Neurocognitive Outcomes of Children with Osteosarcoma Treated with High-dose Intravenous Methotrexate

Haruko Shima[1], Satomi Sato[2], Tetsuya Takimoto[3], Michiko Sakai[1], Noriko Hashida[1], Kyohei Isshiki[1], and Hiroyuki Shimada[1]

[1]Keio University
[2]St Luke's International University
[3]Clinical Research CenterNational Center for Child Health

March 23, 2022

Abstract

Methotrexate (MTX) has been shown to impair neurocognitive outcomes. Because the cumulative dose of MTX used in the standard treatment of osteosarcoma is higher compared to the treatment of other childhood cancers, we analyzed the neurocognitive performance among 12 survivors of childhood osteosarcoma exposed to high-dose MTX at our institution. Prospective longitudinal evaluations of neurocognitive functioning using the Japanese Wechsler Intelligence Scale for Children-4th Edition were performed. As a result, we observed age-appropriate development of neurocognitive performance among osteosarcoma survivors. In conclusion, cognitive development was not adversely affected in this cohort of childhood osteosarcoma survivors treated with HD-MTX.

Title: Neurocognitive Outcomes of Children with Osteosarcoma Treated with High-dose Intravenous Methotrexate

Haruko Shima[1], Satomi Sato[2], Tetsuya Takimoto[3], Michiko Sakai[1], Noriko Hashida[1], Kyohei Isshiki[1], Hiroyuki Shimada[1]

[1]Department of Pediatrics, Keio University School of Medicine, Tokyo, Japan,

[2]Division of Health and Behavioral Sciences, Graduate School of Public Health, St. Luke's International University, Tokyo, Japan,

[3]Department of Data Management, National Center for Child Health and Development, Tokyo, Japan

Corresponding author: Satomi Sato,

Graduate School of Public Health, St. Luke's International University,

3-6-2 Chuo-ku, Tokyo, Japan

Phone: +81-3-5550-4101, FAX: +81-3-5550-4114

E-mail address: satomisa@slcn.ac.jp

Word count: Abstract 98 words, Main text 951 words

1 Table, 1 Figure and 2 Supplemental tables (Supporting information)

A short running Title: Neurocognitive Outcomes of Osteosarcoma Children

Key words: Osteosarcoma, Methotrexate, Neurocognitive outcomes

Abbreviations:

MTX	Methotrexate
CNS	Central nervous system
CRT	Cranial irradiation
WISC-IV	Wechsler Intelligence Scale for Children 4^{th} Edition
FSIQ	Full scale IQ
VCI	Verbal Comprehension Index
PRI	Perception Reasoning Index
WMI	Working Memory Index
PSI	Processing Speed Index

ABSTRACT

Methotrexate (MTX) has been shown to impair neurocognitive outcomes. Because the cumulative dose of MTX used in the standard treatment of osteosarcoma is higher compared to the treatment of other childhood cancers, we analyzed the neurocognitive performance among 12 survivors of childhood osteosarcoma exposed to high-dose MTX at our institution. Prospective longitudinal evaluations of neurocognitive functioning using the Japanese Wechsler Intelligence Scale for Children-4th Edition were performed. As a result, we observed age-appropriate development of neurocognitive performance among osteosarcoma survivors. In conclusion, cognitive development was not adversely affected in this cohort of childhood osteosarcoma survivors treated with HD-MTX.

INTRODUCTION

With growth of the childhood cancer survivor population, increasing attention has focused on how cancer and its treatment affects their neurocognitive function [1]. Among the many systemic chemotherapeutic agents used in the treatment of childhood cancer, the antimetabolite, methotrexate (MTX), has been associated with impairment in neurocognitive outcomes [2]. In particular, methotrexate has been a long-standing component of treatment regimens for acute lymphoblastic leukemia (ALL) and its impact on neurocognitive functioning has been well described [3].

Osteosarcomas, the most common bone sarcoma in children and adolescents, account for approximately 2 to 3% of childhood cancers. High doses of intravenous MTX (HD-MTX) are included in the standard treatment of osteosarcoma, with cumulative doses substantially exceeding those used for ALL (10–12 g/m^2 for osteosarcoma v. 2.5–5.0 g/m^2 for ALL) [4-6]. Treatment of osteosarcoma typically does not require cranial irradiation (CRT) or intrathecal therapy, which have strong links to neurocognitive deficits [3]. Our aim was to characterize the neurocognitive performance among survivors of childhood osteosarcoma exposed to HD-MTX.

METHODS

Patients eligible for this study included those with histologically confirmed osteosarcoma diagnosed between the ages of 5 and 17 years who received or planned to receive chemotherapy including HD-MTX. Three licensed clinical psychologists performed prospective longitudinal evaluations of neurocognitive functioning using the Japanese *Wechsler Intelligence Scale for Children-4thEdition* (WISC-IV) [7] at baseline after study enrollment (T1) and two additional times during follow-up at one-year intervals (T2 and T3). Full scale IQ (FSIQ), Verbal Comprehension Index (VCI), Perception Reasoning Index (PRI), Working Memory Index (WMI) and Processing Speed Index (PSI) were age-adjusted and scaled to have a sample mean of 100 and a sample standard deviation of 15. Testing was conducted during a single two-hour session with order of testing standardized, and participants' schedule were arranged to limit the effect of fatigue and extraneous factors. Only children who had not been subject to WISC-IV testing in the preceding year at the first evaluation were included in the study to exclude the influence of practice effects on the test results.

Descriptive statistics, correlation analysis and the repeated ANOVA were performed using SPSS ver. 25 software. Each patient and/or their legal guardians provided written informed consent for participation. This study was approved by the Ethics Committee of the Keio University School of Medicine.

RESULTS

In total, all 12 pediatric patients diagnosed with osteosarcoma between 2006 and 2016 in our institution were enrolled. Patient characteristics are shown in Table 1. Half of the patients were male, and median age at diagnosis of osteosarcoma and at study entry was 8 (range, 4 – 14) and 12 (range, 7–16) years, respectively. Median duration from diagnosis to the first neurocognitive examination was 3 (range, 0 – 9) years. Three patients underwent their first examination immediately after their first course of HD-MTX, while the remaining patients were evaluated after completion of their HD-MTX. One patient who needed special support at school prior to the treatment was excluded from the analysis. The rest of the cohort attended regular school after completion of treatment and had no chronic health problems requiring medical intervention during the follow-up period of three assessments.

Scores on WISC-IV are shown in Figure 1 and Table S1. Among the 11 evaluable patients, mean FSIQ was 107.00 (SD =15.58) at T1, 108.55 (SD =19.52) at T2, and 115.18 (SD =17.69) at T3, ranging from 90.00 to 133.00. However, these mean differences among FSIQ did not differ significantly over the three evaluation time points. Next, each index was examined using ANOVA. For the four indices (Verbal Comprehension Index; VCI, Perceptual Reasoning Index; PRI, Working Memory Index; WMI, and Processing Speed Index; PSI) scores increased between T1 and T3, but only the increase in PSI was statistically significant with a change from 106.73 at T1 to 115.45 at T3 (p=0.041). Correlation analyses were not significant between intelligence test results at T3 and clinical data (Table S2).

DISCUSSION

In this study, we observed age-appropriate development of neurocognitive performance among survivors of childhood and adolescent osteosarcoma, and none had scores in the disability range following HD-MTX exposure. The difference in neurocognitive outcomes observed in osteosarcoma survivors in our cohort and those previously reported for children with ALL may be related to the additional exposure to CRT or intrathecal therapy as well as younger age at exposure, which have been strongly linked to neurocognitive injury [3]. It is widely recognized that children younger than age five years at diagnosis of ALL are at high risk of neurocognitive sequelae from treatment and older children are less susceptible to neurotoxicity [8]. Most patients in this study showed an increase in FSIQ and four indices from the first to the third assessment. Among all the indexes, only PSI scores significantly increased with time since treatment. This is likely attributable to the learning effect of PSI especially among higher FSIQ patients.

Collectively, cognitive development was not adversely affected in this cohort of childhood osteosarcoma survivors treated with HD-MTX. However, chronic health conditions have been reported to affect neurocognitive functions in adults treated for osteosarcoma during childhood [9,10]. Since patients in this study were younger than 17 years of age and in an early phase of survivorship (mean follow-up time of 66 months, range, 25-144 months), these results may not be generalizable to older survivors with longer elapsed time from treatment. It is reassuring that all patients were able to attend school at the time of assessment. To assure age-appropriate development of neurocognitive functions in pediatric survivors of osteosarcoma, monitoring for emerging deficits that may affect school performance and behavior is important. This study is limited by a relatively small sample size and lack of power for statistical analysis, although these descriptive data provide potentially useful information about a rare pediatric disease.

Conflict of Interest Disclosures: All the authors have no conflicts of interest to disclose.

Funding: This research was supported by Japanese MEXT Grant-in-Aid for Scientific Research (grant number 26780410)

Reference

1. Krull KR, Hardy KK, Kahalley LS, Schuitema I, Kesler SR. Neurocognitive Outcomes and Interventions in Long-Term Survivors of Childhood Cancer. J Clin Oncol. 2018;36(21):2181–2189.

2. Peterson CC, Johnson CE, Ramirez LY, et al. A meta-analysis of the neuropsychological sequelae of chemotherapy-only treatment for pediatric acute lymphoblastic leukemia. Pediatr Blood Cancer. 2008;51:99–104.

3. Buizer AI, de Sonneville LM, Veerman AJ. Effects of chemotherapy on neurocognitive function in children with acute lymphoblastic leukemia: a critical review of the literature. Pediatr Blood Cancer. 2009;52(4):447–454.

4. Marina NM, Smeland S, Bielack SS, Bernstein M, Jovic G, Krailo MD, et al. Comparison of MAPIE versus MAP in patients with a poor response to preoperative chemotherapy for newly diagnosed high-grade osteosarcoma (EURAMOS-1): an open-label, international, randomised controlled trial. Lancet Oncol. 2016;17(10):1396–1408.

5. Reddick WE, Glass JO, Helton KJ, Langston JW, Xiong X, Wu S, Pui CH. Prevalence of leukoencephalopathy in children treated for acute lymphoblastic leukemia with high-dose methotrexate. AJNR Am J Neuroradiol. 2005;26(5):1263–1269.

6. Bacci G, Ferrari S, Ruggieri P, et al. Telangiectatic osteosarcoma of the extremity: neoadjuvant chemotherapy in 24 cases. Acta Orthop Scand. 2001;72(2):167–1672.

7. Wechsler, D. Nihonban WISC-IV chinoukensa jisshi saiten manyuaru [Administration and scoring manual for the Japanese version of the Wechsler Intelligence Scale for Children—Fourth Edition] translators; Ueno K, Hujita K, Maekawa H, et al., Tokyo: Nihon Bunka Kagakusha. Japanese. 2010.

8. Campbell LK, Scaduto M, Sharp W, et al. A meta-analysis of the neurocognitive sequelae of treatment for childhood acute lymphocytic leukemia. Pediatr Blood Cancer 2007;49:65–73.

9. Bishop MW, Ness KK, Li C, et al. Cumulative Burden of Chronic Health Conditions in Adult Survivors of Osteosarcoma and Ewing Sarcoma: A Report from the St. Jude Lifetime Cohort Study. Cancer Epidemiol Biomarkers Prev. 2020;29(8):1627–1638.

10. Edelmann MN, Daryani VM, Bishop MW, et al. Neurocognitive and Patient-Reported Outcomes in Adult Survivors of Childhood Osteosarcoma. JAMA Oncol. 2016;2(2):201–208.

Figure Legend

Figure 1.

Serial change in mean scores of Full-Scale IQ (FSIQ), Verbal Comprehension Index (VCI), Perception Reasoning Index (PRI), Working Memory Index (WMI), and Processing Speed Index (PSI) are shown. 1, 2, 3 indicate the scores of FSIQ and the four indices at T1, T2, and T3.

Hosted file

`TABLE 1 for PBC.docx` available at https://authorea.com/users/466865/articles/561027-neurocognitive-outcomes-of-children-with-osteosarcoma-treated-with-high-dose-intravenous-methotrexate