

Evaluation of Cognitive Function in Childhood Cancer Patients

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Keyword:

Cognitive function,
childhood cancer
patients,
chemotherapy

Abstract

Background Survival rates of children with cancer are currently increasing. The long-term effects of chemotherapy as primary treatment for childhood cancer patients urge physicians' considerations. Cognitive dysfunction, as one of devastating long-term effects of chemotherapy, is known to disrupt quality of life in childhood cancer patients.

Objective This study was to investigate cognitive function in childhood cancer patients.

Methods This cross-sectional study was conducted from April to November 2019 at Haji Adam Malik General Hospital, Medan, North Sumatera, Indonesia. Fifty-four childhood cancer patients who received chemotherapy were enrolled. Cognitive function in childhood cancer patients were measured with Wechsler Intelligence Scale for Children-Revised (WISC-R) test, composed of Full scale IQ (F IQ), Verbal scale IQ (V IQ), and Performance scale IQ (P IQ) scores.

Results The WISC-R test results showed median F IQ, V IQ, and P IQ scores of 86 (47-114), 85 (44-115), and 85 (22-113), respectively. There was no significant difference of IQ scores between male and female patients. Children with age of diagnosis <6 years old had higher F IQ and V IQ [89 (80-105) vs. 84.5 (47-114) and 93.5 (79-109) vs. 81 (44-115); $P=0.04$ and $P=0.02$, respectively). There was no correlation between chemotherapy duration and intrathecal (IT) methotrexate administration with cognitive function. However, administration of high dose intravenous (IV) methotrexate had a negative correlation with F IQ, V IQ, and P IQ ($r=-0.436$, $r=-0.381$, and $r=-0.392$; $P=0.007$, $P=0.017$, and $P=0.015$, respectively).

Conclusion It was concluded that high dose iv methotrexate compromises cognitive function in childhood cancer patients, therefore evaluation of cognitive function is warranted.

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INTRODUCTION

The increase in the survival rate of childhood cancer patients receiving chemotherapy nowadays is 95%. However, long-term effects of chemotherapy are becoming burdensome problems, one of them is cognitive dysfunction.¹ Post-chemotherapy cognitive impairment (PCCI) or cognitive dysfunction due to chemotherapy is defined as a disorder in the process of understanding such as knowledge, memory, attention, judgment, problem-solving, and other behavioral parameters.^{2,3} Cognitive dysfunction associated with chemotherapy occurs in one third or more than 350,000 survivors of childhood cancer patients in America.⁴

Cognitive dysfunction may be experienced by childhood cancer patients who are currently upon treatment or remission period. Janelins et al revealed that 30% and 75% of cancer patients experienced cognitive impairment at the initial and during treatment period, respectively; and as much as 35% of cancer survivors experienced significant cognitive impairment.⁵ Furthermore, cognitive dysfunction may reduce the quality of life cancer patients and their families.⁶

Wechsler Intelligence Scale for Children-Revised (WISC-R) test is a method to evaluate cognitive function. This test allows children to demonstrate pattern recognition, attention to details, memory and spatial reasoning. Previous study showed that childhood cancer patients upon chemotherapy had lower WISC-R test scores than control group. The childhood cancer patients then were receiving radiation and prophylactic central nervous system regimens, such as intrathecal methotrexate.⁷ To the best of our knowledge, this is the first study to investigate the cognitive function in childhood cancer patients who receive chemotherapy in North Sumatera, Indonesia.

METHODS

This study was a cross-sectional study conducted in Haji Adam Malik General Hospital, North Sumatera, Indonesia from April to November 2019. All parents signed an informed consent form prior to evaluation

of cognitive function. This study was approved by the Ethics Committee of Faculty of Medicine, Universitas Sumatera Utara (No. 345/TGL/KEPK FK USU-RSUP HAM/2019) in accordance with the principles of the Helsinki Declaration.

Patients

The inclusion criteria were childhood cancer patients aged 6 – 18 years who had been receiving chemotherapy or had finished serial chemotherapy regimens with no history of cranial irradiation (locally or as part of the total body irradiation). Childhood cancer patients with attention deficit hyperactivity disorder (ADHD), physical or mental disability, and poor compliance to chemotherapy regimens were excluded. Childhood cancer patients involved in our study were receiving chemotherapy regimen prescribed by pediatric hemato-oncology consultant based on the staging and diagnosis of their respective malignancies.

Instrument

Cognitive function in childhood cancer patients were measured with Wechsler Intelligence Scale for Children-Revised (WISC-R) test. The Wechsler Intelligence Scale for Children-Revised is an individually administered intelligence test for children between the ages of 6 and 16. It generates a Full scale, Verbal scale, and Performance scale IQ (F IQ, V IQ, and P IQ) with their respective subtests that represent children's abilities in cognitive domains. IQ scores range and classifications were as follows: (1) above average [IQ 110-119], (2) average [IQ 90-109], (3) low average [IQ 80-89], (4) borderline [IQ 70-79], and (5) mental retardation [IQ <69]. The test was performed by registered child psychologist from Faculty of Psychology, Universitas Sumatera Utara, Medan, Indonesia.

Data analysis

Data had been analyzed using SPSS version 22.0 (IBM Corporation, New York, USA). Mann-Whitney U test was performed to investigate the relationship between intelligence quotient (IQ) test results with

Table 1. Basic characteristics of childhood cancer patients

Variable	n = 54
Ages	
6 - 10 years old, n(%)	28 (51.9)
≥ 10 - <18 years old, n (%)	26 (48.1)
Gender, n (%)	
Male	31 (57.4)
Female	23 (42.6)
Nutritional status, n (%)	
Severe malnutrition	7 (13.0)
Mild-moderate malnutrition	11 (20.4)
Well-nourished	24 (44.4)
Overweight	12 (22.2)
Education, n (%)	
Attending school	13 (24.1)
Not attending school	34 (62.9)
No information	7 (13.0)
Diagnosis, n (%)	
Hematological malignancies	
Acute lymphoblastic leukemia	44 (81.8)
Acute myeloblastic leukemia	3 (5.6)
Hodgkin lymphoma	1 (1.8)
Non-Hodgkin lymphoma	3 (5.6)
Solid tumor	
Adenocarcinoma colon	1 (1.8)
Osteosarcoma	2 (3.4)
Age of diagnosis	
< 6 years old, n(%)	14 (25.9)
≥ 6 years old, n(%)	40 (74.1)
Length of chemotherapy, n (%)	
6– 12 months	32 (59.3)
≥ 1 years	22 (40.7)
Level of WISC-R, n (%)	
Mental retardation (IQ < 69)	3 (5.6)
Borderline (IQ 70 – 79)	8 (14.8)
Low Average (IQ 80 – 89)	27 (50.0)
Average (IQ 90 – 109)	15 (27.8)
Above average (IQ 110-119)	1 (1.9)
Number of patients administered methotrexate, n(%)*	
Intrathecal methotrexate	49 (90.7)
High-dose methotrexate	34 (62.9)

*) one patient may be administered both intrathecal and high-dose methotrexate

gender and age of diagnosis in childhood cancer patients. Spearman correlation test was used to investigate the relationship between cognitive function with duration of chemotherapy and administration of high dose methotrexate. Statistical significance was considered on P value <0.005 .

RESULTS

A total of 54 childhood cancer patients were enrolled in this study. Patients' basic characteristics were described in Table 1. Among the patients enrolled, 57.4% of the patients were male and 42.6% were female with a median age of 9.7 years. Hematological malignancies such as acute lymphoblastic leukemia, acute myeloblastic leukemia, Hodgkin lymphoma and non-Hodgkin lymphoma occurred in 81.8%, 5.6%, 1.8%, and 5.6% patients, respectively. Solid tumor such as adenocarcinoma colon and osteosarcoma only occurred in 1.8% and 3.4% patients, respectively. It was shown that acute lymphoblastic leukemia was the most common diagnosis of childhood cancer patients in our center. Age of diagnosis is an important determinant of the cancer's prognosis. In our study, most patients (74.1%) were diagnosed at the age of more than 6 years old. The duration of chemotherapy in 32 patients (59.3%) were less than 1 year. About 63% of the childhood cancer patients involved in this study were no longer attending the school as their formal education. The results of WISC-R test showed 50.0% and 27.8% of patients had low average and average IQ scores, respectively, while others had borderline or mental retardation IQ scores.

Table 2 showed the WISC-R test results performed by the patients involved in this study. The test was carried out for full scale IQ (F IQ), verbal scale IQ (V IQ), and performance scale IQ (P IQ) assessment. The median score of F IQ was 86 (range 47-114), median score of V IQ was 85 (range 44-115) with varying scores for respective components. The median score of P IQ was 85 (range 22-113); some patients on the component of coding and object assembly were not able to perform the test appropriately.

Only component of similarities subtest for V IQ

Table 2. WISC-R test results

Variable	Median (range)
Fullscale IQ	86 (47-114)
Verbal scale IQ	85 (44-115)
Information	7 (2-14)
Comprehension index	7 (1-15)
Arithmetic	8 (3-15)
Similarities	9 (3-18)
Digital Span (vocabulary)	8 (2-15)
Performance scale IQ	85 (22-113)
Picture completion	6 (1-10)
Picture arrangement	8 (1-18)
Block design	10 (1-14)
Object assembly	6 (0-18)
Coding	9 (0-20)

showed significant score difference between male and female [median score 10 (range 4-18) vs. median score 8 (range 3-16); $P=0.03$], while other components showed no significant IQ score difference between male and female (Table 3). This study showed an association between IQ scores and age of diagnosis of childhood cancer patients. Fullscale and verbal IQ scores of patients with age of diagnosis less than 6 years old were significantly higher than their counterparts [median 89 (range 80-105) vs. median 84.5 (range 47-114) and median 93.5 (range 79-109) vs. median 81 (range 44-115), respectively; $P=0.04$ and $P=0.02$, respectively]. However, there was no significant difference between age of diagnosis with P IQ (Table 4).

There was no correlation between duration of chemotherapy with cognitive function in childhood cancer patients enrolled in our study (Table 5). Many children (59.3%) were exposed to chemotherapy for less than 12 months in this study. The chemotherapeutic drug methotrexate is known to affect the cognitive function in patients with cancer. Based on the protocol of chemotherapy regimen, 49 and 34 patients received intrathecal (IT) methotrexate and high-dose

Table 3. Gender and WISC-R test results in childhood cancer patients

Parameter	Gender		<i>P</i> *
	Male	Female	
F IQ	86 (48-114)	86 (47-107)	0.48
V IQ	85 (56-115)	84 (44-114)	0.45
P IQ	83 (42-113)	87 (22-113)	0.21
Verbal scale IQ subtests			
- Information	7 (4-12)	7 (2-14)	0.43
- Comprehension index	8 (1-13)	7 (1-15)	0.21
- Arithmetic	8 (3-14)	7 (3-15)	0.47
- Similarities	10 (4-18)	8 (3-16)	0.03
- Digital span (vocabulary)	8 (3-15)	9 (2-14)	0.13
Performance scale IQ subtests			
- Picture completion	6 (1-9)	5 (1-10)	0.22
- Picture arrangement	8 (1-14)	8 (1-18)	0.38
- Block design	10 (1-14)	10 (5-14)	0.41
- Object assembly	6 (2-18)	6 (0-13)	0.37
- Coding	9 (3-20)	9 (0-20)	0.35

Mann-Whitney* testTable 4. Age of diagnosis and WISC-R test results in childhood cancer patients**

Parameter	Age of diagnosis		<i>P</i> *
	< 6 years old	≥ 6 years old	
F IQ	89 (80-105)	84,5 (47-114)	0.04
V IQ	93.5 (79-109)	81 (44-115)	0.02
P IQ	88 (78-100)	82.5 (22-113)	0.08
Verbal scale IQ subtests			
- Information	7 (5-12)	7 (2-14)	0.31
- Comprehension index	8 (3-13)	7 (1-15)	0.17
- Arithmetic	10 (7-15)	7 (3-14)	0.001
- Similarities	10 (6-14)	9 (3-18)	0.11
- Digital span (vocabulary)	7 (6-11)	9 (2-15)	0.09
Performance scale IQ subtests			
- Picture completion	6 (4-8)	5 (1-10)	0.01
- Picture arrangement	8 (4-14)	8 (1-18)	0.36
- Block design	9,5 (7-12)	10 (1-14)	0.43
- Object assembly	7 (4-9)	6 (0-18)	0.12
- Coding	9 (5-20)	9 (0-20)	0.48

**Mann-Whitney* test

Table 5. Chemotherapy duration and WISC-R test results in childhood cancer patients

n = 54	Median (range)	r	P*
Chemotherapy duration, weeks	21.5 (1-118)		
F IQ	86 (47-114)	-0.094	0.50
V IQ	85 (44-115)	0.090	0.26
P IQ	85 (22-113)	-0.024	0.43

**Spearman* correlation test

Table 6. Intrathecal (IT) methotrexate administration and WISC-R test results in childhood cancer patients

n = 49	Median (range)	r	P*
Total IT methotrexate administration	9 (1-19)		
F IQ	87 (47-114)	-0.089	0.27
V IQ	85 (44-115)	0.129	0.19
P IQ	85 (22-113)	0.007	0.48

**Spearman* correlation test

Table 7. High-dose intravenous (IV) methotrexate administration and WSIC-R test results in childhood cancer patients

n = 34	Median (range)	r	P*
High-dose IV methotrexate administration, cumulative dosage (g/m ²)	30 (10-60)		
F IQ	87 (47-105)	-0.436	0.007
V IQ	89 (56-114)	-0.381	0.017
P IQ	87 (46-113)	-0.392	0.015

**Spearman* correlation test

intravenous (IV) methotrexate, respectively. This study showed no correlation between the administration of IT methotrexate with cognitive function presented with F IQ, V IQ, and P IQ scores ($r=-0.089$, $r=0.129$, and $r=0.007$; $P=0.27$, $P=0.19$, $P=0.48$, respectively) (Table 6). However, there was correlation found between high-dose IV methotrexate (1 gram/m²BSA) administration with cognitive function presented with F IQ, V IQ, and P IQ scores ($r=-0.436$, $r=-0.381$, and $r=-0.392$; $P=0.007$, $P=0.017$, and $P=0.015$, respectively) (Table 7).

DISCUSSION

Cognitive dysfunction related to chemotherapy in pediatric cancer is characterized by a decrease in F IQ and other functions such as attention, memory, executive function, speed of thinking, visual and motor integration.⁴ In this study, 54 children with chemotherapy, 27 (50%) children had low-average IQ, 8 (14.8%) borderline IQ and 3 children with mental retardation. Difficulties in learning and working together in groups were experienced in daily life. Decreasing quality of life occurred in patients where as many as 34 (63%) patients did not attend school

because of treatment schedules and decreased ability to learn.

Risk factors for cognitive dysfunction in children with cancer depend on the host, cancer itself, and its treatment. In solid tumors, the prevalence of cognitive dysfunction varies from 15 - 50%.⁸ Many studies showed that leukemia survivors had lower IQ compared to children with solid tumors outside the central nervous system.⁹ Several studies had shown gender as a risk factor for cognitive dysfunction in children with cancer. Research by Kotb, et al. in adult patients with leukemia, 62% of patients experienced cognitive dysfunction 6 months after complete chemotherapy. The neurocognitive function did not relate to gender in that study.¹⁰ However, the literature review in children showed that females had worse IQ performance.^{11,12} Based on gender, there was no significant difference of F IQ, V IQ, and P IQ scores between male and female patients involved in this study. Only Similarities subtest examination for V IQ test in male patients had significantly higher score than female patients.

The risk factor in post-chemotherapy cognitive impairment from the host is younger age at the time of diagnosis and starting treatment. Exposure to chemotherapy agents in children from a younger age, especially during the golden period the child's growth and development greatly affects cognitive function.^{13,14,15} Study of children with acute lymphoblastic leukemia by Sherief et al. found that the F IQ and P IQ were significantly lower in children with cancer than controls. Children with age of diagnosis less than 5 years old had lower F IQ and P IQ than children with age of diagnosis more than 5 years old (69.48 vs 45.96, 92.45 vs 98.41, respectively; $P < 0.05$).¹² A large-scale study of 866 children (acute lymphoblastic leukemia and control patients) showed an average F IQ was 101 (SD 15), V IQ was 99.6 (SD 15), and P IQ was 102 (SD 16) at 5 months after diagnosis. Children with aged less than 5 years had lower F IQ than those aged more than 5 years at the initial treatment ($P = 0.005$).¹⁵ Full scale and verbal scale IQ scores of childhood cancer patients diagnosed after aged 6 years were lower

than those who diagnosed below aged 6 years. This results appeared to be contradictory with the previous studies. This may occurred since we have only small number of children with the age of diagnosis below 6 years.

The duration of chemotherapy also has a relationship with cognitive function in children with cancer.¹¹ Cognitive dysfunction in children with cancer can be found before starting the treatment, during treatment, or gradually increase several years after completing chemotherapy protocol for cancer.² Until now it was unclear on how long the time exposure needed for chemotherapy to cause disturbances in cognitive function. On a systematic review, several studies in adults showed that cognitive function changed at a median of 1.9 years post solid tumor chemotherapy. Other study showed cognitive function disturbances after 3.5 years of chemotherapy and even occurred after long-term follow-up to 10 years.⁸

Meta-analyses conducted in children with cancer, especially acute lymphoblastic leukemia, showed a strong relationship between chemotherapy-only treatment and long-term neurocognitive deficiency, especially in intelligence, memory, and speed of information processing.¹⁶ While the long-term study of 94 patients with acute lymphoblastic leukemia described a median F IQ, V IQ, and P IQ scores of 102 (range 94-115), 105 (range 96-115), and 99 (range 88 -111), respectively, on the initial test. All IQ ranges had stable patterns in the second and third tests after 3 and 6 years from the time of initial diagnosis.¹⁷ Our study did not revealed any correlation between the duration of chemotherapy with cognitive function. More patients were exposed to chemotherapy for less than 12 months duration. Further study aimed to evaluate the relationship of cognitive function with long-term chemotherapy duration is warranted.

The drug type, dosage, and administration methods of chemotherapy agents may affect cognitive function of the childhood cancer patients. Parenteral administration of chemotherapy agents has a deteriorating effect on cognitive function. Chemotherapy agents that can cross the blood-brain

barrier such as methotrexate and 5-fluorouracil have a detrimental effect on cognitive function. Chemotherapy agents are unable to be hybridized by the blood-brain barrier because of its large molecular size can cause brain toxicity indirectly through pro-inflammatory cytokine pathways.¹⁰ In the white matter section of the brain, there are neuron cells with various functions. Oligodendrocytes that produce and maintain myelin, fat that forms a protective nerve fiber, and astrocytes to connect neurons with the blood supply that supports them and microglia, immune cells in the brain. Postmortem studies on children who received chemotherapy, found fewer oligodendrocyte cells in the brain compared to controls.^{18,19}

In this study, there was no significant correlation between the mode of administration IT methotrexate chemotherapy agent with cognitive function. However, we found significant negative correlation of the administration of high-dose IV methotrexate with cognitive function. Similar to study on leukemia survivors 5 years after chemotherapy, it had been shown that exposure to high-dose methotrexate was related to flexibility function. The amount of IT methotrexate administration was not associated with poor outcomes of cognitive function.¹ Methotrexate is a common chemotherapy agent in children, given either through parenteral, intrathecal, or intravenous administration. Methotrexate crosses the blood-brain barrier and several studies state the dosage and method of administration correlate with the incidence and severity of cognitive dysfunction.^{20,21} There were several limitations on this study. We only measured cognitive function at one-time period. Most of patients subjects involved in this study were exposed to chemotherapy agents for a short-time period and we have no previous data on the patients' cognitive function. However, this study may serve as preliminary data for further study on cognitive function in childhood cancer patients receiving chemotherapy.

CONCLUSION

Administration of high dose methotrexate compromises cognitive function in childhood cancer

patients. Therefore, evaluation of cognitive function in childhood cancer patients receiving chemotherapy is warranted.

FUNDING SOURCES

The author(s) disclosed receipt of the following financial support for the study and publication of this article: This work was supported by TALENTA Universitas Sumatera Utara, Medan, Indonesia (grant number: 27/UN5.2.3.1/PPM/KP-TALENTA USU/2019).

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