course 3/4, and end of therapy, as well as end of therapy and the 12 month follow-up are seen in group 1. Group 2 shows statistically significant differences for FA and RD between baseline and Day15, and FA has a statistical difference between end of therapy and the 12 month follow-up.

CONCLUSIONS: Two distinct patterns of WM integrity disruption are demonstrated in this population of mature B-cell lymphoma patients. Group 1 shows a pattern consistent with a demyelinating process with subsequent slow remyelination, while group 2 could be explained by restricted diffusion that reflects therapy-related (steroids) contraction of the extracellular space that changes over time, but without actual myelinotoxicity. Implications of these patterns of early DTI change need further long-term follow-up to identify their impact on WM development as well as their neurocognitive ramifications.

REFERENCE: [1] Reddick WE et al. *Neuroradiology*. 2007;49:889-904; [2] Conklin HM et al. *J Natl Cancer Inst*. 2012;84:e363-9; [3] Reddick WE et al. *Am J Neuroradiol*. 2009;30:1947-54.

Figure 1. Average FA and RD of the two groups plotted against the average day from on study date for all patients. Statistical tests reported from paired t-tests.

