Assessment of Neurocognitive Functions in Survivors of Childhood Acute Lymphoblastic Leukemia

Thesis

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By
Shaimaa Nasr Amin
M B, B Ch
Faculty of Medicine
Cairo University

Supervised By

Prof.Dr. **Mohsen Saleh El Alfy**

Professor of Pediatrics
Faculty of Medicine
Ain Shams University

Assistant Prof.Dr. **Enas Ahmed Azab**

Assistant professor of Radiodiagnosis
Faculty of Medicine
Ain Shams University

Dr. **Iman Ahmed Ragab**

Lecturer of Pediatrics
Faculty of Medicine
Ain Shams University

Faculty of Medicine
Ain-Shams University
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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 ٦٠ ALL survivors aged ٥-١٦ years at enrollment; ٢-٩ years at diagnosis, CNS١, treated through ١٩٩٨-٢٠٠٨ and regularly followed up in childhood cancer survivors clinic;. They were compared to ٢٠ 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 ١٩٩٨ to December ٢٠٠٠ were treated with Modified BFM ٨٣. Those diagnosed between January ٢٠٠١ to June٢٠٠٤ were treated with BFM ٩٠ protocol, and those diagnosed From July ٢٠٠٤ to June ٢٠٠٨ were treated with CCG ١٩٩١ for standard risk and CCG ١٩٦١ 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 ٩٠ protocol had a significant lower total IQ, verbal IQ, TMT-partA,

compared to both control and survivors treated with Modified BFM ٨٣, 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 ٨٣ and control group.

Both left and right frontal cortex apparent diffusion coefficient (ADC) was significantly higher in CCG(.٨٨±.٠٦٠, .٩١±.٠٢٨) treated group compared to control(.٦٩٥±.٠٠١٨, .٦٨٤±.٠٠١٨), BFM ٩٠(.٧٩±.٠٧١, .٧٦±.٠٤٨) and modified BFM ٨٣(.٧٦±.٠٣٠, .٨٣±.٠٢٣×١٠−٣mm²/s) groups (p<٠,٠٠٥) yet a significant decrease in FA of right frontal cortex only in CCG (.٢٥٠±.٠٣٩)treated group compared to control(.٦٨٤±.٠٠١٨), BFM ٩٠(.٤٥٠±.٠٤٢) and Modified BFM ٨٣(.٤١±.٠٢٨) groups(p<٠,٠٠٥). FA of right frontal was significantly lower in BFM ٩٠ and Modified BFM ٨٣ 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

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

List of abbreviations

FAB	French-American-British
FRα	Folate receptor-α
GABA	Gamma amino butyric acid
GC	Glucocorticoids
GRP	Glial-restricted precursor
Hcy	Homocysteine
HIF١alpha	Hypoxia-inducible factor-١alpha
HR	High-risk
Ig	Immunoglobulin
IL	Interleukins
IQ	Intelligence quotient
IT	Intrathecal
IV	Intravenous
LPFC	Lateral prefrontal cortex
MD	Mean diffusivity
MLL	Myeloid/lymphoid or mixed lineage leukemia
MMPs	Matrix metalloproteinases
MOPP	Methotrexate, vincristine, prednisone, and procarbazine
MR	Magnetic resonance
MRC	Medical Research Council
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
MS	Methionine synthase

List of abbreviations

MTX	Methotrexate
NMDA	*N*-methyl-D-aspartate
NPCs	Neural progenitor cells
NRP	Neuron-restricted precursor
NSC	Neural stem cell;
NSE	Neuron-specific enolase
NSS	Neurological severity scale
O-٢A/OPC	Oligodendrocyte precursor cell
OS	Overall survival
PCFT	Proton coupled folate transporter
PCR	Polymerase chain reaction
PIQ	Performance IQ
POG	Paediatric Oncology Group
PTSD	Posttraumatic stress disorder
RFC	Reduced folate carrier
SAH	*S*-adenosyl homocysteine
SAM	*S*-adenosyl methionine
SCT	sluggish cognitive tempo
SPOG	Swiss Pediatric Oncology Group
THF	Tetrahydrofolate
TMT	Trail Making Test
TNF	Tumour necrotic factor
VCAM	Vascular cellular adhesion molecule
VEGF	Vascular endothelial growth factor

List of abbreviations

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

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