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Predictors Associated with Delayed Methotrexate Clearance among Patients with Haematological Malignancies

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Abstract

Introduction: High dose methotrexate is commonly utilised in haematological malignancies; however, the prevalence of delayed clearance is not well-defined. The study aimed to determine the prevalence of delayed clearance of methotrexate, to analyse correlation between rate of methotrexate infusions and its concentrations, and to identify the predictors associated with delayed clearance. **Method:** A cross-sectional study was conducted among adult patients with haematological malignancies who received high-dose methotrexate. Spearman's correlation was utilised to analyse correlation between the rates of methotrexate infusions with its concentrations at 48 and 72 hours. Multiple logistic regression was used to identify factors associated with delayed clearance. **Results:** A total of 63 patients with 159 methotrexate infusions were included, with a mean age of 42.2 years (±18.06) and a median body mass index of 23.36 kg/m^2 (19.91-26.14). Delayed methotrexate clearance was observed in 29 (46%) patients, which affected 41 (25.6%) methotrexate infusions. A poor negative correlation was found between the rate of methotrexate infusion and 48-hour concentration (r=-0.206, p=0.009). Older age (odds ratio (OR) 1.06, 95% confidence interval (CI) 1.03-1.10, p<0.001) and dose of methotrexate >3000 mg/m^2 (OR 3.33, 95% CI 6.45-120.88, p<0.001) were identified as the predictors of delayed methotrexate clearance. **Conclusion:** Almost half of the patients experienced delayed methotrexate clearance. A slower rate of infusion was found to correlate with higher 48-hour concentrations. Older age and higher doses of methotrexate were identified as predictors for delayed clearance. Prospective study is needed with larger sample size to ensure generalisability of the outcomes.

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Introduction

High dose methotrexate (HD-MTX) is widely utilised for various types of cancers, including osteosarcoma, lymphoma, and leukaemia. It is defined differently in several works of literature, some reports defined it as 1000 mg/m^2 and above (Kowalski et al., 2021; Li et al., 2019; May et al., 2014), while other defined HD-MTX as 500 mg/m^2 and above (Dhanushkodi, 2021; Howard et al., 2016; Kawakatsu et al., 2019; Shi et al., 2020; Valade et al., 2020). In this study, HD-MTX is defined as 500 mg/m^2 and above. For lymphoma, HD-MTX is utilised in natural killer (NK)/T cell lymphoma, primary central nervous system (CNS) lymphoma and T or B cell lymphoma with CNS involvement (Allen & Lechowicz, 2019; Grommes & DeAngelis, 2017; Li et al., 2016).

In acute lymphoblastic leukaemia (ALL), HD-MTX has been used in adult and paediatric protocols, with the latter utilising higher doses of MTX (Moricke et al., 2008). Some clinicians have incorporated paediatric-inspired protocols to be used in adolescent and young adults (AYA), due to better outcomes in achieving minimal residual disease (MRD) as well as survival outcomes in these population (Ribera et al., 2014; Stock et al., 2019). The Adolescent and Young Adult Oncology Progress Review Group (AYAO PRG) defined the AYA population as comprising individuals aged 15 through 39 years at cancer diagnosis (National Cancer Institute (U.S.), 2006).

Delayed MTX clearance is defined as MTX concentration >1 μmol/L at 48 hours or >0.1 μmol/L at 72 hours from starting of MTX (Kowalski et al., 2021; Nakano et al., 2021; Young et al., 2020). The rationale behind these cutoff points are based on studies demonstrated that these cutoff points were predictive of renal toxicity (Widemann & Adamson, 2006). Furthermore, previous pharmacokinetic study revealed that the toxicity is expected to be present in delayed MTX clearance cases (Stoller et al., 1977).

The prevalence of delayed MTX clearance has been reported by a few literatures in paediatric and adult patients with osteosarcoma, but not well-defined in patients with haematological malignancies. A study among osteosarcoma patients reported that 48.5% of their patients had delayed MTX clearance, in which the dose was 12 g/m^2, higher than those utilised in lymphoma patients (Young et al., 2020). Despite that, a study reported higher incidence in lymphoma patients as compared to osteosarcoma (May et al., 2014). In a recent study, the prevalence of delayed MTX clearance was high, which was reported as 79.9% of the infusions, for osteosarcoma and leukaemia (Mosleh et al., 2023).

Delayed clearance of MTX may increase the risk of adverse effects, including acute kidney injury, myelosuppression, megaloblastic anaemia, oral mucositis, and liver impairment. The incidence of acute kidney injury occurred in 2 to 12% of the patients (Widemann & Adamson, 2006). In terms of hepatotoxicity, elevation of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) most of the time are transient and does not have any clinical significance (Weber et al., 1987).

The factors associated with delayed MTX clearance have been reported in several papers for osteosarcoma and paediatric population, however there was insufficient data available among adult patients with haematological malignancies. A study reported that the prevalence of delayed MTX clearance was significantly associated with male gender and white ethnicity in patients with osteosarcoma (Young et al., 2020). This is further supported by another study that reported the association of delayed clearance with male gender, older age, and higher serum concentration at 24 hours of MTX administration (Zhang et al., 2016). In contrast, a recent paper did not find male gender as a predictive factor; instead, the study reported the diagnosis of leukaemia and reduced urine output on day 1 were associated with delayed MTX clearance (Mosleh et al., 2023). In addition, several studies investigated associations between pharmacogenetics with MTX toxicity, such as ABCC2, MTHFR C677T, and A1298C (Campbell et al., 2016; Razali et al., 2020).

The goal of supportive care during MTX

administration is to increase the solubility of MTX in the urine, promote timely excretion and protection against lethal toxicity by administration of leucovorin rescue therapy. Prior to starting HD-MTX, medication reconciliation needs to be performed in order to prevent potential drug-drug interactions that will interfere with MTX clearance. Drugs that possibly elicit highest risk of adverse drug-drug interaction mechanism are drugs that are competing with MTX for renal tubular secretion, such as non-steroidal anti-inflammatory drugs (NSAIDs), penicillin antibiotics, probenecid, proton-pump inhibitors (PPI), and sulphonamides (Widemann et al., 2006). Another consideration prior HD-MTX administration is the presence of third spacing; this condition may cause delayed elimination of MTX and subsequently severe neutropenia and thrombocytopenia (Goh et al., 1979). Generally in practice, HD-MTX will not commenced in patients presented with third spacing, an alternative regimens will be discussed further.

The next step is hyperhydration and urinary alkalinisation. MTX primarily excreted through kidney, hence the purpose of hyperhydration is to increase urinary flow rates during MTX administration. Urine alkalinisation is defined as a treatment regimen that increases drug elimination by administration of intravenous sodium bicarbonate to produce urine with pH of ≥7.5 (Proudfoot et al. 2004). However, other studies quoted urine pH target as 7 or greater for MTX infusions (Perazella et al., 2010; Widemann et al., 2006). The purpose of alkalinising the urine is to increase MTX solubility and preventing crystals nephropathy. Hyperhydration with 100-150 mL/m^2 per hour starting from 12 hours before commencement of HD-MTX is recommended in many paediatric protocols. Administration of 40 mEq/L of sodium bicarbonate is recommended during and after HD-MTX administration, until MTX concentration is proven to be non-toxic. Urine pH should be monitored to ensure pH is 7 or greater to reduce risk of crystal formation (Perazella et al., 2010; Widemann et al., 2006). Another study suggested to start urine alkalinisation with sodium bicarbonate 150 mEq/mL in 1 litre of dextrose 5% or sterile water, run at 125 mL/hour with target urine pH ≥7.5 (Kowalski et al., 2021).

Another important supportive measure is leucovorin rescue dose. Leucovorin has been used for more than 30 years in HD-MTX treatment, and it is effective in prevention or reduction of adverse effects during HD-MTX treatment, such as myelotoxicity, gastrointestinal toxicity, and neurotoxicity (Ackland et al., 1987; Widemann et al., 2006). The mechanism of action of leucovorin is through bypassing DHFR inhibition by MTX. Leucovorin (5-formyl tetrahydrofolate) enters the cell via the folate carrier and readily converted into a 5,10-methylene tetrahydrofolate without requiring the involvement of DHFR, thus bypassing DHF blockade. Various dosing regimens have been used as rescue dose after HD-MTX administration; however, the usual doses are 10-15 mg/m^2 every 6 hourly until plasma MTX concentration below toxic range. Leucovorin should not be started too early during administration of HD-MTX, as it will nullify the activity of MTX, hence reducing the anti-cancer effects (Howard et al., 2016).

There is an increasing trend on the use of HD-MTX in AYA and adult patients with haematological malignancies. This is due to several studies that showed improved survival outcome in patients who were given paediatric-inspired protocols (Gupta et al., 2019; Hanbali et al., 2021; Stock et al., 2019; Winter et al., 2018). Most of paediatric protocols in ALL utilise a higher dose range of MTX compared to adults (Gökbuget et al., 2000; Moricke et al., 2008). This will render adult population to higher dose of MTX and increase the risk of toxicity. Currently, there is limited data on delayed MTX clearance among AYA and adult haematology patients, hence the risk of delayed MTX excretion each time patients were given HD-MTX is not known. The established data is currently more towards osteosarcoma, which utilise MTX in a different manner; the regimen commonly utilises higher dose of MTX with shorter infusion time, i.e. 4 hours (Young et al., 2020). Furthermore, the dosing approach used in haematological malignancies, particularly paediatric-inspired protocols for leukaemia, utilise doses of 5 g/m^2 over longer infusion time, i.e. 24 hours (Moricke et al., 2008). A study by Mosleh et al.

reported on the delayed clearance in leukaemia patients, however the oldest age was not specified, and the demographic data only presented the proportion of patients aged 15 years and older. Therefore, the inclusion of adults aged 40 years and above remains unclear.

There is a need to identify patients who are at risk of delayed MTX clearance to effectively monitor the patients and carefully decide on the suitable HD-MTX regimen specifically for the patient. In this study, we want to identify the prevalence of delayed MTX clearance and MTX toxicity among patients with haematological malignancies, to analyse correlation between dose and duration of administration with MTX concentrations, and to identify predictors associated with delayed MTX clearance.

Materials and methods

Study Design

This is a single-centre cross-sectional study which was conducted in Hospital Tengku Ampuan Afzan (HTAA) Kuantan. Patients who received HD-MTX were either traced through the system or manual. Demographic data, chemotherapy regimen and infusion data, supportive measures, pharmacokinetic parameters, concomitant drugs, and toxicity profile were collected using data collection form. Purposive sampling method was used in this study. All MTX blood samples of patients with haematological malignancies were included. The calculated sample size was 335 MTX infusions based on single proportion sample size calculation, with 31.9% prevalence reported from previous study (Dhand et al., 2014; May et al., 2014).

Study Population

The target population for this study was all AYA and adult patients diagnosed with haematological malignancies and received HD-MTX. Types of haematological malignancies included were lymphoma and leukaemia, in which the diagnosis were obtained from tumour and bone marrow biopsy, respectively. Inclusion criteria were patients receiving HD-MTX 500 mg/m^2 and above from year 2016 until 2021, comprising of all patients aged more than 15 years old. Renal functions were normal at baseline for all patients, as MTX is contraindicated to be given in patients with renal impairment. Generally, patients presented with third spacing are contraindicated for HD-MTX administration at the included facility; therefore, no patients meeting this criterion were given HD-MTX . All planned on HD-MTX received urine alkalinisation with hydration and sodium bicarbonate, as per recommendation (Howard et al., 2016).

There was no specific in-house urine alkalinisation protocol that was utilised in the hospital; thus, hydration protocol was ordered as per physician's discretion. Generally, patients were started on maintenance hydration with sodium chloride 0.9% with rate of infusion ranging from 125 to 167 mL/H, with intravenous sodium bicarbonate starting from 60 mEq/L. The dose of sodium bicarbonate was adjusted based on urine pH; in some instances, the dose was higher than the general recommendation, which can be titrated up to 160 mEq/L, however, the decision was based on the physicians' discretion (Howard t al., 2016). HD-MTX was administered only when urine pH ≥7.5. Pharmacokinetic monitoring was taken at 48 and 72 hours of starting HD-MTX. Serum MTX concentrations were outsourced to other facilities, Cobas Integra 400+ and Architek assays were used to determine serum MTX concentration. Patients whose data were untraceable or MTX concentration not available were excluded.

Data Collection

The data collection was conducted over 5 months, from March to July 2022. In HTAA, all patients who received HD-MTX from January 2016 until December 2021 were traced from Pharmacy Information System (PhIS) and Laboratory Information System (LIS), whereas for HCTM, data were traced by using Integrated Laboratory Management System. Each patient was assigned a patient identification number (ID), and each MTX infusion was assigned a sample ID.

Statistical Analysis

Statistical Software for Social Sciences (SPSS) version 25 was used for data analysis. All statistical analysis was considered significant if p value <0.05.

Descriptive statistics were used for demographic data. Normality testing was done using skewness and kurtosis. All categorical data were presented as frequencies and percentages, whereas continuous data were presented as mean (standard deviation (SD)) for normally distributed data and median (interquartile range (IQR)) for skewed data. The prevalence of delayed MTX clearance and MTX toxicity were presented as descriptive statistics. Delayed MTX clearance is defined as above. Point of clearance was defined when MTX concentration <0.1 μmol/L. Prevalence of delayed MTX clearance was calculated as:

$$\frac{Cycle\ with\ delayed\ MTX\ clearance}{Total\ chemotherapy\ cycles} \times 100$$

Univariate analyses were performed using independent t-test, Chi-square test, and Mann-Whitney U test, as appropriate. Spearman's rank correlation was utilised to analyse correlation between dose and duration of HD-MTX with MTX concentrations. Degree of correlation is defined by the value of correlation coefficient (r); very strong (≥0.8), moderate (0.6 to 0.8), fair (0.3 to 0.5), and poor (<0.3) (Chan, 2003). Univariate logistic regression was used to identify relationship between the demographic data and prevalence of delayed MTX clearance. Age, gender, race, BMI, dose of MTX, duration of infusion, and concomitant intrathecal (IT) MTX were included for analysis. Concomitant IT MTX is defined as a presence of IT MTX in the chemotherapy regimen alongside with HD-MTX. A p-value cut-off point of 0.25 was used to select variables for inclusion in the multivariate logistic regression analysis, for determination of the predictors (Bursac et al., 2008). All p-values were two sided, and differences were statistically significant when $p<0.05$.

Results

A total of 67 patients with 184 infusions were identified. 4 patients with 25 infusions were excluded from study due to incomplete data on MTX concentrations. Finally, a total of 63 patients with 159 MTX infusions were included and analysed. Mean age was 42.2 years (±18.06), with median BMI of 23.36 kg/m^2 (IQR 19.91 to 26.14) and median body surface area (BSA) of 1.7 m^2 (IQR 1.51 to 1.82). Each patient received median MTX dose of 2000 mg/m^2 (IQR 1500 to 2500) and mean infusion duration of 15.7 hours (±9.94). The details on the chemotherapy regimens received were shown in Figure A1 (Appendix). Delayed MTX clearance occurred in 29 (46%) of the patient, which accounted for 41 (25.6%) of MTX-containing infusion. The difference in median number of MTX cycles was not statistically significant between the groups (3 versus 1.5 cycles, U=363, z=-1.87, p=.061). There was a significant difference between age and delayed MTX clearance (t=2.257, 95% confidence interval (CI) 0.92 to 13.83, p=0.025). Details on the demographic data and associations with delayed MTX clearance were shown in Table 1.

Table 1: Demographic data of patients and associations with delayed MTX clearance. AYA, adolescent and young adults; IQR, interquartile range; IT, intrathecal; MTX, methotrexate; SD, standard deviation. [a]Chi-square test, [b]Fisher's Exact test, [c]Mann-Whitney U test, [d]independent t-test.

Variables	**Delayed MTX clearance**		**Test**	**p Value**
	Yes	**No**		
(n= patients)	**(n = 29)**	**(n = 34)**		
Gender, n (%)				
Male	24 (82.8)	22 (64.7)	2.589[a]	0.108
Female	5 (17.2)	12 (35.3)		
Race, n (%)				
Malay	25 (86.2)	33 (97.1)	2.523[b]	0.171
Non-Malay	4 (13.8)	1 (2.9)		
Age group, n (%)				
AYA	14 (48.3)	17 (50)	0.019[b]	1.000
Adult	15 (51.7)	17 (50)		
Diagnosis, n (%)				
Lymphoma	16 (55.2)	18 (52.9)	0.031[a]	0.859
Leukaemia	13 (44.8)	16 (47.1)		
Median number of MTX cycles (IQR)	3 (1 to 4)	1.5 (1 to 3)	-1.87[c]	0.061

Variables	Delayed MTX clearance		Test	p Value
	Yes	No		
n = infusions)	(n = 41)	(n = 118)		
Mean age, years (SD)	47.73 (19.15)	40.35 (17.43)	2.257[d]	0.025
Median BMI, kg/m² (IQR)	23.52 (18.86 to 26.54)	22.99 (19.93 to 25.78)	-0.353[c]	0.724
Median BSA, m² (IQR)	1.70 (1.52 to 1.85)	1.69 (1.51 to 1.81)	-0.540[c]	0.589
Median dose of MTX, mg/m² (IQR)	2500 (1000 to 4500)	1500 (1500 to 2500)	-1.534[a]	0.125
Mean duration of infusion, hours (±SD)	16.28 (±10.12)	15.48 (±9.93)	-0.434[d]	0.665
IT MTX, n (%)				
Yes	25 (61)	69 (58.5)	0.253[a]	0.615
No	15 (39)	50 (41.5)		

Correlation analysis showed that there was a poor positive correlation between dose of MTX and its concentration at 72 hours (r 0.192, p=.016). Fair positive correlation was found between duration of MTX infusion and the concentration at 48 hours (r 0.301, p<.001). However, when rate of infusion was used, it was found that there was a poor negative correlation between rate of MTX infusion and its concentration at 48 hours (r -0.206, p=.009) (Table 2).

Table 2: Correlations between dose and duration of MTX with its concentrations. MTX, methotrexate. [a]Spearman's rank correlation, *significance at p<0.05.

Variables	MTX concentrations			
	At 48 hours		At 72 hours	
	r[a]	p Value	r[a]	p Value
Dose of MTX	0.043	0.596	0.194	0.015*
Duration of MTX infusion	0.301	<0.001*	0.068	0.393
Rate of MTX infusion	-0.206	0.009*	-0.001	0.991

Figure 1: Correlation between dose of MTX and MTX concentration at 72 hours. MTX, methotrexate.

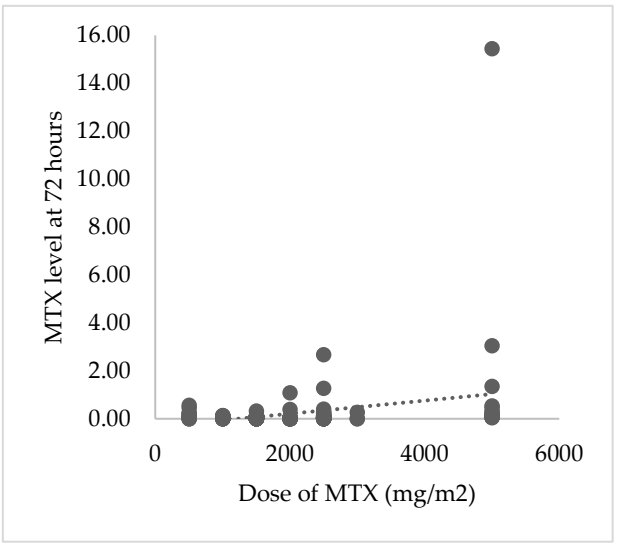
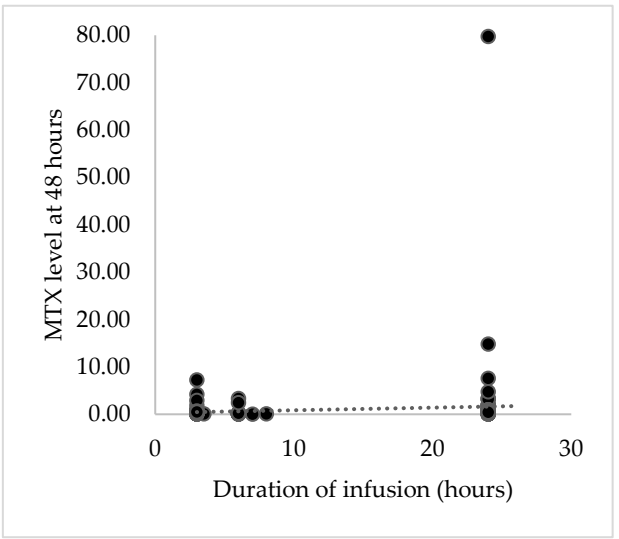


Figure 2: Correlation between duration of MTX infusion and MTX concentration at 48 hours. MTX, methotrexate.



Univariate logistic regression was performed to identify relationship between the selected variables with delayed MTX clearance. Age, gender, and dose of MTX had p value of less than 0.25, hence multivariate logistic regression was performed on these variables. Results showed that for every 1-year increase in age, the odds of having delayed MTX clearance was 6% higher (odds ratio (OR) 1.06, 95% CI 1.03 to 1.07, p<0.001). Dose of MTX >3000 mg/m² has 28 times higher odds of delayed MTX clearance compared to ≤3000 mg/m² (OR 27.91, 95% CI 6.45 to 120.88, p<0.001). Table 3 summarizes the logistic

regression analysis and the significant variables, controlling for other factors. The model equation is as follow:

$$logit(odds) = -4.275 + 0.06(\text{Age}) + 3.329(\text{Dose})$$

whereby age is a continuous data, dose ≤3000 mg/m²=0, and dose >3000 mg/m²=1. The model has been checked for goodness-of-fit, multicollinearity, interaction, and outliers. The multicollinearity was assessed using tolerance and variance inflation factor (VIF). Both variables included had the same tolerance value and VIF (0.85 and 1.177, respectively), which indicates no multicollinearity. The final model met all the assumptions, and demonstrated a good model, whereby 76.7% of the cases can be predicted correctly.

Discussions

We present an analysis of AYA and adult patients who received HD-MTX. The prevalence of delayed MTX clearance was 25% in this study. This prevalence was slightly lower compared to other published studies, whereby delayed MTX clearance was reported to be 31.9% of the lymphoma cases (May et al., 2014). Another study reported prevalence of 29% delayed clearance among total MTX infusions given (Young et al., 2020). Furthermore, another study found a higher occurrence of delayed MTX clearance, which was 41.4% (Ng et al, 2016). The reason for this difference may be due to single centre study, which may not be representative of the whole population; some of the cases might not be counted. The results across studies suggest that delayed MTX clearance is prevalent across all cancer diagnosis, and prompt intervention is needed.

A weak positive correlation was found between dose of MTX and 72-hour concentration (Figure 1) and a fair positive correlation between duration of MTX infusion and 48-hour concentration (Figure 2). When both data combined into rate of infusion it showed poor negative correlation (Table 2). These poor correlations might be due to low concentrations of MTX in most of the samples, especially concentration at 72 hours. Furthermore, there were outliers, which may drive towards the significance. These outliers were the toxic cases encountered during the data collection.

On the other hand, there was no correlation found between dose and 48-hour concentrations. Based on the two pharmacokinetic studies, the relationship between dose and peak concentration (C_{max}) was seen in HD-MTX infused over 6 hours (Bacci et al., 2006; Lin et al., 2009). However, this association was not observed in 24 and 48-hour concentration (Lin et al., 2009). The lack of correlation between the dose and 48-hour concentration may be due to interindividual variability in renal clearance. This may be due to a higher drug clearance when higher C_{max} was reached, as suggested by previous study (Cano et al., 1981).

In contrast, previous pharmacokinetic study revealed that the toxicity of MTX was related with the infusion time, in this case haematological toxicity and liver derangement (Goldie et al., 1972). This may be due to the longer exposure of MTX when it is being administered over longer period, rendering patient to elevated risk of MTX toxicity. However, our data showed inconsistent results, whereby the dose was related to delayed MTX clearance instead. It was noted that Goldie et al. did not report any statistical analysis to back up the findings; it was more of a trend observed descriptively rather that a true significance.

Multivariate logistic regression showed that age and dose MTX of >3000 mg/m² were independent predictors associated with delayed MTX clearance. Similar results have been demonstrated in a study which identified dose as a predictor (Ng et al., 2016). Increasing the dose of MTX will ultimately increase the drug exposure, hence elevating the risk of delayed MTX clearance. A study by Nakano et al reported that age could not be identified as risk factor although there was a significant association with delayed MTX clearance (Nakano et al., 2021). MTX was primarily excreted through urine, hence renal function plays an important role in the drug clearance. Older age may have a decline in renal function compared to young age, which may explain this situation even though patients had a

Table 3: Multivariate logistic regression on the predictors associated with delayed MTX clearance. CI, confidence interval, IT, intrathecal; MTX, methotrexate; OR, odds ratio. [a]Method: Forward Stepwise (likelihood ratio). *Variables that have p<0.25 were included for multivariate logistic regression.

Variables	Univariate Logistic Regression				Multivariate Logistic Regression			
	B	OR	95% CI	p Value	B[a]	Adjusted OR	95% CI	p Value
Age	0.023	1.02	1.00 to 1.05	0.028*	0.060	1.06	1.03 to 1.10	<0.001
Gender								
Male	0.743	2.10	0.89 to 4.98	0.091*	-	-	-	-
Female		1.00						
Race								
Non-Malay	0.28	0.76	0.27 to 2.12	0.594	-	-	-	-
Malay		1.00						
BMI	-0.017	0.98	0.93 to 1.04	0.565	-	-	-	-
Dose of MTX								
>3000 mg/m^2	1.674	5.33	1.87 to 15.19	0.002*	3.329	27.91	6.45 to 120.88	<0.001
≤3000 mg/m^2		1.00				1.00		
Duration of MTX infusion	0.008	1.01	0.97 to 1.05	0.662	-	-	-	-
Concomitant IT MTX								
Yes	0.189	1.21	0.58 to 2.52	0.615	-	-	-	-
No		1.00						

normal renal function at baseline.

We could not find gender as a significant predictor for delayed MTX excretion. This finding was supported by other studies which did not find any relationship between gender and delayed MTX clearance (Barreto et al., 2021; Nakano et al., 2021). A study among osteosarcoma patients reported that female gender was associated with delayed MTX excretion (Misaka et al., 2020; Zhang et al., 2016). In contrast, two studies found an association between male gender and delayed MTX clearance (May et al., 2014; Young et al., 2020). These inconsistent results showed that gender may not be a clear predictor, it may be explained by genetic polymorphism which may varies among gender.

Overall, the understanding of the predictors may be beneficial for individualizing therapy among patients and provide the best supportive care measures. Further exploration of pharmacogenetics and its relationship with specific types of toxicity may further improve predictions and patient outcome, and a betterment towards personalized medicine.

There are some limitations in this study that may restrict the application of the outcome. First, this is an underpowered study, with post-hoc power calculation of 38.4% due to insufficient samples. A larger sample size is required to address the generalisability of the outcomes in this study. There are a few potential biases in this study. The first one is selection bias, as this study was a single centre study. In addition, the use of purposive sampling may introduce bias, as it may not represent a broader population. Secondly, information bias also may be present; there was no standardised urine alkalinisation protocol throughout Malaysia which may lead to variability in patient management. Furthermore, the use of different laboratory assays might introduce the inconsistency in the reported MTX concentrations. Thirdly, confounding bias also could not be excluded totally, as there may be other variables which could not affect the outcome, such as genetic polymorphism and variations in chemotherapy regimen. Standardisation of urine alkalinisation regimen among facilities is recommended to reduce variability among patients.

Conclusion

In conclusion, the prevalence of delayed MTX clearance is prominent among adult patients with haematological malignancies in our study population. A weak positive correlation was found between the rate of MTX infusion with 48 hours' concentrations. Older age and higher dose of MTX were identified as the predictors for delayed clearance. Further prospective study is needed with larger sample size to ensure generalisability of the outcomes.

Authors contributions

M. N. Y. designed and conducted the research, performed data collection and analysis, and wrote the manuscript; N. M. S. and N. A. M. T. supervised the whole research, provided ideas, verified the analytical methods, and reviewed the write-up; S. N. N. A. J. conceived the idea for research method, assisted in data collection; A. N. K. provided conceptualization of ideas. A. N. K. and N. R. T. provided expert opinions in the field of haematology. All authors provided critical feedback and helped shape the research, analysis, and manuscript.

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Ethical approval statement

Ethical approvals were obtained from National Medical Research and Ethics Committee (MREC) of the Ministry of Health (MOH) Malaysia (Ref No: NMRR ID-22-00022-1TH (IIR)) and Research Ethics Committee UKM (REC UKM) (Ref No: UKM PPI/111/8/JEP-2022-238).

Informed consent statement

Patient consent was waived due to retrospective nature of the study.

Conflict of interest

The authors declare that there are no conflicts of interest.

Declaration of generative AI and AI-assisted technologies in the writing process

The authors declare that no generative artificial intelligence (AI) or AI-assisted technologies was used for the preparation of this manuscript.

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Appendix A

Figure A1: Chemotherapy regimens used for HD-MTX, total of 159 HD-MTX infusions. HD-MTX, high dose methotrexate; R, rituximab.

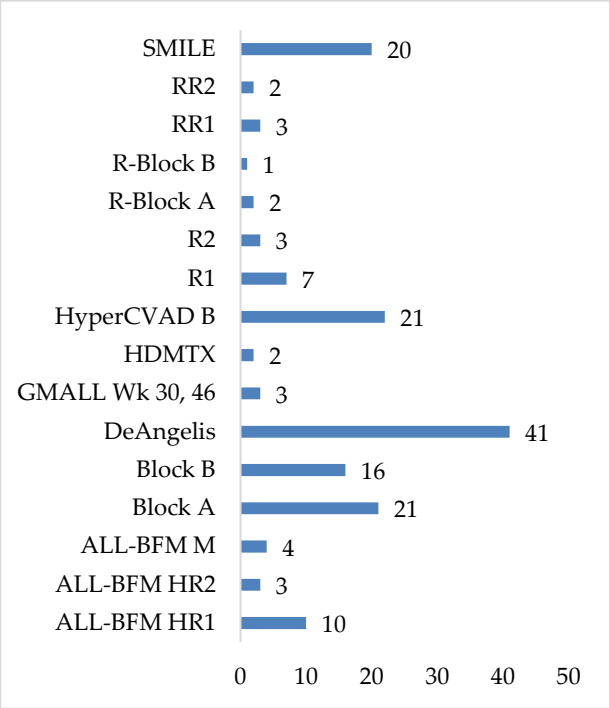
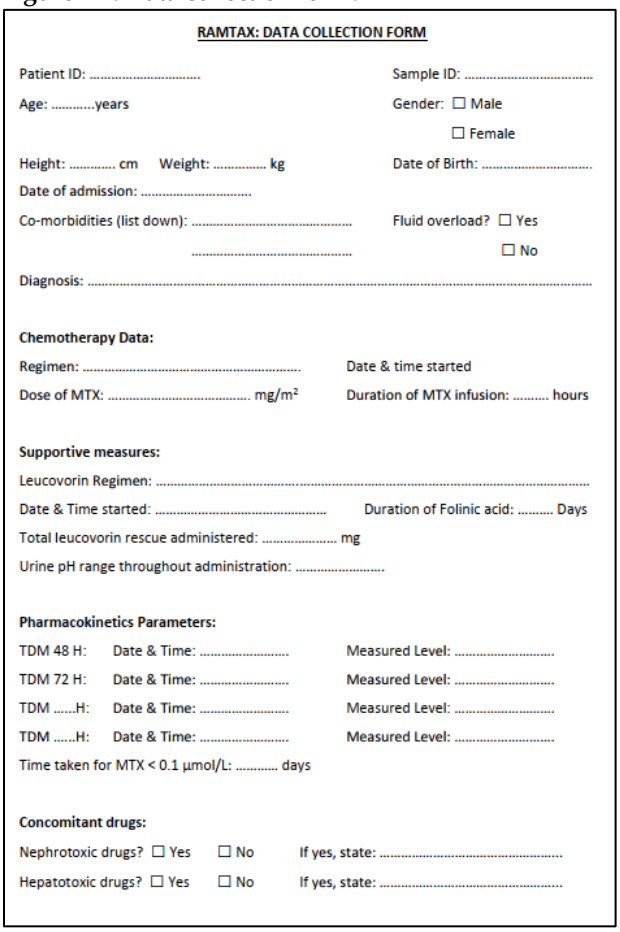


Figure A2: Data collection form.



RAMTAX: DATA COLLECTION FORM

Patient ID: ..... Sample ID: .....

Age: .....years Gender: ☐ Male ☐ Female

Height: ..... cm Weight: ..... kg Date of Birth: .....

Date of admission: .....

Co-morbidities (list down): ..... Fluid overload? ☐ Yes ☐ No

.....

Diagnosis: .....

Chemotherapy Data:

Regimen: ..... Date & time started

Dose of MTX: ..... mg/m² Duration of MTX infusion: ..... hours

Supportive measures:

Leucovorin Regimen: .....

Date & Time started: ..... Duration of Folinic acid: ..... Days

Total leucovorin rescue administered: ..... mg

Urine pH range throughout administration: .....

Pharmacokinetics Parameters:

TDM 48 H: Date & Time: ..... Measured Level: .....

TDM 72 H: Date & Time: ..... Measured Level: .....

TDM .....H: Date & Time: ..... Measured Level: .....

TDM .....H: Date & Time: ..... Measured Level: .....

Time taken for MTX < 0.1 µmol/L: ..... days

Concomitant drugs:

Nephrotoxic drugs? ☐ Yes ☐ No If yes, state: .....

Hepatotoxic drugs? ☐ Yes ☐ No If yes, state: .....

1 **Table A1:** Chemotherapy agents used in HD-MTX regimens. MTX, methotrexate; IT, intrathecal

Protocol Name	Chemotherapy Agents	Leucovorin Rescue Dose	Duration of MTX Infusion (hours)
ALL-BFM HR1	Methotrexate 5000 mg/m² D1 Vincristine 1.5 mg/m² (max 2 mg) D1,6 Cyclophosphamide 200 mg/m² BD × 5 doses D2-4 Cytarabine 2000 mg/m² bd D5 L-Asparaginase 25,000 u/m² D6 IT Methotrexate 12 mg D1 IT Cytarabine 30 mg D1	15 mg/m² QID start at 42H of MTX	24
ALL-BFM HR2	Methotrexate 5000 mg/m² D1 Vindesine 3 mg/m² (max 5 mg) D1,6 Ifosfamide 800 mg/m² × 5 doses D2-4 Daunorubicin 30mg/m² D5 L-Asparaginase 25,000 u/m² D6 IT Methotrexate 12 mg D1 IT Cytarabine 30 mg D1	15 mg/m² QID start at 42H of MTX	24
ALL-BFM M	6-Mercaptopurine 25 mg/m² D1-56 Methotrexate 5000 mg/m² D8,22,36,50 IT Methotrexate 12 mg D8,22,36,50	15 mg/m² QID start at 42H of MTX	24
Block A	Methotrexate 1500 mg/m² D1 Vincristine 2 mg D1 Ifosfamide 800 mg/m² D1-5 Cytarabine 150 mg/m² BD D4-5 Etoposide 100 mg/m² D4-5 IT Methotrexate 15 mg D1,5 IT Cytarabine 40 mg D1,5	30 mg/m² start at 42 & 48H of MTX, then 15 mg/m² QID	24

Block B	Methotrexate 1500 mg/m^2 D1 Vincristine 2 mg D1 Cyclophosphamide 200 mg/m^2 D1-5 Doxorubicin 25 mg/m^2 D4-5 Etoposide 100 mg/m^2 D4-5 IT Methotrexate 15 mg D1,5 IT Cytarabine 40 mg D1,5	30 mg/m^2 start at 42 & 48H of MTX, then 15 mg/m^2 QID	24
DeAngelis (Week 1,3,5,7,9)	Methotrexate 2500 mg/m^2 D1 Vincristine 1.4 mg/m^2 (max 2.8 mg) D1 Procarbazine 100 mg/m^2 (max 150 mg) D1-7 (Week 1,5,9)	20 mg QID start at 24H of MTX	3
GMALL Week 30, 46	Methotrexate 1500 mg/m^2 D1,15 L-Asparaginase 10,000 u/m2 D2,16 6-Mercaptopurine 60mg/m^2 OD D1-7,15-21 IT Methotrexate 15 mg D1 IT Cytarabine 40 mg D1	30 mg/m^2 start at 42 & 48H of MTX, then 15 mg/m^2 QID	24
HD-MTX	Methotrexate 3000 mg/m^2 D1	20 mg QID start at 24H of MTX	3
HyperCVAD B	Methotrexate 1000 mg/m^2 D1 Cytarabine 3000 mg/m^2 BD D2- 3 IT Methotrexate 12 mg D2 IT Cytarabine 100 mg D2	15 mg QID start at 48H of MTX	24
R1	Methotrexate 500 mg/m^2 D1 Vincristine 1.5 mg/m^2 (max 2 mg) D1 Cytarabine 300 mg/m^2 D5 Etoposide 100 mg/m^2 D5 L-Asparaginase 10,000 u/m^2 D6-8 6-Mercaptopurine 100 mg/m^2 OD D1-5 IT Methotrexate 15 mg D1	15 mg/m^2 start at 42 & 48H of MTX, then 10 mg/m^2 QID	24
R2	Methotrexate 500 mg/m^2 D1 Vincristine 1.5 mg/m^2 (max 2 mg) D1 Cytarabine 300 mg/m^2 D5 Daunorubicin 50 mg/m^2 D5 Ifosfamide 400 mg/m^2 D1-5 6-Thioguanine 50 mg/m^2 BD D1-5 IT Methotrexate 15 mg D1	15 mg/m^2 start at 42 & 48H of MTX, then 10 mg/m^2 QID	24
SMILE	Methotrexate 2000 mg/m^2 D1 Ifosfamide 1500 mg/m^2 D2-4 Etoposide 100 mg/m^2 D2-4 L-Asparaginase 6000 u/m^2 D8,10,12,14,16,18,20	30 mg/m^2 start at 30H & 36H of MTX, then 15 mg/m^2 QID	6

1