Intrainfusion Drug Monitoring and Algorithm-Based Dose Adjustments for Children With ALL Receiving High-Dose Methotrexate Are Feasible and Safe in Costa Rica, a Low- and Middle-Income Country

Karol Acevedo, MD[1]; Gabriela Soto, MD[1]; Mary C. Shapiro, MD[2,3]; Jennifer H. Foster, MD, MPH[2,3]; Kathia Valverde, MD[1]; Eric S. Schafer, MD, MHS[2,3]; and Judith Margolin, MD[2,3]

DOI https://doi.org/10.1200/GO-24-00450

ABSTRACT

PURPOSE Infusions of high-dose methotrexate at 5 g/m² over 24 (HDMTX) as a single infusion for pediatric patients with high-risk precursor B-cell ALL are known to lead to superior outcomes. The Hospital Nacional de Niños Dr Carlos Sáenz Herrera, part of the public system Caja Costarricense de Seguro Social in Costa Rica (HNN), has been historically unable to provide this therapy secondary to the required intensive monitoring and cost-prohibitive toxicity support.

METHODS We report our experience providing HDMTX at HNN, to our knowledge, for the first time using an algorithm-based individualized HDMTX protocol designed to prevent toxic levels of methotrexate. The protocol checks intrainfusion methotrexate levels at hours 2 and 6 or 8, with adjustments in the infusion downward if levels predict a high/toxic end infusion concentration.

RESULTS Fifty-two patients (who received 196 total evaluable infusions between 2017 and 2019) were included. Rate adjustments were required during 51 infusions (24.6%). Significant methotrexate-related toxicities were rare and included acute kidney injury (≥grade 3, 0.5%, n = 1), neurotoxicity (≥grade 3, 1%, n = 2), mucositis (≥grade 3, 4.8%, n = 10), and neutropenia (≥grade 3, 24.6%, n = 51). No ≥grade 4 toxicities occurred.

CONCLUSION A real-time, algorithm-based individualized HDMTX infusion is a practical and safe way to administer HDMTX in a low- and middle-income country.

Accepted January 22, 2025
Published March 7, 2025

JCO Global Oncol 11:e2400450

INTRODUCTION

Methotrexate, a synthetic folate antimetabolite, is one of the most versatile and effective chemotherapeutic agents in the treatment of ALL but has common adverse effects (AEs) including myelosuppression, mucositis, and liver, kidney, and neurologic toxicities. It has been shown that high-dose methotrexate at 5g/m² infusions as single dose over 24 hours (HDMTX) is a key component in the treatment of high-risk (HR) pediatric precursor B-cell (preB) ALL.[1] The cytotoxic effect on bone marrow disease and its ability to penetrate the blood-brain barrier have decreased the requirement for cranial radiation and improved event-free survival in children with ALL. To avoid immediate, life-threatening nephrotoxicity, this form of HDMTX requires extensive supportive care including alkalinized intravenous fluids, methotrexate concentration monitoring, leucovorin rescue, and the availability of glucarpidase—an expensive (approximately $40,000 US dollars [USD] per administration[2]) folate-inactivating, carboxypeptidase-containing medication and/or dialysis.[3-7] However, even with supportive care, some patients receiving HDMTX experience significant toxicities. An estimated 2%-19% of patients will experience acute kidney injury (AKI) with a mortality rate, in those patients, of 4.4%.[8-10]

In Costa Rica, we have traditionally not been able to provide the superior HDMTX of 5 g/m² over 24 hours secondary to our inability to perform the extensive laboratory monitoring required or appropriately rescue with glucarpidase or dialysis the small number of patients who might develop high methotrexate exposure–based, life-threatening AKI. Our previous protocol to treat patients with HR ALL included four cycles of 5 g/m² methotrexate as a single dose over 4 hours during consolidation. While we were able to deliver these doses over 4 hours without excessive toxicity in our patients, our relapse-free survival and disease-free survival were only approximately half the rates reported for such patients in

CONTEXT

Key Objective

To describe the provision of 5 g/m^2 methotrexate over 24-hour infusions, typically given once every 14 days × 4 doses, to children with high-risk (HR) ALL, to our knowledge, for the first time in Costa Rica.

Knowledge Generated

Measuring methotrexate levels at two time points during the infusion (hours 2 and 6 or 8) and adjusting the infusion rate on the basis of a static, bedside algorithm before discontinuing the infusion at 24 hours allowed all children to receive this therapy with minimal/reversible toxicities. Only 1 of 196 infusions resulted in ≥grade 3 renal toxicity, and no grade 4/5 toxicities occurred. Incorporation of this method required minimal additional cost and effort.

Relevance

Low- and middle-income countries, which do not have ready access to methotrexate toxicity rescue agents/methods such as dialysis or glucarpidase, can incorporate this method of providing superior therapy (at least in HR B-cell ALL) and should improve outcomes without incurring significant extra costs or compromising safety.

high-income countries (HICs).[1,11] To improve the efficacy of the HDMTX treatments, we sought a safe way to maintain therapeutic MTX levels in steady state (Cp_{ss}; approximately 65 μM ± 15 μM) in patients, during a 24-hour infusion (the level normally achieved during 5 g/m^2 as a single dose over 24 hours[12]), while minimizing the possibility that they would require the aforementioned interventions that are not possible in our practice setting.

We adapted treatment for HR preB ALL from the Children's Oncology Group (COG) protocol AALL1131[13] to our setting. In an effort to safely give 5 g/m^2 as a single dose over 24 hours, to be in line with AALL1131, we incorporated an individualized intensive methotrexate monitoring and intrainfusion dose adjustment algorithm for HDMTX, which has been successfully used with patients at Texas Children's Hospital (TCH; Houston, TX) for over a decade. At TCH, the algorithm is used for patients who have known pre-existing renal impairment and/or history of methotrexate renal intolerance and has been shown to have an outstanding safety and efficacy record.[9,14]

We report the use of HDMTX in a low- and middle-income country (LMIC) following an interinfusion real-time methotrexate adjustment safety algorithm.

METHODS

Overview

The medical records of patients 1 year and older and younger than 13 years, with National Cancer Institute (NCI)-Rome criteria HR or very HR (VHR; as defined by COG AALL1131) preB ALL and T-cell ALL, admitted from May 2017 to May 2019, to Hospital Nacional de Niños Dr Carlos Sáenz Herrera, part of the public system Caja Costarricense de Seguro Social (HNN) in Costa Rica, were retrospectively reviewed (Table 1). Patients were consented to therapy per local standards and treated according to the national protocol (CR LLA 1-16), which is based on COG AALL1131.[13] Patients who were found to be Philadelphia Chromosome [t(9;22)]–positive (Ph+) were designated and treated as VHR patients. These Ph+ patients were treated on protocol but had imatinib added to their regimen. The CR LLA 1-16 protocol was approved by both the local independent ethics committee and the Baylor College of Medicine (Houston, TX) Intuitional Review Board.

As part of therapy, during an Interim Maintenance phase, patients received HDMTX as a planned 24-hour infusion of 5 g/m^2 as a single dose over 24 hours, for a total of four doses. HDMTX was given according to an intensive monitoring protocol previously published.[9,14] Because of cost, glucarpidase was not available in Costa Rica at the time of our study. Appropriate high-flow hemodialysis was emergently available if catastrophic acute renal failure were to occur.

The intensive monitoring HDMTX protocol has been described previously[9,14] (Fig 1). It was designed to anticipate the development of toxic methotrexate levels during a HDMTX infusion and make changes to the infusion in real time to avoid acute renal injury and the need for hemodialysis and/or glucarpidase administration. Briefly, before the start of the HDMTX infusion, patients receive a 4-hour prehydration with half-normal saline with sodium bicarbonate at 200 mL/m^2/hour for urinary alkalization. To ensure that the critical laboratory tests (methotrexate and creatinine levels) were drawn and resulted early in the day, the clinical laboratory was made aware ahead of time when the infusions were planned/scheduled. All patients were admitted the day/evening before the planned HDMTX infusions. The prehydration started at 3 am with the methotrexate infusion beginning at 7 am. Infusions were not planned on weekends or holidays. The methotrexate infusion was ordered as a 5 g/m^2 infusion given as a

TABLE 1. Patient Demographics

Characteristic	Patients (N = 52), No. (%)	Cycles (Total = 196), No. (%)
Age, years, median (range)	6 (1-13)	
Sex		
Male	33 (63.5)	119 (59.6)
Female	19 (36.5)	77 (40.4)
Risk		
High	25 (48.1)	94 (48)
Very high	27 (51.9)	102 (52)
Lineage		
B-ALL	47 (90.4)	176 (89.8)
T-ALL	5 (9.6)	20 (10.2)

Abbreviations: B-ALL, B-cell ALL; T-ALL, T-cell ALL.

500 mg/m² bolus over 0.5 hours followed immediately by 4,500 mg/m² over 23.5 hours. Adjustments were then made to the methotrexate infusion rate in real time on the basis of a fixed bedside algorithm (Fig 1), which responds to methotrexate plasma concentrations drawn at hour 2 (safety check) and either hour 6 or hour 8 (presumed steady state). The time between drawn levels and response to the algorithm directions is to be completed within 2 hours. These adjustments target a 24-hour Cp_{ss} of 65 μM ± 15 μM. As this is a safety algorithm, only decreases in the infusion rate (ie, dose) are performed if the algorithm predicts that the Cp_{ss} will be >80 μM. The infusion is discontinued at 24 hours without regard to methotrexate left in the infusion line or bag; it is in fact expected that if infusion rates are decreased on the basis of the algorithm, some methotrexate will remain uninfused at the end of 24 hours. As such, decreases in infusion rate equate to decreases in administered dose. The hydration continues until a level of methotrexate of <0.2 μM has been achieved.[9,14]

A standard rescue regimen with leucovorin was started 42 hours after the initiation of methotrexate (Table 2). Fluid rates remained at the hyperhydration rate of 200 mL/m²/hour, which is high relative to the recommended 125-150 mL/m²/hour starting level used in most HDMTX regimens, but the increased rate is known to reduce rates of toxic methotrexate concentrations without resulting in levels that are substantially lower than those achieved with standard hydration.[12]

Sample Collection

Blood samples were collected from all patients with the purpose of methotrexate concentration monitoring and renal function testing at hours 2, 6 or 8, 24, 36, and 48 after the beginning of the infusion and every 24 hours thereafter until the methotrexate levels were <0.2 μM. Hour 8 methotrexate levels were obtained only if a change in the dose was performed on the basis of the hour 2 levels.

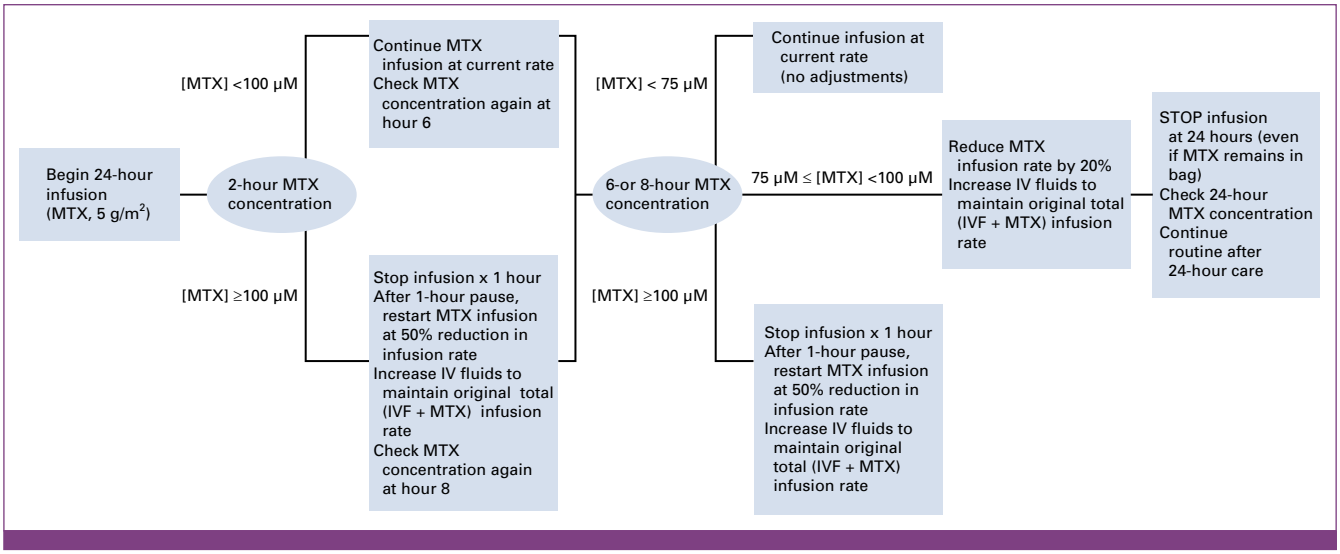

FIG 1. Protocol algorithm, intrainfusion concentration monitoring, and algorithm-based dose adjustments. IV, intravenous; IVF, intravenous fluids; MTX, methotrexate.

TABLE 2. Laboratory Testing and Leucovorin Schedule

Hour From the Infusion Start	Methotrexate Concentration	Leucovorin Administration	Next Laboratory Testing
42	≤1 μM	15 mg/m^2 dose once every 6 hours	Hour 48
	1.01-9.9 μM	15 mg/m^2 dose once every 6 hours	Hour 48
	10-19.9 μM	15 mg/m^2 dose once every 3 hours OR 30 mg/m^2 dose once every 6 hours	Hour 48
	20-200 μM	100 mg/m^2 dose once every 6 hours	Hour 48
	>200 μM	1,000 mg/m^2 dose once every 6 hours	Hour 48
48	≤0.4 μM	15 mg/m^2 dose once every 6 hours to complete a minimum of 3 doses	No further laboratory draws
	0.41-4.9 μM	15 mg/m^2 dose once every 6 hours until methotrexate is <0.2 μM	Draw every 12 hours until the methotrexate level is <0.2 μM
	5-9.9 μM	15 mg/m^2 dose once every 3 hours OR 30 mg/m^2 dose once every 6 hours and continue until methotrexate is <0.2 μM	Draw every 12 hours until the methotrexate level is <0.2 μM
	10-100 μM	100 mg/m^2 dose once every 6 hours and continue until methotrexate is <0.2 μM	Draw every 12 hours until the methotrexate level is <0.2 μM
	>100 μM	1,000 mg/m^2 dose once every 6 hours and continue until methotrexate is <0.2 μM	Draw every 12 hours until the methotrexate level is <0.2 μM

Methotrexate Concentration Assessment

The serum methotrexate quantitative concentration was measured using the chemiluminescent microparticle immunoassay technology with ARCHITECT *i* SYSTEM (Abbott Laboratories, Abbott Park, IL), with a cost of $5 USD for each test.

Data Analysis

Descriptive statistics were calculated, including counts and percentages for categorical variables and means (with standard deviations) or median (range) for continuous variables. Patient characteristics were analyzed on the basis of the number of enrolled eligible subjects, whereas analyses of cycles were analyzed, for those included, assuming each cycle as an independent observation. Associations between categorical variables were evaluated using the Fisher's exact or chi-square tests. Associations between continuous variables were evaluated using one-way ANOVA tests. All *P* values were two-sided, and a value <.05 was considered significant.

RESULTS

Between May 2017 and May 2019, 52 patients, with a median age of 6 years (range, 1-13 years), received 207 infusions of HDMTX according to the intensive monitoring methotrexate algorithm. Of the 207 infusions, 11 infusions (5.3%) were excluded for not having a complete set of creatinine values. Of the excluded values, no patient had more than one cycle excluded and there was a relatively even distribution of excluded cycles per cycle number (n = 2 from cycle 1, n = 3 from cycle 2, n = 3 from cycle 3, and n = 3 from cycle 4). The population included 63.5% (n = 33) males and 36.5% (n = 19) females. Stratification according to the type of protocol arm included 48.1% (n = 25) patients in the HR arm and 51.9% (n = 27) in the VHR arm (Table 1).

Toxicities were classified according to the NCI Common Terminology Criteria for Adverse Events (CTCAE version 5.0).[15] Greater than or equal to grade 3 AEs up to 3 days after the infusion included vomiting (11.6%, n = 24), fever (7.3%, n = 15), diarrhea (6.3%, n = 13), and AKI (0.5%, n = 1). Similar AEs at the 1-week follow-up included neutropenia (24.6%, n = 51, mean duration 10.7 days [range, 3-19]), thrombocytopenia (9.2%, n = 19, mean duration of 10.2 days [range, 6-15]), mucositis (4.8%, n = 10), and neurotoxicity (1%, n = 2). Neutropenia also caused a delay in next cycle initiation for 7.7% patients (n = 16). No hepatotoxicity was recorded. No ≥grade 4 AEs occurred.

The mean hour 24 methotrexate Cp_{ss} for the 196 infusions was 53.68 μM (range, 12.54-117 μM). Infusion rate adjustments occurred in 51 infusions (24.6%) involving 29 unique patients (55.7%). Of these, three infusions (1.4%) were modified because of high methotrexate levels at 2 hours postinitiation and 48 infusions (23.1%) were modified because of elevated methotrexate levels at 6 hours postinitiation. No infusions required dose adjustments at more than one time point. For infusions where no dose adjustment was required (75.3%, n = 156), the mean hour 24 methotrexate level was 51.65 μM (range, 12.54-117 μM). For infusions with dose adjustments at hour 6 (23.2%, n = 48), the mean hour 24 methotrexate level was 59.98 μM (range, 23.6 μM-116 μM). For all infusions, we were able to achieve a mean hour 24 methotrexate level close to the projected 65 ± 15 μM. There were no statistically significant differences in the occurrence of toxicities during methotrexate infusions for patients who required dose adjustments per protocol compared with those who did not. There was no statistically significant difference in renal toxicity per cycle. The mean creatinine elevations compared with baseline/2 hours for cycles 1, 2, 3, and 4 were 1.16, 1.11, 1.19, and 1.07 times the baseline, respectively (one-way ANOVA, *P* = .17).

TABLE 3. Kidney Injury Grading for All Included Cycles

Toxicity	Category	AE Grading System	CTCAE/AKIN Toxicity Grade					
			NT	1	2	3	4	5
Creatinine ≥25% of baseline	No (n =161)	CTCAE	80	81	0	0	0	0
		AKIN	161	0	0	0	NA	NA
	Yes (n = 35)	CTCAE	0	23	11	1	0	0
		AKIN	23	8	3	1	NA	NA

Abbreviations: AKIN, Acute Kidney Injury Network Classification/staging system for acute kidney injury; CTCAE, Common Terminology Criteria for Adverse Events, National Cancer Institute, Version 5; NA, not applicable; NT, no toxicity.

Analysis of the effect of the elevation of the creatinine (baseline/hour 2 versus those collected at ≥hour 24) was performed to see if there was any correlation with the incidence of renal toxicity involvement and other toxicities. Renal toxicity was considered to have occurred if there was an elevation of creatinine by ≥25%. Renal toxicity occurred in 35 infusions (17.8%) with all but one patient experiencing <grade 3 toxicity according to both the CTCAE and the Acute Kidney Injury Network (AKIN) scales (Table 3).[16-18] Other toxicities of vomiting, fever, diarrhea, mucositis, neutropenia, thrombocytopenia, and neurotoxicity did not statistically significantly differ between patients with renal toxicity involvement and those without (Table 4). AKI was defined as those who have ≥grade 3 creatinine increased per CTCAEv5.0.

DISCUSSION

Long-infusion HDMTX therapy is challenging to provide in LMICs secondary to the inability to provide the advanced and/or expensive rescue care required for those who experience high-exposure-based toxicities. To our knowledge, we report the successful first experience of providing this form of HDMTX to children in Costa Rica, which we were able to do by using the TCH individualized intensive methotrexate monitoring algorithm.[9,14] Multiple studies have demonstrated the superiority in outcomes of giving methotrexate 5 g/m² as a single dose over 24 hours to children with HR preB ALL over other forms of methotrexate,[1,19,20] and additional studies have demonstrated its benefit in other populations as well.[21] Admittedly, some recent studies have shown superiority or equipollence between Capizzi-style methotrexate and HDMTX in pediatric patients with T-ALL when incorporated into certain HIC chemotherapy cassettes.[22,23]

The TCH protocol[9,14] allows for individualized adjustments in methotrexate dose administered by lowering the infusion rate in response to high methotrexate levels obtained in real time during the infusion. The protocol was determined to be successful in our setting as there were no logistical failures in implementation of the protocol, and the mean 24-hour Cp_{ss}

TABLE 4. Comparison of Complications According to the Presence of Kidney Involvement in ALL Patient Cycles

Adverse Events	Kidney Involvement[a]		P
	Yes (n = 35/196)	No (n = 161/196)	
	No. Experienced of 35 Yes Patients (%)	No. Experienced of 161 No Patients (%)	
Complications during infusion			
Vomiting	2 (5.55)	15 (9.37)	.46
Fever	2 (5.55)	8 (5)	.89
Diarrhea	0 (0)	6 (3.75)	.24
AKI[b]	1 (2.77)	0 (0)	.03[a]
Postevaluation (day 7 poststart of the infusion)			
Mucositis	2 (5.55)	13 (8.12)	.60
Neutropenia	4 (11.11)	43 (26.87)	.05
Thrombocytopenia	4 (11.11)	14 (8.75)	.66
Nephrotoxicity	0 (0)	0 (0)	NC
Neurotoxicity	0 (0)	2 (1.25)	.50

NOTE. Estimate adjusted by means of Fisher's exact test because of small sample.
Abbreviations: AKI, acute kidney injury; NC, not calculable.
[a]Kidney involvement is defined as an elevation of at least 25% of the basal creatinine level 6 hours after the start of the methotrexate infusion.
[b]AKI is defined as those who have ≥grade 3 creatinine increased per Common Terminology Criteria for Adverse Events v5.

TABLE 5. Comparison of Published High-Dose Methotrexate Delivery Methods in LMICs

Study	Location	Disease	Age, Years Range	Dose Range, g/m^2	Infusions (patients)	Infusions ≥4 g/m^2 as a Single Infusion (% of total)	Modifications for the LMIC Setting	Cycles Resulting in Kidney Injury (%)	Cycles Requiring Next Cycle Delay (%)	Other Significant Events During the MTX Cycle
Kapoor et al[25]	Delhi, India	B-ALL, T-ALL	1-15	5	149 (41)	149 (100)	None	0 (not clear how defined)	15	9 (22%) patients did not get all four cycles (n = 4 received 3 cycles, n = 4 received 2 cycles, n = 1 received one cycle)
Vaishnavi et al[17]	Chandigarh, India	B-ALL, T-ALL, T-NHL	1-13	3-5	100 (53)	50 (50)	No MTX monitoring, increased hydration, increased doses of LCV	23 (defined as ≥25% Cr increase)	72	1 death (dengue shock syndrome)
Sajith et al[26]	Maharashtra, India	B-ALL, T-ALL	1-18	2-5	244 (62)	37 (15.2)	None	0.4 (not clear how defined)	32.3	
Khera et al[27]	Delhi, India	B-ALL, T-ALL	1-11	2-5	100 (29)	40 (40)	MTX analyzed only at hour 36 (MTX_{36}) with discharge at hour 66 if MTX_{36} < 1 μM, and fluid and LCV continued with discharge at hour 78 if MTX_{36} ≥ 1 μM	24 (defined as ≥25% Cr increase)	Not reported	
Totadri et al[28]	Vellore, India	B-ALL, B-NHL, T-ALL, T-NHL	1-15	3-5	284 (71)	88 (30.9)	MTX analyzed at hour 42 only; if hour 42 concentration was >1 μM additional LCV was given and prolonged hydration with then repeat MTX level every 12 hours until <0.1 μM	Not monitored (Cr was only measured at baseline before each MTX cycle)	9.9	
Acevedo (current study)	San Jose, Costa Rica	B-ALL, T-ALL	1-13	5[a]	196 (52)	196 (100)	Increased hydration, intrainfusion dose reductions on the basis of MTX levels measured at hours 2 and 6 or 8 of infusion	29.6 (defined as ≥25% Cr increase) 0.5 (defined as ≥CTCAE grade 3) 0.5 (defined as ≥AKIN grade 3)	7.7	

Abbreviations: B-ALL, B-cell ALL; CTCAE, Common Terminology Criteria for Adverse Events; Cr, creatinine; LCV, leucovorin; LMIC, low- and middle-income country; MTX, methotrexate; T-ALL, T-cell ALL.

[a]All patients ordered for 5 g/m^2 as a single dose but with allowable intrainfusion dose reductions on the basis of the algorithm.

values for all groups of patients fell well within the 65 ± 15 μM predicted by pharmacokinetic modeling. In addition, we had no 24-hour Cp_{ss} levels <16 μM, a level which is known to be inadequate for lowing risk of relapse.[24] This confirmed it unnecessary to require a protocol/algorithm, which adjusts infusion rates upward for levels predicted by the modeling to be lower than expected.

The toxicity rates in our study were similar to those reported in other studies.[5,12,13,25,26] There were also no statistically significant differences in the occurrence of AEs during or after the methotrexate infusions for patients who required adjustments according to the individualized intensive methotrexate-monitoring algorithm, compared with those who did not. This suggests that early monitoring methotrexate levels ensures timely intervention to prevent toxicity. One of the biggest concerns of using HDMTX is the risk of nephrotoxicity.[3] Preventive strategies, such as increased hydration, high-dose leucovorin, and glucarpidase, are interventions that may be sufficient to allow renal recovery without the need for dialysis.[3] In this study, of 196 HDMTX infusions, only one patient presented with ≥grade 3 AKI (0.5%). This patient experienced intractable vomiting during the infusion, which might have adversely affected his methotrexate clearance and renal function.[12] Had his vomiting been better controlled, we might have had no patients experience ≥grade 3 nephrotoxicities. This patient also recovered from his toxicity and was able to safely receive the fourth HDMTX infusion later in his course, without any undue toxicity.

With our protocol, we are now at the LMIC forefront of consistently and safely providing 5 g/m² as a single dose over 24 hours. Understanding the importance of this therapy, several groups in India have published on giving HDMTX in a LMIC with limited resources (Table 5).[17,25–28] These studies certainly offer acceptable methods of providing HDMTX. However, they often gave 5 g/m² as a single dose over 24 hours during an infusion or had high percentages of patients not receive all four doses of HDMTX in a cycle. In addition, some studies analyzed few kidney function time points, making it unclear as to the grade of nephrotoxicities experienced. Finally, while our rates of nephrotoxicity are largely similar to previous publications, our rates of next cycle delays were significantly better, suggesting that other methods produced toxicities which made proceeding to the next cycle on time unacceptable. Outside of India, a recent survey of 20 pediatric oncology centers in Central and South America noted that 17 (85%) gave 5 g/m² as a single dose over 24 hours to their patients with HR ALL[29]; however, no published data on the logistics or safety of these protocols appear to be available. The reporting of the logistics and safety of 5 g/m² as a single dose over 24 hours in Latin America specifically is of particular importance because Hispanic patients who receive HDMTX in the United States are known to have increased toxicities and delayed clearance parameters in comparison with their non-Hispanic counterparts.[30–32] However, in our study within a Latin American population, AKI was noted in 0.5% (n = 1) of patients and neutropenia was documented in 24.6% (n = 51) of patients.

We believe that this successful therapy would be feasible to implement in other LMIC settings. Similar to many other LMIC centers, we already had the ability to deliver alkalized fluids and leucovorin and have the infrastructure to admit patients for monitoring during HDMTX, which had done for our 2-5 g/m² infusions as single doses over 4 hours. The nursing staff was educated on the protocol by several authors (K.A., G.S., K.V., and J.M.). The medical staff was trained to draw methotrexate and creatinine levels at time points required. Methotrexate and creatinine levels were returned via our electronic medical record. All medical staff were trained to be vigilant in retrieving results and on how, if required, to change the infusion rate orders. The nursing staff was trained to discontinue the infusion at 24 hours even if some of the initially ordered amount of methotrexate was left in the administration bag. Laboratory staff were trained on the protocol by the authors. The only increased cost was individual methotrexate assay kits, which were obtained at $5 USD per kit. To not incur additional cost of laboratory staff over time or additional personnel, patients were admitted the day before, so that methotrexate infusions could begin at 7 AM, with all levels drawn during the daytime hours: 9 AM and 1 PM and then at 24 hours and 48 hours. This also ensured adequate prehydration before the start of the methotrexate infusions.

Despite some intrinsic limitations to our study, including the sample size and its retrospective nature, we conclude that using this individualized intensive methotrexate-monitoring algorithm is safe for the administration of HDMTX in LMICs, even without the availability of glucarpidase. Administration of 5 g/m² as a single dose over 24 hour HDMTX in this manner is a safe and practical opportunity for delivering therapy known to improve survival outcomes and long-term cure for higher-risk patients. To our knowledge, this is the first implementation of this type of HDMTX monitoring protocol in LMICs.

AFFILIATIONS

[1]Hematology Department, Hospital Nacional de Niños, Dr Carlos Sáenz Herrera, Caja Costarricense de Seguro Social, San José, Costa Rica
[2]Department of Pediatrics, Baylor College of Medicine, Houston, TX
[3]Texas Children's Cancer and Hematology Center, Texas Children's Hospital, Houston, TX

CORRESPONDING AUTHOR

Judith Margolin, MD; e-mail: jfmargol@texaschildrens.org.

EQUAL CONTRIBUTION

E.S.S. and J.M. contributed equally to this work.

PRIOR PRESENTATION

Presented in part in published abstract form after the 2020 Annual meeting of the American Society of Pediatric Hematology/Oncology scheduled to take place in Fort Worth, TX was canceled due to COVID restrictions. The abstract was published as: Acevedo K et al. High dose methotrexate use in pediatric acute lymphoblastic leukemia in a middle income country. 2020 American Society of Pediatric Hematology/Oncology. Poster # 706. *Pediatric Blood and Cancer*. 2020; 76(S2): e28321, 706.

DATA SHARING STATEMENT

Data sets and unmanipulated data used in the manuscript are available upon reasonable written request to the corresponding author.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Provision of study materials or patients: Gabriela Soto, Kathia Valverde
Collection and assembly of data: Karol Acevedo, Gabriela Soto, Kathia Valverde, Eric S. Schafer, Judith Margolin
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/go/authors/author-center.
Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Mary C. Shapiro
Open Payments Link: https://openpaymentsdata.cms.gov/physician/1374935

Jennifer H. Foster
Consulting or Advisory Role: Ymabs Therapeutics Inc, Alkermes, US WorldMeds, Fennec Pharma

Eric S. Schafer
Consulting or Advisory Role: Beam Therapeutics, Jazz Pharmaceuticals

No other potential conflicts of interest were reported.

ACKNOWLEDGMENT

We thank all the physicians who contributed to accomplishing the HDMTX algorithm in our patients and the statisticians Dr Roy Wong and Erick Mendez who contributed to the statistical analysis.

REFERECES

1. Larsen EC, Devidas M, Chen S, et al: Dexamethasone and high-dose methotrexate improve outcome for children and young adults with high-risk B-acute lymphoblastic leukemia: A report from Children's Oncology Group study AALL0232. J Clin Oncol 34:2380-2388, 2016
2. Kala J, Nelson R, Drudge C, et al: Glucarpidase for treating adults with delayed methotrexate elimination due to impaired renal function: An economic simulation analysis. Clinicoecon Outcomes Res 15:165-179, 2023
3. Howard SC, McCormick J, Pui CH, et al: Preventing and managing toxicities of high-dose methotrexate. Oncologist 21:1471-1482, 2016
4. Ramsey LB, Balis FM, O'Brien MM, et al: Consensus guideline for use of glucarpidase in patients with high-dose methotrexate induced acute kidney injury and delayed methotrexate clearance. Oncologist 23:52-61, 2018
5. Schmiegelow K: Advances in individual prediction of methotrexate toxicity: A review. Br J Haematol 146:489-503, 2009
6. Widemann BC, Adamson PC: Understanding and managing methotrexate nephrotoxicity. Oncologist 11:694-703, 2006
7. Widemann BC, Balis FM, Shalabi A, et al: Treatment of accidental intrathecal methotrexate overdose with intrathecal carboxypeptidase G2. J Natl Cancer Inst 96:1557-1559, 2004
8. Cheng DH, Lu H, Liu TT, et al: Identification of risk factors in high-dose methotrexate-induced acute kidney injury in childhood acute lymphoblastic leukemia. Chemotherapy 63:101-107, 2018
9. Foster JH, Thompson PA, Bernhardt MB, et al: A prospective study of a simple algorithm to individually dose high-dose methotrexate for children with leukemia at risk for methotrexate toxicities. Cancer Chemother Pharmacol 83:349-360, 2019
10. Ylinen E, Jahnukainen K, Saarinen-Pihkala UM, et al: Assessment of renal function during high-dose methotrexate treatment in children with acute lymphoblastic leukemia. Pediatr Blood Cancer 61:2199-2202, 2014
11. Navarrete M, Rossi E, Brivio E, et al: Treatment of childhood acute lymphoblastic leukemia in central America: A lower-middle income countries experience. Pediatr Blood Cancer 61:803-809, 2014
12. Relling MV, Fairclough D, Ayers D, et al: Patient characteristics associated with high-risk methotrexate concentrations and toxicity. J Clin Oncol 12:1667-1672, 1994
13. Salzer WL, Burke MJ, Devidas M, et al: Impact of intrathecal triple therapy versus intrathecal methotrexate on disease-free survival for high-risk B-lymphoblastic leukemia: Children's Oncology Group study AALL1131. J Clin Oncol 38:2628-2638, 2020
14. Foster JH, Bernhardt MB, Thompson PA, et al: Using a bedside algorithm to individually dose high-dose methotrexate for patients at risk for toxicity. J Pediatr Hematol Oncol 39:72-76, 2017
15. National Cancer Institute (US): Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. 2017. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50
16. Mehta RL, Kellum JA, Shah SV, et al: Acute Kidney Injury Network: Report of an initiative to improve outcomes in acute kidney injury. Crit Care 11:R31, 2007
17. Vaishnavi K, Bansal D, Trehan A, et al: Improving the safety of high-dose methotrexate for children with hematologic cancers in settings without access to MTX levels using extended hydration and additional leucovorin. Pediatr Blood Cancer 65:e27241, 2018
18. Wight J, Ku M, Garwood M, et al: Toxicity associated with high-dose intravenous methotrexate for hematological malignancies. Leuk Lymphoma 63:2375-2382, 2022
19. Niemeyer CM, Gelber RD, Tarbell NJ, et al: Low-dose versus high-dose methotrexate during remission induction in childhood acute lymphoblastic leukemia (Protocol 81-01 update). Blood 78: 2514-2519, 1991
20. Reiter A, Schrappe M, Ludwig WD, et al: Favorable outcome of B-cell acute lymphoblastic leukemia in childhood: A report of three consecutive studies of the BFM group. Blood 80:2471-2478, 1992
21. Lonnerholm G, Valsecchi MG, De Lorenzo P, et al: Pharmacokinetics of high-dose methotrexate in infants treated for acute lymphoblastic leukemia. Pediatr Blood Cancer 52:596-601, 2009
22. Jastaniah W, Elimam N, Abdalla K, et al: High-dose methotrexate vs. Capizzi methotrexate for the treatment of childhood T-cell acute lymphoblastic leukemia. Leuk Res Rep 10:44-51, 2018
23. Kirkwood AA, Goulden N, Moppett J, et al: High dose methotrexate does not reduce the risk of CNS relapse in children and young adults with acute lymphoblastic leukaemia and lymphoblastic lymphoma. Results of the randomised phase III study UKALL 2011. Blood 140:516-518, 2022
24. Evans WE, Abromowitch M, Crom WR, et al: Clinical pharmacodynamic studies of high-dose methotrexate in acute lymphocytic leukemia. NCI Monogr 5:81-85, 1987
25. Kapoor G, Sinha R, Abedin S: Experience with high dose methotrexate therapy in childhood acute lymphoblastic leukemia in a tertiary care cancer centre of a developing country. Pediatr Blood Cancer 59:448-453, 2012
26. Sajith M, Pawar A, Bafna V, et al: Serum methotrexate level and side effects of high dose methotrexate infusion in pediatric patients with acute lymphoblastic leukaemia (ALL). Indian J Hematol Blood Transfus 36:51-58, 2020
27. Khera S, Kapoor R, Pramanik SK: Solitary serum methotrexate level 36 hours post high-dose methotrexate: A safe, efficacious, and cost-effective strategy to monitor methotrexate toxicities in childhood leukemia in resource-limited centers. Pediatr Blood Cancer 67:e28387, 2020

28. Totadri S Srinivasan HN, Joseph LL, et al: A single assessment of methotrexate levels at 42 hours permits safe administration and early discharge in children with lymphoblastic lymphoma and leukemia receiving high-dose methotrexate. Pediatr Hematol Oncol 38:434-443, 2021
29. Villanueva G, Lowe J, Tentoni N, et al: Access to methotrexate monitoring in Latin America: A multicountry survey of supportive care capacity. Pediatr Hematol Oncol 41:135-149, 2024
30. Harris RD, Bernhardt MB, Zobeck MC, et al: Ethnic-specific predictors of neurotoxicity among patients with pediatric acute lymphoblastic leukemia after high-dose methotrexate. Cancer 129: 1287-1294, 2023
31. Mullikin D, Ranch D, Khalfe Y, et al: Hispanic ethnicity is associated with prolonged clearance of high dose methotrexate and severe nephrotoxicity in children and adolescents with acute lymphoblastic leukemia. Leuk Lymphoma 61:2771-2774, 2020
32. Schafer ES, Bernhardt MB, Reichert KE, et al: Hispanic ethnicity as a risk factor for requiring glucarpidase rescue in pediatric patients receiving high-dose methotrexate. Am J Hematol 93: E40-E42, 2018