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Medium and High-Dose Methotrexate-Induced Toxicity in Children with Acute Lymphoblastic Leukemia

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Abstract

Background: Methotrexate has an important role in treatment of acute leukemia. We measured methotrexate level in CSF and blood of children with acute lymphoblastic leukemia to determine complications and outcomes.

Materials and Methods: One hundred and twenty patients (73 male, 47 female), with mean age at diagnosis of 6.1 years (11mo_15years) entered the study. Patients were divided into two groups receiving consolidation therapy of medium-dose MTX 2g/m2/24hrs, or high- dose MTX 5g/m2/24hrs respectively. Clinical features, concentration and pharmacokinetic parameters of MTX, as well as serum creatinine were assessed.

Results: The mean serum MTX levels (24 hours after therapy) was 8.9_ 9.8 µmol/L after 4 courses. The mean serum MTX level 48 hours after therapy was 0.3-0.42 µmol/L after 4 courses. The mean CSF MTX levels after therapy was 0.22 µmol/L. The mean serum creatinine before and after MTX therapy were not different between two groups. Mucositis was observed as grade 0; in 65.8%, grade 1 in 15%, grade 2in 15%, grade 3 in 3.3% and grade 4 in 0.8% of patients. CNS relapse was observed in 20.8% patients. The mean MTX level after 24 hours in patients with CNS relapse were lower than the mean MTX level in patients with no CNS relapse. Mortality in patients with severe mucositis was higher than patients with mild mucositis (P value <.001). Mortality in patients with CNS relapse was greater than patients without CNS relapse.

Conclusion: Routine assessment of the serum MTX levels for medium dose MTX is not necessary, however, careful clinical monitoring of these patient is mandatory. Monitoring the plasma concentration of MTX is necessary in high dose MTX therapy.

Keywords: Leukemia, treatment, side effect, methotrexate

Introduction

Acute lymphoblastic leukemia (ALL) and Non-Hodgkin Lymphoma (NHL) are the most common malignancies causing mortality and morbidity in children [1].

Various therapeutic protocols are being used to treat these malignancies and high dose methotrexate (HD-MTX) is the main therapeutic agent used [2-9]. In contrast with many beneficial effects of HD-MTX, dangerous side effects must be considered [3-7].

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A vast study done in the United States has reported HD-MTX induced mortality to be about 6% [7]. Different pharmacokinetic characteristics of patients has highlighted the necessity of MTX blood level measurement to avoid likely toxicity. Since 1972 different laboratory measurement methods have been applied and high pressure liquid chromatography (HPLC) is still the outstanding method [2, 8,9].

Because the inapt proliferation of bone marrow originated leukocytes determines the pathogenesis of leukemia, the therapeutic protocols have focused on cell proliferation inhibitory agents[10-12]. Such drugs act through different mechanisms to abort malignant cells proliferation; for example direct cell killing or disruption of cell metabolism. If a single drug is used, malignant cells encounter it by changing their metabolic pathways therefore multi-drug protocols are always recommended[13-15]. Multi-drug therapy invades and overwhelms malignant cells and disarms them [16-19].

Berlin-Frankfurt-Munster (BMF) protocol is used to treat all children with ALL, except those with B-cell ALL or aged less than 1 year [15].

The present study intends to determine the incidence of MTX dose-based toxicity (5g/m2/24hrs compared to 2g/m2/24hrs), the age based MTX toxicity and MTX plasma level based toxicity.

Materials and Method

This was a prospective-cohort study conducted in Ali-Asghar hospital. One hundred and twenty children referred to this center with ALL aged 1 to15 years were involved (2004-2007).

All of patients with ALL entered the study after filling written informed consent and underwent the IC-BFM 2002 chemotherapy protocol . After induction phase, children with standard risk were given 6 mercaptopurine 25mg/m2, before lunch, once fortnightly, and MTX 2000mg/m2/24hrs, every 14 days (×4) as consolidation phase (M protocol). On the other hand children with high risk were given MTX 4000 mg/m2/24hours, every 14 days (×4). Ten percent of MTX was administered in 30 minutes and the rest was administered in 23.5 hours; moreover calcium leukoverin was administered 15mg/m2/dose, 42, 48 and 54 hours after MTX administration commencement.

The inclusion criteria were complete remission, body well being, absence of infection or mucositis, normal plasma creatinine level (based on age), absence of urinary stasis, satisfactory liver function tests (AST and ALT <5 times and bilirubin < 3 times over than the normal range), and satisfactory complete blood counts (WBC>1500/µl, neutrophil> 500/µl and platelets> 50000/µl). Also urine flow had to be within the normal range with PH>7 (4hours

Table 1: Mean plasma and CSF methotrexate levels through different therapeutic courses.

	Methotrexate											
	BLOOD								CSF			
	A		B		C		D		A	B	C	D
	24 hr	48 hr	24 hr	48 hr	24 hr	48 hr	24 hr	48 hr	24 hr	24 hr	24 hr	24 hr
Mean	9.79	0.42	8.90	0.30	9.10	0.29	8.80	0.30	0.22	0.25	0.23	0.21
SD	9.52	0.47	7.30	0.25	7.70	0.26	6.78	0.29	0.14	0.12	0.10	0.20
Min	0.20	0.10	0.60	0.10	0.30	0.20	0.50	0.10	0.50	0.60	0.40	0.50
Max	51.00	3.30	33.00	1.40	50.00	1.50	37.00	1.50	0.70	0.80	0.65	0.70

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before till 72 hours after MTX administration). Body fluid balance was be checked twice daily and if fluid intake was 400 ml/ m2 or more than its output per 12 hours, then lasix 0.5 mg/kg was injected.

When MTX administration ended, its serum level was measured 24, 48 and 72 hours later. Patients' hydration and urine alkalization as well as plasma creatinine were checked in first and second days and patients were monitored daily to find possible MTX side effects such as abdominal discomfort, mucositis, nephrotoxicity and neurotoxicity. The characteristics of patients including age, gender, plasma creatinine before, 24 and 48 hours after MTX administration, MTX plasma levels 14, 48 and 72 hours after administration were recorded. Also MTX level in CSF, abdominal discomfort, mucositis, nephrotoxicity and neurotoxicity were recorded after each course of treatment.

Results

In totall 120 children entered our study with 73 patients (61%) being male and 47 patients (39%) being female. The mean age among patients was 3.38±6.14years. Twenty one patients (17.5%) were in high-risk group and the rest were in standard risk group.

The mean MTX plasma level after 24 and 48 hours of chemotherapy were 8.9-9.8µmol/l and 0.3-0.42µmol/l respectively (less than toxic level) (Figure1). The mean MTX level in CSF was 0.22µmol/l (Table1). The mean plasma creatinine values before and after MTX therapy, were 0.56-0.63mg/dl and 0.59-0.62mg/dl respectively; with no statistically significant difference. Maximum plasma creatinine value was 1.1 after course 1 (Figure 1). In addition mucositis was seen in grades 0, 1, 2, 3 and 4 in 65.8%, 15%, 15%, 3.3% and 0.8% of patients respectively (Table2). Relapse in CNS happened in 20.8% of children and 21% of patients died. Although, the mean MTX plasma level of children aged less than 6 years was lower than those aged more than 6 years, no statistically significant difference was observed. Both groups showed no significant difference considering the mucositis within first 24 hours of therapy. The mean MTX plasma level of patients with relapse in CNS was lower than the rest of patients, but no statistically significant difference was found. Mortality and morbidity rates were significantly different between patients aged >6y (8 cases, 12.1%) and patients aged ≤6y (17 cases, 31.5%) (P=0.01, OR=3.3). In contrast, relapse in CNS was not significantly different between patients aged >6y (10 cases, 15.2%) and patients aged ≤6y (15 cases, 27.8%). Patients with relapse in CNS showed higher mortality compared to the rest (64% compared to 9.5%, P<0.001). Patients with mucositis showed higher mortality too (79.6% compared to 9.3%, P<0.001). The reference MTX plasma levels after 24, 48 and 72 hours of therapy were <5µmol/l, <0.5µmol/l and <0.05µmol/l respectively.

Discussion

MTX still plays the most principal role in leukemia treatment. Leukoverin is often used to diminish the side effects and toxicities (16-18). Despite more than 40 studies on HD-MTX, no study shows a perfect guideline for definite cure of relapse in CNS [1-8, 19].

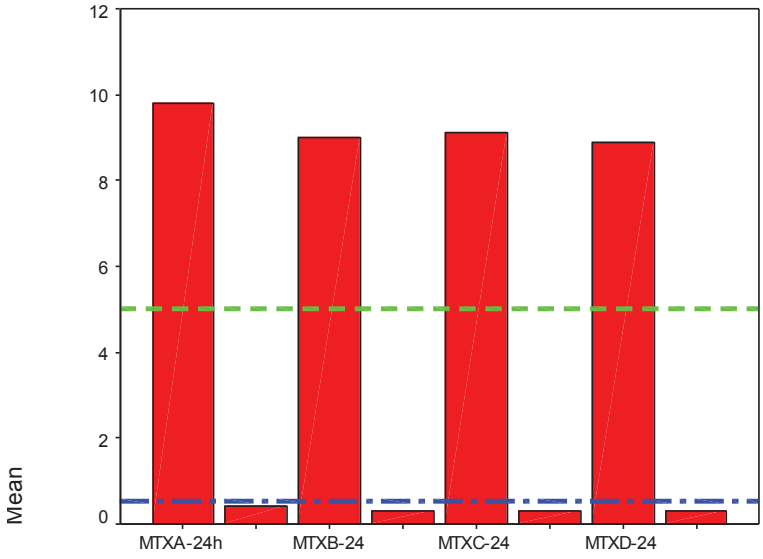
Many previous studies have included 60-70% of patients in standard-risk group similar

Table 2: Prevalence of the various grades of mucositis.

Percent	Frequency	Mucositis Grade
65.80	79	None
15.00	18	Erythema
15.00	18	Patchy pseudomembrane
3.30	4	Confluent Pseudomembrane
0.80	1	Necrosis

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Figure 1: Mean plasma and CSF methotrexate levels through different therapeutic courses.



to our study [4-9]. A Dutch study on patients with ALL (1984-1988) showed that the mean MTX dose of 2gr/m2 led to beneficial effects on 291 patients and cure rate of 81% [11].

In the present study, patients were randomly classified into 2 groups and MTX was administered then its plasma level were measured 24, 48 and 72 hours after administration, showing no statistically significant difference between two groups. Also the mean plasma creatinine values before and after MTX therapy, were 0.56-0.63mg/dl and 0.59-0.62mg/dl respectively indicating no significant difference.

Joannon et al. have suggested that medium-dose MTX (2gr/m2) induced toxicity can be minimal and does not require plasma level monitoring if leukoverin is added [8]. The present study showed that 48 hours after medium-dose MTX therapy (2gr/m2), the mean MTX plasma level in all courses were within the range of 0.3-0.42 µmol/l (lower than the toxic level) therefore, adequate hydration, alkalization and use of leukoverin can obviate the need for MTX plasma level monitoring.

Relling et al. examined MTX on 134 children with ALL through various protocols comprising diferent therapeutic courses (900-3700 mg/m2, 481 courses in overall) and the major observed toxicity was mucositis (22%) [7], similar to what we found in our study. No significant difference was found among the grades.

Shuper et al. believed that both low and high doses of leukoverin can be detrimental for the cure[14]; low dose of leukoverin leads to appearance of MTX side effects such as abdominal discomfort, nephrotoxicity, neurotoxicity, myelosuppression and mucositis, and the high dose of leukovern neutralizes antitumoral effects of MTX and thus lets malignant cells relapse in CNS [12-13, 20].

MTX makes a brief concentration in CNS and is expelled by multi-drug resistance proteins [1-3]. Our study showed that mean MTX level in CSF (24 hours after therapy) in patients with relapse in CNS was lower than those without relapse, but no significant difference was found. Relapse in CNS leads to high mortality (64% compared to 9.5%, P<0.001). It is strongly suggested to use leukoverin at 42, 48 and 72 hours after MTX initiation [8-12, 21], moreover intratechal MTX administration must be 1 hour after its intravenous administration to achieve satisfactory drug levels in CSF [12,13].

Conclusion

Routine assessment of the serum MTX levels for medium dose MTX is not necessary, however, careful clinical monitoring of these patient is mandatory. Monitoring the plasma concentration of MTX is necessary for high dose MTX therapy.

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