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Disparities in Neurotoxicity Risk and Outcomes among Pediatric Acute Lymphoblastic Leukemia Patients

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Abstract

Purpose: Methotrexate chemotherapy can be associated with neurologic complications during therapy and long-term neurologic deficits. This study evaluated demographic and clinical factors associated with incidence of methotrexate neurotoxicity and described the impact of neurotoxicity on acute lymphoblastic leukemia (ALL) therapy in pediatric patients.

Experimental Design: Patients were enrolled between 2012 and 2017 from three pediatric cancer treatment centers in the United States. Medical records for suspected cases of methotrexate neurotoxicity, defined as an acute neurologic event following methotrexate therapy, were reviewed. Cox proportional hazards models were used to estimate the association between race/ethnicity and methotrexate neurotoxicity. Multivariable linear regression models compared treatment outcomes between patients with and without methotrexate neurotoxicity.

Results: Of the 280 newly diagnosed patients enrolled, 39 patients (13.9%) experienced methotrexate neurotoxicity. Compared with non-Hispanic whites, Hispanic patients experienced the greatest risk of methotrexate neurotoxicity (adjusted HR, 2.43; 95% CI, 1.06–5.58) after accounting for sex, age at diagnosis, BMI *Z*-score at diagnosis, and ALL risk stratification. Patients who experienced a neurotoxic event received an average of 2.25 fewer doses of intrathecal methotrexate. Six of the 39 cases of neurotoxicity (15.4%) experienced relapse during the study period, compared with 13 of the 241 (2.1%) patients without neurotoxicity ($P = 0.0038$).

Conclusions: Hispanic ethnicity was associated with increased risk of methotrexate neurotoxicity, which was associated with treatment modifications and relapse. Understanding the mechanism and predictors of methotrexate neurotoxicity is important to improving treatment outcomes in pediatric ALL.
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Introduction

Methotrexate is a key component of contemporary chemotherapy for acute lymphoblastic leukemia (ALL), the most common malignancy diagnosed among those less than 15 years of age in the United States (1). However, methotrexate chemotherapy can be associated with profound neurologic complications during therapy, as well as long-term neurologic deficits (2, 3). Specifically, central nervous system–directed intrathecal and high-dose intravenous methotrexate have been linked to acute and subacute neurotoxicity, with a reported incidence among patients with pediatric ALL ranging between 3% and 12% depending on treatment regimen (4–8). The clinical presentation of methotrexate-induced neurotoxicity, which typically occurs within 2 weeks of intrathecal and/or intravenous high-dose methotrexate, includes altered mental status, seizures, and stroke-like symptoms (9, 10). Although symptoms typically resolve with time, the incidence of neurotoxicity often results in hospitalization and modifications to leukemia therapy, which may reduce treatment efficacy and jeopardize long-term survival (9). Despite the potentially serious implications of neurotoxicity, information as to why some patients experience methotrexate-induced neurotoxicity, whereas others do not, is limited.

Several recent case series have reported a high prevalence of methotrexate subacute neurotoxicity among Hispanic patients with ALL, suggesting sensitivity to methotrexate therapy may differ by race and ethnicity (11, 12). Disparities and mortality in pediatric ALL have been narrowing over time (13–15). Differences in susceptibility to treatment-related toxicity may contribute to well-documented racial/ethnic disparities in ALL treatment efficacy (16–19). However, risk factors for methotrexate neurotoxicity and the impact of neurotoxic events on subsequent ALL treatment have not been well described in large, diverse populations. Therefore, the objectives of this study were to: (i) evaluate demographic and clinical factors associated with incidence of acute and subacute methotrexate neurotoxicity and (ii) describe the impact of neurotoxicity on therapy in a large and well-characterized, multi-institutional prospective cohort of pediatric patients treated according to contemporary ALL protocols.

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

Children from minority populations continue to experience inferior outcomes after being diagnosed with acute leukemia, despite improvements in treatment regimens. Treatment-related toxicities resulting in treatment modifications or delays may contribute to racial and ethnic differences in survival. For example, we report here that Hispanic patients experience more episodes of neurotoxicity than other groups. Accordingly, patients who experienced neurotoxicity received significantly fewer doses of intrathecal methotrexate and slightly lower cumulative doses of intravenous methotrexate. These findings add to the growing body of evidence indicating that minority patients, in particular Hispanics, often encounter significant disparities in terms of treatment outcomes for pediatric ALL. Understanding the mechanisms and predictors of neurotoxicity is critical to improving treatment outcomes. Future studies are needed to evaluate biologic factors that may modify the risk of neurotoxicity among vulnerable patients, including Hispanics. Extended follow-up time is also needed to evaluate the long-term effects of neurotoxicity in pediatric patients.

Materials and Methods

Study population

Patients undergoing therapy on a leukemia treatment protocol at three major pediatric cancer treatment centers in the United States [University of Arizona (Tucson, AZ), Children's Minnesota (Minneapolis, MN), and Texas Children's Cancer Center (Houston, TX)] between November 2012 and February 2017 were enrolled on a prospective study of treatment-related toxicity. Institutional review boards at each participating site approved the study, which was conducted in accordance with guidelines in the U.S. Common Rule and Belmont Report. Informed consent was obtained from parents or legal guardians of each participant, and when appropriate, assent was obtained from subjects. Subjects were eligible for the study if they were diagnosed between 2 and 18 years of age and treated on or according to one of the following Children's Oncology Group (COG) leukemia protocols: AALL0932, AALL1231, AALL1131, AALL0434, AALL1122, AALL0031. Summary of leukemia treatment in reference to methotrexate therapy is provided in Supplementary Table S1. Specific treatment information for each protocol can be accessed on www.clinicaltrials.gov (20). Subjects with preexisting medical history of developmental disability or neurologic disorders were excluded.

Data collection

Methotrexate neurotoxicity. Patients were prospectively monitored for the incidence of toxicity during treatment through June 2017. Electronic medical records were reviewed for suspected cases of acute or subacute methotrexate neurotoxicity. Suspected cases were defined as patients with a neurologic event including stroke-like symptoms, aphasia, and seizures following intrathecal and/or intravenous methotrexate that resulted in modifications in intrathecal and/or intravenous methotrexate therapy. Suspected cases were independently reviewed by two pediatric oncologists to confirm the diagnosis of acute or subacute methotrexate neurotoxicity. No discrepancies in case ascertainment were reported between reviewers.

Study covariates. Demographic (i.e., patient sex, race, ethnicity) and clinical information [i.e., diagnosis, chemotherapy dose, treatment risk group assignment, minimal residual disease (MRD) status at day 29 of therapy, height and weight at diagnosis, date of relapse or death] were abstracted from electronic medical records. Bone marrow evaluation on COG leukemia protocols is performed at the end of induction on D29 to determine risk assignment and postinduction therapy course (21, 22). Information on race and ethnicity was obtained using the standard NIH self-report form. Cumulative intrathecal (number of doses) and intravenous (dose in g/m^2) methotrexate were calculated through the end of the postinduction therapy. Body mass index (BMI) *Z*-scores were calculated from diagnostic heights and weights using sex- and age-specific growth charts (23).

Statistical analysis

Statistical analyses were conducted in Stata version 14 (StataCorp) at a 5% significance threshold. Appropriate descriptive statistics for continuous (i.e., mean, SD) and categorical (i.e., frequency, proportion of the total) covariates were calculated to characterize the study population. Differences in covariates by neurotoxicity status were evaluated using a *t* test for continuous or Fisher exact test for categorical covariates. The incidence of methotrexate neurotoxicity by race/ethnicity groups was graphically compared using Nelson–Aalen cumulative hazard curves and statistically evaluated with the log-rank test. Cox proportional hazards models were used to estimate the crude and adjusted HR and corresponding 95% confidence interval (95% CI) for the association between race/ethnicity and methotrexate neurotoxicity. Adjusted models included terms for age at diagnosis, BMI *Z*-score at diagnosis, sex, and treatment risk arm. We also evaluated the association between methotrexate neurotoxicity and clinical outcomes. Multivariable linear regression models were generated to compare treatment differences between patients with and without methotrexate neurotoxicity, adjusting for treatment risk arm, BMI *Z*-score at diagnosis, sex, and age at diagnosis. Separate regression models were constructed for the dependent variables of cumulative cycles of intrathecal methotrexate, cumulative intravenous methotrexate dose, and time from diagnosis to start of maintenance/continuation therapy. The frequency of all-cause and central nervous system (CNS) relapse was compared between patients with and without methotrexate neurotoxicity using the log-rank test and Cox regression models. We performed regression diagnostics to confirm that modeling assumptions were satisfied, such as the proportionality assumption of Cox regression and the multivariate normality assumption of linear regression.

Results

A total of 280 newly diagnosed patients were eligible and enrolled in the parent study between November, 2012, and February, 2017. Individuals were followed from diagnosis of ALL to start of maintenance/continuation therapy. As of June 1, 2017, 39 patients (13.9%) experienced acute or subacute methotrexate neurotoxicity (median follow-up = 22.6 months; range, 1.3–55.6 months). All patients with suspected neurotoxicity presented with

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Table 1. Clinical and demographic characteristics of patients treated on ALL protocols, 2012–2017

	Overall	MTX neurotoxicity		
	(*n* = 280)	Yes (*n* = 39)	No (*n* = 241)	*P*
Age at diagnosis, mean (SD)	8.40 (4.36)	12.20 (3.27)	7.79 (4.21)	<0.01
BMI *Z*-score, mean (SD)	0.23 (1.31)	0.80 (1.20)	0.14 (1.31)	<0.01
Patient sex, *n* (%)				0.99
Male	146 (52.1)	20 (51.3)	126 (52.3)	
Female	134 (47.9)	19 (48.7)	115 (47.7)	
Race/ethnicity, *n* (%)				<0.01
Non-Hispanic white	100 (36.2)	8 (20.5)	92 (38.8)	
Hispanic	133 (48.2)	29 (74.4)	104 (43.9)	
Non-Hispanic black	23 (8.3)	2 (5.1)	21 (8.9)	
Non-Hispanic other	20 (7.3)	0 (0.0)	20 (8.4)	
Diagnosis, *n* (%)				0.28
B-ALL	240 (85.7)	31 (79.5)	209 (86.7)	
T-ALL	30 (10.7)	7 (18.0)	23 (9.5)	
Lymphoblastic lymphoma	10 (3.6)	1 (2.5)	9 (3.7)	
Treatment arm, *n* (%)				<0.01
Low/standard risk	115 (41.5)	6 (15.4)	109 (45.8)	
High/very high risk	162 (58.5)	33 (84.6)	129 (54.2)	
Triple IT therapy, *n* (%)				0.99
None	248 (89.9)	34 (89.5)	214 (89.9)	
Any	28 (10.1)	4 (10.5)	24 (10.1)	
Day 29 MRD, *n* (%)				0.11
<0.01%	200 (74.1)	24 (63.2)	176 (75.9)	
≥0.01%	70 (25.9)	14 (36.8)	56 (24.1)	

NOTE: *P* value from *t* test for continuous variable or Fisher exact test for categorical variables.
Abbreviations: IT, intrathecal; MTX, methotrexate; T-ALL, T-cell acute lymphoblastic leukemia.

common manifestations (e.g., aphasia, seizure, stroke) and were independently reviewed by two pediatric oncologists (J. Brackett and Z.E. Dreyer). Most cases of neurotoxicity presented with stroke-like symptoms ($n = 24$), seizures ($n = 6$), altered mental status ($n = 3$), or both altered mental status and stroke-like symptoms ($n = 2$). There were individual cases of each of the following presentations: seizure and stroke-like symptoms, aphasia, vision changes with difficulty word finding, and syncopal episode (Supplementary Table S2). All suspected cases of neurotoxicity received at least one MRI, with evidence of methotrexate-induced neurotoxicity detected in 72% ($n = 28$) of cases. The demographic and clinical characteristics of the study population are presented in Table 1. The mean age at ALL diagnosis of patients included in this analysis was 8.4 years (range, 2.5–18.8 years). Most participants included in the analysis were male (52.1%), diagnosed with pre B-cell leukemia (85.7%), treated on high or very high-risk treatment arms (58.5%). Compared with patients without neurotoxicity, patients with acute or subacute methotrexate neurotoxicity were significantly older at diagnosis (12.2 years vs. 7.8 years), had greater BMI *Z*-scores (0.80 vs. 0.14), and were more likely to receive high or very high-risk treatment (84.6% vs. 54.2%). Of the patients who experienced neurotoxicity, 74.4% ($n = 29$) were Hispanic compared with 43.9% ($n = 104$) of those without methotrexate neurotoxicity ($P < 0.01$). There was no statistically significant difference in the type of ALL (B-cell vs. T-cell) by race/ethnicity (χ^2, $P = 0.362$); therefore, the differences noted in neurotoxicity by race/ethnicity are not likely due to differences in ALL type.

The incidence of acute and subacute neurotoxicity differed significantly by race/ethnic group (Fig. 1, log-rank $P = 0.0049$). Compared with non-Hispanic whites (Table 2), Hispanic patients experienced the greatest risk of methotrexate neurotoxicity (unadjusted HR, 2.93; 95% CI, 1.34–6.42). Hispanic ethnicity remained robustly associated with neurotoxicity risk even after accounting for sex, age at diagnosis, BMI *Z*-score at diagnosis, and ALL risk stratification (adjusted HR, 2.43; 95% CI, 1.06–5.58). A sensitivity analysis restricted to the cases with MRI evidence of methotrexate neurotoxicity ($n = 28$) did not meaningfully impact the findings.

Relative to non-Hispanic whites, Hispanic patients in the sensitivity analysis remained at increased risk of MRI-confirmed neurotoxicity in both unadjusted models (HR, 2.81; 95% CI, 1.13–6.67) and models accounting for treatment risk arm, age at diagnosis, BMI *Z*-score at diagnosis, and gender (HR, 2.39; 95% CI, 0.91–6.26). A total of nine of the 39 patients with neurotoxicity (23.1%) experienced a second neurotoxic event, all of whom were Hispanic ($P = 0.079$). The second events were similar in nature to the symptoms in the first event: three patients presented with seizure; five with stroke-like symptoms; and one with altered

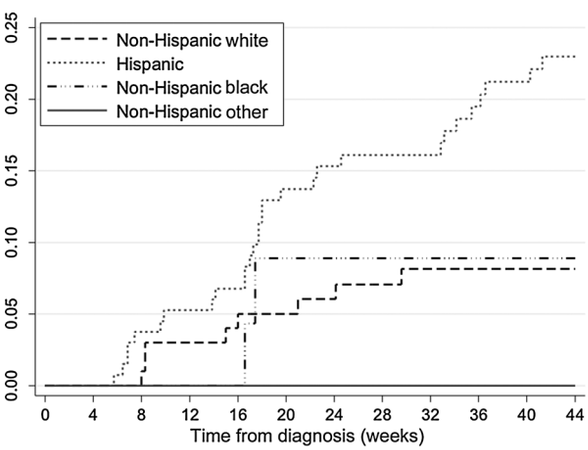

Figure 1.
Cumulative incidence of methotrexate neurotoxicity by race/ethnicity.

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Table 2. Association between race/ethnicity and incidence of methotrexate neurotoxicity among patients treated on ALL protocols, 2012–2017

			Unadjusted model		Adjusted model[a]	
	Patients at baseline	Neurotoxic events	HR (95% CI)	*P*	HR (95% CI)	*P*
Race/ethnicity						
Non-Hispanic white	100	8	Ref.		Ref.	
Hispanic	133	29	2.93 (1.34–6.42)	0.01	2.43 (1.06–5.58)	0.036
Non-Hispanic black	23	2	1.15 (0.24–5.40)	0.86	1.23 (0.25–5.91)	0.80
Non-Hispanic other	20	0	—	—	—	—

[a]Model adjusted for treatment risk arm, age at diagnosis, BMI *Z*-score at diagnosis, and sex.

mental status. Independent of Hispanic ethnicity, only age at diagnosis (HR, 1.18; 95% CI, 1.09–1.29) remained a statistically significant predictor of neurotoxicity in multivariable models, with the risk increasing linearly with increasing age. Although not statistically significant, there was evidence of an increased risk of neurotoxicity in females (HR, 1.45; 95% CI, 0.76–2.79) and patients in high/very high treatment risk arms (HR, 1.44; 95% CI, 0.52–4.03).

Independent of treatment risk arm, sex, BMI *Z*-score at diagnosis, and age at diagnosis, patients who experienced a neurotoxic event received an average of 2.25 (95% CI, 1.73–2.77) fewer doses of intrathecal methotrexate (Table 3). The most common treatment modification was holding lumbar punctures (LPs) and replacing intrathecal methotrexate with intrathecal cytarabine/hydrocortisone (AraC/HC) for at least one subsequent LP after the neurotoxic event (43.6%), followed by holding at least next scheduled LP and resuming intrathecal methotrexate with leucovorin rescue (38.5%). LPs were generally held for 4 to 6 weeks pending symptom resolution and/or abnormality improvement on MRI. Summary of all intravenous and intrathecal methotrexate treatment changes are presented in Supplementary Table S3. Of the 39 cases of methotrexate neurotoxicity, 24 (61.5%) were rechallenged with intrathecal methotrexate and leucovorin rescue, 7 (17.9%) were never rechallenged, and 5 (12.8%) continued to receive intrathecal methotrexate with leucovorin without interruption in previously scheduled therapy. Three (7.7%) are pending final clinical decision. Six of the 39 cases of neurotoxicity (15.4%) experienced relapse during the study period, compared with 13 of the 241 (2.1%) patients without methotrexate neurotoxicity (Supplementary Fig. S1A, log-rank $P = 0.0038$). Similarly, CNS relapse was significantly more frequent among patients with neurotoxicity (4/39, 10.3%) than patients without neurotoxicity (5/241, 2.1%) in this study (Supplementary Fig. S1B, log-rank $P = 0.0014$). In univariate Cox regression models, methotrexate neurotoxicity was significantly associated with CNS relapse (unadjusted HR, 3.80; 95% CI, 1.44–10.02; $P = 0.007$), a trend that remained after accounting for treatment risk arm (HR, 2.92; 95% CI, 1.07–7.95; $P = 0.036$), MRD status at day 29 (HR, 3.49; 95% CI, 1.32–9.24; $P = 0.012$), race and ethnicity (HR, 3.15; 95% CI, 1.13–8.79; $P = 0.028$), age at diagnosis (HR, 2.56; 95% CI, 0.91–7.21; $P = 0.076$), and gender (HR, 3.82; 95% CI, 1.44–10.10; $P = 0.007$).

Table 3. Treatment comparison by neurotoxicity status among patients treated on ALL protocols, 2012–2017

	Mean (95% CI) treatment comparison by neurotoxicity		
	Neurotoxicity ($n = 28$)	No neurotoxicity ($n = 181$)	*P*
IV MTX dose, g/m^2	10.23 (8.33–12.13)	12.04 (11.37–12.71)	0.084
Number IT MTX doses	8.84 (8.36–9.33)	11.09 (10.92–11.26)	<0.01
Time to maintenance, days	296.9 (284.8–311.9)	290.0 (284.8–295.3)	0.408

NOTE: Model adjusted for treatment risk arm, age at diagnosis, BMI Z-score at diagnosis, and sex.
Abbreviations: IT, intrathecal; IV, intravenous; MTX, methotrexate.

Discussion

To our knowledge, this is the first multi-institutional prospective study to evaluate demographic and clinical factors associated with incidence of methotrexate neurotoxicity and subsequent impact on pediatric ALL treatment. The overall incidence of methotrexate neurotoxicity in our patient population (13.9%) is slightly higher than previous reports, ranging from 3% to 12% (4–8). It is worth noting that the frequency of neurotoxicity among non-Hispanic patients in this study (6.8%) was consistent with previous studies. It appears the higher frequency of neurotoxicity observed in our study (13.9%) is a consequence of the high incidence of neurotoxicity among Hispanics (21.8%) and a high proportion of Hispanics included in the study population (47.5%), which are underrepresented in other studies of pediatric ALL neurotoxicity. Because our study eligibility limited subjects under 2 years of age at diagnosis, our study population is slightly older than the population of children with ALL in the United States. Our gender distribution is similar to the United States; however, our population is overrepresented for Hispanics patients even though it is representative of our local populations. All reported events occurred following intrathecal and/or intravenous methotrexate (~14 days from last intrathecal/intravenous methotrexate). This time frame is consistent with other studies of acute and subacute methotrexate neurotoxicity (4–8). We also found that Hispanic ethnicity was associated with increased risk of methotrexate neurotoxicity. Of the patients who experienced a neurotoxic event in our cohort, 74.4% were Hispanic, and, of the patients who experienced a second neurotoxic event, all were Hispanic. Our suggestion that Hispanics are at an increased risk of developing methotrexate neurotoxicity is supported by two recent case series that also reported high proportion of Hispanic patients with subacute neurotoxicity (11, 12). Specifically, Afshar and colleagues reported on 18 cases of neurotoxicity, of which 66.7% ($n = 12$) were Hispanic (11). Similarly, Giordano and colleagues described a series of five Hispanic patients who developed methotrexate neurotoxicity (12).

The higher overall incidence of methotrexate neurotoxicity in our study population could be attributed to different case definitions for methotrexate acute or subacute neurotoxicity. For example, Bjowani and colleagues reported that all cases included in their study had MRI findings consistent with methotrexate neurotoxicity, while MRI evidence of neurotoxicity was observed in just 72% of the cases included in our study (5). Notably, restricting our analysis to cases with MRI evidence of neurotoxicity did not meaningfully impact our results.

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Alternatively, the high prevalence of neurotoxicity observed in this study may reflect recent advances in ALL treatment, which have improved overall survival of pediatric ALL, but may also be associated with more toxicity. A recent Children's Oncology Group Study reported that patients with high-risk B-cell acute lymphoblastic leukemia (B-ALL) who received intravenous high-dose methotrexate versus Capizzi escalating-dose intravenous methotrexate had a significantly higher 5-year event-free survival (82% compared with 75%; $P = 0.006$; ref. 24). These findings resulted in changes to intravenous methotrexate therapy, and subsequently, high-dose intravenous methotrexate was recommended for pediatric patients with high-risk B-ALL. This shift in the standard of care exposes more patients to high-dose intravenous methotrexate, possibly increasing their risk of developing treatment-related toxicities including neurotoxicity.

Racial and ethnic minorities continue to experience inferior outcomes after being diagnosed with pediatric ALL, despite improvements in treatment regimens (16–19). Treatment-related toxicities resulting in treatment modifications or delays may contribute to racial and ethnic differences in survival. In our study, methotrexate neurotoxicity was significantly associated with time to any relapse as well as CNS relapse. The relapse rate of 15.4% in our patient populations is consistent with the rate reported in a small case series of five patients by Giordano and colleagues where one (20%) relapsed and died. Changes in intravenous and/or intrathecal methotrexate therapy were made for patients who experienced a neurotoxic event to allow for symptom resolution and recovery from onset of neurologic changes. Accordingly, patients who experienced neurotoxicity in this study received significantly fewer doses of intrathecal methotrexate and slightly lower cumulative doses of intravenous methotrexate. In addition, 29 cases (74.4%) received leucovorin rescue after intrathecal methotrexate. Several publications suggest that leucovorin doses may interact with methotrexate to reduce efficacy and cure rate of pediatric ALL (25, 26). These findings may help us better understand what factors contribute to poorer survival among Hispanic patients with ALL.

Our findings add to the growing body of evidence indicating that minority patients, in particular Hispanics, often encounter significant disparities in terms of treatment outcomes for pediatric ALL. These findings should be further examined in larger cohort studies. Extended follow-up is also needed to further evaluate outcomes and long-term effects of methotrexate neurotoxicity in pediatric patients. Although we did not differentiate between acute and subacute methotrexate neurotoxicity, future studies with larger sample sizes should examine possible differences between acute and subacute neurotoxic events. In addition, within each type of ALL, numerous cytogenetic subtypes exist, and the impact of these subtypes on outcomes should be examined in future studies. Future studies are also needed to evaluate biologic factors that may modify the risk of methotrexate neurotoxicity among vulnerable patients, including Hispanics. Understanding the mechanism and predictors of methotrexate neurotoxicity is critical to improving treatment outcomes. Future research from our group is investigating biomarkers for neurotoxicity, which could benefit increased surveillance during therapy for these adverse treatment outcomes.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Conception and design: O.A. Taylor, A.L. Brown, I.K. Moore, M.J. Hockenberry, P.J. Lupo, M.E. Scheurer

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): O.A. Taylor, A.L. Brown, Z.E. Dreyer, I.K. Moore, P. Mitby, M.C. Hooke, M.E. Scheurer

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): O.A. Taylor, A.L. Brown, J. Brackett, Z.E. Dreyer, M.J. Hockenberry, P.J. Lupo, M.E. Scheurer

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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): O.A. Taylor, A.L. Brown, J. Brackett, Z.E. Dreyer, M.J. Hockenberry, M.E. Scheurer

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