

# Assessment of Neurocognitive Functions in Survivors of Childhood Acute Lymphoblastic Leukemia

*Thesis*

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**Pediatrics**

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## Abstract

Patients with childhood ALL achieve long-term disease-free survival, making reducing complications of therapy of major concerns. *The aim* of this study was to assess the prevalence and degree of neurocognitive dysfunction in survivors of childhood ALL treated with different protocols and the effect of time since end of chemotherapy.

**Patients and methods:** A cross-sectional study including 60 ALL survivors aged 0-16 years at enrollment; 2-9 years at diagnosis, CNS<sup>1</sup>, treated through 1998-2008 and regularly followed up in childhood cancer survivors clinic;. They were compared to 50 healthy age and sex matched controls. Grade of school, scholastic achievement in the previous year were reported followed by revision of hospital records including type and risk of ALL, protocol of treatment, number, type and dose of intrathecal chemotherapy, number and doses of high dose I.V methotrexate, data of cranial radiotherapy . Three different protocols were applied to these patients according to the time of diagnosis; patients diagnosed between January 1998 to December 2000 were treated with Modified BFM 83. Those diagnosed between January 2001 to June 2003 were treated with BFM 90 protocol, and those diagnosed From July 2003 to June 2008 were treated with CCG 1991 for standard risk and CCG 1961 for high risk patients. Neurocognitive functions were tested using Wechsler Intelligence Scale for Children, Benton visual retention (BVR) test and Trail making test (part A and B were done. MRI Brain was performed to the patients and control group using diffusion weighed images and diffusion tensor magnetic resonance imaging (DTI).

### Results:

Survivors treated with CCG protocol showed a significant decrease in all cognitive tests results compared to control ( $p < 0.05$ ). Survivors treated with BFM 90 protocol had a significant lower total IQ, verbal IQ, TMT-partA,

compared to both control and survivors treated with Modified BFM  $\wedge\text{r}$ , and a significant decrease in performance IQ, BVRT and TMT-partB compared to control only. No significant difference between results of cognitive tests in survivors treated with Modified BFM  $\wedge\text{r}$  and control group.

Both left and right frontal cortex apparent diffusion coefficient (ADC) was significantly higher in CCG( $.88 \pm .06$ ,  $.91 \pm .02$ ) treated group compared to control( $.79 \pm .01$ ,  $.78 \pm .01$ ), BFM  $90$ ( $.79 \pm .07$ ,  $.76 \pm .04$ ) and modified BFM  $\wedge\text{r}$ ( $.76 \pm .03$ ,  $.83 \pm .03 \times 10^{-3} \text{mm}^2/\text{s}$ ) groups ( $p < .05$ ) yet a significant decrease in FA of right frontal cortex only in CCG ( $.20 \pm .03$ ) treated group compared to control( $.78 \pm .01$ ), BFM  $90$ ( $.40 \pm .04$ ) and Modified BFM  $\wedge\text{r}$ ( $.41 \pm .02$ ) groups( $p < .05$ ). FA of right frontal was significantly lower in BFM  $90$  and Modified BFM  $\wedge\text{r}$  treated group compared to control group.

No significant correlation was found between cognitive tests results with age at diagnosis, time since the end of therapy, total number of intrathecal injections, age at radiotherapy treatment, dose and time of radiotherapy. Cognitive tests didn't differ between survivors treated with triple intrathecal therapy(ITTT) compared to those treated with intrathecal methotrexate, yet significant decrease in FA of right hippocampus in survivors who received ITTT compared to survivors treated with intrathecal monotherapy,

*Conclusion:* Neurocognitive dysfunction was a common sequelae of childhood ALL treatment. It was more related to protocol of therapy rather than the duration of follow-up since end of chemotherapy. Frontal lobe FA may be a clinically useful biomarker for the assessment of neurotoxicity in post-treatment childhood ALL survivors.

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# List of abbreviations

<b>o-MeTHF</b>	o-methyltetrahydrofolate
<b>ACC</b>	The anterior cingulate cortex
<b>ADHD</b>	Attention deficit hyperactivity disorder
<b>Ado</b>	Adenosine
<b>AL</b>	Acute lymphoblastic leukemia
<b>AML</b>	Acute myeloid leukemia
<b>APC</b>	Astrocyte precursor cell
<b>BFM</b>	Berlin-Frankfurt-Munster
<b>BVRT</b>	Benton Visual Retention Test
<b>CCG</b>	Children's Cancer Group
<b>CI</b>	Cranial irradiation
<b>Cig</b>	Cytoplasmic immunoglobulin
<b>CNS</b>	Central nervous system
<b>COG</b>	Children Oncology Group
<b>CR</b>	Complete remission
<b>CRT</b>	Cranial radiation therapy
<b>CSF</b>	Cerebrospinal fluid
<b>DFS</b>	Disease-free survival
<b>DHF</b>	Dihydrofolate
<b>DHFR</b>	Dihydrofolate reductase
<b>DTI</b>	Diffusion tensor imaging
<b>EAA</b> s	Excitatory aminoacids
<b>EFS</b>	Event-free survival

# List of abbreviations

<b>FAB</b>	French-American-British
<b>FR<math>\alpha</math></b>	Folate receptor- $\alpha$
<b>GABA</b>	Gamma amino butyric acid
<b>GC</b>	Glucocorticoids
<b>GRP</b>	Glial-restricted precursor
<b>Hcy</b>	Homocysteine
<b>HIF-<math>\alpha</math></b>	Hypoxia-inducible factor- $\alpha$
<b>HR</b>	High-risk
<b>Ig</b>	Immunoglobulin
<b>IL</b>	Interleukins
<b>IQ</b>	Intelligence quotient
<b>IT</b>	Intrathecal
<b>IV</b>	Intravenous
<b>LPFC</b>	Lateral prefrontal cortex
<b>MD</b>	Mean diffusivity
<b>MLL</b>	Myeloid/lymphoid or mixed lineage leukemia
<b>MMPs</b>	Matrix metalloproteinases
<b>MOPP</b>	Methotrexate, vincristine, prednisone, and procarbazine
<b>MR</b>	Magnetic resonance
<b>MRC</b>	Medical Research Council
<b>MRD</b>	Minimal residual disease
<b>MRI</b>	Magnetic resonance imaging
<b>MS</b>	Methionine synthase

# List of abbreviations

<b>MTX</b>	Methotrexate
<b>NMDA</b>	<i>N</i> -methyl-D-aspartate
<b>NPCs</b>	Neural progenitor cells
<b>NRP</b>	Neuron-restricted precursor
<b>NSC</b>	Neural stem cell;
<b>NSE</b>	Neuron-specific enolase
<b>NSS</b>	Neurological severity scale
<b>O-<math>\gamma</math>A/OPC</b>	Oligodendrocyte precursor cell
<b>OS</b>	Overall survival
<b>PCFT</b>	Proton coupled folate transporter
<b>PCR</b>	Polymerase chain reaction
<b>PIQ</b>	Performance IQ
<b>POG</b>	Paediatric Oncology Group
<b>PTSD</b>	Posttraumatic stress disorder
<b>RFC</b>	Reduced folate carrier
<b>SAH</b>	<i>S</i> -adenosyl homocysteine
<b>SAM</b>	<i>S</i> -adenosyl methionine
<b>SCT</b>	sluggish cognitive tempo
<b>SPOG</b>	Swiss Pediatric Oncology Group
<b>THF</b>	Tetrahydrofolate
<b>TMT</b>	Trail Making Test
<b>TNF</b>	Tumour necrotic factor
<b>VCAM</b>	Vascular cellular adhesion molecule
<b>VEGF</b>	Vascular endothelial growth factor

# List of abbreviations

<b>VHR</b>	Very high-risk
<b>VIQ</b>	Verbal intelligence quotient
<b>WBC</b>	White blood cell
<b>WHO</b>	World Health Organization
<b>WISC</b>	Wechsler Intelligence Scale for Children
<b>WMFA</b>	White matter fractional anisotropy

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