Neurocognitive and Patient-Reported Outcomes in Adult Survivors of Childhood Osteosarcoma

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**IMPORTANCE** This study provides the first objective data documenting neurocognitive impairment in long-term survivors of childhood osteosarcoma.

**OBJECTIVE** To examine neurocognitive, neurobehavioral, emotional, and quality-of-life outcomes in long-term survivors of childhood osteosarcoma.

**DESIGN, SETTING, AND PARTICIPANTS** Cross-sectional cohort study at an academic research hospital, with prospective treatment and chronic health predictors. Outcome data were collected from June 2008 to August 2014. Data analysis was completed in April 2015. Survivors of osteosarcoma recruited from the St Jude Lifetime Cohort Study were compared with community controls.

**MAIN OUTCOMES AND MEASURES** Neurocognitive function, neurobehavioral symptoms, emotional distress, and quality of life. Outcomes were examined in relation to pharmacokinetic indices of methotrexate exposure and current chronic health conditions, which were assessed through medical examination and coded according to Common Terminology Criteria for Adverse Events, Version 4.03.

**RESULTS** Eighty survivors of osteosarcoma (mean [SD] age, 38.9 [7.6] years; time since diagnosis, 24.7 [6.6] years; 42% female) were compared with 39 community controls (age, 39.0 [11.7] years; 56% female). Survivors demonstrated lower mean scores in reading skills (−0.21 [95% CI, −0.32 to −0.10] vs 0.05 [95% CI, −0.13 to 0.23]; P = .01), attention (−0.78 [95% CI, −1.32 to −0.24] vs 0.24 [95% CI, −0.07 to 0.55]; P = .002), memory (−0.24 [95% CI, −0.48 to 0] vs 0.27 [95% CI, −0.08 to 0.62]; P = .01), and processing speed (−0.15 [95% CI, −0.35 to 0.05] vs 0.74 [95% CI, 0.44 to 1.03]; P < .001). Results of pharmacokinetic analysis showed that high-dose methotrexate maximum plasma concentration (estimate = 0; P = .48), median clearance (estimate = −0.11; P = .76), and median/cumulative exposure (estimate = 0; P = .45) were not associated with neurocognitive outcomes. Any grade 3 or 4 Common Terminology Criteria for Adverse Events cardiac, pulmonary, or endocrine condition was associated with poorer memory (t = 2.93; P = .006) and slower processing speed (t = 3.03; P = .002). Survivor-reported poor general health was associated with decreased sustained attention (estimate = 0.24; P = .05) and processing speed (estimate = 0.34; P = .005).

**CONCLUSIONS AND RELEVANCE** Long-term survivors of osteosarcoma are at risk for neurocognitive impairment, which is related to current chronic health conditions and not to original treatment with high-dose methotrexate. Prospective longitudinal studies are needed to identify onset and progression of impairment to inform optimal interventions.
The survival rate for patients with a diagnosis of osteosarcoma has improved from less than 20% in the 1970s to approximately 70% today. This progress is largely due to advances in treatment, including adjuvant chemotherapy with intravenous high-dose methotrexate. Because high-dose methotrexate has been associated with neurotoxic effects among survivors of childhood acute lymphoblastic leukemia (ALL), the Children’s Oncology Group recommends neurocognitive screening for all survivors of childhood and adolescent cancer exposed to high-dose methotrexate. This recommendation has been applied to osteosarcoma survivors who received high-dose methotrexate at cumulative dosages 4- to 5-fold greater than the patients with ALL. However, to our knowledge, there are no reports in the literature describing neurocognitive outcomes in osteosarcoma survivors, who do not receive intrathecal methotrexate like patients with ALL.

Previous reports in patients with ALL examining the relationship between high-dose methotrexate dosage and long-term neurocognitive outcomes have conflicting results. This may be due to the inability of investigations to account for wide interpatient variability in high-dose methotrexate pharmacokinetics, which can result in variability of pharmacological effect. High-dose methotrexate dosage is a poor surrogate for overall drug exposure and limits elucidation of the dosage-drug exposure-response relationship, affecting accuracy of results. An analysis that includes measures of systemic exposure may provide more insight into the relationship between high-dose methotrexate therapy and neurocognitive outcomes.

Along with high-dose methotrexate, historical treatment regimens for children and adolescents with osteosarcoma have incorporated anthracyclines, bleomycin sulfate, and alkylating agents, which have been associated with cardiac, pulmonary, and endocrine morbidities. Long-term survivors of childhood cancer are at risk for fatigue, as well as physical inactivity and poor nutrition, which can increase the risk for metabolic syndrome. We have recently reported associations between cardiopulmonary disease and neurocognitive impairment in adult survivors of Hodgkin lymphoma, who did not receive neurotoxic therapies (ie, cranial radiotherapy, high-dose methotrexate, intrathecal chemotherapy). In the general population, endocrine morbidity is associated with neurocognitive impairment.

Long-term survivors of osteosarcoma may be at risk for neurocognitive problems either due to direct neurotoxicity associated with exposure to high-dose methotrexate or due to the secondary effects of chronic health conditions associated with use of chemotherapy agents or health behaviors. The purpose of the present study was to report the first comprehensive assessment of objective neurocognitive outcomes in long-term survivors of childhood osteosarcoma and to examine associations between these outcomes and treatment factors and chronic health conditions.

Methods

The present study was approved by the institutional review board at St Jude Children’s Research Hospital. All participants provided written informed consent. Data analysis was completed in April 2015.

Participants

Survivors of childhood osteosarcoma treated with high-dose methotrexate were recruited from the St Jude Lifetime Cohort (SJLIFE) study. To be eligible for SJLIFE, survivors had to have been treated at St Jude Children’s Research Hospital, and currently be at least 18 years old and 10 or more years from the time of diagnosis. Participants were excluded if they had a secondary brain tumor or other subsequent cancer that required neurotoxic therapies, had a non–cancer-related neurological disorder, or were not proficient in the English language. Of the 126 potentially eligible participants identified in SJLIFE, 6 met exclusion criteria (n = 1 secondary brain tumor, n = 4 non–cancer-related neurological disorders, n = 1 not proficient in English). Of the remaining 120 eligible survivors, 80 (66.7%) participated in the present study (see eFigure I in the Supplement). Direct testing was completed on 71 survivors, while 9 survivors completed only patient-reported outcomes (PROs). Community controls were recruited from among friends and relatives of patients and hospital staff, based on frequency matching of sex, age, and race of a related survivor sample. Controls (n = 39) who were unrelated to the osteosarcoma survivors were used in the present analyses as a comparison group.

Procedures

Medical record abstraction was performed to capture treatment data, surgical history, secondary malignant neoplasm, and chronic medical conditions. Participants completed a core battery of tests, including electrocardiography, complete blood cell count with differential, comprehensive metabolic panel, fasting lipid profile, insulin and glycated hemoglobin levels, thyroid and gonadal function, and urinalysis. Risk-based clinical evaluation was also conducted, including echocardiography and pulmonary function tests. Chronic conditions were graded for cardiac, pulmonary, and endocrine...
High-Dose Methotrexate Pharmacokinetic Analysis

All patients receiving high-dose methotrexate had serial blood samples collected to measure methotrexate serum concentrations as part of their clinical care. Patients treated on St Jude Osteosarcoma Protocol 72 received high-dose methotrexate at 2.5 g/m² over 6 hours and serum methotrexate concentrations were analyzed by spectrophotometric immunoassay. Patients treated on St Jude Osteosarcoma Protocol 77 received high-dose methotrexate at a dosage of 5 g/m² and serum methotrexate concentrations were analyzed by isotopic immunoassay. Patients enrolled on the Multi-Institutional Osteosarcoma Protocol, St Jude Osteosarcoma Protocol 86, and St Jude Osteosarcoma Protocol 91 received high-dose methotrexate at a dosage of 12 g/m² over 4 hours and serum methotrexate concentrations were measured by a fluorescence polarization immunoassay. The introduction of each new immunoassay involved rigorous testing to ensure the validity against the previous immunoassay. Observed variability related to assay was accounted for by use of a separate statistical (residual) error model in the population pharmacokinetic model.

To estimate population pharmacokinetic parameters and overall exposure to methotrexate, nonlinear mixed-effects modeling was used and a 2-compartment model was fit to serum concentration-time data from all individuals. Pharmacokinetic parameters included systemic clearance, volume of the central compartment \( V_c \), and intercompartmental rate constants \( k_{12} \) and \( k_{21} \). The estimate of the area under the concentration-time curve (AUC\(_{0-\infty}\) for each patient was calculated as the high-dose methotrexate dose divided by the post hoc estimate of clearance. The maximum concentration \( C_{\text{max}} \) was reported from the observed or simulated concentration-time data. Individual measures of systemic clearance, \( C_{\text{max}} \), and AUC\(_{0-\infty}\) were summarized for each patient to analyze the relationship between different measures of methotrexate exposure and neurocognitive outcomes.

Neurocognitive Evaluations

Neurocognitive evaluations were completed with licensed and/or certified examiners under the general supervision of a board-certified clinical neuropsychologist. Assessed neurocognitive domains (and instruments) included intelligence (Wechsler Abbreviated Scale of Intelligence\(^{18}\), academic skills (Woodcock-Johnson-III Tests of Achievement\(^{19}\) [letter-word identification and calculation subtests]), attention (Trail Making Test Part A,\(^{20}\) Conner’s Continuous Performance Test-II\(^{21}\) [omissions, variability]), memory (California Verbal Learning Test-II\(^{22}\)), processing speed (hit rate, the Grooved Pegboard Test\(^{23}\) [dominant hand], Wechsler Adult Intelligence Scale-III\(^{23}\) [WAIS-III; coding, symbol search]), and executive function (Trail Making Test Part B,\(^{20}\) Controlled Oral Word Association Test,\(^{20}\) WAIS-III [digit span backward]). Patient-reported outcomes were collected for neurobehavioral symptoms, using the Behavior Rating Inventory of Executive Function—adult version,\(^{24}\) for emotional symptoms using the Brief Symptom Inventory 18,\(^{25}\) and for health-related quality of life using the Short Form 36\(^{26}\) health survey. Testing was conducted during a single 2-hour session, with order of testing standardized, and participants’ schedules were arranged to limit the effect of fatigue and extraneous factors.

Statistical Analysis

Descriptive statistics were calculated for demographic and treatment characteristics. The \( \chi^2 \) test and 2-sample \( t \) test were used to compare participant and nonparticipant characteristics and cumulative treatment variables. Scores on neurocognitive functions, neurobehavioral symptoms, emotional symptoms, and health-related quality of life were converted to standard scores using normative population data, where lower scores represent poorer neurocognitive functioning or worse PRO symptoms. One-sample \( t \) tests were used to compare performances and symptoms between survivors and population norms, and 2-group \( t \) tests were used to compare survivors with community controls. Only those neurocognitive, neurobehavioral, and emotional measures that differed from the normative sample and between survivors and community controls, with at least 1 comparison having \( P \leq .01 \) (to adjust for multiple comparisons), were examined for associations with high-dose methotrexate exposure. Univariate and multivariable model analyses were examined between survivors’ performance and high-dose methotrexate dose and pharmacokinetic indices. Associations between neurocognitive performance and chronic health conditions were examined by dichotomizing the cohort into those with vs without a grade 3 or 4 cardiac, pulmonary, or endocrine event, and then 2-group \( t \) tests were conducted to compare groups. Among survivors, the association between neurocognitive impairment and social outcome was examined.

Results

Demographic characteristics did not significantly differ between survivor participants and nonparticipants (see eTable 1 in the Supplement). Survivor participants were treated with marginally higher doses of doxorubicin, carboplatin, cyclophosphamide, and bleomycin, and slightly lower doses of cisplatin than nonparticipants. No difference in high-dose methotrexate cumulative dose was apparent (\( P = .61 \)). No differences were found between community controls and survivor participants in sex \( (22 \% [56\%] \) female controls, \( 34 \% [42\%] \) survivors; \( P = .15 \)), mean (SD) present age \( (39.0 \pm 11.7 \) years controls, \( 38.9 \pm 7.1 \) years survivors; \( P = .82 \)), or social attainment, with the exception of marital status (see eTable 2 in the Supplement). Survivor participants had a mean (SD) age of 14.2 (3.7) years at diagnosis and participated in the study a mean (SD) of 24.7 (6.6) years after diagnosis. The majority of survi-
vors underwent amputation (63 \(84\%\)) and had cancer in a lower extremity (74 \(92\%\)).

Neurocognitive performance and PROs for neurobehavioral and emotional outcomes of survivors and community controls are presented in Table 1. Compared with community controls, survivors demonstrated lower reading scores (\(P = .01\)), more variability in sustained attention (\(P = .002\)), poorer short-term memory (\(P = .01\)), slower motor processing speed (\(P < .001\)), and poorer cognitive fluency (\(P = .006\)). Survivors also scored significantly below population norms on these same measures, whereas community controls did not differ significantly from population norms. Within survivors, performance on neurocognitive measures was related to attainment of less than a college education (relative risk [RR], 1.25 [95% CI, 1.02-1.53], for each 1.0 \(z\) score below the mean on short-term memory), less than full-time employment (RR, 3.75 [95% CI, 1.15-12.22], for each 1.0 \(z\) score below the mean on reading), and less than $40 000 annual income (RR, 2.76 [95% CI, 1.04-7.36] and RR, 1.11 [95% CI, 1.02-1.20], for each 1.0 \(z\) score below the mean on reading and sustained attention, respectively), adjusting for present age and sex (see eTable 3 in the Supplement). Osteosarcoma survivors self-reported more problems with working memory compared with controls (\(P < .001\)) and national norms (\(P = .004\)). Although survivors reported more somatic complaints on the Brief Symptom Inventory 18 compared with controls (\(P < .001\) and \(P = .004\), respectively).
Table 3. Number of Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03, Grades

<table>
<thead>
<tr>
<th>Adverse Event Type</th>
<th>CTCAE Grade, No. (%)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>3 or 4*</th>
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<tbody>
<tr>
<td>Cardiac</td>
<td>19 (23)</td>
<td>23 (29)</td>
<td>23 (29)</td>
<td>14 (18)</td>
<td>1 (1)</td>
<td>15 (19)</td>
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<tr>
<td>Fractional shortening</td>
<td>53 (75)</td>
<td>0</td>
<td>8 (11)</td>
<td>10 (14)</td>
<td>0</td>
<td>10 (14)</td>
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<tr>
<td>Pulmonary</td>
<td>41 (51)</td>
<td>27 (34)</td>
<td>7 (9)</td>
<td>4 (5)</td>
<td>1 (1)</td>
<td>5 (6)</td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td>31 (39)</td>
<td>9 (11)</td>
<td>25 (31)</td>
<td>14 (18)</td>
<td>1 (1)</td>
<td>15 (19)</td>
<td></td>
</tr>
</tbody>
</table>

* There were 33 unique survivors with any grade 3 or 4 condition (41%).

b Fractional shortening grading based on echocardiography also depicted with the cardiac system.
tation fractions assessed through echocardiography. Although most survivors demonstrated normal ejection fraction, 10 survivors had a grade 3/4 fractional shortening condition (ie, ejection fraction <40%). Survivors with grade 3/4 fractional shortening demonstrated lower sustained attention compared with survivors with no fractional shortening (mean [SD], –2.22 [5.43] vs –0.52 [1.28], respectively; $P = .04$).

Discussion

When compared with community controls and population normative data, long-term survivors of childhood osteosarcoma demonstrate significant neurocognitive problems in attention, memory, processing speed, executive function, and academics, as well as significant self-reported symptoms of poor working memory. Survivors do not report significant symptoms of emotional distress, poor mental health, bodily pain, or physical role limitations, although they do report decreased physical health-related quality of life compared with the general population. Given the frequent occurrence of amputation in these survivors, this pattern may suggest positive adaption to their physical disabilities. These results provide, to our knowledge, the first objective assessment of neurocognitive skills in long-term survivors of this disease and demonstrate a clear risk for adverse events.

At a mean of nearly 25 years after diagnosis, neurocognitive outcomes in the survivors were not related to cumulative dose or pharmacokinetic indices of high-dose methotrexate exposure. These parameters were based on population pharmacokinetic modeling and model-predicted estimates of $C_{\text{max}}$, clearance, and $\text{AUC}_{0-\text{max}}$ generated from serum concentrations obtained through comprehensive medical record review across each course of methotrexate. This approach permits the novel examination of the association between functional outcomes and high-dose methotrexate exposure in long-term survivors of osteosarcoma. The high-dose methotrexate pharmacokinetic parameters were not related to any of the significant areas of impairment, either in unadjusted univariate models or when controlling for sex, age at diagnosis, and time since diagnosis.

Although we did not observe a significant association between high-dose methotrexate therapy and neurocognitive outcomes, it is important to consider the patient population treated and study design implemented when making comparisons to the available literature. In survivors of childhood ALL who were treated with high-dose methotrexate and were roughly 5 years from diagnosis, higher dosages of high-dose methotrexate were associated with more attention problems compared with those survivors receiving lower high-dose methotrexate dosages. We recently examined neurocognitive outcomes in 567 adult survivors of childhood ALL, 214 of whom were treated only with chemotherapy. At a mean of 20.9 years after diagnosis, the chemotherapy-only patients demonstrated impairment in intelligence, academics, attention, memory, processing speed, and executive function. Through multivariate analysis, cumulative dosages of high-dose methotrexate were found to be significantly associated with increasing risk for slowed processing speed. However, with the osteosarcoma survivors in the present study, who were roughly 25 years after diagnosis, we did not find such an association. This discrepancy may be explained by a younger mean age at diagnosis in our patients with ALL than in the osteosarcoma cohort (6.9 vs 14.2 years) and the fact that patients with ALL received concomitant intrathecal chemotherapy. In addition, the extended time since diagnosis may have resulted in a shift from variance explained by high-dose methotrexate to other factors that emerge with age.

Other investigators have made conflicting reports on the associations between high-dose methotrexate therapy and neurocognitive problems in long-term survivors of ALL. Ochs and colleagues performed a prospective neurocognitive study in patients with ALL and found a significant difference in full-scale and verbal intelligence, along with arithmetic scores, when comparing baseline and end-of-therapy performance within the parenteral methotrexate group. Spiegler and colleagues performed an evaluation of neurocognitive impairment in long-term survivors of childhood ALL at a mean of 10 years from diagnosis and found no significant difference in neurocognitive outcomes of patients treated with high-dose or very high-dose methotrexate (defined as 3 doses of 8 or 33.6 g/m², respectively) when compared with age-matched controls. However, we recently demonstrated that neurocognitive impairment in ALL survivors is also associated with genetic polymorphisms in methionine synthase, which may affect the pharmacokinetic indices of high-dose methotrexate exposure. Thus, interpatient variability in methotrexate pharmacokinetic parameters, which likely results in variability in pharmacological effect, along with pharmacogenetic polymorphisms may be the driving force in high-dose methotrexate–related neurocognitive impairment.

Recent literature has demonstrated that chronic health conditions can also affect neurocognitive functions in adult survivors of childhood cancer. Adverse cardiac, pulmonary, and endocrine function occurs in 50% to 60% of long-term adult survivors. In adult survivors of Hodgkin lymphoma, who were a mean of 27 years after diagnosis, we previously demonstrated that abnormal cardiac function was associated with impaired executive function, while abnormal pulmonary function was related to impaired attention and processing speed. Moreover, neurocognitive impairment was also correlated with structural abnormalities on magnetic resonance imaging. Our present results with osteosarcoma survivors demonstrate that grade 3 or 4 adverse chronic health conditions were associated with poorer memory and processing speed. Those with grade 3 or 4 conditions demonstrated performances below the population mean on measures of reading, attention, memory, and processing speed compared with those with less than grade 3 or 4 conditions. However, those with chronic health conditions of less than grade 3 demonstrated performances below the mean on measures of attention, processing speed, and executive function. This pattern suggests not only an impact of chronic health conditions on neurocognitive function but also contributions from other factors yet to be determined. Prospective testing of patients with osteosarcoma is needed to
thoroughly evaluate the impact of high-dose methotrexate pharmacokinetics independent of the chronic health conditions that develop over time.

This study is not without limitations. Our cohort of 80 long-term survivors of childhood osteosarcoma is relatively small, particularly when compared with recent cohorts of survivors of childhood ALL. The sample size may be insufficient to pick up subtle effects of high-dose methotrexate therapy and does not permit complex multivariable modeling, particularly analyses that include both treatment and chronic condition variables. Thus, omitted-variable bias is a potential concern because the present models may have left out 1 or more important causal factors. The frequency of grade 3 or 4 chronic conditions does not permit separate examination of cardiac, pulmonary, and endocrine factors. However, osteosarcoma is not nearly as common as ALL and there are no other reports of direct neurocognitive and high-dose methotrexate pharmacokinetics in the current literature. Furthermore, our use of a community control group equated on age and sex permits us to identify neurocognitive deficits referenced to population norms, as well as a community standard.

Conclusions

Limitations notwithstanding, our study is the first to use objective neurocognitive testing to demonstrate impairment in long-term survivors of childhood osteosarcoma, to analyze the relationship between neurocognitive outcomes and pharmacokinetic parameters of high-dose methotrexate therapy, and to demonstrate associations between this impairment and chronic health conditions in the survivors. Treatment-related neurocognitive problems have not been systematically evaluated in osteosarcoma survivors, with the literature in childhood cancer survivors focused almost entirely on survivors of ALL or central nervous system tumors. Our results demonstrate the need for increased attention in this diagnosis, with prospective studies to delineate the evolution of impairment over the course of therapy and long-term survival. In addition, we recommend initial screening for neurocognitive deficits in survivors of osteosarcoma as they enter long-term follow-up (ie, 2 years following completion of therapy), and periodically thereafter as they manifest new chronic health conditions.


