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Population Pharmacokinetic and Toxicity Analysis of High-Dose Methotrexate in Patients with Central Nervous System Lymphoma

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Abstract

Background High-dose methotrexate (HD-MTX)-based polychemotherapy is widely used for patients with central nervous system (CNS) lymphoma. The pharmacokinetic (PK) variability and unpredictable occurrence of toxicity remain major concerns in HD-MTX treatment.

Objectives This study aimed to characterize the population PK of HD-MTX in patients with CNS lymphoma and to identify baseline predictors and exposure thresholds that predict a high risk of nephro- and hepatotoxicity.

Methods Routinely monitored serum MTX concentrations after intravenous infusion of HD-MTX and MTX dosing information were collected retrospectively. Acute event of toxicity ($\geq$ grade 1) was defined according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 on the basis of serum creatinine and alanine aminotransferase. A population PK model was developed in NONMEM. Toxicity data were analyzed using a logistic regression model, and potential baseline and exposure-related predictors were investigated.

Results In total, 1584 MTX concentrations from 110 patients were available for analysis. A two-compartment population PK model adequately described the data. Estimated glomerular filtration rate (eGFR), treatment regimen, albumin, alkaline phosphatase, and body weight were identified as significant covariates that explain the PK variability of HD-MTX. Baseline eGFR and sex were identified as significant predictors for renal toxicity, and MTX dose (mg/m^2) was the strongest predictor for hepatotoxicity. The MTX area under the concentration–time curve ($\text{AUC}_{24-\infty}$) and concentration at 24 h ($C_{24\text{h}}$) were shown to correlate with renal toxicity only, and $49,800 \mu\text{g}/\text{L} \times \text{h}$ ($109.6 \mu\text{mol}/\text{L} \times \text{h}$) and $C_{24\text{h}} > 3930 \mu\text{g}/\text{L}$ ($8.65 \mu\text{mol}/\text{L}$) were potential exposure thresholds predicting high risk (proportion $> 60\%$).

Conclusions A population PK model was developed for HD-MTX in patients with CNS lymphoma. The toxicity analysis showed that lower baseline eGFR and male sex, and higher MTX dose are associated with increased risk of acute nephro- and hepatotoxicity, respectively. The proposed exposure thresholds that predict high risk of renal toxicity and the developed models hold the potential to guide HD-MTX dosage individualization and better prevent acute toxicity.

1 Introduction

High-dose methotrexate (HD-MTX)-based polychemotherapy is the standard therapy for patients with primary central nervous system (CNS) lymphoma [1, 2]. It is also widely used for patients with secondary CNS involvement of diffuse large B-cell lymphoma (DLBCL), mainly for those who are naive to HD-MTX [3].

The standard dose of HD-MTX for patients with CNS lymphoma is $3 \text{ g}/\text{m}^2$ and is administrated by intravenous infusion. Methotrexate (MTX) has approximately 50%

protein binding and is eliminated primarily unchanged by renal excretion ($> 80\%$), while a small fraction is eliminated as a metabolite 7-hydroxymethotrexate [4, 5].

In routine HD-MTX treatment, MTX concentrations are monitored after each administration until they reach a safe target ($< 0.2 \mu\text{mol}/\text{L}$). Although HD-MTX dose is based on patient body surface area (BSA), significant inter- and intraindividual variability in its pharmacokinetics (PK) is observed [6–8]. Delayed elimination of MTX due to impaired renal function or extravascular fluid collections can occur, which will result in a prolonged period of MTX exposure and a higher risk of toxicity [4, 7, 8]. Furthermore, the unpredictable occurrence of acute toxicity during HD-MTX treatment, including kidney dysfunction and hepatotoxicity,

Key Points

A population PK model was developed for high-dose methotrexate (HD-MTX) on the basis of data collected from patients with CNS lymphoma and subsequently used for exposure-toxicity analysis

Lower baseline eGFR and male sex are associated with increased risk of acute renal toxicity (grade ≥ 1). Higher MTX dose (mg/m^2) is associated with increased risk of acute hepatotoxicity (grade ≥ 1)

The analysis identified that MTX exposure metrics correlate with renal toxicity only, and area under the concentration–time curve from 24 h to infinite ($\text{AUC}_{24-\infty}$) $> 49,800 \mu\text{g}/\text{L} \times \text{h}$ ($109.6 \mu\text{mol}/\text{L} \times \text{h}$) and concentration at 24 h ($C_{24\text{h}}$) $> 3930 \mu\text{g}/\text{L}$ ($8.65 \mu\text{mol}/\text{L}$) predicted high risk of renal toxicity (proportion $> 60\%$)

may result in treatment interruption or delay, which could cause unfavorable treatment outcome [6, 7]. To improve the outcomes of HD-MTX therapy, further individualizing HD-MTX dosage and identifying factors that predict a high risk of HD-MTX induced toxicity are desired.

The risk factors that have been identified for HD-MTX-induced renal toxicity in patients with lymphoid or hematological malignancy are mostly dose or exposure related: doses $\geq 6 \text{ g}/\text{m}^2$, area under the concentration–time curve (AUC) in the first administration cycle, and dose-normalized concentration at 24 and 48 h [9–11]. For HD-MTX-induced hepatotoxicity, studies on risk factors are limited. One study suggests that the AUC of HD-MTX is associated with hepatotoxicity, and another study suggests that prior alanine aminotransferase (ALAT) elevation may predict increased hepatotoxicity risk [12, 13]. However, an exposure threshold for toxicity that would facilitate better supportive care and treatment individualization for HD-MTX is still lacking. Moreover, the predictors at baseline for HD-MTX-induced toxicities are less studied. In addition to the ALAT elevation for hepatotoxicity, studies have shown that baseline lactate dehydrogenase, albumin, and interacting/nephrotoxic drugs correlated with the risk of acute kidney injury or nephrotoxicity [9, 14, 15]. Further exploration of potential risk factors at baseline for both nephro- and hepatotoxicity would therefore be beneficial to guide HD-MTX therapy.

Population PK–pharmacodynamic (PD) modeling with mixed-effect models enables quantitative characterization

as well as the prediction of drug PK, response, or toxicity profiles and their relationships at both population and individual levels. This approach also enables the identification of covariates that explain the observed inter- and intraindividual variabilities [16]. Combined with simulations, the developed model can be applied to guide treatment rationally [17]. Until now, several population PK models of HD-MTX in patients with lymphoid malignancy have been published, but many were not specifically focused on patients with CNS lymphoma [8, 11, 12, 18–23]. Subsequent quantitative pharmacology-based toxicity analysis of HD-MTX for patients with CNS lymphoma with a model-based approach is still lacking.

In the current study, on the basis of retrospectively collected data, we performed a population PK analysis to characterize HD-MTX PK in patients with CNS lymphoma who received various treatment regimens, and explored covariates that explain the variability. Subsequently, the occurrence of acute nephro- and hepatotoxicity were analyzed with a model-based approach that aims to identify baseline predictors and exposure threshold that predict a high risk of toxicity for each HD-MTX administration cycle.

2 Patients and Methods

2.1 Patients and Data

Patients who were diagnosed with CNS lymphoma and treated with HD-MTX-based polychemotherapy with available dosing information and MTX concentrations in the period ranging from 2010 to March 2021 from the Leiden University Medical Center (LUMC), Erasmus Medical Center (EMC), and University Medical Center Groningen (UMCG) were included. Patients received HD-MTX by intravenous infusion and were dosed per body surface area (BSA). All medications that have potential drug–drug interaction with MTX [e.g., benzimidazoles and nonsteroidal antiinflammatory drugs (NSAIDs)] were stopped 72 h prior to the use of HD-MTX. Details on the preventive and mitigation protocol for toxicity are described in Online Resource 3. Glucarpidase was not used in these patients since it was not reimbursed in the Netherlands before 2024.

The routinely monitored MTX concentrations were retrospectively collected from the laboratory information system (LIS). MTX concentrations were analyzed with ARKTM assay [24] with a lower limit of quantification (LLOQ) of $18.2 \mu\text{g}/\text{L}$ ($0.04 \mu\text{mol}/\text{L}$) in the LUMC and the EMC and $15 \mu\text{g}/\text{L}$ in the UMCG. If the detected MTX was above $22722 \mu\text{g}/\text{L}$ ($50 \mu\text{mol}/\text{L}$) at 24 h, above $2272.2 \mu\text{g}/\text{L}$ ($5 \mu\text{mol}/\text{L}$) at 48 h, or above $90.9 \mu\text{g}/\text{L}$ ($0.2 \mu\text{mol}/\text{L}$) at 72 h after administration of HD-MTX, it was defined as delayed elimination

[4]. Patient demographic characteristics, drug dosing information (i.e., treatment regimen, infusion hours, and dose), and laboratory results (i.e., serum creatinine (SCr), alkaline phosphatase (ALP), aspartate aminotransferase (ASAT), ALAT, albumin, and bilirubin) were collected from patients' electronic health care records. On the basis of available data, estimated glomerular filtration rate (eGFR) was also estimated by using the CKD-EPI creatinine equation and included in the analysis [25].

This study is approved by the local Ethical Committee of each institute (number G20.126), and did not fall within the scope of the WMO (Medical Scientific Research Act). A waiver for informed consent was granted. All performed procedures were in accordance with the ethical standards of the institutional medical ethical committee and the 1964 Declaration of Helsinki and its later amendments.

2.2 Population PK Modeling

A population PK model was developed on the basis of the available MTX PK data. The unit of MTX concentrations was unified to $\mu\text{g/L}$ by multiplying the data reported in $\mu\text{mol/L}$ by the molar mass of MTX (454.44 g/mol). Data below the LLOQ were omitted from the analysis owing to the small proportion ($< 10\%$) [26].

One-, two-, and three-compartment models with first-order elimination were explored as the structural model. Parameters were assumed to be log-normally distributed, and interindividual variability (IIV) was quantified. Interoccasion variability (IOV) was incorporated on the PK parameter clearance (CL) to account for the intraindividual variability, and each administration cycle was defined as an occasion. A combined proportional and additive error model was applied to characterize the residual errors. The residual errors of data from different medical centers were set to follow the same distribution. The structural model was selected based on goodness of fit (GOF), objective function value (OFV), and the stability of the model.

Subsequently, the covariate effects of patient demographic information, treatment regimen (which covers the effect of the infusion duration, patient status, and the comedications in the polychemotherapy setting), time-varying laboratory results on CL, and body-size-related characteristics on volumes of distribution were investigated. The stepwise covariate modeling (SCM) function was applied with assistance of Perl-speaks NONMEM (version 4.9) [27]. Model selection was based on a reduction in OFV assuming a χ^2 distribution, a reduction in IIV or IOV, and physiological plausibility. Both a forward inclusion ($p < 0.05$, $\Delta\text{OFV} < -3.84$, degrees freedom of 1) and a backward elimination process ($p < 0.01$, $\Delta\text{OFV} > 6.64$, degrees freedom of 1) were performed to identify significant covariates.

2.3 Toxicity Analysis

At each HD-MTX administration cycle, the renal and hepatotoxicity were graded on the basis of monitored SCr and ALAT results according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, respectively [28], to increase the clinical translatability compared with continuous variable analysis. The $\geq$ grade 1 toxicity was defined as a toxicity event (dichotomous) in case each single CTCAE category had an incidence of $< 15\%$. The data were analyzed with a logistic regression model where the probability of having toxicity was estimated. The logit function is shown in Eqs. 1–3, where “base” represents the baseline logit score, θ is the typical population probability operator, and η_i represents the random IIV, which was assumed to be normally distributed with mean of 0 and variance of ω^2 .

Individual PK parameters obtained from the final PK model were applied to simulate and estimate the MTX exposure metrics of interest for each administration cycle: AUC between 24 h after drug administration to infinity ($\text{AUC}_{24-\infty}$) and MTX concentration at 24 h ($C_{24\text{h}}$). $\text{AUC}_{24-\infty}$ was estimated by integrating the individual concentration–time curves from 24 h to last sample time plus AUC from the last sample time to infinity, which was approximated as the last concentration divided by the terminal elimination rate constant (β).

The potential predictors (baseline and exposure-related predictors) for nephro- and hepatotoxicity were investigated by being included linearly into the logit function (Eq. 4). Separate analyses were performed to identify the baseline predictors and to explore the correlation between MTX exposure metrics (i.e., $\text{AUC}_{24-\infty}$ and $C_{24\text{h}}$) and toxicity. The inclusion of covariates was based on the reduction in OFV and physiological plausibility. A forward inclusion process was performed when investigating the baseline predictors. Factors that result in a $\Delta\text{OFV} < -3.84$ were considered to be significant ($p < 0.05$, degrees freedom of 1).

The evaluated baseline factors include patient demographic information, baseline eGFR, ALAT, ASAT, and albumin of each administration cycle, dose amount, treatment regimen, dose divided by baseline CL as an AUC approximation (AUC_{base}) of each administration cycle, $\text{AUC}_{24-\infty}$ from previous administration course ($\text{pAUC}_{24-\infty}$), and $C_{24\text{h}}$ from previous administration course ($\text{pC}_{24\text{h}}$). The toxicity status in the previous administration course was also evaluated as a potential predictive factor.

Using the final model where the covariate effect of exposure metrics were identified to be significant, 500 simulations were performed for the subjects in the dataset, and the median of the proportion of patients having toxicity across 10 exposure intervals was derived to determine the exposure threshold.

$$\text{base} = \ln\left(\frac{\theta}{1 - \theta}\right) \quad (1)$$

$$\text{logit}_i = \text{base} + \sum_{k=1}^n E_{\text{cov}_k} + \eta_i \quad (2)$$

$$P_i = \frac{e^{\text{logit}_i}}{1 + e^{\text{logit}_i}} \quad (3)$$

$$E_{\text{cov}_k} = \begin{cases} \text{categorical} : \theta_{\text{cov}} \\ \text{continuous} : \left(\frac{\text{COV}}{\text{median}(\text{COV})}\right)^{\theta_{\text{cov}}} \end{cases} \quad (4)$$

2.4 Model Evaluation

The final PK model was evaluated with GOF plots, prediction-corrected visual predictive check (pcVPC), and a bootstrap based on 1000 runs of replicated datasets sampled from the original dataset with replacement.

The pcVPC plot was generated on the basis of 1000 times of simulation. MTX concentrations were commonly monitored at 24 h, 48 h, and 72 h, and thereafter every 24 h after the start of infusion until the concentration was below a threshold. Consequently, patients with delayed elimination had a longer follow-up and more samples per patient. The same sampling strategy was applied when performing simulations for the pcVPC plot; i.e., if the simulated concentration after day 3 fell below 45.4 µg/L (0.1 µmol/L), the next data point would not be sampled. The set threshold of 45.4 µg/L is the median of the second last monitored concentration of the collected data after day 3.

The adequacy of the toxicity model was evaluated with a visual predictive check (VPC). The original dataset was simulated 500 times to derive the median and 90% prediction interval of the proportion of patients having toxicity at each administration cycle and over a range of covariate values. The prediction interval was compared with the observed results.

2.5 Software and Estimation Method

The population modeling analysis was performed with NONMEM (version 7.4.4, ICON Development Solutions, Ellicott City, MD, USA) aided with Perl-speaks-NONMEM (PsN) (version 4.9, Uppsala University, Uppsala, Sweden) [29]. Parameters of the population PK model were estimated using the first-order conditional estimation method with interaction (FOCEI). The conditional Laplacian method was used to approximate the marginal likelihood in the toxicity analysis. Data management and plot generation were

performed with R statistics software (version 4.2.1, R Foundation for Statistical Computing, Vienna, Austria).

3 Results

3.1 Patients and PK Data

In total, 110 patients with CNS lymphoma (56 males and 54 females) were included from the LUMC ($n = 75$), the UMCG ($n = 17$), and the EMC ($n = 18$). Among the included patients, 80 patients (73%) were diagnosed with primary CNS lymphoma, 11 patients (10%) were diagnosed with secondary CNS lymphoma, and 11 patients (10%) had secondary CNS involvement of systemic DLBCL. The baseline characteristics of the included patients from the three medical centers are shown in Table 1.

In total, 1584 monitored MTX concentrations from 412 administration cycles were collected, of which 124 (7.8%) were below the LLOQ and were omitted from the analysis. The concentrations were monitored daily after the start of MTX infusion until the concentrations fell to a level below 90.9 µg/L (0.2 µmol/L) or the LLOQ. The median number of concentrations contributed by each patient to the analysis was 12, ranging from 2 to 35. The delayed elimination was observed in 47 (31.3%) patients, and the longest follow-up time during one administration cycle was 454 h. Five patients had a treatment interruption of more than 2.5 months, and their data before and after the interruption were treated as data from two separate subjects. This resulted in 115 subjects in the dataset eventually. The time course of all collected MTX concentrations is shown in Online Resource 1, Fig. S1.

The treatment regimen differs among medical centers (Table 1, Online Resource 1, Table S1). The LUMC patients were separated into two treatment groups. Older and/or less fit patients received HD-MTX with rituximab and procarbazine (RMP). For younger and fit patients (< 70 years old), HD-MTX was given with high-dose cytarabine (HD-AraC), thiotepa, and rituximab (MATRIX). For the UMCG and EMC patients, HD-MTX was administered with teniposide, carmustine, prednisolone, with or without rituximab or HD-AraC (MBVP). Details about the treatment regimens including infusion durations can be found in Online Resource 1, Table S1.

3.2 Population PK Model

A two-compartment population PK model with first-order elimination provided the best fit to the obtained data in HD-MTX in patients with CNS lymphoma. Compared with the one-compartment model, the objective function value (OFV)

Table 1. Baseline characteristics of the patients included in the current study

Item	N (%) / median (range)		
	LUMC	UMCG	EMC
Center			
Number of patients	75	17	18
Age (years)	66 (22–83)	66 (52–73)	67 (51–76)
Sex			
Male	42 (56%)	6 (35%)	8 (44%)
Female	33 (44%)	11 (65%)	10 (56%)
Body weight (kg)	78 (53.4–115)	76.5 (46.4–108)	70.1 (49.5–96.3)
Height (cm)	176 (155–195)	169 (158–192)	168 (148–186)
Body mass index (kg/m ²)	25.0 (17.6–38.0)	25.0 (17.9–35.4)	23.7 (18.9–34.5)
Body surface area (m ²)	1.94 (1.58–2.34)	1.94 (1.44–2.40)	1.8 (1.41–2.05)
ASAT (IU/L)	20 (9–100)	20.3 (10–53)	22.5 (14–58)
ALAT (IU/L)	30.5 (9–286)	43 (16–213)	41 (13–215)
SCr (μmol/L)	64 (37–125)	66 (43–94)	65 (45–98)
eGFR (mL/(min × 1.73 m ²)) ^a	93.8 (52.9–159)	89.3 (54–113)	90.3 (66.9–115)
Albumin (g/L)	38.5 (28–49)	37.5 (32.5–45.4)	40 (34–49)
ALP (U/L)	67 (25–297)	60 (44–82)	62.5 (28–118)
Bilirubin (μmol/L)	8 (3–23)	7.7 (3–25.3)	8 (4–19)
Disease type			
PCNSL	45 (60%)	17 (100%)	18 (100%)
SCNSL	11 (14.7%)	0	0
Stage IV DLBCL with CNS involvement	11 (14.7%)	0	0
Other lymphoma with CNS involvement ^b	8 (10.7%)	0	0
Number of administration cycles per patient	4 (1–8)	4 (3–4)	4 (1–8)
Dose of MTX (mg/m ²)	3000 (1500–8000)	3000 (1950–3000)	3000 (1500–3200)
Treatment regimens ^c			
RMP	35 (46.7%)	0	0
MATRIX	40 (53.3%)	0	0
MBVP	0	17 (100%)	18 (100%)

ALAT alanine aminotransferase, ALP alkaline phosphatase, ASAT aspartate aminotransferase, CNS central nervous system, DLBCL diffuse large B-cell lymphoma, eGFR estimated glomerular filtration rate, MTX methotrexate, PCNSL primary CNS lymphoma, SCNSL secondary CNS lymphoma, SCr serum creatinine

^aeGFR was estimated with the CKD-EPI creatinine equation

^bIncluding T cell lymphoma, follicular lymphoma, and Burkitt lymphoma

^cRMP, contains high-dose MTX (HD-MTX), rituximab, and procarbazine; MATRIX, contains HD-MTX, high-dose cytarabine (HD-AraC), thiopeta, and rituximab; MBVP, contains HD-MTX, teniposide, carmustine, prednisolone, with or without rituximab or HD-AraC. Details can be found in Online Resource, Table S1

of the two-compartment model was 1843.772 units lower ($p < 0.01$, degrees of freedom 4). Although the three-compartment model was shown to further improve the model fit, the estimated relative standard errors (RSEs) of parameters indicated unreliable parameter estimates. Therefore, the two-compartment model was selected as the structural model. The model code of the final PK model can be found in Online Resource 2.

The covariate analysis identified eGFR, treatment regimen, albumin, and ALP as significant covariates on CL of MTX ($p < 0.01$). Body weight was a significant covariate on the volume of distribution of the central compartment

(V_1). The RSEs indicate an acceptable precision ($< 40\%$) of most parameters, except for the coefficient of ALP effect (Table 2). The typical MTX CL in patients in the RMP group was estimated to be 16.0% lower than that in the MATRIX group, while the CL differences between the MATRIX and MBVP groups were not significant (Table 2, Online Resource 1, Fig. S2). The coefficient of variation (CV%) of random IIV and IOV for CL decreased from 29.2% and 23.1% to 15.5% and 12.3%, respectively, after covariate inclusions. The inclusion of IIV on V_1 became insignificant after covariate inclusions and was therefore fixed to zero (OFV increased by 2.265). The estimated standard deviation

Table 2 Parameter estimates of the final population PK model of HD-MTX in patients with CNS lymphoma

	Estimate (RSE)	IIV (CV%) (RSE%) [shrink- age]	IOV (CV%) (RSE%)	Bootstrap	
				Median	95% CI
CL (L/h)	21.2 (13%)	15.5 (8%) [10%]	12.3 (6%)	21.4	[17.2, 27.2]
θ_{eGFR}	0.0104 (5%)	–		0.0104	[0.0093, 0.011]
θ_{TREAT}					
MATRIX	1	–		–	–
RMP	0.840 (4%)	–		0.839	[0.772, 0.913]
MBVP	1.03 (3%)	–		1.03	[0.952, 1.11]
θ_{ALB}	0.225 (28%)	–		0.225	[0.0715, 0.369]
θ_{ALP}	–0.0624 (41%)	–		–0.0656	[–0.115, –0.0186]
V_1 (L)	125 (16%)	0 FIX		126.4	[98.1, 172]
θ_{WT}	0.00370 (34%)	–		0.00369	[0.00127, 0.00629]
V_2 (L)	36.7 (27%)	55.7 (11%) [13%]		38.1	[23.9, 62.4]
Q (L/h)	0.593 (21%)	30.2 (15%) [15%]		0.605	[0.418 0.920]
Residual errors					
Prop. (CV%)	25.2% (4%)	[18%] ^a		25.0%	[23.0%, 26.9%]
Add. (SD, µg/L)	0.0001 FIX	–		0.0001 FIX	–

$$V_{1i} = 125 \times (1 + \theta_{\text{WT}} \times (\text{WT} - 75.8)) \times e^{\eta_i}$$

$$\text{CL}_i = 21.2 \times (1 + \theta_{\text{eGFR}} \times (\text{eGFR} - 82.93)) \times \left(\frac{\text{ALB}}{37.31}\right)^{\theta_{\text{ALB}}} \times \left(\frac{\text{ALP}}{73.81}\right)^{\theta_{\text{ALP}}} \times \theta_{\text{TREAT}} \times e^{\eta_i}$$

Add. additive residual error, ALB albumin, ALP alkaline phosphatase, CI confidence interval, CL clearance, CV coefficient of variation, eGFR estimated glomerular filtration rate, IIV interindividual variability, IOV interoccasion variability, Prop. proportional residual error, Q intercompartment clearance, RSE relative standard error, SD standard deviation, V_1 distribution volume of the central compartment, V_2 distribution volume of the peripheral compartment, WT weight, MATRIX, RMP, and MBVP three different treatment regimens

^aEpsilon shrinkage

(SD) of the additive residual error approached zero and was therefore fixed to 0.0001 µg/L.

The GOF plots on both normal and logarithmic scale showed that the model predictions were generally in good accordance with the observations, while the population predictions underpredicted the observations at lower concentrations (Fig. 1). The deviations between model predictions and observations were also observed when the concentrations were above 20,000 µg/L. However, when removal of these data points was explored, the new parameter estimates were still within the estimated 95% confidence interval (CI) of the current parameter estimates. The conditional weighted residual errors (CWRES) were distributed around zero without obvious trends over time, but trends over population predictions at lower concentrations can be observed (Fig. 1). The pcVPC plot demonstrated an adequate predictability of the model (Fig. 2). The final parameter estimates were in good agreement with the bootstrap results (Table 2).

3.3 Toxicity Analysis

Among the 115 subjects, 51 (44.3%) and 76 (66.1%) subjects developed acute nephron- and hepatotoxicity during at least one administration cycle, respectively. The majority of subjects received ≤ 4 courses of treatment (98/115, 85.2%). The

observed proportion of patients having each grade of renal or hepatotoxicity during each administration cycle is shown in Online Resource 1, Fig. S3. The dose was reduced in 13 subjects after they had either nephro- or hepatotoxicity or both.

3.3.1 Baseline Predictor

The modeling analysis of renal toxicity showed that, among the investigated baseline factors, the inclusion of age, sex, dose in mg/m², AUC_{base}, pC_{24h}, pAUC_{24–∞}, or eGFR resulted in a significant decrease in OFV in the univariable covariate analysis, among which the baseline eGFR was the most significant predictor ($\Delta\text{OFV} = -52.8$). The inclusion of toxicity status of the previous administration course did not result in a significant decrease in OFV. The treatment regimen itself was also not identified to affect the toxicity probability. The final model of renal toxicity included baseline eGFR (range 40.2–158.7 mL/min/1.73m², maximum predicted probability change (max ΔP) = –0.929) and sex (for female, $\Delta P = -0.103$) as significant covariates.

For the hepatotoxicity model, AUC_{base}, dose in mg, and dose in mg/m² resulted in significant decreases in OFV in the univariable covariate analysis, among which dose in mg/

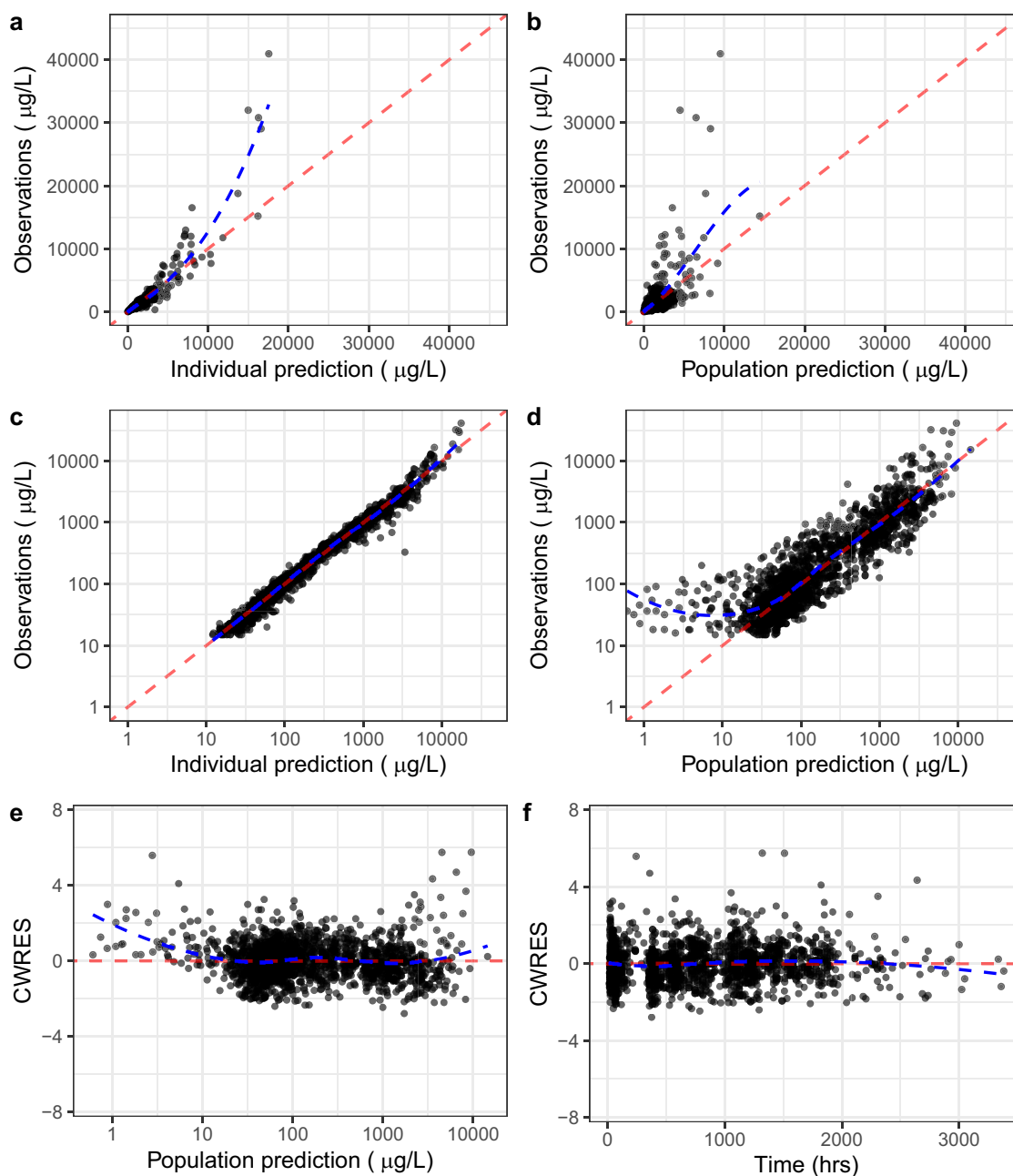


Fig. 1 Goodness-of-fit plots of the developed population PK model, including observations versus individual predictions on both normal (a) and logarithmic scale (c), observations versus population predictions on both normal (b) and logarithmic scale (d), and conditional

weighted residual errors (CWRES) versus populations predictions (e) and time after last dose (f). The red dashed lines represent $y = x$ (a, b, c, d) and $y = 0$ (e, f). Blue dashed lines represent corresponding loess regressions

m^2 was shown to be the most significant predictor ($\Delta\text{OFV} = -14.7$). The inclusion of toxicity status of the previous administration cycle did not decrease OFV significantly. No additional covariates were significant after the inclusion of dose in mg/m^2 ; i.e., the final model of hepatotoxicity only included dose in mg/m^2 (range 1500–8000 mg/m^2 , $\text{max}\Delta\text{P} = 0.86$) as the most significant covariate.

The parameter estimates of the base and final toxicity models are shown in Table 3. The model code of the final toxicity models can be found in Online Resource 2. The RSE values of all the parameters are $< 40\%$, indicating acceptable precision. The inclusion of covariates largely reduced the variance of the random IIV in both models. The VPC plots demonstrated adequate model predictability for the

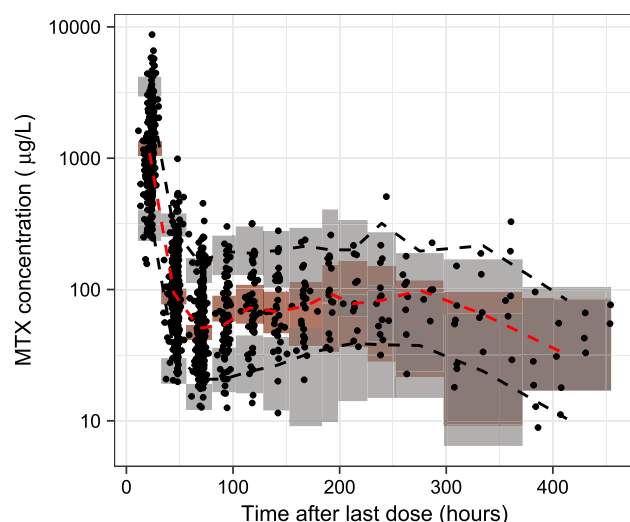


Fig. 2 Prediction-corrected visual predictive check (pcVPC) of the final HD-MTX pharmacokinetics model. Black points represent observations, black dashed lines represent 95th and 5th percentile of the observations, red dashed line represents the 50th percentile of the observations, grey shaded areas represent 95% confidence interval of the 95th and 5th percentiles of the simulations, and red shaded area represents 95% confidence interval of the 50th percentile of the simulations

probability of having renal toxicity, while the decreasing trend of hepatotoxicity over treatment courses was not well captured (Online Resource 1, Fig. S4). The wider 90% prediction interval after the fourth administration cycle was due to the relatively small sample size at those cycles. Figure 3 demonstrates the change of observed and predicted renal and hepatotoxicity probability as predictor values change. The simulation results showed that the median predicted probability of having renal toxicity decreased to less than 25% when baseline eGFR was higher than 66.6 mL/min/1.73m², and the median predicted probability of having hepatotoxicity increased to above 38.5% when the dose was raised above 3500 mg/m².

3.3.2 Exposure–Toxicity Relationship

The exposure metrics C_{24h} and $AUC_{24-\infty}$ were identified to correlate with renal toxicity ($\Delta OFV = -75.3$ and -85.6 , respectively) in the univariable covariate analysis but not for hepatotoxicity. The parameter estimates can be found in Online Resource 1, Table S2. The observed proportion of patients with renal toxicity was 61% when $C_{24h} > 3930$ µg/L (8.65 µmol/L) and 68.3 % when $AUC_{24-\infty} > 49,800$ µg/L × h (109.6 µmol/L × h). According to the model simulations, the predicted median proportions of renal toxicity decreased from 61% to 9.8–29.3 % when C_{24h} decreased to ≤ 3930 µg/L, and from 61% to 9.8–26.8% when $AUC_{24-\infty}$

Table 3 Parameter estimates of the base and final logistic regression model of renal and hepatotoxicity

	Base model		Final model	
	Estimate	RSE (%) / [Shrinkage (%)]	Estimate	RSE (%) / [Shrinkage (%)]
Renal toxicity model				
θ	0.112	29%	0.0595	26%
θ_{eGFR}	–	–	–3.06	9%
θ_{SEX}	–	–	–1.32	32%
$IIV (\omega^2)$	3.29	43% [35%]	1.11	61% [50%]
Hepatotoxicity model				
θ	0.289	11%	0.118	15%
θ_{DOSE}	–	–	2.25	38%
$IIV (\omega^2)$	0.922	48% [41%]	0.708	52% [45%]

BSA body surface area, IIV interindividual variability, RSE relative standard error, $eGFR$ estimated glomerular filtration rate

decreased to $\leq 49,800$ µg/L × h, respectively. The distribution of estimated $AUC_{24-\infty}$ and C_{24h} of all treatment cycles and observed and predicted probability of renal toxicity over $AUC_{24-\infty}$ and C_{24h} are shown in Fig. 4.

4 Discussion

In this study, a population PK model was developed for HD-MTX in patients with CNS lymphoma, and covariates that explain HD-MTX PK variability were identified. Toxicity analysis identified baseline predictors for nephron- and hepatotoxicity, and the models allow estimation of the toxicity probability before each administration cycle. Additionally, potential exposure thresholds of $AUC_{24-\infty}$ and C_{24h} that indicate a high risk of renal toxicity were suggested, to support better HD-MTX treatment.

The identified covariates on CL of MTX in the final model include albumin and indicators of renal function, which are in accordance with the known PK characteristics of MTX [4, 5]. In addition, the CL of MTX was also shown to vary among treatment regimens, which might suggest a need to alter the dose when targeting the same level of exposure. The possible explanations for this finding could be the differences in infusion duration/rate of HD-MTX, patient status, and the combined medications among these treatment groups. However, the impact of those factors cannot be distinguished as they highly overlapped with each other. A potential correlation between infusion duration/rate and MTX clearance has been mentioned previously. In those studies, higher CL or lower AUC has been observed in patients receiving HD-MTX with long infusion durations (24 h) compared with short infusion durations (2–6 h) [11, 30, 31], which may be due to

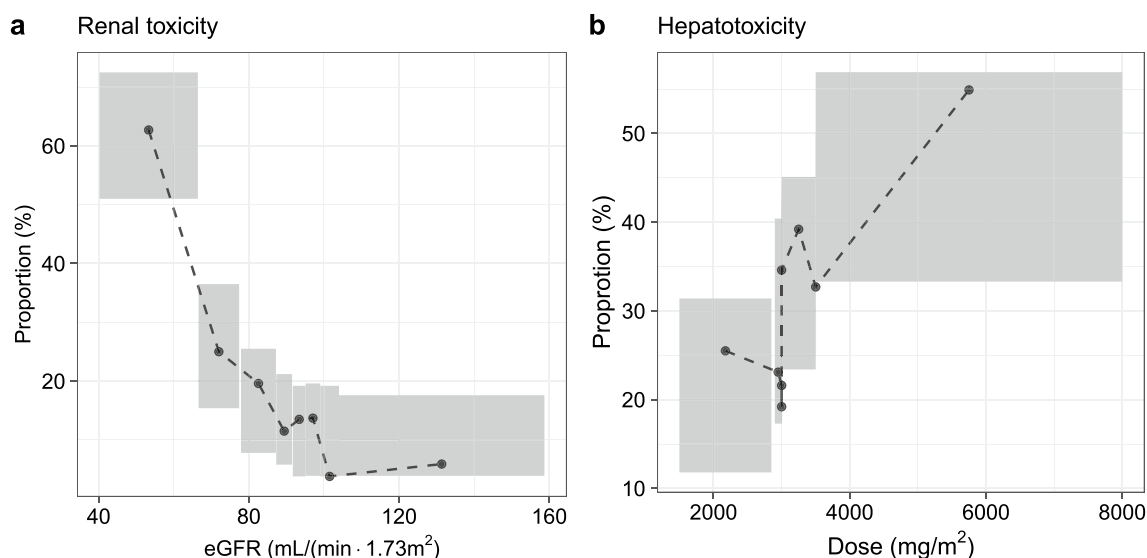


Fig. 3 Visual predictive check of the model for renal toxicity probability over estimated glomerular filtration rate (eGFR) (a) and hepatotoxicity probability over dose (mg/m²) (b). Black points represent

the observations, and shaded areas are the 90% prediction interval of the final models where binning was done on the basis of the number of observations

the saturation of MTX elimination at high concentrations. In our study, high CL estimates under 24-h infusion were also observed. However, 4-h infusion was shown to correlate with lower CL estimates compared with 1- or 3.25-h infusion in our results (Online Resource 1, Fig. S2). A clear physiological explanation for this observed phenomenon could not be found, and therefore dose alterations based on infusion duration specifically are not recommended.

Currently, HD-MTX is dosed per BSA in CNS lymphoma patients. However, our study demonstrated that the influence of BSA on MTX PK is less significant than that of body weight, although these two factors are highly correlated and BSA has been identified as a covariate in previous PK studies [19, 22]. The estimated MTX AUC_{24-∞} and C_{24h} in our study population also show an increasing trend over BSA (Pearson correlation coefficients 0.19 ($p = 0.000152$) and 0.23 ($p = 2.079 \times 10^{-6}$) between BSA and log(AUC_{24-∞}) and log(C_{24h}), respectively), suggesting a potential overdose or underdose for part of the patients (Online Resource 1, Fig. S5). A few other studies have also pointed out that BSA is not the most predictive factor to MTX PK, and BSA-guided dosing should be reconsidered, especially for overweight patients [11, 32, 33]. Moreover, a dose reduction for HD-MTX has been suggested for patients with reduced renal function [7, 34]. Taking these facts into account, adjusting the MTX dose with the developed PK model, which involves multiple covariates including renal function, to approach the exposure target is considered to be more rational and accurate than BSA-guided dosing, and can help to further reduce PK variability.

The GOF plot of the final PK model showed that the population predictions underpredicted the lower concentrations (data points collected after 200 h after last drug intake) while the individual predictions fit well to the observations. These underpredicted concentrations all came from the treatment cycles where delayed elimination was observed. This suggests that the model structure could still be improved to better characterize the concentration–time curves in case of delayed elimination. For example, an interaction between renal function and MTX PK, which may result in time-dependent MTX elimination, and nonlinear elimination at low concentrations can be considered [35, 36]. A three-compartment model could also slightly better capture the delayed elimination. However, a reliable and stable three-compartment model could not be identified on the basis of the current dataset. Since the individual fit of our model is considered to be adequate, a more complicated model was eventually not applied.

The toxicity analysis identified baseline predictors for HD-MTX-induced nephro- and hepatotoxicity which allow estimation of the toxicity probability before an administration cycle. Sex and eGFR were identified as significant baseline predictors for renal toxicity probability. Dose (mg/m²) and age were also identified as significant predictors in the univariable analysis, which is consistent with previous findings [9, 14]. However, their influence did not remain significant after including eGFR in the model. Female sex showing to be associated with decreased risk of renal toxicity may be due to the lower MTX exposure in females (median C_{24h} was 1276 µg/L for males and 785 µg/L for females). Our findings suggest that, to lower the probability of renal toxicity, the use of HD-MTX for patients with CNS lymphoma

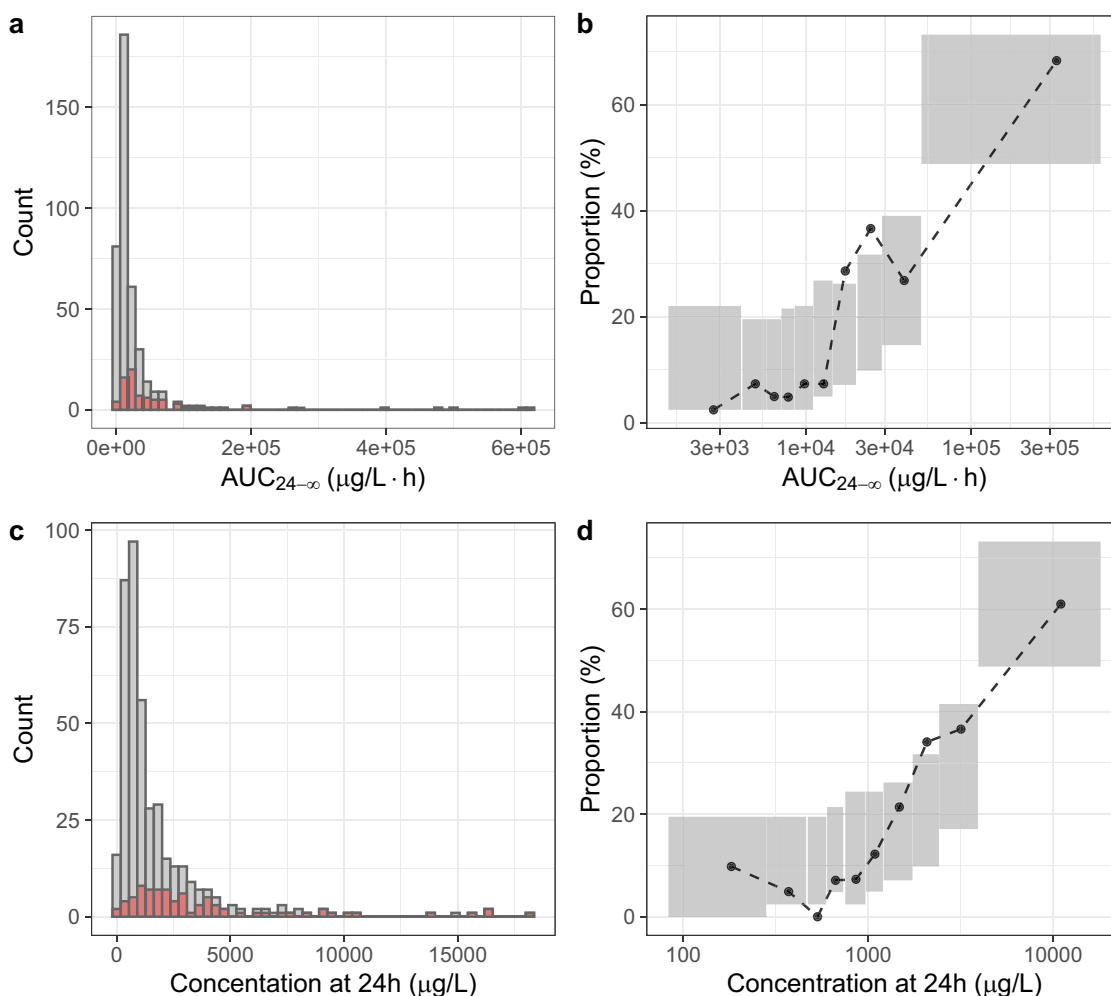


Fig. 4 Distribution of (a) estimated $AUC_{24-\infty}$ and (c) simulated concentration at 24 h (C_{24h}) of all treatment cycles (grey) and treatment cycles with renal toxicity (red), and observed and predicted probability of renal toxicity over (b) $AUC_{24-\infty}$ and (d) C_{24h}

is recommended when $eGFR > 66.6 \text{ mL/min/1.73m}^2$. This is in accordance with a previous review indicating that renal function is a key prognostic factor for the tolerance of HD-MTX [34]. Accurately estimating the renal function of patients before HD-MTX treatment may therefore be key in preventing toxicity during HD-MTX treatment. In patients with relatively low muscle mass, other $eGFR$ measurement techniques such as an iohexol $eGFR$ test could be applied [37]. Patients with higher risk of toxicity who still need HD-MTX treatment should be carefully monitored, and rescue therapy with high-dose folate or in severe cases glucarpidase could be considered [38–40].

The dose of HD-MTX (mg/m^2) was identified to be the strongest predictor of hepatotoxicity. The results suggest that a high risk for hepatotoxicity in patients with CNS lymphoma is foreseeable if the administered dose of HD-MTX is higher than 3500 mg/m^2 . The actual dose in mg was not as strong a predictor as the dose per BSA, and neither BSA nor

the MTX exposure metrics were identified to correlate with hepatotoxicity, suggesting a more complex mechanism and relationship that warrant further investigation. In addition, the probability of hepatotoxicity appeared to decrease over treatment cycles, which was not fully captured by the model. A possible explanation could be that patients tend to tolerate MTX better when treated for a longer period of time. Dropout due to toxicity is considered to be a less likely reason, since less than 50% of subjects who stopped treatment after the first to third treatment courses had hepatotoxicity. Since information on reason for dropout was not available, it was not considered in the analysis.

MTX exposure metrics were only identified to correlate with renal toxicity in patients with CNS lymphoma. To avoid the impact of possible inaccurate prediction of peak concentrations, $AUC_{24-\infty}$ was estimated and included in the analysis instead of $AUC_{0-\infty}$. We also investigated the correlation between C_{24h} and toxicity, as a threshold on C_{24h} is valuable

for early identification of patients at risk and early application of rescue treatment. Our results show that $AUC_{24-\infty} > 49,800 \mu\text{g/L} \times \text{h}$ or $C_{24\text{h}} > 3930 \mu\text{g/L}$ correlate with high risk of renal toxicity in CNS lymphoma patients (proportion $> 60\%$). The threshold of $C_{24\text{h}}$ is also in line with what was found in a previous study ($4540 \mu\text{g/L}$, i.e., $10 \mu\text{mol/L}$) [7].

Although high MTX exposure can result in toxicity, sufficient exposure is still essential to guarantee efficacy. To better apply our findings to facilitate the individualization and optimization of HD-MTX therapy in patients with CNS lymphoma, an investigation on the exposure–efficacy relationship is still needed. Previous studies suggested that $AUC_{0-\infty} > 1100 \mu\text{mol/L} \times \text{h}$ is associated with a favorable treatment outcome [12, 30]. The same group later developed a dosing algorithm that aims for a $AUC_{0-\infty}$ target of $1000\text{--}1100 \mu\text{mol/L} \times \text{h}$ for an optimal treatment outcome [18]. Owing to an identified correlation of $AUC_{0-\infty}$ with $C_{24\text{h}}$, a $C_{24\text{h}}$ target of $4\text{--}5 \mu\text{mol/L}$ was recommended [18]. Nonetheless, the direct relationship between $C_{24\text{h}}$ or $AUC_{24-\infty}$ and efficacy has not been reported. Thus, a further investigation on the relationship between $C_{24\text{h}}$ or $AUC_{24-\infty}$ and efficacy would be beneficial to establish a therapeutic range for HD-MTX to support the individualization of HD-MTX dosage.

The current study has some limitations. First of all, owing to the lack of data sampled in the first 12 h after the start of MTX infusion, the developed model may not be able to well capture peak concentrations and provide a precise estimate of $AUC_{0-\infty}$. Nevertheless, our study demonstrated that $AUC_{24-\infty}$ and $C_{24\text{h}}$ estimated with the model are also predictive of HD-MTX-induced renal toxicity. Additionally, for the majority of administration cycles, only ≤ 4 PK samples were available for the PK analysis. However, the population modeling approach allows one to handle sparsely and unevenly distributed samples very well. Secondly, this study was based on real-world data, and the possibility of data not being recorded adequately enough may impact our analysis. Nevertheless, our findings may be more representative of real-world patients and are more translatable to clinical practice. Thirdly, the low incidence of grade 2 and higher toxicities in our population forced us to analyze the data as a dichotomous variable (grade 1 and higher versus no toxicity), therefore it was not possible to specifically look for prognostic factors of grade 2 and higher toxicities. Finally, although identified predictors explained a large proportion of variability in HD-MTX-induced toxicities, the unexplained variability remains large. Identifying covariates for the remaining variability would be beneficial to further improve the prediction. Previous studies have reported the influence of ABCC2 on PK of HD-MTX and the potential association of gene MTHFR, SLC19A1, and ABCB1 with MTX-induced hepatic toxicity [8, 23, 41]. Thus, the potential impact of pharmacogenetic polymorphisms would be of interest for future studies.

5 Conclusions

A population PK model was developed and adequately characterized the PK profile of HD-MTX in patients with CNS lymphoma. eGFR, treatment regimen, albumin, ALP, and body weight were identified as significant covariates that explain inter- and intraindividual variabilities in PK of HD-MTX. The toxicity analysis identified lower eGFR and male sex, and higher MTX dose (mg/m^2) as baseline predictors that are associated with higher risk of acute nephro- and hepatotoxicity, respectively. $AUC_{24-\infty} > 49,800 \mu\text{g/L} \times \text{h}$ ($109.6 \mu\text{mol/L} \times \text{h}$) and $C_{24\text{h}} > 3930 \mu\text{g/L}$ ($8.65 \mu\text{mol/L}$) were suggested to be potential exposure thresholds that predict a high risk of renal toxicity. These results hold great potential for further individualizing HD-MTX dosage and preventing acute organ toxicity, which can improve HD-MTX therapy in CNS lymphoma patients.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s40262-024-01452-6>

Declarations

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Conflict of interest The authors have no competing interests to declare that are relevant to the content of this article. Daan Touw is an Editorial Board member of Clinical Pharmacokinetics. Daan Touw was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions.

Availability of data The datasets generated during and/or analyzed during the current study are not openly available owing to reasons of privacy but are available from the corresponding author on reasonable request.

Ethical approval This study is approved by the local Ethical Committee of each institute (number G20.126) and did not fall within the scope of the WMO (Medical Scientific Research Act). A waiver for informed consent was granted. All performed procedures were in accordance with the ethical standards of the institutional medical ethical committee and the 1964 Declaration of Helsinki and its later amendments.

Consent to participate This study is approved by the local Ethical Committee of each institute (number G20.126), and did not fall within the scope of the WMO (Medical Scientific Research Act). A waiver for informed consent was granted.

Consent for publication Not applicable.

Code availability The population modeling analysis was performed with NONMEM (version 7.4.4, ICON Development Solutions, Ellicott City, MD, USA) aided with Perl-speaks-NONMEM (PsN) (version 4.9, Uppsala University, Uppsala, Sweden). Data management and plots generation were performed with R statistics software (version 4.2.1, R Foundation for Statistical Computing, Vienna, Austria).

Author contributions Dirk Jan A.R. Moes and Joost S.P. Vermaat contributed to the study conception and design. Fleur A. de Groot, Marcel

Nijland, Jeanette K. Doorduijn, Daan J. Touw, Thijs Oude Munnink, Brenda C.M. de Winter, and Anyue Yin contributed to the collection of data. Anyue Yin and Dirk Jan A.R. Moes performed the analysis. Fleur A. de Groot, Lena E. Friberg, Henk-Jan Guchelaar, and Joost S.P. Vermaat contributed to the data analysis and result interpretation. The initial draft of the manuscript was written by Anyue Yin and Dirk Jan A.R. Moes, and all authors commented on the manuscript. All authors reviewed and approved the final manuscript.

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