Original Article

Monitoring Methotrexate Level in Adult Patients with Osteosarcoma: A Proposed Algorithm for Thai Patients

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Objective: Plasma methotrexate [MTX] concentrations monitoring is important in high-dose MTX [HDMTX]. However, the availability of drug monitoring and its cost are problematic. The goal of this study was to study the MTX clearance in adult Thai patients and propose the simplified guideline.

Materials and Methods: This is a retrospective study examined osteosarcoma patients treated with multi-agent chemotherapy including HDMTX (12 g/m^2) during 2011 to 2013. MTX serum levels were obtained every 24 h until the concentration fell below the threshold concentration of 0.1 mM. Leucovorin was given per standard protocol.

Results: A total of 326 MTX serum levels in 76 HDMTX courses were analyzed. The mean MTX serum peak values were 1,300 (980 to 1,618) mM. MTX serum level fell rapidly in the first 72 hours then gradually decreased over time. In 45% of the cases, leucovorin could be stopped at 96 hours after the infusion of MTX.

Conclusion: MTX serum level monitoring is mandatory in HDMTX regimen. Drug monitoring should start at 72 hours after HDMTX infusion and every 24 hours until the level is below 0.1 mM.

Keywords: Osteosarcoma, Methotrexate, Therapeutic drug monitoring

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Osteosarcoma is a common malignant bone tumor in children and adolescents but quite rare in adults[1,2]. The primary tumors usually located in the metaphyseal regions of the long bones especially around the knee[3]. The surgical treatment is the mainstay modality with the corporation of neoadjuvant and adjuvant chemotherapy[4].

Doxorubicin, cisplatin, and high-dose methotrexate [HDMTX] are the backbone drugs which are commonly used in combination before and after surgery[5,6]. Despite the effective of HDMTX, the toxicity is substantial. Plasma MTX concentrations may become very high in some patients and result in toxicities in many organs including renal and liver dysfunction, bone marrow suppression, mucositis, and neurological disorder[7,8].

To prevent the catastrophic event, leucovorin rescue is usually given after the HDMTX infusion along with aggressive hydration and alkalinization. Monitoring of plasma MTX concentrations is crucial to adjust the dosage of MTX and leucovorin[9,10]. In Thailand, unfortunately, monitoring the MTX level is not always feasible due to lack of facility, staff, and the cost of the procedure.

Herein, the authors present the plasma MTX concentrations and pharmacokinetics variables to predict subsequent MTX concentrations. An algorithm for MTX monitoring in resource-limited setting was introduced.

Materials and Methods

This is a retrospective study examined osteosarcoma patients treated during 2011 to 2013. Adult patients (>15 years) with primary osteosarcoma received neoadjuvant or adjuvant chemotherapy with HDMTX (12 g/m^2), cisplatin, and doxorubicin were

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included. The treatment regimen is given in Figure 1. Clinical and methotrexate data of 25 patients with osteosarcoma were reviewed.

From Figure 1, MAP regimen (Methotrexate, Doxorubicin, and Cisplatin) was given every 3 weeks, 2 cycles before and 2 cycles after the surgery. The surgery of primary tumor consisted of limb-sparing surgery or amputation and was based on the surgeon's decision. All patients received hydration and alkalinization with sodium bicarbonate before and after HDMTX. HDMTX was administered as a 4-hour infusion dissolved in 0.9% NaCl 1,000 ml. Intravenous leucovorin 50 mg every 6 hours was administered starting 6 hours following completion of the MTX infusion. MTX serum levels were obtained every 24 h until the MTX concentration fell under the threshold concentration of 0.1 µM.

Baseline and clinical characteristics were analyzed using descriptive statistics and presented in percentage, mean, and standard deviation [SD]. All data analysis was performed using STATA software (StataCorp LP, College Station, TX, USA). The study was conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by institution's ethics review board.

Pharmacokinetics parameters

Pharmacokinetic parameters of MTX were calculated as follows:

$$K_e = \frac{\ln C_2 - \ln C_1}{\Delta t}$$

$$T_{1/2} = \frac{0.693}{K_e}$$

K_e is the elimination rate constant (hr^{-1}), C_1 is the concentration of MTX at time t_1 (µM), C_2 is the concentration of MTX at time t_2 (µM), and Δt is time between C_1 and C_2 (hr).

After 72 hours from the start of MTX infusion, almost all patients eliminated the drugs with the half-life of terminal half-life ($T_{1/2\text{-}\beta}$). The decline rate was resembling the first order kinetics elimination, therefore we calculated the elimination rate constant (K_e) from the drug concentration at different time point using the first order kinetics equation;

$$K_e = \frac{\ln C_2 - \ln C_1}{\Delta t}$$

K_e: Elimination rate constant (hr^{-1})
C_1: MTX concentration at t_1 (µM)
C_2: MTX concentration at t_2 (µM)
Δt: Time difference between C_1 and C_2 (hr)

After we obtained the K_e at different time points, the half-lives ($T_{1/2}$) were calculated using the equation as follows;

$$T_{1/2} = \frac{0.693}{Ke}$$

$T_{1/2}$: Half-life (hours)
K_e: Elimination rate constant (hr^{-1})

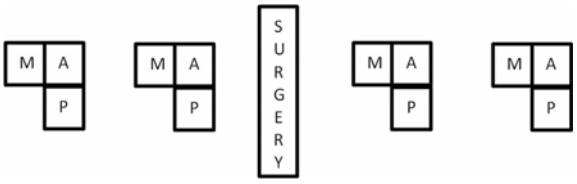

Figure 1. Chemotherapy regimen. A, doxorubicin; M, Methotrexate; P, cisplatin.

Results

A total of 25 patients (17 males; 8 females) with high-grade osteosarcoma treated with HDMTX at the Srinagarind hospital were included. The patient characteristics are summarized in Table 1. Most of the patients were under 20 years old (mean 20.8 years). The mean body surface area was 1.54 kg/m^2 and all had normal baseline kidney function.

A total of 326 MTX serum levels in 76 HDMTX courses were analyzed. The overall mean MTX value at the different time is shown in Figure 2. The mean MTX serum peak value was 1,300 (980-1,618) µmol/L. There were a great inter-patient and intra-patient variability of MTX serum levels.

According to the MTX concentrations in

Table 1. Demographic data of osteosarcoma patients received HDMTX

n = 25	Mean, SD
Age (years)	20.8, 7.45
Gender, n (%)	
Male	17 (68%)
Female	8 (32%)
Height (cm)	165.6, 10.19
Weight (kg)	52.1, 11.16
BSA (kg/m^2)	1.54, 0.19
GFR (ml/min/m^2)*	118.6, 29.65

BSA = body surface area; GFR = glomerular filtration rate, calculated by Cockroft-Gault formula

different time point, the graph could be divided into two parts; 24 to 72 hours and after 72 hours (Figure 2). During the first 72 hours, the concentration of MTX fell rapidly which was explained by two-compartment open model; the drug was distributed from the central compartment to the peripheral compartment. After 72 hours, the level gradually decreased from the elimination phase from first order kinetics.

At 72 hours after the start of MTX, the level is lower than 0.5 □M in more than half of the patients (59%) and the mean serum MTX concentrations was

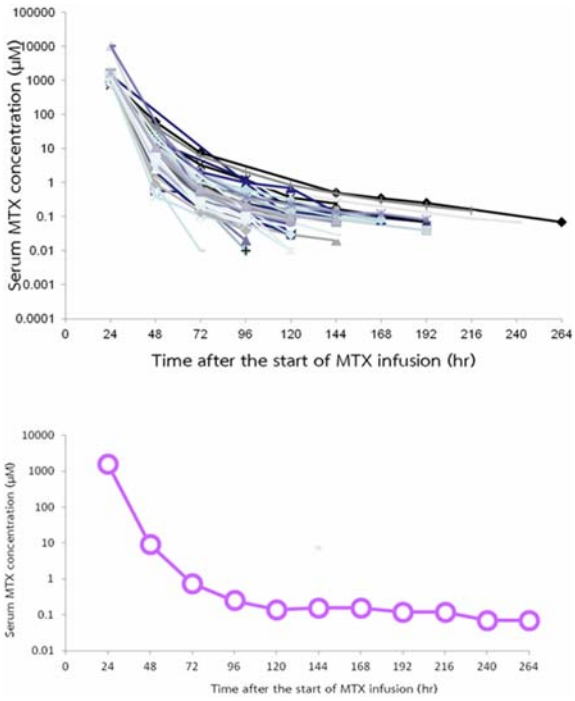

Figure 2. Serum methotrexate concentration at different time points. A) Individual data, B) Mean level.

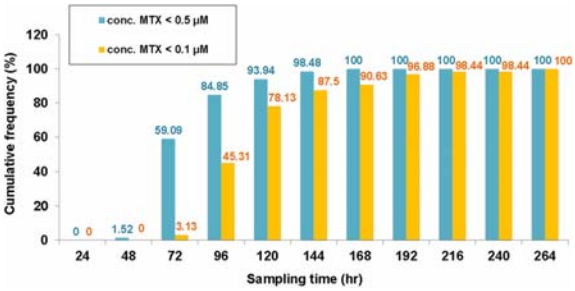

Figure 3. Percentage of patients with MTX concentration of less than 0.1 μM and 0.5 μM at different time points.

0.26±0.12 μM. The leucovorin could be stopped in 3.13% of the patients at 72 hours and 45.31% of the patients at 96 hours after MTX infusion (Figure 3).

From Table 2, the K_e gradually declined as time passed resulting in the increase of $T_{1/2}$. When the drug elimination was in first order kinetics and the half-life was $T_{1/2-\square}$, the elimination time was longer.

The authors predicted the MTX concentration by using the equation as follows;

$$C_t = C_0 \times e^{-Ket}$$

C_t: MTX concentration at Time t (μM)
C_0: MTX concentration at start (μM)
K_e: Elimination rate constant (hr^{-1})
t: Time difference between C_0 and C_t (hr)

The authors compared the predicted and measured MTX concentration at the different time point. The concentration difference was calculated as shown in Table 3.

Compared to other time points, the smallest difference was observed at 144 hours after infusion. After 96 hours, the elimination half-life of 85% of the patients was $T_{1/2-\beta}$, therefore using K_e at 96 to 120 hours to predict the MTX concentration would be more accurate than other periods. However, the intra-patient variability was still observed, even after 96 hours.

Discussion

HDMTX plays a major role in the treatment of osteosarcoma. However, the adverse events are also well established including but not limited to renal toxicity, neurologic dysfunction, hematologic toxicity, and elevated liver enzymes[7,8]. Monitoring for MTX level, serum creatinine and giving leucovorin rescue are crucial in the protocol of HDMTX.

The findings in the present study are in agreement with earlier reports that MTX elimination is a two-compartment open model[10-12]. Holmboe et al also demonstrated the biphasic curve of drug elimination

Table 2. The Elimination rate constant (K_e) and half-life ($T_{1/2}$) at different time points

Time (number of cases)	K_e (hr^{-1})	$T_{1/2}$ (hr)
72 to 96 hr (n = 33)	0.0504±0.0212	15.37±4.79
96 to 120 hr (n = 30)	0.0384±0.0230	22.64±9.30
120 to 144 hr (n = 13)	0.0218±0.0080	36.49±15.08
144 to 168 hr (n = 6)	0.0172±0.0060	48.49±29.83
168 to 192 hr (n = 4)	0.0161±0.0022	43.48±5.68
192 to 216 hr (n = 2)	0.0147±0.0009	47.36±2.92
216 to 240 (n = 1)	0.0105	66.00

Table 3. Predicted and measured MTX concentration

K_e (number of cases)	Time to predict (hr)	$C_{predicted}$(μM)	$C_{measured}$(μM)	Difference (μM)($C_{predicted}$ - $C_{measured}$)
72 to 96 (n = 14)	120	0.0405±0.0176	0.0514±0.0235	0.0203±0.0118
96 to 120 (n = 10)	144	0.0693±0.0435	0.0800±0.0483	0.0141±0.0149
120 to 144 (n = 4)	168	0.0804±0.0299	0.0950±0.0238	0.0198±0.0105
144 to 168 (n = 3)	192	0.1193±0.0580	0.1200±0.0781	0.0168±0.0137
168 to 192 (n = 1)	216	0.1470	0.1500	0.0030
192 to 216 (n = 1)	240	0.0624	0.0700	0.0076

and reported the rapid fall of MTX concentration during the first 72 hours similar to the present study[13].

Many studies also noted the high inter- and intra-patient variability of MTX pharmacokinetics, which required individual adjustment of MTX and leucovorin dosage in each cycle[12,14]. The result also supported the conclusion of Graf et al that the individual adaptation of the MTX dose is not necessary to ensure a peak level or to prevent toxicity[15].

Although it is customary to start the assay plasma MTX levels at 24 hours after MTX infusion[14,16], the authors suggest that it should be started at 72 hours and leucovorin should be given a fixed dose with no adjustment (Figure 4). It is safe and feasible in the resource-restricted setting.

The present study is limited due to the retrospective nature and a small number of patients. In summary, we have found that MTX serum level fell rapidly in the first 72 hours then gradually decreased over time with a wide range of intra- and inter-individual variation in drug elimination. Serum MTX concentration monitoring could be started after 72 hours while continuing leucovorin and this could reduce the cost of the treatment while remaining quality of care.

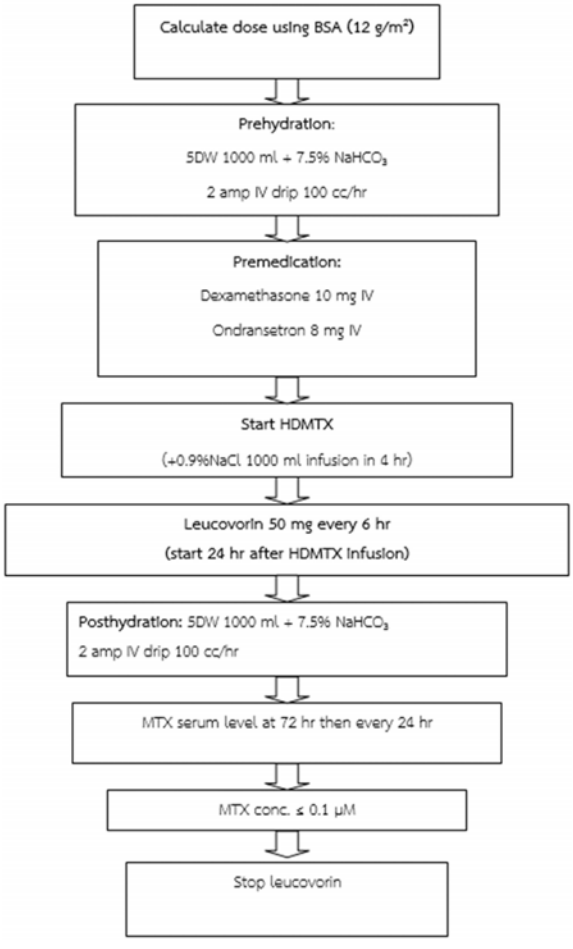

Figure 4. Proposed algorithm for HDMTX monitoring.

What is already known on this topic?

HDMTX plays a major role in the treatment of osteosarcoma but there are many adverse events including renal, hematologic, and liver toxicity. Methotrexate monitoring is essential for high-dose methotrexate treatment.

What this study adds?

The present study showed the MTX pharmacokinetics in Thai adult patients treated with HDMTX for osteosarcoma. MTX serum level fell rapidly in the first 72 hours then gradually decreased over time with a wide range of intra- and inter-individual variation in drug elimination. The authors proposed an algorithm to start serum MTX concentration monitoring after 72 hours while continuing leucovorin in order to reduce the cost while remaining quality of care.

Acknowledgements

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Potential conflicts of interest

The authors declare no conflict of interest.

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