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Assessment of High Dose Methotrexate Serum Level in Hematological Diseases

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ABSTRACT

The Methtrexateoncology drug has a significant role in treatment of acute lymphoblastic leukemia. Although this effective role of Methotrexate, it has many adverse effects especially if administered in high dose. To estimate of the serum level of Methotrexate and clearance, pharmacokinetic and pharmacodynamic of Methotrexate. A clinical prospective follow up study conducted in Baghdad Hematology center of Medical city during the period from 1st of November, 2018 to 20th of April, 2019on sample of 53 Iraqi patients with hematological malignancy. The diagnosis of acute lymphoblastic leukemia or non-Hodgkin's lymphoma was done by the physicians through proper investigations. The Methotrexate dose and infusion rate were designed by the responsible Hematologist. The patients were followed through serum collection and examination of Methotrexate level by Apput Machine. The Methotrexate adverse effects were present in 6 (11.3%) patients with hematological malignancy; 55% mucositis, 18% hepatic adverse effects, 18% renal adverse effects and 9% central nervous system side effects. Mean serum Methotrexate 24 hr for patients with hematological malignancy was significantly higher among patients with positive hepatic, renal and central nervous system adverse effects ($p<0.05$). Mean serum Methotrexate 72 hr for patients with hematological malignancy was significantly higher among patients with positive hepatic and renal adverse effects ($p<0.05$). The common Methotrexate adverse effects after 24 hours and after 72 hours in treatment of hematological malignancy in patients are hepatic, renal and central nervous system adverse effects.

1. INTRODUCTION

The pharmacological and medical management of complex chemotherapy regimens are vast and complex, requiring an intimate understanding of physiology, particularly when novel biologic agents are utilized with commonly used regimens. The pharmacological and medical management of hematologic malignancies with a tendency to have central nervous system (CNS) involvement is complex and requires an understanding of physiology and pharmacology. Many chemotherapy regimens used to treat hematologic malignancies with

either CNS involvement or high risk for CNS disease will include the administration of high dose methotrexate [1]. MTX, a chemotherapy antineoblastic drug of antifolate metabolism, that has a similar chemical structure to folic acid and can inhibit DNA synthesis by inhibiting the activity of dihydrofolate reductase in cells, has been proven to have a high application value in ALL [2]. MTX has increased affinity for its target enzymes when MTX is polyglutamated intracellularly and the polyglutamated MTX (MTXp) is intracellularly retained far longer than the administered monoglutamated MTX. The antileukemic effect of MTX is well documented and it has been shown that intracellular and extracellular concentrations of MTX and its active polyglutamylated metabolites are significant for the antileukemic effect and cure rate [3]. It is also likely that MTX has inhibitory effects on the intracellular transport of glucose. MTX kills cells during the S phase of the cell cycle and has the highest efficacy on rapidly dividing cells. In high-dose MTX treatment, the cells are depleted and the patient will die, if leucovorin rescue is not given. Leucovorin, a reduce folate coenzyme, repletes the intracellular pool of tetrahydrofolate cofactors. The effect of low-dose MTX treatment is probably more due to longlasting effect of the polyglutamation [4].

Pharmacokinetics: Between 50-60% of plasma MTX is bound to proteins, and at low doses this may be up to 95%. Between 80-90% of low-dose MTX is eliminated unmetabolised by renal excretion within 48 hours. The plasma-MTX half-live is 3 to 10 hours after low oral doses. After high intravenous doses, MTX disappears in a triphasic way: a rapid distribution phase, followed by the second phase reflecting renal clearance with a half-life of 2 to 3 hours, and the third phase with a half-life of 8 to 15 hours [5].

Potential Toxicities of High-Dose Methotrexate (HD-MTX): Nephrotoxicity caused by HDMTX arises through crystal nephropathy, which occurs when methotrexate and its metabolites precipitate within the renal tubules. Because methotrexate is acidic, drug crystals are not present in urine with an alkaline pH, as alkalinization greatly increases methotrexate solubility and excretion [6]. Transient liver toxicity may include reversible chemical hepatitis in up to 60% and hyperbilirubinemia in 25% of courses, respectively [7]. In up to 15% of HDMTX courses, patients report transient disturbances of the central nervous system (CNS), and a subset of these experience significant symptoms, such as cortical blindness, hemiparesis, and seizure [8]. Other common side effects are nausea, vomiting, diarrhoea, stomatitis, megaloblastic anaemia, leucopenia, trombocytopenia, transient elevation of the hepatic transaminases and bone marrow suppression. Lowering or postponing the doses can reduce the toxic side effects. In both intravenous and intrathecal therapy, neurological toxicity can occur [9].

Risk Factors of HD-MTX Toxicity: Several patient-related factors can increase the risk for AKI. Volume depletion is perhaps the most important and can result from fluid losses due to vomiting or diarrhea, adrenal insufficiency, or renal salt wasting. Reductions in intravascular volume lead to renal hypoperfusion with subsequent decreased urine output [10]. In most patients with normal renal function, HDMTX can be given safely with the use of several supportive care strategies. These should include adjusting medications with potential interactions, vigorous hydration, and urinary alkalinization (target pH $\geq$ 7) before starting methotrexate infusions. The goal is to enhance the solubility and dilution of methotrexate in the urine and apply Folinic acid guided by serial serum methotrexate levels to protect against potentially lethal toxicity [11].

2. Patients and Methods

2.1 Study design & settings

This study is a clinical prospective study conducted in Baghdad Hematology center of Medical city during the period from 1st of November, 2018 to 20th of April, 2019.

2.2 Study population

patients with hematological malignancy (47 ALL patients and 6 NHL patients) admitted to Baghdad Hematology center of Medical city for Methotrexate treatment were enrolled in the study.

2.3 Inclusion criteria

1. Patients age (≥14 years old).
2. Acute lymphoblastic leukemia.
3. Non-Hodgkin's lymphoma.

2.4 Exclusion criteria

1. <14 years old.
2. Moderate to sever liver disorder.
3. Known renal failure.
4. Known neurological disorder.
5. Refused to participate.

2.5 Sampling

A convenient sample of 53 Iraqi patients with hematological malignancy admitted to Baghdad Hematology center of Medical city for Methotrexate treatment according to chemotherapy protocol was selected after eligibility to inclusion and exclusion criteria. The MTX dose and infusion rate were designed by the protocols. The patients were followed through serum collection and examination of MTX level by Apput Machine. The dose of 15 mg every 6 hour Folinic acid was administered 12 hours after finishing MTX infusion.

3. Results

This study included 53 Iraqi patients with hematological malignancy presented to Baghdad Hematology center of Medical City. Mean Methotrexate (MTX) dose for patients with hematological malignancy was 2904.4±1463.1 mg and mean body surface area of them as 1.85±1.41 $cm^2$with mean dose/BSA as 1756.1±950.9 mg/cm^2. Mean serum level of MTX 24 hr was 0.53±0.67 mg, for 48 hr was 0.37±0.49 mg and for 72 hr was 0.47±0.86 mg. All these findings were shown in table 3.

Table 1: Methotrexate dose and serum levels of patients with hematological malignancy.

Variable	No. of patients	%
Total dose of MTXmean±SD (2904.4±1463.1 mg)		
BSA mean±SD (1.85±1.41 cm^2)		
Dose/BSAmean±SD (1756.1±950.9 mg/cm^2)		
Serum level of MTX 24 hrsmean±SD (0.53±0.67 mg)		
Serum level of MTX 48 hrsmean±SD (0.37±0.49 mg)		
Serum level of MTX 72 hrsmean±SD (0.47±0.86 mg)		

The MTX adverse effects were present in 6 (11.3%) patients with hematological malignancy; 55% mucositis, 18% hepatic adverse effects, 18% renal adverse effects and 9% central nervous system side effects. All these findings were shown in table 4 and figure 3.

Table 2: MTX adverse effects of patients with hematological malignancy.

Variable	No. of patients	%
Adverse effects		
Negative	47	88.7
Positive	6	11.3
Total	53	100.0
Adverse effects types		
Mucositis	6	55.0
Hepatic	2	18.0
Renal	2	18.0
CNS	1	9.0
Total	11	100.0

Most (98.1%) of patients with hematological malignancy were treated with 15 mg/mg folinic acid and only one patient was treated with 300 mg folinic acid. Number of folinic acid doses was 4 doses for 50.9% of patients with hematological malignancy, 8 doses for 37.8% of them and 12 doses for 11.3% of them. All these findings were shown in table 7.

Table 3: Folinic acid doses of patients with hematological malignancy.

Variable	No. of patients	%
Folinic acid dosemean±SD (20.4±39.1 mg)		
15 mg	52	98.1
300 mg	1	1.9
Total	53	100.0
Number of folinic acid doses		
4 doses	27	50.9
8 doses	20	37.8
12 doses	6	11.3
Total	53	100.0

Table 4: Distribution of serum MTX levels according to adverse effects.

Variable	Negative Mean±SD	Positive Mean±SD	P
			Mucositis
Serum MTX 24hr	0.49±0.64	0.79±0.86	0.3*^{NS}
Serum MTX 48hr	0.29±0.35	0.89±1.1	0.1*^{NS}
Serum MTX 72hr	0.12±0.05	0.69±1.1	0.5*^{NS}

Hepatic			
Serum MTX 24hr	0.48±0.63	1.8±0.2	**0.004***S
Serum MTX 48hr	0.29±0.35	0.89±1.1	0.1*NS
Serum MTX 72hr	0.08±0.05	2±0.0	**<0.001***S
Renal			
Serum MTX 24hr	0.48±0.63	1.8±0.2	**0.004***S
Serum MTX 48hr	0.29±0.35	0.89±1.1	0.1*NS
Serum MTX 72hr	0.08±0.05	1.9±0.0	**<0.001***S
CNS			
Serum MTX 24hr	0.5±0.64	2±0.0	**0.02***S
Serum MTX 48hr	0.39±0.49	0.08±0.0	0.5*NS
Serum MTX 72hr	0.46±0.85	-	-

*Independent sample t-test, NS=Not significant, S=Significant.

Table 5: Distribution of serum MTX levels according to protocols.

Variable	Hyper CVAD Mean±SD	UKALL Mean±SD	HDMTX Mean±SD	P
Serum MTX 24hr	0.3±0.5	0.68±0.6	0.89±0.8	**0.02***S
Serum MTX 48hr	0.31±0.2	0.22±0.25	0.56±0.73	0.4*NS
Serum MTX 72hr	0.11±0.06	-	0.7±1.1	0.5**NS

*One way ANOVA analysis, **Independent sample t-test, NS=Not significant, S=Significant.

Table 6: Distribution of serum MTX levels according to time of infusion.

Variable	24 hr Mean±SD	4 hr Mean±SD	P
Serum MTX 24hr	0.46±0.6	1.2±0.9	**0.01***S
Serum MTX 48hr	0.33±0.46	0.52±0.67	0.5*NS
Serum MTX 72hr	0.56±0.96	0.08±0.0	0.6*NS

*Independent sample t-test, NS=Not significant.

4. Discussion

Current study showed no significant relationship between high MTX dose and oral mucosistis. This finding is in agreement with results of [11] study in Japan which reported no significant relationship between high MTX serum concentration and oral mucositis. In present study, the high dose serum MTX levels (24 hours and 72 hours) of Iraqi adults with hematological malignancy were significantly related to hepatic adverse effects. This finding regarding hepatic adverse effects of high dose MTX is similar to results of [12] study in Turkey. Current study revealed that high dose serum MTX levels (24 hours and 72 hours) of Iraqi patients with hematological malignancy were significantly related to renal adverse effects. This finding is consistent with results of [13] study in Japan. However, longer duration of a high serum concentration of MTX must be

prevented42, as MTX is highly cytotoxic and has many other adverse effects like hepatotoxicity, digestive tract and hematologic toxicity and long-term high serum MTX level must be in less than 0.1 nmol/mL [14]. Present study showed that high dose serum MTX levels (24 hours) of Iraqi patients with hematological malignancy were significantly related to central nervous system adverse effects. This finding coincides with results of [15]. In current study, mean serum MTX level 24 hours for hematological malignancy patients on HDMTX protocol was significantly higher than serum MTX 24 hours levels for patients on Hyper CVAD and UKALL protocols (P=0.02). These findings are in agreement with results of [16] study in USA Our study showed that mean serum MTX level 24 hours for hematological malignancy patients on 4 hours infusion was significantly higher than serum MTX 24 hours levels for patients on 24 hours infusion (P=0.01). This finding is similar to results of [17] study in Chile.

5. Conclusion

- The common Methptrexate adverse effects without hematological events after 24 hours and after 72 hours in treatment of hematological malignancy in patients are hepatic, renal and central nervous system adverse effects.
- The hepatic and renal adverse effects of Methotrexate are shown after 24 and 72 hours elevation of serum concentration, while neurotoxicity is shown after 24 hours.
- The high serum concentration of Methotrexate is related to high dose Methtrexate protocol and high infusion rate of Methotrexate administration.

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