Cancer Chemotherapy and Pharmacology
https://doi.org/10.1007/s00280-024-04687-z

ORIGINAL ARTICLE

Development of a novel nomogram for predicting delayed methotrexate excretion following high-dose methotrexate in adult patients with hematologic malignancies

Daisuke Ikeda[1] · Tatsuya Isezaki[2] · Kentaro Narita[1] · Satoshi Yuyama[2] · Mitsuaki Oura[1] · Atsushi Uehara[1] · Rikako Tabata[1] · Masami Takeuchi[1] · Kosei Matsue[1]

Received: 23 February 2024 / Accepted: 13 June 2024

Abstract

Purpose High-dose methotrexate (HDMTX) is integral in treating hematologic malignancies but carries risks of severe toxicities due to prolonged MTX exposure. However, knowledge of delayed MTX excretion is primarily derived from pediatric and adolescent cohorts, with the reported predictors being presented as rough dichotomous values. This study aimed to identify risk factors for delayed MTX excretion exclusively in adult patients with hematologic malignancies and develop a more applicable predictive nomogram based on continuous clinical and laboratory variables.

Methods 517 HDMTX cycles in 194 patients were retrospectively analyzed. Delayed MTX excretion was defined as either MTX concentration ≥ 1.0 μmol/L at 48 h or ≥ 0.1 μmol/L at 72 h after HDMTX initiation. Multivariate logistic regression analysis was used to construct the nomogram internally validated with the bootstrap method.

Results Delayed MTX excretion was observed in 24.0% of cycles. Six significant predictors were identified: relapsed/refractory disease (Odds ratio [OR] 2.03), fewer HDMTX cycles (OR 0.771), treatment intent (OR 2.13), lower albumin (OR 0.563) and creatinine clearance levels (OR 0.993), and increased γ-glutamyl transpeptidase levels (OR 1.004, all $P < 0.05$). These were incorporated into a web-based nomogram as continuous variables with good prediction accuracy (area under the curve, 0.73) and without significant overfitting. Delayed MTX excretion increased risks of developing acute kidney injury, even solely at the 72 h timepoint (OR 2.57, $P = 0.025$), without providing any benefit of clinical outcomes.

Conclusion This study comprehensively characterized MTX elimination failure following HDMTX in adult patients and could pave the way for individualized risk prediction.

Keywords HDMTX · Delayed excretion and hematologic malignancies

Abbreviations

MTX	Methotrexate
R/R	Relapsed/refractory
Alb	Albumin
CrCl	Creatinine clearance
GGT	γ-glutamyl transpeptidase
ROC	Receiver operating characteristic
AUC	Area under the curve

Introduction

High-dose methotrexate (HDMTX) is the cornerstone of the treatment and prevention of central nervous system diseases in hematologic malignancies [1]. Despite the advantage of overcoming the blood-brain barrier, HDMTX carries the risk of unacceptable toxicities, including acute kidney injury (AKI), myelosuppression, and central nervous system (CNS) symptoms [2]. These adverse events can lead

Daisuke Ikeda, Tatsuya Isezaki, Kentaro Narita and Satoshi Yuyama contributed equally to this work.

✉ Daisuke Ikeda
dskikd.2409@gmail.com

[1] Division of Hematology/Oncology, Department of Medicine, Kameda Medical Center, 929 Higashi-chou, Kamogawa-shi 296-8602, Chiba, Japan

[2] Department of Pharmacy, Kameda Medical Center, Chiba, Japan

Published online: 21 June 2024

to the interruption of chemotherapy and occasionally to life-threatening conditions. Consequently, rigorous supportive care including aggressive hydration, urine alkalinisation, and leucovorin rescue has evolved over the past few decades [3, 4].

Predicting the delayed excretion of MTX offers an alternative strategy to avoid unnecessary adverse events associated with HDMTX. Various risk factors for delayed MTX clearance have been reported, including older age [5, 6], sex [5, 7, 8], impaired renal function [5, 6, 9], hypoalbuminemia [6, 10, 11], fluid retention [12], and drug-drug interactions [13, 14]. However, most identified predictors are presented as rough dichotomous values, such as creatinine clearance (CrCl) < 60 mL/min [5] and albumin (Alb) < 3.4 g/dL or < 3.7 g/dL [10, 11]. These arbitrary cut-offs may preclude the more precise calculation of individual risk probabilities, which in turn could diminish their generalizability. Genotyping to identify variants in the *SLCO1B1* gene [15, 16], and more recently developed machine learning-based models [6, 8], may provide robust predictive value; however, these advanced tools have not yet been implemented in routine clinical practice. Moreover, previous studies on HDMTX have predominantly focused on pediatric and adolescent patients with acute lymphoblastic leukemia (ALL) or osteosarcoma [8, 9, 17–19]. Even studies involving elderly cohorts often include a mix of lymphoma and solid tumors [5, 10, 13, 20, 21], which compromises the direct application of findings to these more vulnerable populations. For instance, conflicting results have been reported regarding MTX concentration and renal function, with no relationship reported only in childhood ALL [19].

Therefore, the aims of this study were to (1) comprehensively analyze the clinical characteristics and identify risk factors for delayed MTX excretion exclusively in adult patients with hematologic malignancies and (2) develop a more applicable predictive nomogram based on continuous clinical and laboratory variables.

Materials and methods

Study design, patient, definition, and data collection

We performed a single-center retrospective analysis of consecutive adult patients (18 years or older) with ALL or malignant lymphoma who received HDMTX therapy at the Kameda Medical Center between January 2011 and December 2022. Because we included elderly patients with lower levels of CrCl who required MTX dose reduction [22], we defined HDMTX using the widely accepted threshold of ≥ 500 mg/m^2 [2], rather than ≥ 1000 mg/m^2. According to previous studies, delayed MTX excretion was defined as plasma MTX levels ≥ 1 μmol/L at 48 h or ≥ 0.1 μmol/L 72 h from the start of MTX infusion [23, 24]. AKI was graded as grade 1, 2, and 3 in accordance with the Kidney Disease: Improving Global Outcomes (KDIGO) guideline [25]. The exclusion criteria were missing data on either 48–72 h MTX concentration. To assess the association with MTX clearance, the following clinical and laboratory data were collected from electronic chart review: patient factors (age, gender, disease type, disease status, body surface area [BSA]), biochemical parameters (CrCl, Alb, aspartate aminotransferase [AST], alanine transaminase [ALT], γ-glutamyl transpeptidase [GGT], total bilirubin [TBil], calcium, phosphorus, urine acid [UA]), details of HDMTX administration (cycle numbers, doses, infusion manner [drip or continuous infusion], concurrent chemotherapy and purpose [prophylactic or treatment]) and well-known co-medications that potentially have drug-drug interactions [proton pump inhibitors, nonsteroidal anti-inflammatory drugs [NSAIDs], antibiotic agents, and phenytoin]) [26]. The presence of pleural effusion was examined using chest radiography prior to HDMTX initiation. The dataset was locked on 31 July 2023. This study was approved by our institutional review board and was conducted in accordance with the Declaration of Helsinki (approval number: 22-132-240205).

HDMTX procedures and supportive care

HDMTX was administered using a formula of either a 3.5 mg/m^2 3 h drip [27] or a 1.0 mg/m^2 24 h continuous infusion [28], with the dose adjusted based on age and CrCl. Standardised supportive care was implemented throughout the study period according to our institutional protocol. Briefly, patients were administered adequate hydration and diuresis with acetazolamide, and their urine pH was monitored every 6 h along with intravenous alkalinization to maintain a urine pH > 7.0. Serum MTX concentrations were measured at mandatory 48 h and 72 h time-points (ARCHITECT i2000SR, Abbott Japan, Tokyo), with subsequent monitoring of patients with delayed MTX excretion at the physician's discretion. The principal leucovorin rescue schedule depended on the MTX administration method: for 3 h drip infusions, leucovorin calcium was administered at a dose of 15 mg/m^2 every 6 h starting 24 h after the beginning of the MTX infusion [27]; for continuous infusions, a single dose of 50 mg/body was administered 36 h after the start of MTX infusion, followed by 15 mg/body every 6 h [28]. If delayed MTX excretion occurred, leucovorin rescue was intensified to 50 mg/body every 6 h until the MTX level dropped below 0.1 μmol/L.

Statistical analysis

Continuous variables were analyed using the Mann–Whitney U test, whereas categorical variables were compared using Fisher's exact test. Univariate and multivariate analysis using logistic regression were performed to identify risk factors for delayed MTX excretion. These identified factors were also evaluated to determine whether they can predict the development of clinically more relevant events, such as the development of AKI and more toxic MTX concentrations (≥ 5 µmol/L at 48 h), which is a defined indicator for glucarpidase use [29]. Similarly, the odds ratios (ORs) for delayed MTX clearance associated with AKI development were assessed. To create a nomogram, backward stepwise logistic regression was used to select the most predictive variables. Internal validation of the nomogram was conducted using the bootstrap method (1000 bootstrap resample). The apparent and optimism-corrected receiver operating characteristic areas under the curve (ROC AUC) and calibration slopes were calculated [30]. The Hosmer–Lemeshow test was used to assess the goodness-of-fit in the logistic regression [31]. The developed nomogram is freely available on the interactive online Shiny website (https://predicting-delayed-mtx-excretion.shinyapps.io/MTX_shiny/). Different outcome measures were applied for HDMTX purposes. For patients with prophylactic use, the Fine-Gray test was applied to test the cumulative incidence of CNS recurrence with the competing risk of death. For patients with CNS disease, the survival time after CNS disease development was estimated using the Kaplan-Meier method with the log-rank test. All statistical analysis were performed using R version 1.4.1717 (R Foundation, Vienna, Austria). Statistical significance was defined as a two-sided P-value < 0.05.

Results

Baseline patient characteristics and detailed HDMTX administration pattern

Of the 209 patients treated with 567 cycles of HD-MTX-containing chemotherapy, 15 patients and 50 cycles were excluded because of missing MTX concentration data. A total of 194 patients and 517 cycles (median, 2, range 1–14) were analyzed. The median age was 67 years (range 59–72), with a slight male predominance (58.4%). Most patients ($n = 162$, [83.5%]) had an underlying malignant lymphoma, of whom 110 (67.9%) had diffuse large B-cell lymphoma (DLBCL) and 16 (9.9%) had primary central nervous system lymphoma (PCNSL) (Supplementary Table 1). The median doses were 2429 mg/m^2 (interquartile range [IQR] 1034–3344). Doses in the ranges of 500–1000, 1000–2000, 2000–3000, and > 3000 mg/m^2 accounted for 106 (20.5%), 100 (19.3%), 122 (23.6%), and 189 (36.5%) cases, respectively. When dichotomized by median age, older patients received approximately two-thirds of the HDMTX dose compared to younger patients (median 2051 mg/m^2 vs. 3005 mg/m^2, $P < 0.001$). Regarding other details of HDMTX administration, most patients received a drip infusion ($n = 377$ [72.9%]). The proportions of patients who received HDMTX at diagnosis, for prophylactic intent, and with concurrent chemotherapy were 63.2%, 53.6%, and 50.9%, respectively.

Comparison of clinical and laboratory data between HDMTX cycles with or without delayed excretion

Delayed MTX excretion occurred in 124 of the 517 cycles (24.0%) (Supplementary Fig. 1). Specifically, 39 events (7.5%) occurred at 48 h and 122 (23.6%) occurred 72 h after the initiation of HDMTX. Among these 39 patients, almost all ($n = 37$ [94.9%]) exhibited clearance failure at the 72 h timepoint. In contrast, of the 122 patients with toxic MTX concentrations at 72 h, 106 (86.9%) were monitored at the 96 h MTX concentration, and approximately half ($n = 49$ [46.2%]) continued to have incomplete MTX clearance.

Table 1 shows a comparison of clinical and laboratory parameters between HDMTX cycles with and without delayed excretion. In terms of patient and disease factors, patients with delayed MTX excretion were more likely to be elderly (median age 68, IQR 64–73 vs. 67 IQR 57–71, $P = 0.006$), male (66.1% vs. 56.0%, $P = 0.047$), and have relapsed/refractory (R/R) disease (46.0% vs. 33.9%, $P = 0.018$) than those without delayed MTX excretion. The biochemical results showed the significantly lower levels of Alb (median 3.4 g/dL vs. 3.6 g/dL, $P < 0.001$), CrCl (75.7 mL/min vs. 84.3 mL/min, $P = 0.007$), and phosphorus (3.1 mg/dL vs. 3.3 mg/dL, $P = 0.013$) in the delayed clearance group. No significant differences were observed in liver function tests. Notably, HDMTX doses were not significantly different in terms of MTX excretion status (median 2276 mg/m^2 vs. 2485 mg/m^2, $P = 0.147$). Fewer cumulative HDMTX cycles were observed in the delayed excretion group, with marginal significance ($P = 0.064$), and a higher proportion of patients with delayed MTX excretion received HDMTX for treatment (57.2% vs. 43.0%, $P = 0.007$). The frequency of specific co-medications did not significantly differ between the two groups.

Risk factors of MTX elimination failure and construction of the predictive nomogram

The univariate analysis showed that older age; male sex; R/R status; fewer HDMTX cycle counts; HDMTX with

Table 1 Comparison of baseline characteristics between cycles with and without delayed MTX excretion

	Cycles with delayed MTX excretion ($n=124$)	Cycles without delayed MTX excretion ($n=393$)	*P*-value
Patient factors			
Age, median (IQR)	68 (64–73)	67 (57–71)	0.006
Male, *n* (%)	82 (66.1%)	220 (56.0)	0.047
BSA, m², median (IQR)	1.59 (1.48–1.7)	1.58 (1.45–1.7)	0.587
Disease factors, *n* (%)			
Acute lymphoblastic leukemia	16 (12.9)	64 (16.3)	0.396
Malignant lymphoma	108 (87.1)	329 (83.7)	-
Newly diagnosed	67 (54.0)	260 (66.1)	0.018
Relapsed/refractory	57 (46.0)	133 (33.9)	-
Laboratory data, median (IQR)			
Alb, g/dL	3.4 (3.0–3.6)	3.6 (3.2–3.9)	<0.001
AST, U/L	19 (15–25)	20 (15–27)	0.344
ALT, U/L	20 (13–32)	20 (13–31)	0.718
GGT, U/L	43 (27–81)	38 (27–65)	0.239
TBil mg/dL	0.4 (0.3–0.6)	0.4 (0.3–0.6)	0.081
CrCl, mL/min*	75.7 (60.2–102.4)	84.3 (66.3–108.2)	0.007
Ca, mg/dL	8.6 (8.3–8.9)	8.7 (8.3–9.0)	0.212
P, mg/dL	3.1 (2.7–3.6)	3.3 (2.9–3.9)	0.013
UA, mg/dL	4.4 (3.3–5.5)	4.3 (3.4–5.2)	0.548
Details of HDMTX			
Doses, mg/m² (IQR)	2276 (1027–3063)	2485 (1073–3388)	0.147
Drip infusion, *n* (%)	93 (75.0)	284 (72.3)	0.643
Concurrent chemotherapy, *n* (%)	65 (52.4)	198 (50.4)	0.757
Cycle counts, median (IQR)	2 (1–3)	2 (1–4)	0.064
Treatment intent, *n* (%)	71 (57.2)	169 (43.0)	0.007
Co-medication, *n* (%)			
PPI	13 (10.5)	50 (12.7)	0.637
NSAIDs	3 (2.4)	2 (0.5)	0.09
SMX/TMP	8 (6.4)	26 (6.6)	1
Penicillin-type drugs or CPFX	0 (0)	0 (0)	NA
Phenytoin	0 (0)	0 (0)	NA

Abbreviations: HDMTX, high-dose methotrexate; IQR, interquartile range; BSA, body surface area; Alb, albumin; CrCl, creatinine clearance; AST, aspartate aminotransferase; ALT, alanine transaminase; GGT, γ-glutamyl transpeptidase; TBil, total bilirubin; Ca, calcium; P, phosphorus; UA; PPI, proton pump inhibitor; NSAIDs, nonsteroidal anti-inflammatory drugs; SMX/TMP, sulfamethoxazole-trimethoprim; CPFX, ciprofloxacin

* CrCl was calculated by Cockcroft-Gault equation

treatment intent; and lower levels of Alb, CrCl, and phosphorus were significantly associated with an increased risk of delayed MTX excretion (all $P<0.05$) (Table 2). Interestingly, only elevated GGT levels were identified as a significant predictor of liver function ($P=0.012$). As expected, the presence of pleural effusion was highly associated with inadequate MTX clearance (OR 34.4, 95% confidence interval [CI] 4.36–271, $P<0.001$). With regard to co-administered drugs, only NSAIDs showed a trend toward a higher risk of MTX clearance failure (OR 4.85, 95% CI 0.8–29.3, $P=0.085$). Next, the association with the development of AKI was evaluated as a more direct outcome measure (Supplementary Table 2). Possibly due to the fewer event numbers, none of the factors can significantly predict either any grade ($n=28$) or grade 2–3 ($n=10$) AKI development. On the other hand, lower albumin levels and the presence of pleural effusion were significantly associated with the risks of a more toxic MTX concentration of 5 μmol/L at 48-hour time points ($n=5$) (Supplementary Table 2).

To create a predictive nomogram, backward stepwise selection, including all of the above significant variables, was performed. Age, male sex, and serum phosphorus levels were excluded because they were not statistically significant. Three clinical data (R/R status [OR 2.03, 95% CI 1.17–3.53, $P=0.011$], cycle counts [OR 0.771, 95% CI 0.671–0.886, $P<0.001$] and treatment intent [OR 2.13, 95% CI 1.21–3.75, $P=0.008$]), three laboratory parameters (Alb [OR 0.563, 95% CI 0.602–0.874, $P=0.01$], CrCl [OR 0.993, 95% CI 0.985–1.000, $P=0.044$] and GGT [OR 1.004, 95% CI 1.001–1.007, $P=0.014$]), and pleural effusion (OR 23.1, 95% CI 2.75–194, $P=0.003$) were identified as a candidate for constructing a nomogram. Owing to concerns regarding the subjective interpretations of chest radiographs and the potential for observer bias, pleural effusion was deemed inappropriate for inclusion in the model. Excluding pleural effusion, six variables remained significant risk factors (Supplementary Table 3), and a novel nomogram was constructed based on these variables (Fig. 1A).

The nomogram showed the higher ROC AUC of 0.73 (95% CI 0.68–0.78) compared to that of standalone values of Alb (0.62, 95% CI 0.57–0.68), CrCl (0.58, 95% CI 0.52–0.63), and GGT (0.54, 95% CI 0.47–0.59) in predicting delayed MTX excretion (Fig. 1B). Internal validation using the bootstrap method yielded an optimism-corrected ROC AUC of 0.71, which was close to the apparent value. The calibration curve indicated a good agreement between the predicted and observed values, with an acceptable optimism slope of 0.103, although the performance slightly decreased at higher probability levels (Fig. 1C). The Hosmer–Lemeshow test also supported the good fitness of the nomogram ($P=0.217$). The nomogram was made available on a freely accessible web server, allowing us to calculate individual risk probabilities, as shown in Supplementary Fig. 2.

Table 2 Univariate and multivariate analysis for predicting delayed MTX excretion

	Univariate analysis			Multivariate analysis (Backward stepwise selection)		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Patient and disease factors						
Age (continuous variables)	1.03	1.01–1.05	0.002	NA	NA	> 0.05
Male				NA	NA	> 0.05
BSA (continuous variables)	1.47	0.533–4.08	0.455	-	-	-
Acute leukemia				-	-	-
R/R disease status				2.03	1.17–3.53	0.011
MTX administration details						
Dose (continuous variables)	1.000	1.000–1.000	0.188	-	-	-
Dose > 3000 mg/m^2	0.818	0.534–1.25	0.355	-	-	-
3 h drip infusion	1.15	0.725–1.83	0.55	-	-	-
Concurrent chemotherapy	1.09	0.724–1.63	0.692	-	-	-
Cycle counts (continuous variables)	0.885	0.794–0.985	0.025	0.771	0.671–0.886	< 0.001
Treatment intent	1.78	1.18–2.67	0.005	2.13	1.21–3.75	0.008
Laboratory data (all continuous variables)						
Alb	0.437	0.295–0.647	< 0.001	0.563	0.602–0.874	0.01
CrCl	0.99	0.984–0.997	0.004	0.993	0.985–1.000	0.044
AST	0.993	0.978–1.01	0.369	-	-	-
ALT	1.001	0.993–1.009	0.808	-	-	-
GGT	1.004	1.001–1.007	0.012	1.004	1.001–1.007	0.014
TBil	1.54	0.682–3.5	0.298	-	-	-
Ca	0.699	0.464–1.05	0.087	-	-	-
P	0.718	0.54–0.955	0.022	NA	NA	> 0.05
UA	1.05	0.912–1.21	0.495	-	-	-
Other known risk factors						
Pleural effusion	34.4	4.36–271	< 0.001	23.1	2.75–194	0.003
Co-medications						
PPI use	0.803	0.421–1.53	0.507	-	-	-
NSAIDs use	4.85	0.8–29.3	0.085	-	-	-
SMX/TMP use	0.973	0.42–2.21	0.949	-	-	-

Abbreviations: OR, odds ratio; CI, confidence interval; BSA, body surface area; R/R, relapsed/refractory; MTX, methotrexate; Alb, albumin; CrCl, creatinine clearance; AST, aspartate aminotransferase; ALT, alanine transaminase; GGT, γ-glutamyl transpeptidase; TBil, total bilirubin; Ca, calcium; P, phosphorus; UA; PPI, proton pump inhibitor; NSAIDs, nonsteroidal anti-inflammatory drugs; SMX/TMP, sulfamethoxazole-trimethoprim; NA, not assessed

Association of delayed MTX excretion with clinical outcomes

Finally, we evaluated the effect of MTX elimination failure on the clinical outcomes. Overall, 28 (5.4%) patients developed AKI of any grade (grade 1 [$n = 18$], grade 2 [$n = 7$], and grade 3 [$n = 3$]), with the majority ($n = 24$ [85.7%]) showing reversibility of kidney function. None of the specific co-medications showed a skewed distribution toward patients with more severe AKI (grade 1 vs. 2–3). Three patients (0.6%) required hemodialysis, one of whom did not improve and succumbed directly to MTX-related complication. Since glucarpidase was not approved in Japan during this study period, none of the life-threatening patients were treated with that antidote. Whereas only three patients with effective MTX clearance developed AKI (0.7% [3/393]), 25 (20.2% [25/124]) with delayed MTX excretion developed AKI, 16 (12.9%) with grade 1, six (4.8%) with grade 2, and three (2.4%) with grade 3. Regardless of timing, MTX elimination failure was associated with an increased risk of AKI of any grade, observed even solely at the 72 h timepoint (OR 2.57, 95% CI 1.12–5.9, $P = 0.025$) (Fig. 2A). Moreover, even when considering only grade 2–3 AKI, ineffective MTX excretion significantly increased the risks, except the delay occurring only at the 72-hour after HDMTX initiation (Fig. 2B).

Among the 146 patients who received HDMTX to prevent CNS relapse, 14 (9.6%) experienced CNS recurrence (Supplementary Fig. 3). The 2-year cumulative incidence of CNS relapse did not significantly differ by MTX elimination status: 5.7% (95% CI 2.3%-11.4%) in the normal group versus 2.6% (95% CI 0.2–11.7%, $P = 0.273$) (Supplementary Fig. 4A). Moreover, for the 62 patients with CNS disease (two relapsed ALL, 44 secondary CNS lymphoma [SCNSL]

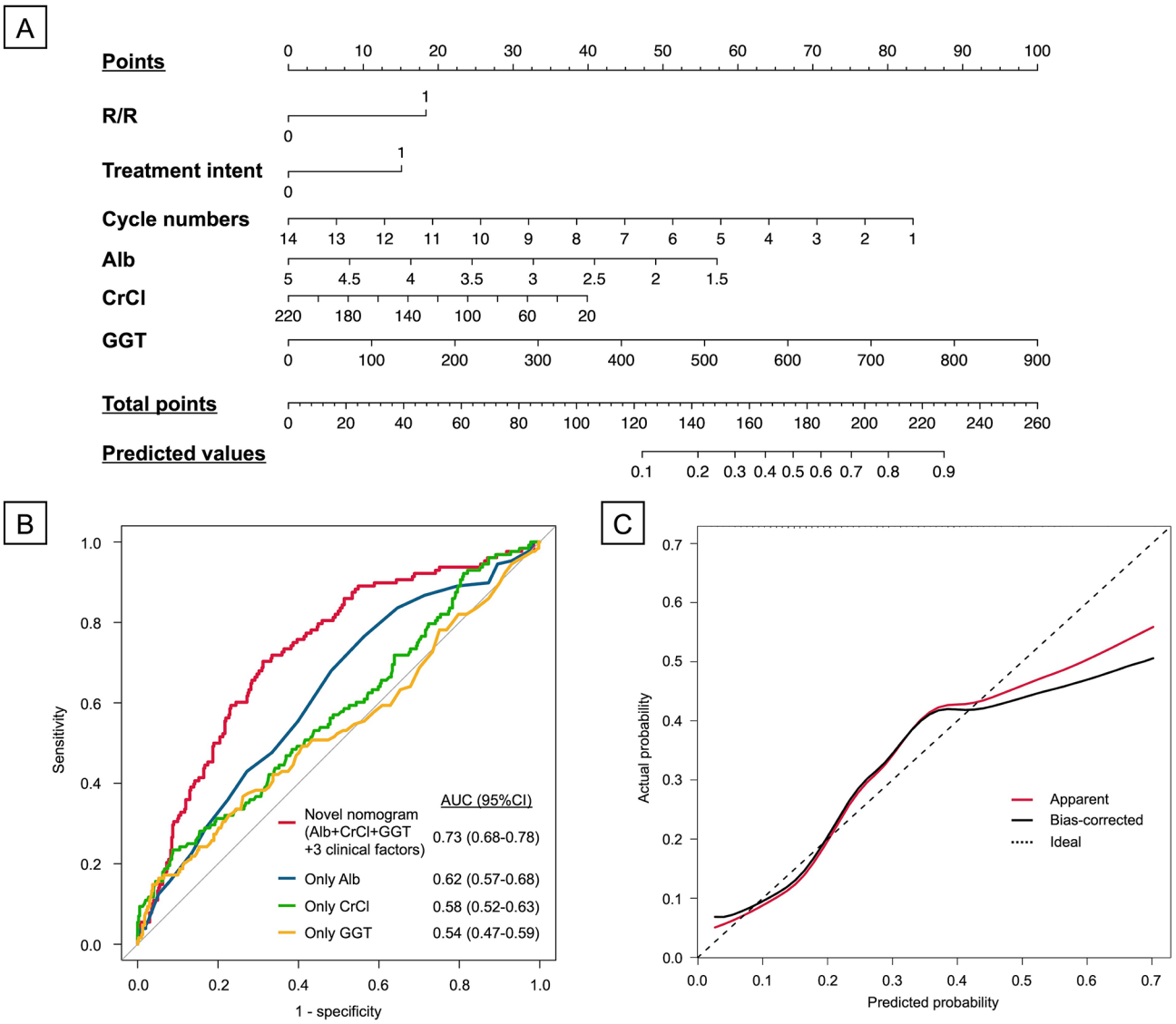

Fig. 1 Nomogram of predicting delayed MTX excretion. **(A)** A nomogram model for predicting delayed MTX excretion. The clinical and laboratory parameters of patients are plotted vertically on the nomogram, with each parameter's contribution quantified by an assigned score that corresponds to the predicted risk of delayed MTX excretion. The sum of these scores was calculated and marked on the total score line to obtain the probability of delayed MTX clearance. **(B)** ROC analysis was performed to compare the novel nomogram (red line), standalone uses of albumin (blue line), CrCl (green line) and GGT levels (orange line). **(C)** The calibration curves for the nomogram. The X-axis represents the predicted probability of delayed MTX excretion, and the Y-axis represents the actual probability. The black dashed line denotes the perfect prediction of an ideal model, the red solid line represents the nomogram prediction, and the black solid line denotes the bootstrap-corrected prediction

and 16 PCNSL), the survival time from CNS disease development was also not significantly different (the 2-year survival: 56.1%, 95% CI 33.7–73.6 in the non-delayed vs. 35.2%, 95% CI 19.8–51.0 in the delayed group, $P = 0.324$) (Supplementary Fig. 4B). Although the numbers are small, subgroup analyses confined to malignant lymphoma—split into patients with prophylactic HDMTX, SCNSL, and PCNSL—also showed no statistically significant differences in outcomes (Supplementary Fig. 5).

Discussion

To examine the characteristics of delayed MTX excretion and its associated risk factors, we analyzed one of the largest datasets consisting of more than 500 HDMTX cycles administered, with a particular focus on adult hematologic oncology patients. Three clinical factors and three biochemical parameters, represented as continuous variables, were identified and integrated to create an easy-to-use nomogram

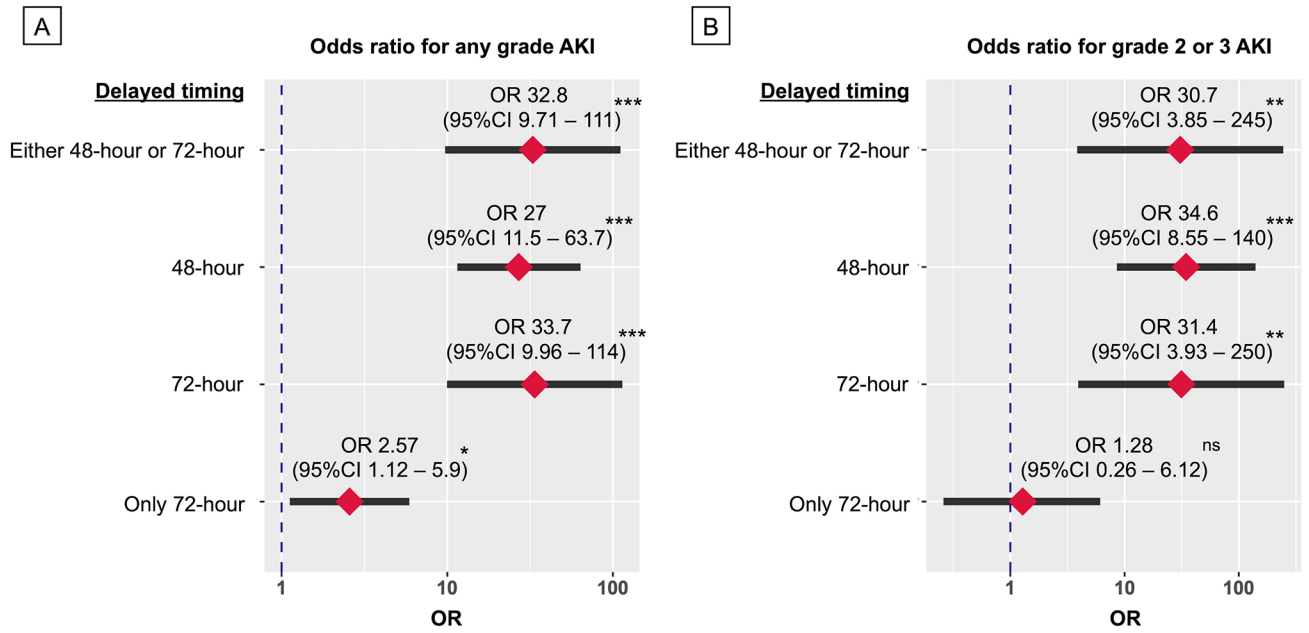

Fig. 2 Association of delayed MTX excretion with clinical outcomes. Forest plot depicting the odds ratio of developing AKI of **(A)** any grade and **(B)** grade 2 or 3. Red diamonds represent the corresponding odds ratios with the black line indicating the 95% CI. *, ** and *** indicate P-value < 0.05, < 0.01 and < 0.001, respectively

for predicting the failure to eliminate MTX. Delayed MTX excretion is harmful, as it is associated with an increased risk of developing AKI, rather than providing any benefit, such as reducing the incidence of CNS relapse or improving survival.

Despite the establishment of optimal supportive care, HDMTX poses the risk of devastating complications. HDMTX-induced nephrotoxicity typically occurs in approximately 10% cases [17, 20, 23], with single studies reporting nephrotoxicity rates as high as 38% [32]. These adverse effects pose a greater challenge to adult patients with lymphoma, who are commonly over 70 years of age and have multiple comorbidities. Recently, several large studies have suggested the limited efficacy of universal CNS prophylaxis using HDMTX in high-risk DLBCL patients [33, 34]. Alongside identifying patients who benefit from HDMTX, as evidenced by these studies, efforts should also be made to identify those who were likely to suffer from its toxicities. Given the higher interpatient variability in organ function among the elderly population, findings derived from children and adolescents may not be directly extrapolatable. For patients with ALL, even in the era of novel drugs such as T-cell engagers, HDMTX remains an integral part of curative intent regimen due to the absence of established alternative options with CNS-penetrating properties [35].

An important finding of our study was the lower predictive value of chronological age and the higher MTX doses, in contrast to several pediatric cohort studies [6, 18, 36]. Although Reiss et al. observed an association between higher doses (≥ 6000 mg/m^2) and prolonged MTX clearance times [11], their cohort included younger patients with a median age of 51 years, which may not accurately represent the adult patient population. The diminished significance of these two factors in our study could be due to dose adjustments. Elderly patients (older than the median age of 67 years) underwent dose reductions, with the median HDMTX dose reduced to two-thirds. As demonstrated in a pivotal study by Jahnke et al. [1]. , adherence to the appropriate dose reductions can facilitate safe administration of HDMTX, mitigating the risk of delayed MTX excretion.

In addition to well-known predictors, such as Alb and CrCl, GGT was also chosen to construct a nomogram. Although the reason for the superiority of GGT over other liver function tests remains unclear, numerous studies have highlighted the importance of non-renal clearance of MTX via liver metabolism [18, 19, 37–39]. Regarding clinical aspects, later cycles of HDMTX were significantly associated with a decreased risk of delayed MTX excretion. Consistent with previous studies [40, 41], cycle number may act as a surrogate for identifying patients who are more tolerant to repeated MTX exposure. The last two risk factors, R/R disease and treatment intent (i.e. the presence of CNS disease), can lead to a reduced performance status, which, in turn, might influence overall MTX clearance. Some studies have suggested that a lower baseline CrCl level or AKI development is paradoxically associated with better survival

[21, 42], possibly due to higher MTX exposure. Although the small subgroup analysis showed the numerically better 2-year survival rate in PCNSL with MTX clearance failure (83.3% vs. 58.3%, $P = 0.23$), our study did not support these findings overall and emphasized the importance of avoiding delays in MTX excretion.

The major limitations of our study are its retrospective nature and lack of external validation. Although the bootstrap method suggests minimal overfitting, external validation from an independent cohort is essential to implement the developed nomogram in clinical practice. We made the web-based simulation model accessible to a broad audience, which may have helped to validate our findings. Moreover, the nomogram can inform us of the individual predicted probabilities of delayed MTX excretion. However, our data are insufficient to determine how many probabilities dictate our therapeutic decision-making (i.e. avoiding HDMTX or intensifying supportive care). There are growing evidence on novel agents that shows preliminary but promising efficacy against CNS diseases [43]. Ibrutinib, a Bruton tyrosine kinase inhibitor, has been shown to reach therapeutic levels in the CNS and achieve an overall response rate of 69% and 88% for patients with SCNSL and PCNSL, respectively, in a phase II study [44]. While robust validation is needed, once such a novel CNS-directed therapy without HDMTX is established, it would be more feasible to use the proposed predictive model as a guide for treatment decisions.

In conclusion, this study underscores that MTX clearance following HDMTX therapy in adult patients did not only simply depends on renal function and is influenced by albumin levels, liver function, and patient condition. The novel nomogram developed in this study could pave the way for individualized risk prediction.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00280-024-04687-z.

Acknowledgements We thank Editage (https://www.editage.jp) for providing excellent assistance with English language editing.

Author contributions DI, KN, and KM designed the study. DI interpreted the data, performed statistical analysis, and wrote the manuscript. DI, TI, KN, and SY collected the clinical data. MO, AU, RT, KN and MT provided patient care. All authors critically reviewed and approved the manuscript.

Data availability The datasets generated in this study are available from Daisuke Ikeda upon request (dskikd.2409@gmail.com).

Declarations

Ethics approval The present study was conducted in accordance with the Declaration of Helsinki and approved by our institutional review board (approval number: 22-132-240205).

Conflict of interest KM received the research grant for AstraZeneca. Other authors declare no competing financial interests.

References

1. Jahnke K, Korfel A, Martus P, Weller M, Herrlinger U, Schmittel A et al (2005) High-dose methotrexate toxicity in elderly patients with primary central nervous system lymphoma. Ann Oncol 16(3):445–449. https://doi.org/10.1093/annonc/mdi075
2. Howard SC, McCormick J, Pui CH, Buddington RK, Harvey RD (2016) Preventing and managing toxicities of high-dose methotrexate. Oncologist 21(12):1471–1482. https://doi.org/10.1634/theoncologist.2015-0164
3. Relling MV, Fairclough D, Ayers D, Crom WR, Rodman JH, Pui CH et al (1994) Patient characteristics associated with high-risk methotrexate concentrations and toxicity. J Clin Oncol 12(8):1667–1672. https://doi.org/10.1200/JCO.1994.12.8.1667
4. Alsdorf WH, Karagiannis P, Langebrake C, Bokemeyer C, Frenzel C (2021) Standardized supportive care documentation improves Safety of High-Dose Methotrexate Treatment. Oncologist 26(2):e327–e32. https://doi.org/10.1002/onco.13603
5. May J, Carson KR, Butler S, Liu W, Bartlett NL, Wagner-Johnston ND (2014) High incidence of methotrexate associated renal toxicity in patients with lymphoma: a retrospective analysis. Leuk Lymphoma 55(6):1345–1349. https://doi.org/10.3109/10428194.2013.840780
6. Jian C, Chen S, Wang Z, Zhou Y, Zhang Y, Li Z et al (2023) Predicting delayed methotrexate elimination in pediatric acute lymphoblastic leukemia patients: an innovative web-based machine learning tool developed through a multicenter, retrospective analysis. BMC Med Inf Decis Mak 23(1):148. https://doi.org/10.1186/s12911-023-02248-7
7. Zhang W, Zhang Q, Zheng TT, Zhen JC, Niu XH (2016) Delayed high-dose methotrexate excretion and influencing factors in Osteosarcoma patients. Chin Med J (Engl) 129(21):2530–2534. https://doi.org/10.4103/0366-6999.192781
8. Zhan M, Chen Z, Ding C, Qu Q, Wang G, Liu S et al (2021) Risk prediction for delayed clearance of high-dose methotrexate in pediatric hematological malignancies by machine learning. Int J Hematol 114(4):483–493. https://doi.org/10.1007/s12185-021-03184-w
9. Xu WQ, Zhang LY, Chen XY, Pan BH, Mao JQ, Song H et al (2014) Serum creatinine and creatinine clearance for predicting plasma methotrexate concentrations after high-dose methotrexate chemotherapy for the treatment for childhood lymphoblastic malignancies. Cancer Chemother Pharmacol 73(1):79–86. https://doi.org/10.1007/s00280-013-2319-2
10. Kataoka T, Sakurashita H, Kajikawa K, Saeki Y, Taogoshi T, Matsuo H (2021) Low serum albumin level is a risk factor for delayed Methotrexate Elimination in High-Dose Methotrexate Treatment. Ann Pharmacother 55(10):1195–1202. https://doi.org/10.1177/1060028021992767
11. Reiss SN, Buie LW, Adel N, Goldman DA, Devlin SM, Douer D (2016) Hypoalbuminemia is significantly associated with increased clearance time of high dose methotrexate in patients being treated for lymphoma or leukemia. Ann Hematol 95(12):2009–2015. https://doi.org/10.1007/s00277-016-2795-7
12. Evans WE, Pratt CB (1978) Effect of pleural effusion on high-dose methotrexate kinetics. Clin Pharmacol Ther 23(1):68–72. https://doi.org/10.1002/cpt197823168
13. Mosleh E, Snyder S, Wu N, Willis DN, Malone R, Hayashi RJ (2023) Factors influencing delayed clearance of high dose methotrexate (HDMTX) in pediatric, adolescent, and young

adult oncology patients. Front Oncol 13:1280587. https://doi.org/10.3389/fonc.2023.1280587
14. Suzuki K, Doki K, Homma M, Tamaki H, Hori S, Ohtani H et al (2009) Co-administration of Proton pump inhibitors delays elimination of plasma methotrexate in high-dose methotrexate therapy. Br J Clin Pharmacol 67(1):44–49. https://doi.org/10.1111/j.1365-2125.2008.03303.x
15. Ramsey LB, Panetta JC, Smith C, Yang W, Fan Y, Winick NJ et al (2013) Genome-wide study of methotrexate clearance replicates SLCO1B1. Blood 121(6):898–904. https://doi.org/10.1182/blood-2012-08-452839
16. Taylor ZL, Vang J, Lopez-Lopez E, Oosterom N, Mikkelsen T, Ramsey LB (2021) Systematic review of pharmacogenetic factors that Influence High-Dose Methotrexate Pharmacokinetics in Pediatric malignancies. Cancers (Basel) 13(11). https://doi.org/10.3390/cancers13112837
17. Khera S, Sharma G, Negi V, Shaw SC (2022) Hypoalbuminemia and not undernutrition predicts high-dose methotrexate-induced nephrotoxicity in children with acute lymphoblastic leukemia in resource-constrained centers. Pediatr Blood Cancer 69(9):e29738. https://doi.org/10.1002/pbc.29738
18. Nakano T, Kobayashi R, Matsushima S, Hori D, Yanagi M, Suzuki D et al (2021) Risk factors for delayed elimination of high-dose methotrexate in childhood acute lymphoblastic leukemia and lymphoma. Int J Hematol 113(5):744–750. https://doi.org/10.1007/s12185-020-03071-w
19. Joannon P, Oviedo I, Campbell M, Tordecilla J (2004) High-dose methotrexate therapy of childhood acute lymphoblastic leukemia: lack of relation between serum methotrexate concentration and creatinine clearance. Pediatr Blood Cancer 43(1):17–22. https://doi.org/10.1002/pbc.20032
20. Gros L, Roldan A, Cabero-Martinez A, Dominguez-Pinilla N, de la Fuente A, Gonzalez-Barca E et al (2023) Incidence and management of patients with methotrexate delayed elimination in the clinical practice: a Delphi study. J Oncol Pharm Pract 29(4):794–801. https://doi.org/10.1177/10781552221079568
21. Latcha S, Gupta M, Lin IH, Jaimes EA (2023) High Dose Methotrexate-Induced Acute kidney Injury: incidence, risk factors, and recovery. Kidney Int Rep 8(2):360–364. https://doi.org/10.1016/j.ekir.2022.10.029
22. Aronoff GR (2005) Dose adjustment in renal impairment: response from Drug Prescribing in Renal failure. BMJ 331(7511):293–294. https://doi.org/10.1136/bmj.331.7511.293-a
23. Kawaguchi S, Fujiwara SI, Murahashi R, Nakashima H, Matsuoka S, Ikeda T et al (2021) Risk factors for high-dose methotrexate-induced nephrotoxicity. Int J Hematol 114(1):79–84. https://doi.org/10.1007/s12185-021-03132-8
24. Nirenberg A, Mosende C, Mehta BM, Gisolfi AL, Rosen G (1977) High-dose methotrexate with citrovorum factor rescue: predictive value of serum methotrexate concentrations and corrective measures to avert toxicity. Cancer Treat Rep 61(5):779–783
25. Kellum JA, Lameire N, Group KAGW (2013) Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (part 1). Crit Care 17(1):204. https://doi.org/10.1186/cc11454
26. Green MR, Chowdhary S, Lombardi KM, Chalmers LM, Chamberlain M (2006) Clinical utility and pharmacology of high-dose methotrexate in the treatment of primary CNS lymphoma. Expert Rev Neurother 6(5):635–652
27. Ferreri AJ, Reni M, Foppoli M, Martelli M, Pangalis GA, Frezzato M et al (2009) High-dose cytarabine plus high-dose methotrexate versus high-dose methotrexate alone in patients with primary CNS lymphoma: a randomised phase 2 trial. Lancet 374(9700):1512–1520. https://doi.org/10.1016/S0140-6736(09)61416-1
28. Thomas DA, Faderl S, O'Brien S, Bueso-Ramos C, Cortes J, Garcia-Manero G et al (2006) Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. Cancer 106(7):1569–1580. https://doi.org/10.1002/cncr.21776
29. Ramsey LB, Balis FM, O'Brien MM, Schmiegelow K, Pauley JL, Bleyer A et al (2018) Consensus Guideline for Use of glucarpidase in patients with high-dose Methotrexate Induced Acute kidney Injury and delayed Methotrexate Clearance. Oncologist 23(1):52–61
30. Tammemagi CM, Pinsky PF, Caporaso NE, Kvale PA, Hocking WG, Church TR et al (2011) Lung cancer risk prediction: prostate, lung, colorectal and ovarian Cancer screening trial models and validation. J Natl Cancer Inst 103(13):1058–1068. https://doi.org/10.1093/jnci/djr173
31. Hosmer DW, Hosmer T, Le Cessie S, Lemeshow S (1997) A comparison of goodness-of-fit tests for the logistic regression model. Stat Med 16(9):965–980. https://doi.org/10.1002/(SICI)1097-0258(19970515)16:9%3C965::AID-SIM509%3E3.0.CO;2-O
32. Wiczer T, Dotson E, Tuten A, Phillips G, Maddocks K (2016) Evaluation of incidence and risk factors for high-dose methotrexate-induced nephrotoxicity. J Oncol Pharm Pract 22(3):430–436. https://doi.org/10.1177/1078155215594417
33. Wilson MR, Eyre TA, Kirkwood AA, Wong Doo N, Soussain C, Choquet S et al (2022) Timing of high-dose methotrexate CNS prophylaxis in DLBCL: a multicenter international analysis of 1384 patients. Blood 139(16):2499–2511. https://doi.org/10.1182/blood.2021014506
34. Lewis KL, Jakobsen LH, Villa D, Smedby KE, Savage KJ, Eyre TA et al (2023) High-dose methotrexate as CNS prophylaxis in high-risk aggressive B-Cell lymphoma. J Clin Oncol 41(35):5376–5387. https://doi.org/10.1200/JCO.23.00365
35. Kopmar NE, Cassaday RD (2023) How I prevent and treat central nervous system disease in adults with acute lymphoblastic leukemia. Blood 141(12):1379–1388
36. Xu W, Tang Y, Song H, Shi S, Yang S (2007) Retrospective study on elimination delay of methotrexate in high-dose therapy of childhood acute lymphoblastic leukemia in China. J Pediatr Hematol Oncol 29(10):688–693. https://doi.org/10.1097/MPH.0b013e31814d6777
37. Ito K, Oleschuk CJ, Westlake C, Vasa MZ, Deeley RG, Cole SP (2001) Mutation of Trp1254 in the multispecific organic anion transporter, multidrug resistance protein 2 (MRP2) (ABCC2), alters substrate specificity and results in loss of methotrexate transport activity. J Biol Chem 276(41):38108–38114. https://doi.org/10.1074/jbc.M105160200
38. Comandone A, Passera R, Boglione A, Tagini V, Ferrari S, Cattel L (2005) High dose methotrexate in adult patients with osteosarcoma: clinical and pharmacokinetic results. Acta Oncol 44(4):406–411. https://doi.org/10.1080/02841860510029770
39. Dupuis C, Mercier C, Yang C, Monjanel-Mouterde S, Ciccolini J, Fanciullino R et al (2008) High-dose methotrexate in adults with osteosarcoma: a population pharmacokinetics study and validation of a new limited sampling strategy. Anticancer Drugs 19(3):267–273. https://doi.org/10.1097/CAD.0b013e3282f21376
40. Bacci G, Ferrari S, Longhi A, Forni C, Loro L, Beghelli C et al (2003) Delayed methotrexate clearance in osteosarcoma patients treated with multiagent regimens of neoadjuvant chemotherapy. Oncol Rep 10(4):851–857. https://doi.org/10.3892/or.10.4.851
41. Kawakatsu S, Nikanjam M, Lin M, Le S, Saunders I, Kuo DJ et al (2019) Population pharmacokinetic analysis of high-dose methotrexate in pediatric and adult oncology patients. Cancer Chemother Pharmacol 84(6):1339–1348. https://doi.org/10.1007/s00280-019-03966-4
42. Ferreri AJ, Guerra E, Regazzi M, Pasini F, Ambrosetti A, Pivnik A et al (2004) Area under the curve of methotrexate and creatinine clearance are outcome-determining factors in primary CNS lymphomas. Br J Cancer 90(2):353–358. https://doi.org/10.1038/sj.bjc.6601472

43. Bobillo S, Khwaja J, Ferreri AJM, Cwynarski K (2023) Prevention and management of secondary central nervous system lymphoma. Haematologica 108(3):673–689
44. Grommes C, Wolfe J, Gavrilovic I, Kaley T, Stone J, Daras M et al (2018) Phase II of single-agent Ibrutinib in recurrent/refractory primary (PCNSL) and secondary CNS lymphoma (SCNSL). Blood 132(Suppl 1):2965