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Neurocognitive Evaluation of Japanese Childhood Cancer Survivors

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Abstract: Long-term cognitive effects following acute lymphoblastic leukemia treatment have been reported for Caucasians; however, these data remain unclear for other ethnicities and the treatment of other cancers. Here, we assessed cognitive function in Japanese childhood cancer survivors. This study enrolled 53 Japanese survivors of childhood cancer (mean age, 9.5 years; 36 boys and 17 girls). We evaluated performance-based cognitive function using the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-Ⅳ). Deviation intelligence quotients (IQ) for verbal comprehension (VC), perceptual reasoning (PR), processing speed (PS), and working memory (WM) were compared with the standardized mean and standard deviation (SD; 100 and 15, respectively). We classified patients into three groups depending on the cumulative methotrexate (MTX) dose (none, 1-19 g / m^2, and $>$ 20 g / m^2). Full-scale IQ was within normal range at 104.8 (SD, 12.9), although there were significant differences among the four WISC-Ⅳ index scores ($P < 0.001$). The PS score (97.1 ± 15.5) was significantly lower than the VC (107.2 ± 15.8) and PR (105.3 ± 14.2) scores (both $P < 0.005$). WM performance decreased in an MTX dose-dependent manner (107.8, 102.6, and 96.5 for none, 1-19 g / m^2, and higher than 20 g / m^2, respectively; $P = 0.05$). Japanese childhood cancer survivors, including those in the non-MTX group, demonstrated significant PS impairment. High-dose MTX treatment might be associated with neurocognitive deficiencies, particularly in WM. Although current treatments are associated with high cure rates, future research and interventions are required to improve cognitive function in these patients.

Key words: chemotherapy-induced cognitive impairment, childhood cancer survivors, cognitive function, methotrexate

Introduction

Treatment for childhood cancer has improved dramatically in recent years, resulting in estimated survival rates higher than 70%[1)]. Nevertheless, childhood cancer survivors, especially those with acute lymphoblastic leukemia (ALL), are at risk of late, adverse, neurocognitive effects, including difficulties with attention, visual-motor function, processing speed, and working

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memory[2,3]. Risk factors for neurocognitive difficulties include the need for greater intensity of cranial radiation therapy (CRT)[4-6], high-dose methotrexate (MTX) treatment[6,7], and younger age at diagnosis[8,9]. While late neurocognitive adverse effects have been reported in childhood ALL especially for Caucasians, there has been a limited focus on other types of childhood cancer and ethnicities. To our knowledge, no published reports have examined the effects of treatment in Japanese patients with childhood cancer. This study aimed to assess cognitive function in Japanese patients with childhood cancer whose conditions remained stable after acute-phase treatment.

Patients and Methods

1. Participants (Table 1)

This study was part of a larger cross-sectional survey of cognitive function following treatment for childhood cancer. Participants were 53 Japanese survivors of childhood cancer (mean age, 9.5±3.2 [range, 5-16] years; 36 boys and 17 girls; ALL, n=37; acute myeloid leukemia [AML], n=6; chronic myeloid leukemia [CML], n=1; lymphoma, n=2; and solid tumors, n=7), recruited from the outpatient pediatric clinic of Showa University Fujigaoka Hospital. All participants completed acute-phase treatment and remained stable with no history of neurological disease or injury. None of the patients had a history of premorbid learning disabilities or other developmental conditions before the initial treatment. The treatment protocols varied by participant, but mostly included systemic corticosteroid, systemic MTX, and / or cytarabine administration. Four patients received CRT. Written informed consent was obtained from the parents, while the children agreed to be interviewed and to undergo the assessment. The study was approved by the Ethics Committee of Showa University Fujigaoka Hospital, Institutional Review Board (Permit Number: 2016037) and was conducted following the provisions of the Declaration of Helsinki.

Table 1. Patient characteristics

Number of patients	53
Sex: male / female	36 / 17
Age: median (range)	9.5years (5-16 years)
Day of examination post hospital discharge: median (range)	1,369 days (62-4,815 days)
ALL / AML / CML / ML / ST	37 / 6 / 1 / 2 / 7
Cranial irradiation (+ / -)	4 / 49
HD-MTX (+ / -)	39 / 14
IT (+ / -)	46 / 7

ALL: acute lymphoblastic leukemia, AML: acute myeloid leukemia, CML: chronic myeloid leukemia, ML: malignant lymphoma, ST: solid tumor,
Cranial irradiation: cranial irradiation with 12 to 24grays,
HD-MTX: high-dose methotrexate (10 g / m^2 or 20 g / m^2),
IT: intrathecal therapy (MTX, cytarabine, and steroids).

2 Assessments

We evaluated performance-based cognitive function using the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV). Examiners were Master-level licensed psychologists qualified and experienced in administering the WISC-IV. The WISC-IV provides a full-scale intelligence quotient (FSIQ) score, as well as four composite Index Scores, and has a standardized mean and standard deviation (SD) of 100 and 15, respectively. The Index Scores for four domains were calculated based on the following subtests; Verbal Comprehension (VC; composed of the Vocabulary and Similarities subtests), Perceptual Reasoning (PR; Block Design and Matrix Reasoning subtests), Working Memory (WM; Digit Span and Letter-Number Sequencing subtests), and Processing Speed (PS; Coding and Symbol Search subtests). All scaled scores and Index Scores were derived from the raw scores based on the Japanese standardization sample data. The WISC-V was not released in Japan at the time of data collection.

3. Data analysis

All data were analyzed using the Statistical Package for the Social Sciences (IBM Corp., Armonk, NY). The box plot revealed no extreme outliers, and the WISC-IV FSIQ and all WISC-IV Index Scores were normally distributed. Repeated-measures analysis of variance was performed to examine differences among the cognitive performance domains using the four WISC-IV Index Scores as intra-individual factors. Bonferroni post-hoc pairwise comparisons were also conducted, while Spearman's correlations were used to examine the relationships between age at diagnosis, counts of intrathecal therapy (IT), counts of high-dose MTX therapy, counts of cytarabine therapy, days between complete response and testing, and cognitive performance. We divided the patients in three groups depending on the cumulative MTX dose (none, moderate [1-19 g / m^2], and high [higher than 20 g / m^2]) to explore associations between the cumulative MTX dose and cognitive function. Finally, we performed subgroup analysis of the high, cumulative MTX-dose group because previous studies indicated that MTX treatment could affect cognitive function. To avoid type I error due to multiple comparisons, the significance level for all analyses was set to 0.005 (two-tailed).

Results

The FSIQ was 104.8±15.5, which was within the age-matched average range for the general population. Meanwhile, there were significant differences among the four WISC-IV Index Scores ($F[3,156]=7.893$, $P<0.001$). Post-hoc analysis revealed the PS score (97.1±15.5) to be significantly lower than the VC (107.2±15.8) and PR (105.3±14.2) scores (each $P<0.005$, Bonferroni corrected) (Fig. 1). In addition, although age at diagnosis, counts of IT, counts of cytarabine therapy, and days between complete response and testing were not associated with a cognitive function domain, the counts of high-dose MTX therapy were significantly correlated with poor WM performance ($r=-0.342$, $P=0.013$) (Table 2). Accordingly, we observed a decreasing trend in WM performance as the MTX dose increased; WM scores for none,

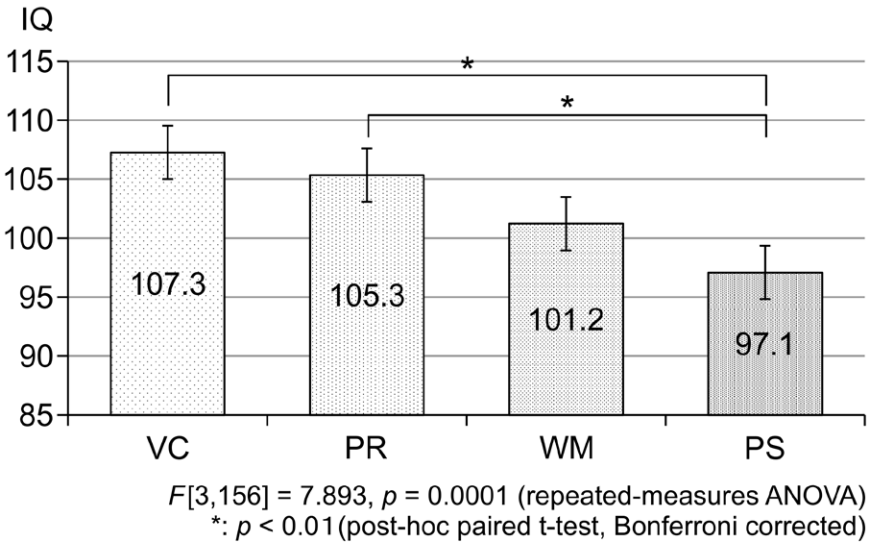

Fig. 1. Cognitive performance (Wechsler Intelligence Scale for Children–Fourth Edition) of childhood cancer survivors
IQ: intelligence quotient, VC: verbal comprehension, PR: perceptual reasoning, WM: working memory, PS: processing speed, ANOVA: analysis of variance.

Table 2. Relationship between cognitive function and each factor

	FSIQ	VC	PR	WM	PS	VC-WM
Age	.069	.124	.039	−.124	−.195	.217
	.621	.375	.779	.375	.162	.119
IT	−.135	−.032	−.157	−.198	.054	.113
	.339	.824	.267	.160	.706	.424
HD−MTX	.008	.186	−.086	−.342	.148	.433
	.958	.186	.543	.013	.294	.001
AraC	−.171	−.201	−.239	.035	−.063	−.242
	.225	.154	.088	.805	.656	.084
Day of examination post hospital discharge	.113	.120	.008	.076	−.066	.105
	.422	.391	.955	.590	.638	.453

FSIQ: full scale intelligence quotient, VC: verbal comprehension, PR: perceptual reasoning, WM: working memory, PS: processing speed, IT: intrathecal therapy (MTX, cytarabine, and steroids), HD-MTX: high-dose methotrexate ($10\,g/m^2$ or $20\,g/m^2$), AraC: cytarabine is a chemotherapy drug.

moderate, and high-dose groups were 107.8, 102.6, and 96.5, respectively ($P=0.05$). Post-hoc analysis revealed a significantly lower WM score in the high-MTX group (96.5) than in the non-MTX group (107.8; $P<0.05$, Bonferroni corrected) (Fig. 2), while the PS score was decreased in all groups including the non-MTX group (including patients with AML, CML, and solid tumors) (Fig. 3). Finally, sub-group analysis in the high MTX group revealed a significantly lower WM

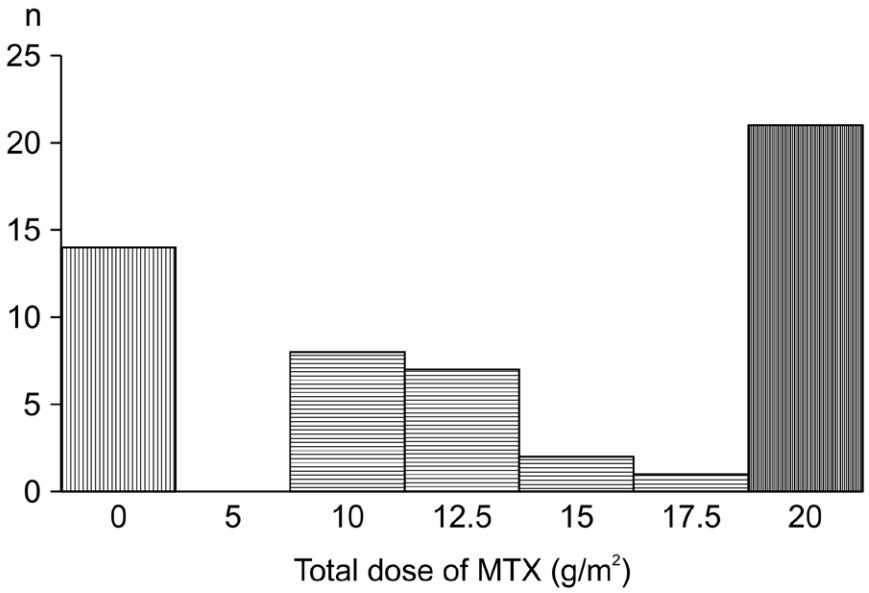

Fig. 2. Histogram of total methotrexate (MTX) dose

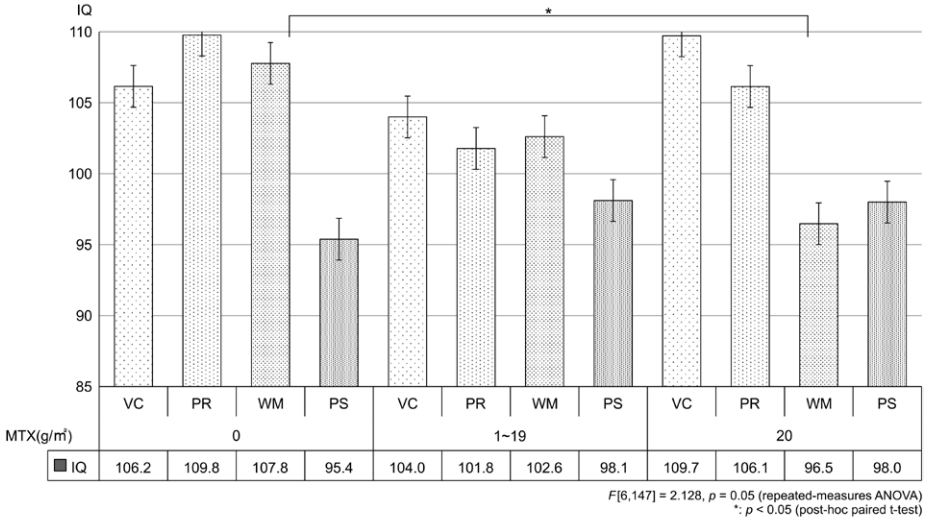

Fig. 3. Cognitive performance (Wechsler Intelligence Scale for Children–Fourth Edition) impairment by methotrexate (MTX) dose
IQ: intelligence quotient, VC: verbal comprehension, PR: perceptual reasoning, WM: working memory, PS: processing speed, ANOVA: analysis of variance.

score (96.5) than the VC (109.6) and PR (106.1) scores (P<0.01 and P<0.05, respectively, Bonferroni corrected) (Fig. 4).

Discussion

The childhood cancer survivors studied herein had intact FSIQ compared with the population

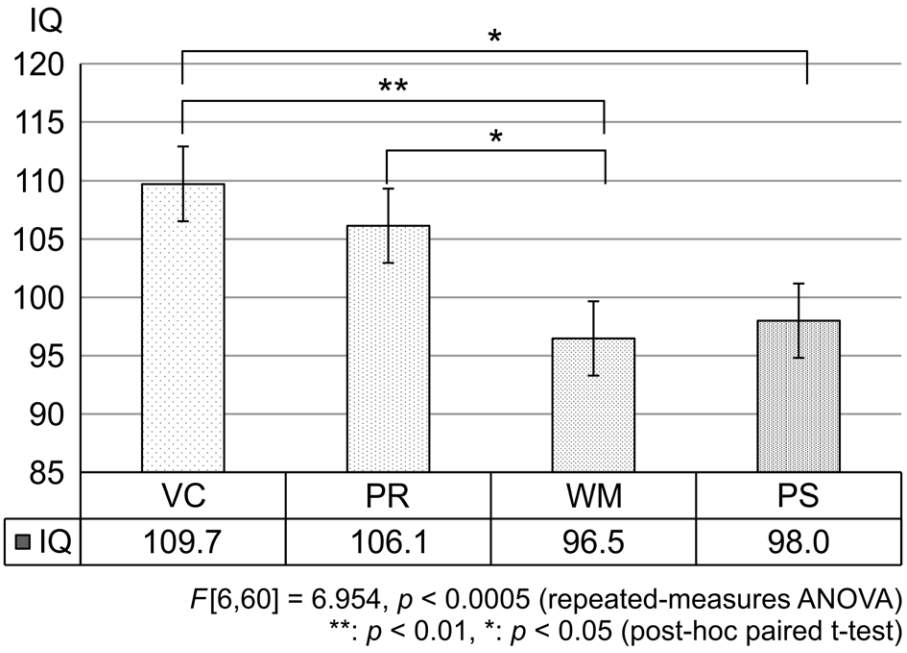

Fig. 4. Cognitive performance (Wechsler Intelligence Scale for Children–Fourth Edition) of childhood cancer survivors in the high-methotrexate group (>20 g / m^2)
IQ: intelligence quotient, VC: verbal comprehension, PR: perceptual reasoning, WM: working memory, PS: processing speed, ANOVA: analysis of variance.

normative data; however, they showed significant PS deficits on the group level. Several previous studies found that although general intellectual ability in ALL survivors is not affected by chemotherapy alone, their PS is significantly lower than that of comparison peers[10–12], and this is supported by our findings. Generally, central nervous system (CNS) -directed chemotherapy, such as CRT and high-dose MTX, is required for ALL and it is well known that patients with ALL may have cognitive dysfunction[13]. In the current study, PS was also decreased in the other types of cancer examined. To our knowledge, this is the first study investigating the association between cognitive function and childhood cancer in patients not receiving CNS-directed chemotherapy. Interestingly, our study patients with childhood cancer who did not receive high-dose MTX (i.e., those with AML, CML, and solid tumors) also had decreased PS. While little is known about the association between PS impairment and childhood cancer treatment other than high-dose MTX, depression, the effects of long-term hospitalization, and parenting stress could play a role. Indeed, there is some evidence from adult cancer survivors that perceived depressive symptoms might strongly affect cognitive performance[14], while Patel *et al*[15]. reported an association between PS impairment and parenting stress.

In the current study, a negative correlation was found between MTX dose and WM performance. In support of this finding, previous meta-analysis data indicated that PS and WM are significantly impaired in childhood cancer survivors[16]. In addition, although some studies

found no association between MTX dose and neurocognitive outcome[7, 17], other investigators reported that childhood ALL survivors who received high-dose intravenous MTX had a greater degree of neurocognitive problems than those administered low-dose MTX[18–20], as indicated by the present study results. All previous studies were conducted with Caucasian samples, and our study is the first to confirm the same results in an Asian population.

Recently, a cognitive and problem-solving program was implemented for leukemia and brain tumor survivors[21, 22]. Hardy *et al*[22]. reported good feasibility and acceptability of the program with significant increases in WM and parent reports of decreased attention problems following the 12-week program, while Moore *et al*[23]. reported that early mathematics intervention can prevent a decline in mathematical ability and cognitive function in patients with childhood ALL. Accordingly, we plan to implement an early intervention involving a computerized cognitive training program for patients with childhood cancer undergoing chemotherapy.

Although age at diagnosis, counts of IT, counts of cytarabine therapy, and days between complete response and testing were not associated with any cognitive function domain, the counts of high-dose MTX therapy were significantly correlated with poor WM performance. The patients who received high-dose MTX therapy were almost all ALL patients and were hospitalized for approximately 1 year, whereas the hospitalization of other patients varied between 6 months and 1 year. There was no significant difference in the age at first onset with or without high-dose MTX. Based on the above findings, long-term hospitalization is considered a confounding factor related to the WM decrease in the high-dose MTX administration group.

In this study, the general comparison was difficult because only a small number of the patients who were hospitalized for approximately 1 year in the control group did not receive high-dose MTX. Accordingly, accumulating a larger number of cases is necessary in the future because the effects of long-term hospitalization in childhood and high-dose MTX therapy should also be considered.

Conflict of interest disclosure

The authors declare no conflicts of interest.

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