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Original article

UTILITY OF REPEATED DRUG LEVEL MEASUREMENTS AFTER HIGH DOSE METHOTREXATE INFUSION FOR TREATMENT PLANNING IN PEDIATRIC LEUKEMIA

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Abstract: **Introduction:** Although high-dose Methotrexate (MTX) is a successful chemotherapeutic agent used in the treatment of acute lymphoblastic leukemia in childhood, life-threatening toxic effects are rarely seen. Therefore, frequent follow-up of drug levels is recommended. The study researched the necessity of drug level measurement and a minimum safe number of measurements.

Materials and Methods: The files of pediatric patients with Acute Lymphoblastic Leukemia receiving high-dose MTX treatment in a single center between 2018 and 2021 were retrospectively reviewed. The treatment protocol was: 3000 mL/m^2 alkaline hydration fluid was continued until the 72nd hour together with 2 gr/m^2 continuous MTX infusion in the low-risk group and 5 gr/m^2 in moderate and high-risk groups, and 15 mg/m^2/dose folinic acid was given at the 42nd, 48th and 54th hours.

Findings: 456 MTX treatments were evaluated in 114 patients. Similar results ($p > 0.05$) were obtained in the MTX level measurements performed at the 24th, 42nd, 48th, and 54th hours after MTX administration. In the repeated measurements, the data at the 42nd hour were similar ($p = 0.021$). The number of cases that were > 150 µmol/L at the 24th hour of methotrexate infusion and above 1 µmol/L at the 42nd, 48th, and 52nd hours were found to be similar in the repeated measurements.

Conclusion: Although recommended, frequent follow-up of MTX levels might not always indicate toxicity. In centers with limited laboratory facilities, the MTX level measured at the 42nd hour in the first treatment might be a practical approach to guide the management of other MTX treatments.

Keywords: leukemia, methotrexate, toxicity, drug level.

INTRODUCTION

The most frequent type of cancer in childhood is acute leukemia. 80% of this is acute lymphoblastic leukemia (ALL). Methotrexate (MTX) is the principal chemotherapeutic agent used in the treatment of ALL and also for the prevention of relapse (1-5). One of the main factors increasing the treatment success in childhood ALL is dose intensity, and it is established that MTX administered in high doses positively affects prognosis (6, 7).

The mechanism of the MTX effect is to bind to the methylenetetrahydrofolate reductase enzyme, preventing the conversion of dihydrofolate to tetrahydrofolate, the active form of folic acid. With single-carbon presentation, tetrahydrofolate is indispensable in the synthesis of purine nucleotides and thymidylates. The effect of MTX, therefore, is to inhibit DNA synthesis and repair and prevent cell proliferation (8). MTX prevents the proliferation of rapidly proliferating healthy cell types, such as bone marrow, oral and intestinal mucosal cells, and urinary bladder cells, as well as malignant cells. One of the main drugs in the treatment of acute lymphoblastic leukemia, MTX, may cause life-threatening toxic effects, such as liver toxicity, nephrotoxicity, bone marrow suppression, and especially oro-intestinal mucositis, in 2-12% of the patients, even if the effect of MTX is therapeutically curtailed by calcium folinate treatment within 18-24 hours after the administration of MTX in high doses (9).

Standard doses have been determined for the amount of folic acid to be administered. However, the amount and number of doses are estimated according to serum MTX levels (9-11). In studies conducted to date, a wide range of recommendations based on MTX level has been made, ranging from "this measurement is not required" to "a single measurement is sufficient" or "a follow-up at six-hour intervals is needed until MTX level falls below the determined level" (9, 12-14). This study reviewed the similarities and differences among the repeated MTX levels in pediatric patients who were given repeated high-dose MTX due to ALL and researched the utility of these repeated measurements.

MATERIALS AND METHODS

MTX levels of pediatric patients treated according to ALL IC BFM 2009 protocol in a single Pediatric Hematology and Oncology Clinic, Basaksehir Cam and Sakura Training and Research Hospital, Istanbul 2018-2021, were evaluated. Each patient received four cycles of high-dose MTX. Complete blood count, creatinine, and alanine aminotransferase values were checked for suitability for MTX administration before each cycle. The treatment protocol was: 3000 mL/m^2 alkaline hydration was given together with 2 g/m^2 continuous MTX infusion in the low-risk ALL group and 5 g/m^2 in moderate and high-risk ALL groups for 24 hours. Hydrationfluids were continued until the 72nd hour. MTX clearance was determined by measuring the MTX level from peripheral blood samples four times at the 24th, 42nd, 48th, and 54th hours from the beginning of the first MTX infusion, and 15 mg/m^2/dose folinic acid was administered at the 42nd, 48th and 54th hours. From the 42nd hour, an additional dose of folinic acid of 15 mg/m^2/dose, if MTX is higher than 1 μmol/L, 30 mg/m^2/dose if higher than 2 μmol/L, 45 mg/m^2/dose if higher than 3 μmol/L, 60 mg/m^2/dose if higher than 4 μmol/L was given. Calcium folinate was continued until the MTX level in the peripheral blood fell below 0.25 μmol/L. Regular 6-hour follow-up MTX measurement was stopped in patients who showed sufficient clearance of MTX. The results of these measurements were compared.

MTX level was measured by a homogeneous competitive binding immunoassay based on competition between MTX in the sample and reagent containing MTX labeled with glucose-6-phosphate dehydrogenase (G6PDH) enzyme to bind to the anti-MTX antibody (Ark^{TM}Metotrexateassay). As the latter binds the antibody, G6PDH enzyme activity decreases. In the presence of the drug in the sample, enzyme activity increases, and this is directly proportional to the sample drug concentration. Uninhibited G6DPH enzyme converts coenzyme nicotinamide adenine dinucleotide (NAD) to NADH which is measured spectrophotometrically as the rate of change in absorbance. Endogenous serum G6PDHdoes not interfere with the results because the coenzyme NAD operates only with the bacterial G6PDH enzyme used in the assay.

Approval for this study was obtained from the hospital ethics committee (23.09.2021; 2021.09.190). All procedures performed in the study were in accordance with the institutional and national research committee's ethical standards and with the 1964 Helsinki declaration and its later amendments.

Statistical Analysis

All statistical analyses were performed using SPSS for Windows, version 22.0 (IBM Inc., Armonk, NY, USA). The normality of the distribution of the variables was analyzed by the Kolmogorov-Smirnov test. Data with normal distribution are presented as mean ± standard deviation (SD), and those with non-normal distribution are shown as median (minimum-maximum). Independent groups were compared with the Student T-test and Mann Whitney U-Test and Kruskal-Wallis test, as appropriate, and the repeated measurements were compared with the Friedman tests. Chi-Square Test and Fisher's Exact Test were used to compare ratios. A $p < 0.05$ was considered significant.

RESULTS

During the study, 456 MTX levels following high-dose therapy in 114 patients were analyzed. The median age of the patients was 6 (2-17) years. Most (68; 60%) of the patients were male. The majority (101; 89%) were diagnosed with B cell ALL, of whom 14 (13.9%) were low-risk, 76 (75.25%) were moderate-risk, and 11 (10.9%) were in the high-risk groups. The remaining 13 (11%) patients were diagnosed with T cell ALL and 10 (76.9%) were in the moderate-risk group, and 3 (23.1%) were in the high-risk group.

In the level measurements performed four times at the 24th, 42nd, 48th, and 54th hours following each MTX cycle (given at two-week intervals), no statistically significant difference was found from cycle to cycle at each of the four-time points (Table 1). Analysis of the data indicated that the values at the 42nd hour were similar (p = 0.021) and that the 42nd-hour measurement of the first MTX treatment was guiding for determining the level in other MTX treatments (Table 1). The number of cases that were > 150 μmol/Lat at the 24th hour of the methotrexate infusion and above 1 μmol/L at the 42nd, 48th, and 52nd hours were similar in the repeated measurements at the same time points in the subsequent infusion cycles (Table 2).

Table 1. *Median interquartile MTX levels at the 24th, 42nd, 48th, and 54th hours by the cycle of treatment*

Hour of measurement	Cycle of high-dose methotrexate				
	First	Second	Third	Fourth	*p**
24	31.8 (41)	24.5 (42.6)	33.4 (42.1)	20.1 (15.9)	0.123
42	0.63 (0.62)	0.5 (0.32)	0.45 (0.43)	0.48 (0.4)	0.135
48	0.38 (0.24)	0.44 (0.21)	0.3 (0.13)	0.24 (0.37)	0.064
54	0.27 (0.2)	0.26 (.69)	0.26 (0.45)	0.21 (0.24)	0.937

Kruskal - Wallis test

Table 2. *Number of cases above 150 µmol/L24 hours after the infusion and above 1 µmol/Lat the 42nd, 48th, and 52nd hours after the first, second, third, and fourth cycle of high dose MTX*

	Time of measurement (hour)	Cycle of high-dose methotrexate				
		First	Second	Third	Fourth	*P*
> 150 micmol/L	24	74	47	45	34	NA
> 1 (micmol/L)	42	64	73	73	63	0.224
	48	79	66	58	50	NA
	52	66	46	33	27	NA

Chi-square; NA, not applicable.

Severe toxicity requiring hospitalization developed in three (2.6%) patients, consisting of nephrotoxicity in two and severe mucositis in one. Serum creatinine values prior to MTX infusion of the patients who developed nephrotoxicity were within the normal range (0.4-0.6 mg/dL). One was on the third high-dose MTX cycle, and when the 42nd-hour serum MTX level was found to be 34 µmol/L, serum creatinine was 1.3 mg/dl. Later, on the eleventh day, when the serum MTX level was 0.98 µmol/L, serum creatinine was persistently high at 0.72 mg/dL. MTX level and creatinine levels continued to decrease gradually and correlatedly during these 11 days. On the twelfth day, when the MTX level was 0.13 µmol/L, serum creatinine normalized for the first time at 0.47 mg/dL. No toxicity was observed when this same patient underwent their fourth MTX treatment. In the other patient with nephrotoxicity, the MTX level was 29.5 µmol/L when serum creatinine was 2.04 mg/dL after the fourth high dose of MTX. Although both levels were persistently high and correlated for 11 days, serum creatinine returned to normal (0.5 mg/dL) for the first time on the eleventh day of follow-up, when the MTX level was 0.28 µmol/L. Acute renal failure developed with elevated serum creatinine in both of these patients, but indications for dialysis, such as persistent hypercalcemia, acidosis, or uremic symptoms, did not develop and no permanent damage was observed in their follow-up.

DISCUSSION

In pediatric patients receiving MTX (2 to 5 g/m^2) for ALL, terminal half-life is known to change between 0.7 to 5.8 hours. Renal excretion is the primary way of elimination through active tubular secretion with glomerular filtration after iv administration, and 80% to 90% of the administered dose is excreted unchanged within 24 hours, while 10% or less of the administered dose is excreted via the biliary route. To detect delayed drug clearance, it is recommended to measure plasma MTX concentrations three times, at the 24th, 42nd, and 48th hours after the start of the MTX infusion; furthermore, the folinic acid recovery dose and regimen are determined with these measurements (15, 16, 17). The level of drug measured at the end of the first 24 hours following MTX infusion is important to assess the risk of toxicity at a time point 18 hours before the first calcium folinate treatment would be given. Drug level measurement is frequently used, especially in drugs with antidotes, to predict the toxic effects of the drugs. However, practical guidance is needed as it is not generally possible to get reliable results in a few hours in centers with limited laboratory facilities. In this study, the results of the repeated MTX level measurements were assessed to guide the safe administration of high-dose MTX treatment in pediatric patients with ALL. Moreover, the ethical territory requires the bioethical reflect, argue and provide constructions of knowledge

towards the choices and decisions made in concrete cases and situations (18).

Several studies have suggested that serial monitoring of drug levels until the MTX level becomes < 0.1 μmol/L is critical for the successful management of MTX-related toxicity (9, 10, 11). However, some studies have reported that a safety/toxicity balance can be obtained through clinical and laboratory findings in centers where level monitoring cannot be carried out, while other studies have suggested that only one or two post-infusion blood MTX measurements are sufficient (14, 16, 19). Vaishnavi et al. monitored 100 MTX cycles and reported that administration of 3 or 5 g/m^2 MTX without measuring MTX levels is safe by monitoring long-term hydration, additional leucovorin doses, and serum creatinine and urine pH (12). In a study conducted with 32 pediatric patients, Sari et al. analyzed 68 treatment cycles following ≥ 1 g/m^2/day MTX administration, two measurements were carried out at the 24th and 48th hours, and no correlation was found between the MTX level and clinical toxicity in these measurements (20). In the study by Dhingra et al., consisting of 184 patients, it was reported that a single plasma drug level measurement at the 54th hour, together with long-term hydration, was sufficient for the safe management of MTX in 89% of the 598 MTX treatments (14). In another study, 231 MTX infusions given to 61 pediatric patients were analyzed, and it was declared that pharmacokinetic parameters could be determined precisely and accurately by two-level measurements at the 24th and 48th hours, and thus the time when MTX concentration reached the prescribed threshold could be predicted (16). Our study also shows that the benefit of repeated measurements is extremely low after analysis of 456 high-dose MTX levels over four cycles in 114 patients.

Studies indicating that serum creatinine levels can be used to predict MTX nephrotoxicity have been published (21-24). In a study where high-dose MTX treatments given to 264 pediatric patients with acute leukemia were examined, it was concluded that an increase of more than 50% in serum creatinine level was a better guide for delayed MTX elimination than serum MTX level (20). In a similar study, it was reported that serum creatinine and creatinine clearance were closely correlated with plasma MTX concentrations after high dose MTX and that it could be used in follow-up (21). In the study by Howard et al., it was reported that urine pH, serum creatinine value, urination, and examination of mucous membranes twice a day allowed the administration of hundreds of high-dose MTXcycles without too much toxicity (14). In our study, we also found that serum creatinine levels were increased only in two patients, and this resulted in acute renal failure, that MTX level and serum creatinine levels were high in the measurements at the same time and decreased to normal levels simultaneously. We also found that serum creatinine was compatible with MTX concentration when MTX level measurements could not be conducted.

To avoid the toxic effects of MTX, alkaline hydration and folinic acid are used, as well as MTX level measurements (12). As more than 90% of MTX is eliminated by the kidneys and dissolves poorly at acidic pH, alkaline hydration is performed (10, 19, 25). Alkaline hydration was reported to last for a minimum of three days (12, 26, 27) and in our study, hydration was also given for this duration. Folinic acid was started at the 42nd hour as it will neutralize MTX. However, studies have shown that the risk of relapse may increase when given in high amounts with additional doses (5, 10). In contrast, it has been questioned whether long-term folinic acid is harmful or reduces the efficacy of MTX (28). In the present study, folinic acid was administered to the patients at the 42nd, 48th, and 54th hours of MTX infusion, and only those with higher blood MTX levels than expected were given additional doses.

The probability of side effects increases with the increase in the dose of MTX (29). Mucositis is the most frequently reported toxic effect of MTX (12, 26, 29-31). MTX-related toxicity may require hospitalization (27, 29). In our study, only three individuals of the 114 patients had side effects requiring hospitalization and subsequent delay in the next chemotherapy cycle. In these three, nephrotoxicity was more frequent than mucositis, but the numbers are too small to draw any firm conclusion.

Despite the delayed clearance of MTX, considering that toxicity symptoms rarely develop in patients, it was observed that drug levels might not be directly related to toxicity, although measurements are still clinically useful. However, although high-dose MTX has been used without level follow-up, if MTX levels are available but repeated testing is not possible, it seems advisable to perform at least a limited number of MTX level measurements after infusion. As a preventive measure, it may be reasonable to follow up on MTX levels earlier and use more measurements in patients with toxicity in earlier high-dose MTX cycles. Although more comprehensive studies are required, this study showed that MTX level measurement at the 42nd hour in the first MTX treatment cycle might offer reliable guidance. Thus, we believe this may be a pragmatic solution to repeated measurements in a resource-limited setting, enable better planning for other subsequent treatments, and provide an effective, reliable, and cost-efficient solution to the problem of

repeated MTX measurement when giving high-dose treatment.

A limitation of this study was that, due to the retrospective nature of the study, some data was missing from the comparison of the levels between the four sequential cycles.

Conclusion

It was considered that in the high-dose MTX treatments after the first dose, the contribution of the blood MTX levels measured every 6 hours to the forming of the treatment was extremely limited. MTX level measured at the 42nd hour in the first treatment might be a practical approach to guide the management of other MTX treatments.

Abbreviations

MTX — Methotrexate
ALL — Acute Lymphoblastic Leukemia
G6PDH — Glucose-6-Phosphate Dehydrogenase
NAD — Nicotinamide Adenine Dinucleotide

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Licensing

Sažetak

KORISNOST PONOVLJENIH MERENJA NIVOA LEKA NAKON INFUZIJE VISOKE DOZE METOTREKSATA ZA PLANIRANJE LEČENJA KOD PEDIJATRIJSKE LEUKEMIJE

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Uvod: Iako je visoka doza metotreksata (MTX) uspešan hemoterapeutski agens koji se koristi u lečenju akutne limfoblastne leukemije u detinjstvu, toksični efekti opasni po život retko se primećuju. Zbog toga se preporučuje često praćenje nivoa leka. Studija je istraživala neophodnost merenja nivoa leka i minimalnog bezbednog broja merenja.

Materijali i metode: Retrospektivno su pregledani dosijei pedijatrijskih pacijenata sa akutnom limfoblastnom leukemijom koji su primali terapiju u visokim dozama MTX u jednom centru između 2018. i 2021. godine. Protokol tretmana je bio: 3000 mL/m^2 alkalne hidratantne tečnosti je nastavljeno do 72. sata zajedno sa 2 gr/m^2 kontinuiranom infuzijom MTX u niskorizičnoj grupi i 5 gr/m^2 u umereno i visoko rizičnim grupama i 15 mg/m^2/doza folinske kiseline je davana u 42. 48. i 54. satu.

Rezultati: Evaluirana su 456 tretmana metotreksatom (MTKS) kod 114 pacijenata. Slični rezultati ($p > 0,05$) dobijeni su u merenjima nivoa MTKS-a 24., 42., 48. i 54. časa nakon primene MTKS-a. U ponovljenim merenjima podaci na 42. satu su bili slični ($p = 0,021$). Broj slučajeva koji su bili >150 mmol/L u 24. satu infuzije metotreksata i iznad 1 μmol/L u 42., 48. i 52. satu su bili slični u ponovljenim merenjima.

Zaključak: Iako se preporučuje, često praćenje nivoa MTX možda neće uvek ukazivati na toksičnost. U centrima sa ograničenim laboratorijskim kapacitetima, nivo MTX meren na 42. satu u prvom tretmanu može biti praktičan pristup za upravljanje drugim MTX tretmanima.

Ključne reči: leukemija, metotreksat, toksičnost, nivo leka.

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