Neurocognitive deficits in survivors of childhood acute myeloid leukemia

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Abstract

Background: Although treatment of acute myeloid leukemia (AML) contains neurotoxic agents, studies investigating neurocognitive outcomes in children with AML are sparse. We evaluated late cognitive effects in children treated with a high-dose cytarabine based regimen, focusing on general intellectual ability and specific neurocognitive domains.

Methods: We evaluated 12 survivors of childhood AML who were treated between 2006 and 2016 and completed the Wechsler Intelligence Scales. One-sample t-tests were used to compare full-scale intelligence quotient (FSIQ) and primary index scores to norms. The overall effect of index scores and subtests was examined with one-way ANOVA. Univariate analyses and multiple regression models examined demographic and clinical characteristics associated with FSIQ.

Results: Participants who underwent the Wechsler Intelligence Scale for Children demonstrated impairment on working memory index and participants who underwent the Wechsler Adult Intelligence Scale showed low score in the subtests that reflect working memory, whereas they exhibited no statistical differences versus the population means for FSIQ. There were no significant differences in the overall effect of index scores and subtests. On univariate analysis, FSIQ were related to time since diagnosis and age at assessment, and both were significant predictors of FSIQ on multiple linear regression.

Conclusions: Survivors of childhood AML exhibited impairment of working memory, even if their FSIQ was within the normal range. Difficulties in specific cognitive domains are associated with reduced quality of life. It is important to identify survivors who are at risk and provide tailored interventions.

Keywords: Acute myeloid leukemia, Neurocognitive deficits, Working memory, Childhood, Quality of life
Because chemotherapy for childhood AML also contains neurotoxic agents and intrathecal therapy (IT) [1, 3], neurocognitive sequelae may occur in AML survivors. Nevertheless, few studies have examined neurocognitive outcomes associated with childhood AML.

This study evaluated the development of late cognitive effects following AML treatment in children with a focus on general intellectual ability and specific neurocognitive domains. In addition, we explored the associations of neurocognitive performance with clinical and demographic factors.

Methods
Participants
The inclusion criteria for this cross-sectional study were as follows: (1) diagnosis of AML or acute undifferentiated leukemia (AUL); (2) < 20 years of age at diagnosis; (3) ≥ 1 year off treatment during a continuous first remission; and (4) receipt of chemotherapy with HD Ara-C. Survivors were excluded if they had been diagnosed with a specific neurodevelopmental disorder such as Down syndrome, if their primary language was not Japanese, or if they had developed any relapse or second malignancy prior to neurocognitive testing. Survivors who underwent allogeneic hematopoietic stem cell transplantation (HSCT) were not excluded. The Institutional Review Board of the Japanese Red Cross Narita Hospital approved this study (Approval Number: 526–01).

Informed consent for participation and medical record release was obtained from survivors or their proxies (for participants younger than 20 years), and assent was obtained from survivors where appropriate.

Treatment protocol
In this study, patients with AML were treated with regimens primarily used in the AML-05 or AML-12 trials, both of which were nationwide multicenter studies conducted by the Japanese Pediatric Leukemia/Lymphoma Study Group. The treatment protocols in these trials consisted of two courses of induction therapy and three to four courses of intensification therapy with cytarabine, etoposide, mitoxantrone, idarubicin, and an age-adjusted dose of triple intrathecal therapy. Central nervous system (CNS) disease was defined as either ≥ 5 white blood cells with blasts in cerebrospinal fluid (CSF) or with clinical and radiographic signs of CNS leukemia. Patients with CNS disease received additional weekly IT until the CSF was clear of blasts. Cranial radiation therapy was not included in the protocols. Allogeneic HSCT was limited to the high-risk group [11–13]. The cumulative doses of cytarabine, anthracyclines, and etoposide in the AML-05 and AML-12 trials are noted in Table 1. Japanese trials used a higher cumulative dose of cytarabine than major studies in other countries [11].

Neurocognitive testing
All participants completed an age-appropriate Japanese version of the Wechsler Intelligence Scales to assess general intelligence: the Wechsler Preschool and Primary Scale of Intelligence—Third Edition (WPPSI-III) for children younger than 5 years, the Wechsler Intelligence Scale for Children—Fourth Edition (WISC-IV) for children aged 5–16 years, and the Wechsler Adult Intelligence Scale—Fourth Edition (WAIS-IV) for survivors aged 17 years or older. One participant was tested using the WPPSI-III, seven patients were tested using the WISC-IV, and four patients were tested using the WAIS-IV. The WISC-IV and WAIS-IV include the full-scale intelligence quotient (FSIQ), verbal comprehension index (VCI), perceptual reasoning index (PRI), working memory index (WMI), and processing speed index (PSI). The WPPSI-III includes FSIQ, VCI, PRI, PSI, and a general language composite (GLC), whereas PSI and GLC are extrapolated from supplemental subtests. FSIQ and each index score have a standardized mean (M) and standard deviation (SD) of 100 and 15, respectively. The test was administered by one experienced psychologist under the supervision of another licensed psychologist.

Statistical analysis
Descriptive statistics were calculated according to the clinical and demographic characteristics of the participants, including gender, age at diagnosis, time since diagnosis, history of HSCT, age at assessment, parental educational history, and household income.

### Table 1 Cumulative doses of cytotoxic agents in the AML-05 and AML-12 studies

|                | AML-05                      | AML-12                      |
|----------------|-----------------------------|-----------------------------|
|                | LR  | IR (HR)                      | LR; A/B                     | IR (HR); A/B                     |
| Cytarabine (g/m²) | 77.4 | 77.4                          | 78.4/95                     | 77.4/94                         |
| Anthracycline equivalent (total, mg/m²)* | 225 | 375                          | 300                         | 375                             |
| Mitoxantrone     | 25  | 55                           | 40                          | 55                              |
| Idarubicin       | 20  | 20                           | 20                          | 20                              |
| Etoposide (mg/m²) | 1750 | 1750                        | 2200                        | 1750                            |

*The cumulative anthracycline dose was calculated relative to the amount of daunorubicin using a conversion rate of 5:1 for daunorubicin to mitoxantrone/idarubicin.
A one-sample \( t \)-test was used to compare FSIQ and primary index scores (VCI, PRI, WMI, and PSI) to standard scores (\( M = 100, SD = 15 \)). The WISC-IV and WAIS-IV scores displayed comparability if all common subtests are performed [14]; however, study participants were only tested for core subtests. For this reason, we separately examined primary indices obtained by a group of participants who underwent the WISC-IV or WAIS-IV. Because only one participant was tested with the WPPSI-III and PSI and GLC were not evaluated, we excluded that subject from the analysis of the primary indices. The overall effect of index scores and subtests was tested by one-way ANOVA. Univariate analyses (Fisher’s exact test, \( t \)-test, Pearson’s correlation, and Spearman’s correlation) examined demographic and clinical characteristics associated with FSIQ. Demographic and clinical variables identified as statistically significant (\( p < 0.05 \)) on univariate analysis were included in multiple regression models. All statistical analyses were performed using EZR for R, a modified version of R commander designed to add statistical functions frequently used in biostatistics [15].

Results
Twenty-eight patients < 20 years of age received a diagnosis of AML \((n = 26)\) or AUL \((n = 2)\) from 2006 to 2016. Among them, 18 patients satisfied the eligibility criteria for this study, and neurocognitive data were obtained from 12 patients. The reasons for exclusion or a lack of participation are noted in Fig. 1. On average, participants were 8.0 years old at diagnosis and 12.9 years old at assessment. Of the 12 participants, five received HSCT, three received total-body irradiation, and one presented with CNS disease at diagnosis. Participant with CNS disease showed \( \geq 5 \) white blood cells with blasts in the CSF but without clinical CNS symptoms. Although brain magnetic resonance imaging performed in all patients before the treatment and an intracranial mass was detected in one patient, this patient was regarded CNS-negative because lack of clinical CNS symptoms. None of the participants developed neurological events or toxicity that affected other nervous systems during chemotherapy. One patient had a history of epilepsy, and none of participants had family medical history, such as psychiatric illnesses and epilepsy. Parental education and household income were used as proxies for family socioeconomic status. The full demographic characteristics of the participants are noted in Table 2.

The participants’ index scores on the Wechsler Intelligence Scales in relation to normative data are summarized in Table 3. The WISC-IV and WAIS-IV were completed by seven and four participants, respectively. Participants who completed the WISC-IV displayed significant impairment on the WMI \((t (6) = -3.36, p = 0.015, M = 83.3 [95\% \text{ confidence interval}=71.1–95.4])\) but no statistical difference from the normative M for FSIQ and other index scores. Among the participants who underwent the WAIS-IV, FSIQ and the four primary
Table 2  Demographic and clinical characteristics of survivors

| No  | Sex       | Total |
|------|-----------|-------|
|      | Male      | 5     |
|      | Female    | 7     |
| Mean age at diagnosis ± SD (range) | 8.0 ± 5.4 (0.4–14.8) |
| Mean time from diagnosis ± SD (range) | 5.2 ± 3.0 (2.3–11.1) |
| Prior CNS involvement | 1 |
| Positive history of HSCT | 5 |
| Mean age at assessment ± SD (range) | 12.9 ± 6.0 (4.1–24.1) |
| Parental education | |
| High school | 2 |
| Vocational school/junior college | 8 |
| University | 1 |
| Unknown | 1 |
| Household income (Japanese yen)* | |
| < 6,000,000 | 6 |
| ≥ 6,000,000 | 4 |
| Unknown | 2 |

* 6,000,000 Japanese yen is approximately 54,000 US dollars

Table 3  Neurocognitive outcomes

| N  | Mean | SD | Range | P* |
|----|------|----|-------|----|
| FSIQ (WISC-IV) | 12 | 97.5 | 12.1 | 81–123 | 0.488 |
| FSIQ (WAIS-IV) | 7 | 93.7 | 9.30 | 81–104 | 0.124 |
| VCI (WISC-IV) | 4 | 105.0 | 15.8 | 87–123 | 0.571 |
| VCI (WAIS-IV) | 12 | 100.3 | 15.7 | 75–121 | 0.943 |
| PRI (WISC-IV) | 7 | 99.3 | 15.8 | 76–115 | 0.098 |
| PRI (WAIS-IV) | 4 | 103.0 | 19.7 | 75–121 | 0.781 |
| WMI (WISC-IV) | 11 | 90.8 | 17.2 | 63–117 | 0.108 |
| WMI (WAIS-IV) | 7 | 83.3 | 13.2 | 63–103 | 0.0152 |
| PSI (WISC-IV) | 4 | 104.0 | 16.7 | 82–117 | 0.665 |
| PSI (WAIS-IV) | 11 | 102.0 | 14.7 | 81–127 | 0.662 |
| PSI (WISC-IV) | 7 | 101.0 | 14.8 | 81–118 | 0.864 |
| PSI (WAIS-IV) | 4 | 103.8 | 16.8 | 87–12 | 0.686 |

* One-sample t-test. P-value for calculated difference between participants and normative means (M = 100, SD = 15). Results with P ≤ 0.05 are regarded as statistically-significant

FSIQ full-scale intelligence quotient, VCI verbal comprehension index, PRI perceptual reasoning index, WMI working memory index, PSI processing speed index

index scores did not differ significantly from the normative M of 100.

As presented in Fig. 2, among the subtest scores, the Letter-Number Sequencing subtest score was the lowest (M = 6.9, SD = 3.2) and the Coding subtest score was the highest (M = 12.0, SD = 2.9) in the WISC-IV cases, whereas the Digit Span subtest score was the highest (M = 9.5, SD = 2.3) and the Arithmetic subtest score was the highest (M = 12.0, SD = 3.7) in the WAIS-IV cases. The Digit Span subtest score was also low in the WISC-IV cases (M = 7.4, SD = 1.8). However, neither group exhibited any significant differences in the overall effect of the index scores and subtests.

The associations between FSIQ and all demographic and clinical variables listed in Table 2 were examined by univariate analysis. The t-test revealed no significant difference in the FSIQ between the WISC-IV and WAIS-IV cases (M = 93.7, SD = 9.3 and M = 105.0, SD = 15.8, respectively, p = 0.16). Among WISC-IV cases, participants aged 10 years and older showed higher FSIQ score than participants under 10 years of age (M = 100.0, SD = 6.1 and M = 85.3, SD = 4.5, respectively, p = 0.017). As presented in Fig. 3, FSIQ was moderately related to the time since diagnosis (rs = 0.59, p = 0.049) and strongly related to age at assessment (r = 0.69, p = 0.013). A longer time since diagnosis and older age at assessment were associated with high FSIQ. Multiple linear regression was performed to predict FSIQ based on the time since diagnosis and age at assessment. A significant regression equation was found (F(2, 9) = 11.74, R2 = 0.66, p = 0.003). The participants’ predicted FSIQ was equal to 76.01 + 2.05 (time since diagnosis) + 0.88 (age at assessment), where time since diagnosis and age at assessment were measured in years. Both time since diagnosis and age at assessment were significant predictors of FSIQ.

Discussion

The results of this study indicate that following treatment with HD Ara-C for AML, survivors exhibit impairment in working memory compared to population norms despite their comparable FSIQ. In multiple linear regression, we revealed that the time since diagnosis and age at assessment were both associated with FSIQ in survivors.

FSIQ did not differ between our AML survivor sample and Japanese population norms; however, deficits in working memory emerged among AML survivors. This is consistent with the findings of a recent report by the CCSS group, which suggested that survivors had a relative risk of impairment in at least one neurocognitive domain [16]. It was previously reported that deficits in specific cognitive domains may be unrelated to general intelligence [17]. In this study, participants who underwent the WISC-IV demonstrated significant impairment
Participants performed poorly on the Digit Span subtest of the WAIS-IV, but impairment in the WMI score disappeared because of a high Arithmetic subtest score. Previous studies suggested that the Arithmetic subtest is a poor predictor of working memory ability, and the Digit Span and Letter-Number Sequencing subtests would be the strongest predictor variables [18, 19]. Because the Digit Span subtest more strongly reflects working memory than the Arithmetic subtest, working memory appears to be the most vulnerable function following childhood AML treatment.

Cerebellar dysfunction may lead to intellectual disorders, such as disturbances of executive function, including deficient planning, set-shifting, abstract reasoning, working memory, and decreased verbal fluency [20]. Cytarabine is known to cause cerebellar toxicity [7–10]. Autopsies demonstrated the loss of Purkinje cells in the cerebellum and reactive Bergmann glial cell proliferation in adults following HD Ara-C treatment [21]. Diffuse heterogeneous brain hypoperfusion, identified by single-photon emission computed tomography, has been reported in children with AML who received HD Ara-C [22]. Although we cannot state so categorically, it can be speculated that HD Ara-C treatment may cause late neurocognitive effects because of cerebellar toxicity. Prior research supported an association between
The neurocognitive sequelae in children with AML have been considered more likely to have been caused by leukemia and its complications at presentation rather than by treatment [31]. By contrast, in our study, only one participant was CNS-positive at diagnosis, and no participants exhibited clinical CNS symptoms during treatment. Therefore, it is conceivable that the influence of the primary disease on cognitive function was small in this study.

Conclusions

Participants displayed no impairment in FSIQ, but they had poor performance in working memory. Working memory is responsible for the temporary storage and manipulation of information. It affects all judgments and activities in everyday life, such as conversation, reading, writing, and calculation. Difficulties in specific cognitive domains, even with good general intellectual ability, may affect the quality of life of survivors of childhood AML. Individually administered intelligence test for survivors of childhood AML might be helpful in detecting domains of cognitive vulnerability. Early detection of neurocognitive late effects and development of interventions for survivors with neurocognitive deficit are required to provide survivors with optimal psychosocial care.

Abbreviations

ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia; AUL: Acute undifferentiated leukemia; CNS: Central nervous system; CSF: Cerebrospinal fluid; FSIQ: Full-scale intelligence quotient; GLC: General language composite; HD Ara-C: High-dose cytarabine; HSCT: Hematopoietic stem cell transplantation; IT: Intrathecal therapy; M: Standardized mean; PPI: Perceptual reasoning index; PSI: Processing speed index; SD: Standard deviation; VCI: Verbal comprehension index; WAIS-IV: The Wechsler Adult Intelligence Scale-Fourth Edition; WISC-IV: The Wechsler Intelligence Scale for Children-Fourth Edition; WMS-IV: The Wechsler Memory Scale-Fourth Edition; WPPSI-III: The Wechsler Preschool and Primary Scale of Intelligence-Third Edition for children.

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Authors’ contributions

ST, SS, YT and TT contributed to the study conception and design. Material preparation, data collection and analysis were performed by ST, SS, SI and HD. YT and TT supervised the project. The first draft of the manuscript was written by ST, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.
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