

Association Between MR Changes Early In Therapy And Later Neurocognitive Performance In Children Treated For Acute Lymphoblastic Leukemia

W. E. Reddick¹, C. L. Dirksen², J. O. Glass¹, C. Cheng³, C-H. Pui⁴

¹Div Translational Imaging Research, St. Jude Children's Research Hospital, Memphis, TN, United States, ²Div Behavioral Medicine, St. Jude Children's Research Hospital, Memphis, TN, United States, ³Dept Biostatistics, St. Jude Children's Research Hospital, Memphis, TN, United States, ⁴Dept Hematology / Oncology, St. Jude Children's Research Hospital, Memphis, TN, United States

Purpose: With improved treatment outcome in children with cancer, current emphasis is placed on the survivors' quality of life, including neurocognitive function. Acute lymphoblastic leukemia (ALL) is the most common childhood cancer, and is affecting 2,400 children annually in the United States. The 5-year event-free survival estimate for pediatric patients with ALL is approximately 80% [1]. Methotrexate given intravenously (IV-MTX) at high dose has been shown to decrease hematological, testicular and central nervous system (CNS) relapse. However, it has significant toxic effects on the CNS and can potentially lead to severe neurological morbidity. Leukoencephalopathy (LE), seen as white matter hyperintensities on T2-weighted MRI, is the most common manifestation and may be either persistent or transient [2]. The impact of these changes on neurocognitive functioning and quality life in survivors remains to be fully determined. This project focuses on the detection of leukoencephalopathy early during therapy for ALL and its association with neurocognitive performance 2.5 years later at the completion of therapy.

Methods: Consecutive patients at least one year of age enrolled on an institutional ALL treatment protocol between June 29, 2000 and June 25, 2002 were eligible for the study. Diagnosis of ALL was established by morphologic, cytochemical, immunophenotyping and genetic studies. Based on a comprehensive risk classification, including blast cell immunophenotype and genotype, presenting clinical features and early treatment response, patients were assigned to one of three risk groups: low-, standard-, and high-risk. During consolidation therapy, low-risk patients received IV-MTX at 2.5 gm/m² every other week for 4 doses, whereas standard- or high-risk patients received it at 5.0 gm/m². Written informed consent was obtained from the patient, parent, or guardian according to Institutional Review Board, NCI, and OHRP guidelines. To ensure equivalent neurocognitive testing, subjects had to be at least five years of age at end of therapy. Patients had to complete both the MR examination after the final course of IV-MTX and the neurocognitive testing at end of therapy. Exclusion criteria resulted in 70 patients eligible for this study: 40 males and 30 females aged 1.9-16.6 (mean 6.9) years at diagnosis. There were 42 subjects (5.8 years at diagnosis) in the low-risk treatment arm and 28 subjects (8.7 years at diagnosis) in the standard-/high-risk treatment arm.

MR imaging was performed on a 1.5T whole-body system using the standard circular polarized volume head coil (Siemens Medical Systems, Iselin, NJ). Nineteen 4 mm thick axial T1-weighted multi-echo inversion recovery images (TR/TE/TI = 8000/20/300 ms, 7 echos), T2/PD-weighted dual spin-echo images (TR/TE1/TE2 = 3500/17/102 ms, 7 echos), and Fluid-attenuated inversion recovery (FLAIR) images (TR/TE/TI = 9000/119/2470 ms; 7 echos) were collected with a 1 mm gap. Imaging sets were registered, RF corrected, and then analyzed with an automated computer-aided detection algorithm for therapy-induced leukoencephalopathy in young children [3].

Neurocognitive assessments included tests of intelligence (Wechsler Intelligence Scales (WISC-III or WAIS-III)), academic achievement (Abbreviated Wechsler Individual Achievement Test (WIAT)), and verbal learning and memory (California Verbal Learning Test (CVLT)). Patients were stratified according to the MR examination at completion of IV-MTX (normal or leukoencephalopathy) and neurocognitive performance at end of therapy was assessed between groups using a two-way ANOVA analysis and the influence of risk arm was assessed using a nonparametric Wilcoxon rank sum test.

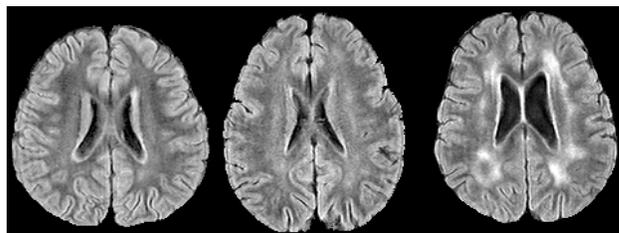


Figure 1 – FLAIR images demonstrating normal, questionable, and definitely abnormal appearance from three different 3.5 year old children.

Results and Discussions: Full Scale, Verbal and Performance IQ were all significantly lower in patients with leukoencephalopathy ($p=0.02$, $p=0.02$, $p=0.04$) and risk arm was a significant influential factor ($p=0.02$, $p=0.03$, $p=0.03$). Long delayed cued recall on the CVLT was significantly below normal for patients with leukoencephalopathy ($p=0.04$) and risk arm was a substantial factor ($p=0.09$). Long delayed free recall was also substantially below normal for patients with leukoencephalopathy ($p=0.06$) but risk was not a factor ($p=0.16$). None of the academic achievement measures were significantly different between patient groups or normative test averages. When risk was a significant factor, patients on the low-risk arm of the protocol accounted for much of the group differences. This may seem counter-intuitive because these patients receive less aggressive therapy but these patients are also significantly younger than the standard-/high-risk patients at the time of diagnosis.

Conclusion: This study establishes a significant relationship between MR changes seen early in therapy and later neurocognitive impact in children treated for ALL. In addition, the youngest patients in the low-risk arm of the treatment protocol accounted for a significant portion of the group differences in many of these measures. Additional statistical analyses are being conducted to account for both age at diagnosis and treatment risk arm.

References:

1. Pui C-H, et al. *N Engl J Med*, 350:1535-48, 2004.
2. Shuper A, et al. *Isr Med Assoc J*, 4:1050-3, 2002.
3. Glass JO, et al. *ISMRM 13th Scientific Meeting*, 2005.