Original article

Estimating duration of leucovorin rescue among patients with non-Hodgkin lymphoma receiving high dose methotrexate therapy

Tiyapong Natiwong and Yingyong Chinthammitr

Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University

Abstract:

Background: *High dose methotrexate (HDMTX) regimen is used in lymphoma with central nervous system (CNS) involvement or as primary CNS prophylaxis. Serum MTX concentrations should be monitored by adjusting leucovorin rescue until reaching the target of < 0.05 μmol/L. However, monitoring MTX level is not feasible in many Thai hospitals.* ***Objective:*** *The study aimed to estimate the most appropriate duration of leucovorin rescue among patients with lymphoma receiving HDMTX.* ***Methods:*** *A retrospective chart review was conducted of patients with lymphoma receiving HDMTX regimen from January 2016 to December 2019. Baseline estimated glomerular filtration rate (eGFR) was categorized into 3 groups: (1) 30-59, (2) 60-89 and (3) ≥ 90 mL/min/1.73 m^2. Patients developing acute kidney injury after HDMTX were excluded. Primary outcome was number of days from HDMTX administration to the MTX level of under 0.05 μmol/L (ΔDay0.05).* ***Results:*** *Sixty-six patients (23 in each eGFR category; 36 men), with mean age of 60±12 years were included. Median dose of HDMTX was 4.0 g/m^2 (range 1.0-4.8). Factor significantly associated with ΔDays0.05 was baseline eGFR category (p < 0.001). Mean ΔDay0.05 in group 1 (eGFR 30-59 mL/min/1.73 m^2) was 6.7±1.7 day (range 4-10), in group 2 (eGFR 60-89) was 4.6±1.3 day (range 3-7), and in group 3 (eGFR ≥ 90) was 3.5±0.5 days (range 3-4).* ***Conclusion:*** *Our result showed that the estimated duration of MTX level under 0.05 μmol/L after HDMTX administration correlated with eGFR value. Notably, physicians could use this data for predicting the stopping date of leucovorin rescue at hospitals where monitoring MTX level was not feasible.*

Keywords : ● *High dose methotrexate* ● *Lymphoma* ● *Leucovorin*

J Hematol Transfus Med. 2023;33:39-47.

Received 5 February 2022 Corrected 27 April 2022 Accepted 1 February 2023

Correspondence should be addressed to Yingyong Chinthammitr, MD, Division of Hematology, Department of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, 2, Wanglang Rd., Siriraj, Bangkok-noi, Bangkok 10700; E-mail: dryingyong@gmail.com

นิพนธ์ต้นฉบับ

การคาดคะเนระยะเวลาการให้ยาลิวโคโวรินในผู้ป่วยโรคมะเร็งต่อมน้ำเหลืองชนิดนอนฮอดจ์กินที่ได้รับยาเมทโทเตรกเสทขนาดสูง

ทิยะพงศ์ เนติวงษ์ และ ยิ่งยง ชินธรรมมิตร์
ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล

บทคัดย่อ

บทนำ *สูตรยาเมทโทเตรกเสทขนาดสูง (HDMTX) นิยมใช้รักษาโรคมะเร็งต่อมน้ำเหลืองในสมองหรือเพื่อป้องกันมะเร็งต่อมน้ำเหลืองเข้าสมอง ทั้งนี้ควรติดตามวัดระดับยาเมทโทเตรกเสทเพื่อปรับขนาดและระยะเวลาของยาลิวโคโวรินจนกว่าระดับยาเมทโทเตรกเสทเหลือน้อยกว่า 0.05 ไมโครโมลต่อลิตร อย่างไรก็ตามการวัดระดับยาเมทโทเตรกเสทในประเทศไทยทำได้ในโรงพยาบาลบางแห่งเท่านั้น* ***วัตถุประสงค์*** *เพื่อคาดคะเนระยะเวลาการให้ยาลิวโคโวรินที่เหมาะสมในผู้ป่วยโรคมะเร็งต่อมน้ำเหลืองที่ได้รับ HDMTX* ***วิธีการศึกษา*** *ศึกษาข้อมูลเวชระเบียนย้อนหลังของผู้ป่วยโรคมะเร็งต่อมน้ำเหลืองที่ได้รับ HDMTX ตั้งแต่เดือนมกราคม 2559 ถึงเดือนธันวาคม 2562 โดยแบ่งผู้ป่วยเป็น 3 กลุ่มตามระดับการทำงานของไต (eGFR) ก่อนได้รับยา HDMTX คือ 30-59, 60-89 และ ≥ 90 มิลลิลิตรต่อนาทีต่อ 1.73 ตารางเมตร ผู้ป่วยที่เกิดภาวะไตเสียหายเฉียบพลันหลังได้รับยา HDMTX ถูกคัดออก ผลลัพธ์หลักคือจำนวนวันตั้งแต่ได้รับยา HDMTX จนระดับยาเมทโทเตรกเสทต่ำกว่า 0.05 ไมโครโมลต่อลิตร (ΔDay0.05)* ***ผลการศึกษา*** *ผู้ป่วย 66 ราย (ชาย 36 ราย) มีอายุเฉลี่ย 60±12 ปี มีผู้ป่วยจำนวน 23 รายในแต่ละกลุ่มของ eGFR ขนาดยา HDMTX เฉลี่ยเท่ากับ 4.0 กรัมต่อตารางเมตร (พิสัย 1.0 ถึง 4.8) ปัจจัยที่สัมพันธ์กับ ΔDay0.05 อย่างมีนัยสำคัญคือ eGFR (p-value < 0.001) โดยค่าเฉลี่ยของ ΔDay0.05 ในกลุ่มหนึ่ง (eGFR 30-59) เท่ากับ 6.7±1.7 วัน (พิสัย 4-10) ในกลุ่มสอง (eGFR 60-89) เท่ากับ 4.6±1.3 วัน (พิสัย 3-7) และในกลุ่ม 3 (eGFR ≥ 90) เท่ากับ 3.5±0.5 วัน (พิสัย 3-4)* ***สรุป*** *ระยะเวลาที่ระดับยาเมทโทเตรกเสทต่ำกว่า 0.05 ไมโครโมลต่อลิตรภายหลังการให้ยา HDMTX ขึ้นกับระดับการทำงานของไต (eGFR) เป็นหลัก ซึ่งอาจนำไปคาดคะเนวันหยุดยาลิวโคโวรินในโรงพยาบาลที่ไม่สามารถติดตามวัดระดับยาเมทโทเตรกเสทได้*

คำสำคัญ : ● *ยาเมทโทเตรกเสทขนาดสูง* ● *มะเร็งต่อมน้ำเหลือง* ● *ลิวโคโวริน*

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2566;33:39-47.

Introduction

Methotrexate (MTX) is an antifolate agent used in treating various cancers and some autoimmune diseases[1]. The mechanism of MTX action is inhibiting dihydrofolate reductase (DHFR). The function of DHFR is conversion of dihydrofolate to tetrahydrofolate (THF). THF is essential for biosynthesis of thymidine and purines, which are needed to synthesize DNA. Blockade of THF synthesis by methotrexate leads to inability of cells to divide and to produce proteins[2].

High dose methotrexate (HDMTX), defined as a dose higher than 1 g/m^2, is used to treat a variety of cancers, including lymphoma with central nervous system (CNS) involvement or as primary CNS prophylaxis[3]. However, HDMTX therapy can cause significant toxicity. To prevent unacceptable toxicity, it must be administered with rigorously standardized supportive care including hydration and alkalinization before starting methotrexate infusions and leucovorin rescue[4].

Leucovorin rescue constitutes the cornerstone of HDMTX treatment because leucovorin effectively neutralizes the effects of methotrexate to protect normal cells. However, it must not be started too early because it would then reduce not only toxicity but also anticancer efficacy[3]. Additionally, continuing leucovorin therapy, until the plasma methotrexate level falls below 0.05 μmol/L, is recommended[3-5].

More than 90% of methotrexate is eliminated by the kidneys[6]. Under conditions of normal renal function, approximately 41% of an intravenously administered dose was excreted unchanged in the urine within six hours after administering, 90% within 24 hours and 95% within 30 hours[2]. Thus, the major factor that affects methotrexate level is renal clearance. Among patients with impaired renal function, MTX clearance may be significantly diminished, and such patients are predisposed to severe toxicity[7-8]. MTX clearance from pleural fluid or ascites also proceeds slowly and may result in prolonged drug half-life in plasma[9-10]. Furthermore, many drug interactions affect MTX clearance such as trimethoprim-sulfamethoxazole (TMP/SMX), NSAID, phenytoin, amiodarone, ciprofloxacin etc[11].

Thus, serum MTX concentrations should be monitored by adjusting leucovorin rescue until reaching the target of < 0.05 μmol/L[12]. However, monitoring MTX level is not feasible in many Thai hospitals. Therefore, this study aimed to estimate the most appropriate duration of leucovorin rescue among patients with lymphoma receiving HDMTX.

Methods

We conducted a single center retrospective chart review of patients with lymphoma receiving HDMTX regimen (> 1 g/m^2) at Siriraj Hospital from January 2016 to December 2019. In this study, patients were included with following criteria 1) Age over 18 years old, 2) diagnosed lymphoma and 3) received HDMTX (> 1 g/m^2) at least once in their chemotherapy regimen. The regimens of HDMTX and leucovorin vary as follow: (1) MTX 200 mg/m^2 IV in 3 hr then 800 mg/m^2 IV in 20 hr, leucovorin 15 mg/m^2 IV push q 6 hr started 12 hr after completing MTX and stopped when MTX level reached < 0.05 μmol/L (HyperCVAD regimen), (2) MTX 2,000 mg/m^2 IV in 6 hr, leucovorin 15 mg/m^2 IV push q 12 hr started 12 hr after completing MTX and stopped when MTX level reached < 0.05 μmol/L (SMILE and IDARAM regimen), (3) MTX 1,500 mg/m^2 IV in 1 hr then 1,500 mg/m^2 IV in 6 hr, leucovorin 15 mg/m^2 IV push q 6 hr started 12 hr after completing MTX and stopped when MTX level reached < 0.05 μmol/L (CNS prophylaxis), (4) MTX 3,000 mg/m^2 IV in 3 hr, leucovorin 15 mg/m^2 IV push q 12 hr started 12 hr after completing MTX and stopped when MTX level reached < 0.05 μmol/L (AspaMetDex regimen), (5) MTX 500 mg/m^2 IV in 15 min then 3,000 mg/m^2 IV in 3 hr (total MTX 3,500 mg/m^2), leucovorin 15 mg/m^2 IV push q 6 hr started 12 hr after completing MTX and stopped when MTX level reached < 0.05 μmol/L and (6) MTX 1,500 mg/m^2 IV over 1 hr then 1,650 mg/m^2 IV in 6 hr x 2 doses (total MTX 4,800 mg/m^2), leucovorin 15 mg/m^2 IV push q 6 hr

started 12 hr after completing MTX and stopped when MTX level reached < 0.05 μmol/L. For all regimens, the MTX level was measured 48 hr after starting HDMTX and then once daily until MTX level reached < 0.05 μmol/L. The dose of leucovorin was later adjusted at the physician's discretion guided by MTX level and standard leucovorin nomogram.

Exclusion criteria included 1) patients whose estimated glomerular filtration rate (eGFR) was < 30 mL/min/1.73 m^2 before starting HDMTX, 2) developed acute kidney injury (AKI) after HDMTX administration defined by KDIGO (definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes) criteria, 3) received following drugs during HDMTX, i.e., phenytoin, NSAID group, amiodarone, ciprofloxacin [except TMP/SMX that was included to compare secondary outcomes because most patients with diagnosed lymphoma had received TMP/SMX for primary prophylaxis of pneumocystis pneumonia (PCP)].

Baseline characteristics of the study participants included age, sex, body weight, height, body surface area (BSA) and HDMTX regimen. Data of potential factors affecting primary outcome were collected including MTX dose (g/m^2), TMP/SMX use, leucovorin dose, hydration regimen, and baseline creatinine before administering HDMTX with eGFR calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation.

We categorized patients into three groups according to baseline eGFR: (1) 30-59, (2) 60-89 and (3) ≥ 90 mL/min/1.73 m^2. Primary outcome was number of days from administering HDMTX to the MTX level reached < 0.05 μmol/L (ΔDay0.05) in each eGFR group and secondary outcome was TMP/SMX effect, leucovorin dose and hydration regimen ΔDay0.05. We categorized MTX dose into five groups: 1, 2-2.4, 3, 3.5, 4.5-4.8 g/m^2, respectively, and we also evaluated effect of MTX dose (g/m^2) on each eGFR group.

Hydration and alkalinized urine protocol for HDMTX regimen at Siriraj Hospital was 5%DW 1,000 mL plus 7.5%$NaHCO_3$ 100 mL IV rate 120 mL/hr at least 12 hours before HDMTX and continuing 48 hours after completing MTX infusion. However, urine pH was not routinely evaluated. Some patients received TMP/SMX for primary prophylaxis of pneumocystis pneumonia, i.e, TMP/SMX (160/800) 1 tablet oral alternate days. Serum creatinine measurement was not routinely indicated after starting HDMTX; therefore, it depended on the physician's discretion. However, all patients were tested for serum creatinine at some days after initiating HDMTX, mostly at three to four days after starting HDMTX and then every three days until MTX level reached < 0.05 μmol/L.

We recruited names of patients from the Siriraj Poison Center Laboratory. We chose the name and hospital number of into patients whose MTX levels were measured from January 2016 to December 2019 and categorized patients into three groups of eGFR sorted by date of admission.

The primary objective was to estimate the number of days from administering HDMTX to the MTX level < 0.05 μmol/L (ΔDay0.05). The secondary objective was to assess factors associated with ΔDay0.05.

A sample size of 69 patients was estimated using One-way analysis of variance (One-way ANOVA) using the nQuery program and the number per group according to eGFR was 23 patients with an effect size of 0.19 and power of test = 90%.

Statistical analysis was conducted using SPSS Software (Version 20; SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean with SD, while categorical data were presented as numbers and percentages. One-way ANOVA was used to compare the mean difference of ΔDay0.05 among eGFR groups and post hoc analysis with multiple comparison using the Dunnett T3 test. Two-way ANOVA was used to analyze interaction between eGFR and MTX dose groups ΔDay0.05. To compare the mean between ΔDay0.05 and hydration regimen, TMP/SMX received and leucovorin increasing dose, the independent t-test was used with *p* values < 0.05 considered to be statistically significant.

The protocol of this study [788/2563(IRB2)] was approved by the Siriraj Institutional Review Board, Faculty of Medicine, Siriraj Hospital, Mahidol University.

Result

Sixty-nine patients with lymphoma receiving HDMTX were included with a mean age of 60±12 years, and were 36 men (52.2%). The most common diagnosis was primary CNS lymphoma [PCNSL; n = 32 (46.4%)]. The most common chemotherapy regimen was HDMTX for PCNSL with an average dose of 3,700 mg/m^2 (Table 1). Hydration before HDMTX was not given among six patients in which HDMTX doses were 1 g/m^2 among five patients and 2 g/m^2 in one patient (IDARAM protocol).

We categorized patients into three groups according to eGFR (30-59, 60-89 and ≥ 90 mL/min/1.73m^2). The mean of ΔDay0.05 that was categorized by eGFR 30-59, 60-89, and ≥ 90 mL/min/1.73 m^2 were 6.7±1.7 day

Table 1 Baseline characteristics

Characteristic	Baseline eGFR (estimated glomerular filtration rate), mL/m^2			total
	> 90 (n = 23)	60-89 (n = 23)	30-59 (n = 23)	
Male sex (%)	9 (39.1)	12 (52.2)	15 (65.2)	36 (52.2)
Mean age (yr)	52.3±14.1	62.7±11.3	65.6±9.1	60±12.9
Mean BW (kg)	56.3±12.6	61.1±9.9	65.8±13.9	61±12.7
Mean height (cm)	160.6±9.3	162.8±8.8	164.6±9.9	162±9.4
Mean BSA (m^2)	1.57±0.2	1.66±0.15	1.71±1.86	1.64±0.18
Mean creatinine (mg/dL)	0.61±0.13	0.94±0.15	1.39±0.3	0.9±0.3
Baseline eGFR	108±13	76±7.1	49.5±8.3	78.1±26
Diagnosis (%)				
Primary CNS lymphoma	11 (47.8)	9 (39.1)	12 (52.2)	32 (46.4)
2nd CNS involvement	3 (13)	2 (8.7)	6 (26.1)	11 (15.9)
Primary CNS prophylaxis	9 (39.1)	12 (52.2)	3 (13.8)	24 (34.8)
Other	0	0	2 (8.7)	2 (2.9)
Regimen (%)				
HDMTX for PCNSL	11 (47.8)	10 (43.5)	12 (52.2)	33 (47.8)
HDMTX + HDAraC	2 (8.7)	1 (4.3)	3 (13)	6 (8.7)
Primary CNS prophylaxis	8 (34.8%)	10 (43.5)	2 (8.7)	20 (29)
Other	2 (8.7)	2 (8.7)	6 (26.1)	10 (14.5)
MTX (g/m^2)				
1	1 (4.3)	0	4 (17.4)	5 (7.2)
2-2.4	1 (4.3)	4 (17.4)	2 (8.7)	7 (10.1)
3	6 (26.1)	5 (21.7)	2 (8.7)	13 (18.8)
3.5	3 (13)	4 (17.4)	4 (17.4)	11 (15.9)
4.5-4.8	12 (52.2)	10 (43.5)	11 (47.8)	33 (47.8)
Increased leucovorin dose				
Yes	10 (43.5)	14 (60.9)	12 (52.2)	36 (52.2)
No	13 (56.5)	9 (39.1)	11 (47.8)	33 (47.8)
Hydration				
Received	21 (91.3)	23 (100)	19 (82.6)	63 (91.3)
Not received	2 (8.7)	0	4 (17.4)	6 (8.7)
Trimethoprim-sulfamethoxazole (TMP/SMX)				
No	19 (82.6)	18 (78.3)	14 (60.9)	51 (73.9)
1DS M,W,F	4 (17.4)	5 (21.7)	8 (34.8)	17 (24.6)
1DS M,Th	0	0	1 (4.3)	1 (1.4)

BW: body weight; BSA: body surface area; PCNSL: primary central nervous system lymphoma; HDAraC: high dose Ara-C; DS: double strength; M: Monday; W: Wednesday; F: Friday; Th: Thursday

(range 4-10), 4.6±1.3 day (range 3-7) and 3.5±0.5 day (range 3-4), respectively [Table 2; $p < 0.001$ (Welch test)].

We categorized the MTX dose into five groups based on gram per body surface area, i.e., 1, 2-2.4, 3, 3.5, 4.5-4.8 g/m^2 (Table 3). We compared mean of ΔDay0.05 between each group of MTX dose and showed no difference of mean of ΔDay0.05 among groups with ANOVA test ($p = 0.346$). Other factors, i.e., hydration before HDMTX, leucovorin dose adjustment and TMP/SMX for primary prophylaxis were analyzed using the independent-sample t-test concerning the effect ΔDay0.05. No significant difference was found among these factors (2-sided p value = 0.252, 0.245, and 0.164, respectively (Table 4). The regimen of HDMTX combined with other chemotherapies, compared with the HDMTX regimen alone, exhibited no difference ΔDay0.05 even when adjusted for eGFR category.

Additionally, we used Two-way ANOVA to evaluate the effect of MTX dose on each group of eGFR. We found that the interaction effect of eGFR and MTX dose ΔDay0.05 was not significant ($p = 0.988$) (Figure 1).

Discussion

Our study demonstrated that eGFR showed a directly significant effect on MTX clearance compatible with the related study of Kristensen and coworkers[15] reporting an excellent correlation between the clearance of methotrexate and endogenous creatinine clearance. Their data could provide a guide to dose adjustment among patients with altered renal function[15].

Table 2 Mean day at MTX level < 0.05 μmol/L according to eGFR

eGFR (mL/min/1.73 m^2)	N	Mean (day)	SD	95%CI	Range
≥ 90	23	3.5	0.51	3.3-3.7	3-4
60-89	23	4.6	1.29	4.1-5.2	3-7
30-59	23	6.7	1.73	6.0-7.5	4-10

MTX: methotrexate; eGFR: estimated glomerular filtration rate; SD: standard deviation; CI: confidence interval

Table 3 Mean day at MTX level < 0.05 μmol/L according to MTX dose

MTX dose (g/m^2)	N	Mean (day)	SD	95%CI	Range
1	5	6.4	2.7	3.0-9.7	3-10
2-2.4	7	4.7	1.7	3.1-6.2	3-7
3	13	4.3	1.7	3.3-5.4	3-9
3.5	11	5	1.4	4.0-5.9	3-7
4.5-4.8	33	5	1.9	4.4-5.7	3-10

MTX: methotrexate; SD: standard deviation; CI: confidence interval

Table 4 Mean day of MTX level at < 0.05 μmol/L according to hydration regimen, TMP/SMX and leucovorin dose adjustment

		N	Mean(day)	SD	*t*	*p*-value
Hydration regimen	Received	63	4.9	1.7	-1.154	0.252
	Not received	6	5.8	2.7		
TMP/SMX	Received	18	5.6	2.5	-1.440	0.164
	Not received	51	4.7	1.5		
Leucovorin dose	Increasing	36	5.2	1.8	-1.172	0.245
	No change	33	4.7	1.8		

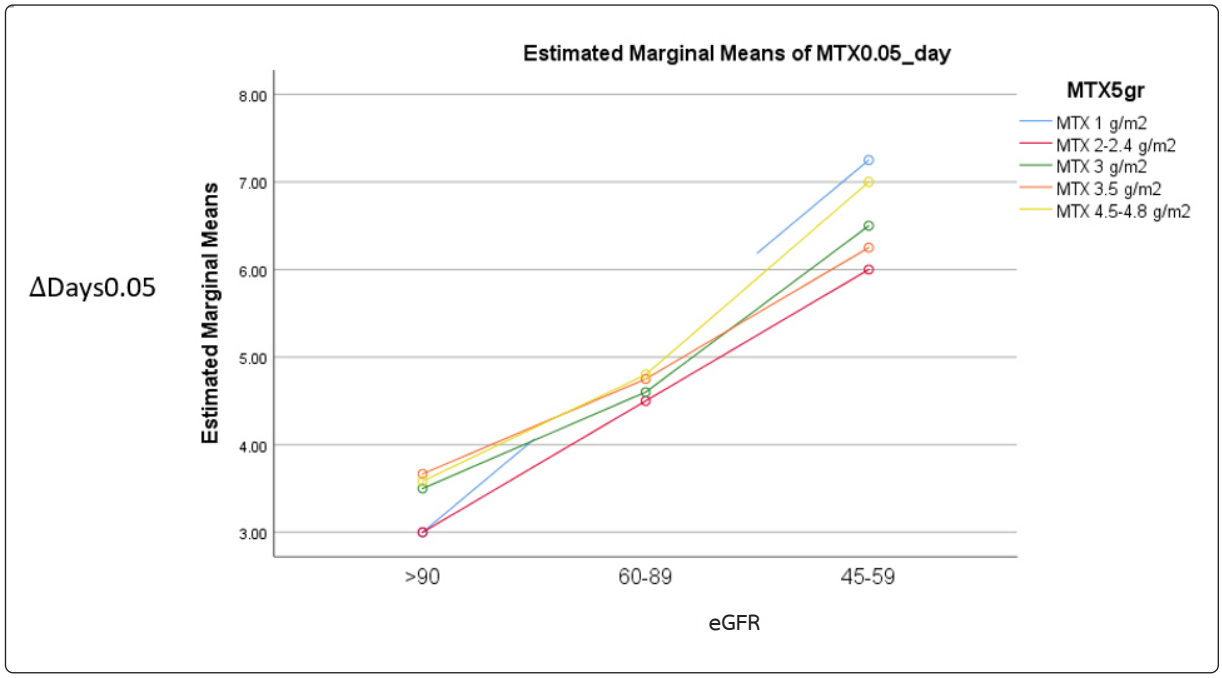

Figure 1 Interaction between eGFR group and MTX dose group on mean day of MTX level < 0.05 μmol/L

Moerover, our study emphasized the mean day that MTX level under 0.05 μmol/L (ΔDay0.05) was achieved in each group of eGFR for the purpose on estimating the duration of leucovorin rescue in clinical practice at hospitals where monitoring MTX level was not feasible. From Table 2, we found the mean ΔDay0.05 in each group of eGFR indicated a narrow range of 95%CI that is about 1 day implying that the mean ΔDay0.05 in this study was reliable.

However, many confounding factors could have affected MTX clearance apart from eGFR. MTX dose was the major factor; therefore, we compared the interaction effect of both eGFR and MTX dose with two-way ANOVA. We found that MTX dose revealed no significant effect on ΔDay0.05. In clinical practice when patients present renal insufficiency, the physician will decrease the MTX dose to avoid renal toxicity. However, specific eGFR cutoff values for dose reduction or omission of subsequent HDMTX have not been established, with upper cutoffs for dose reduction starting at 50 to 60 mL/min and recommendations to omit further HDMTX when eGFR falls below 10 to 30 mL/min[13-14].

With respect to other factors affecting MTX clearance,this study considered other common factors found in clinical practice, i.e., hydration before HDMTX, increased leucovorin dose and TMP/SMX for primary PCP prophylaxis[11,16]. We found no significant effect of these factors on ΔDay0.05. However, regarding hydration before administering MTX, we found that the number in the nonhydration group was too small to compare with those of the hydration group (6 *vs.* 63) because Siriraj Hospital enforces a standard protocol for hydration before administering MTX and most of those in the nonhydration group received hyperCVAD chemotherapy regimen in which no hydration protocol was included.

For TMP/SMX factor, TMP/SMX dose in this study was in primary prophylactic, i.e, given alternate days; hence, its effect on MTX clearance may have been subtle. Regarding the increasing leucovorin dose, physicians considered adjusting the leucovorin dose from MTX level after administering MTX to decrease MTX toxicity. In this study we found no significant effect of increasing leucovorin dose on ΔDay0.05. Leucovorin could prevent mucositis from MTX but may not directly affect MTX clearance.

To apply the result of our study in practice with the main concern on patients' safety at hospitals where MTX level cannot be measured, we suggest using the maximum value range in Table 2 to estimate the number of days that MTX level is less than 0.05 μmol/L categorized by baseline eGFR. Therefore, leucovorin should be continued until reaching MTX level of less than 0.05 μmol/L, which was estimated to be days 10, 7 and 4 (Day 1 = day of starting MTX) according to eGFR of 30-59, 60-89, and ≥ 90 mL/m^2, respectively. In addition, to save the cost of measuring MTX level at hospitals where MTX level measurement was costly and could not be reimbursed, we suggest measuring MTX level for the first time on days 7, 5 and 4 (mean day in table 2) according to eGFR of 30-59, 60-89, and > 90 mL/m^2, respectively. However, we advise that hydration protocol before HDMTX should be provided as in this study to ensure the same condition and outcome.

Limitations of this study included retrospective design leaving uncontrolled confounding factors that might have affected MTX clearance. However, we endeavored to minimize some confounding factors by excluding others such as pleural fluid or ascites[9-10]. Furthermore, we excluded acute kidney injury defined by KDIGO criteria after administering MTX because MTX level cannot be predicted in this condition. If acute kidney injury develops after HDMTX, MTX level will be quite high (usually in the range of 5 to 50 μmol/L) together with delayed MTX clearance. Hence, leucovorin dose must be increased according to standard leucovorin nomogram and provided until MTX level < 0.05 μmol/L. However, when MTX level cannot be measured, leucovorin dose of 100 mg/m^2 every 3 hr might be administered until acute kidney injury subsides and no evidence of MTX toxicity is observed such as mucositis, leukopenia and thrombocytopenia. Another limitation was the small number of patients receiving HDMTX of 3 g/m^2 or more in each category of eGFR level (17 to 21 patients).

Conclusion

Our result showed that the estimated duration of MTX level under 0.05 μmol/L after HDMTX administration correlated to eGFR value, so physicians can use this data to predict the stopping date of leucovorin rescue at hospitals where monitoring MTX level was not feasible.

Acknowledgment

We appreciate the assistance provided by Ms. Khemjira Karnkateklang, Master of Science (Applied Statistics) at the Clinical Epidemiology Sector, Research and Development Subdivision, Department of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University for the statistical analyses in this study.

Conflict of interest

None.

References

1. *Jolivet J, Cowan KH, Curt GA, Clendeninn NJ, Chabner BA. The pharmacology and clinical use of methotrexate. N Engl J Med. 1983;309:1094-104.*
2. *Bleyer WA. The clinical pharmacology of methotrexate: new applications of an old drug. Cancer. 1978;41:36-51.*
3. *Ackland SP, Schilsky RL. High-dose methotrexate: a critical reappraisal. J Clin Oncol. 1987;5:2017-31.*
4. *Howard SC, McCormick J, Pui CH, Buddington RK, Harvey RD. Preventing and Managing Toxicities of High-Dose Methotrexate. Oncologist. 2016;21:1471-82.*
5. *Abelson HT, Fosburg MT, Beardsley GP, Goorin AM, Gorka C, Link M, et al. Methotrexate-induced renal impairment: clinical studies and rescue from systemic toxicity with high-dose leucovorin and thymidine. J Clin Oncol. 1983;1:208-16.*
6. *Shen DD, Azarnoff DL. Clinical pharmacokinetics of methotrexate. Clin Pharmacokinet. 1978;3:1-13.*
7. *Garnick M, Mayer R, Abelson H. Acute renal failure associated with cancer treatment. In: Brenner BM, Lazarus JM, editors. Acute Renal Failure. New York: Churchill Livingstone; 1988. p. 621-657.*
8. *Pitman SW, Parker LM, Tattersall MH. Clinical trial of high-dose methotrexate (NSC-740) with citrovorum factor (NSC-3590)-toxicologic and therapeutic observations. Cancer Chemother Rep. 1975;6:43-9.*
9. *Wan SH, Huffman DH, Azarnoff DL, Stephens R, Hoogstraten B. Effect of route of administration and effusions on methotrexate pharmacokinetics. Cancer Res. 1974;34:3487-91.*

10. *Li J, Gwilt P. The effect of malignant effusions on methotrexate disposition. Cancer Chemother Pharmacol. 2002;50:373-82.*
11. *Levêque D, Santucci R, Gourieux B, Herbrecht R. Pharmacokinetic drug-drug interactions with methotrexate in oncology. Expert Rev Clin Pharmacol. 2011;4:743-50.*
12. *Aumente D, Buelga DS, Lukas JC, Gomez P, Torres A, García MJ. Population pharmacokinetics of high-dose methotrexate in children with acute lymphoblastic leukaemia. Clin Pharmacokinet. 2006;45:1227-38.*
13. *Kintzel PE, Dorr RT. Anticancer drug renal toxicity and elimination: Dosing guidelines for altered renal function. Cancer Treat Rev. 1995;21:33-64.*
14. *Aronoff GR, Berns JS, Brier ME, Golper TA, Morrison G, Singer I, et al, eds. Drug prescribing in renal failure: dosing guidelines for adults. Philadelphia: American College of Physicians; 1999.*
15. *Kristensen LO, Weismann K, Hutters L. Renal function and the rate of disappearance of methotrexate from serum. Eur J Clin Pharmacol. 1975;8:439-44.*
16. *Sand TE, Jacobsen S. Effect of urine pH and flow on renal clearance of methotrexate. Eur J Clin Pharmacol. 1981;19:453-6.*