# High Dose Methotrexat Liver Toxicity

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## Abstract

**Introduction**: Methotrexate (MTX) is an anti folate drug that used in malignant and non malignant patients. The usage of high dose methotrexate was limited to patients with: Osteogenic sarcoma, Ewing sarcoma and Lymphoma. The aim this study was to determine the toxicity or side effects of very high dose methotrexate (8-10 gr/$m^2$/cycle). This study is the first study in Iranian patients and one of few study in world wide with this dosage and number of patients.

**Patients and methods:** In a prospective study on all patients with osteogenic sarcoma, Ewing sarcoma , and lymphoma that candidate for high dose MTX (mean total dosage was 27 gr/$m^2$/case without any underlying disease, and after full physical examination and performing necessary paraclinical tests (Na, K, BUN, Cr, Uric acid, AST, ALT, Bilirubin, and ECG entered and information was filled for all of them prior and after the every cycle. The follow up visit include: repeated physical examination and duration of its was at least 6 months.

**Results:** There were 102 cases, 60 cases were male (58.8%), 42 female (41.2%), median age was 19.5 (5-80), Osteogenic sarcoma and Ewing sarcoma 87 cases (49/male and 38/female), 15 cases were Lymphoma (11/male, 4/female). Total course of MTX therapy was 273 (median courses were 2.67/patient). Our result revealed: Abdominal pain due to hepatomrgally was not obsereved, rising in bilirubin and alkaline phosphetase were not observed, but rising in AST and ALT were the most common liver toxicity due to high dose MTX and detail were: this toxicity was in 23 cases (46.9%) [11/men (18.3%) and 12/female (28.6%)] respectively. The maximum toxicity was grade 2 toxicity according to NCI criteria. All of them resolved spontaneously without any specific management and treatment except watch and wait.

**Conclusion:** This study revealed that the usage of very high dose methotrexate had liver toxicity but these toxicities were limited to abnormal AST and ALT. All of these toxicities were transient and resolved without any scar on liver function after cessation of therapy. After at least 6 months follow up we didn't see any abnormality.

**Key words:** High dose, Methotrexate, Liver toxicity

## Introduction

Methotrexate (MTX) is an anti folate drug that used in malignant and non malignat diseases.(1, 2, 3) High dose MTX usage is MTX more than 1 gr/$m^2$.(4) The determination of MTX toxicity is very important because this drug has many different toxicities. MTX had some histologic liver damage such as: Steoatosis, ITO cell hypertrophy, An iso nucleosis, Liver fibrosis.(5) Other side effects were rising in aminotransferases.(6, 7) Usage of low dose MTX in long period could lead to fibrosis or cirrhosis.(8, 9) High dose MTX could lead to chang and rise in liver enzyme in 50%.(10) Other studies revealed major liver toxicity with high dose MTX.(11, 12) Liver toxicity due to high dose MTX in soth east of iran was limited to rising in aminotransferases less than 2 times the upper limit of normal.(13) Acute rising in aminotransferases

**Table- 1. Patients characteristic.**

| Characteristic | Our results |
|---|---|
| Total number of patients | 102 |
| Median (range) age (in years) | 19.23 (4-82) |
| Sex (%) male/Female | 60 (58.8)/42(41.2) |
| Total cycles of HDMTX given all patients | 273 |
| Average (range) cycles of HDMTX per patient | 2.67 (2-5) |

**Table- 2. Disease frequency.**

| Primary disease | Sex | | Total |
|---|---|---|---|
| | Male | Female | |
| Osteosarcoma | 38 | 34 | 72 |
| % within osteosarcoma | 52.8% | 47.2% | 100% |
| % within all patients | 37.2% | 33.3% | 70.6% |
| Ewing sarcoma | 11 | 4 | 15 |
| % within Ewing sarcoma | 73.3% | 26.7% | 100% |
| % within all patients | 10.8% | 3.9% | 0.47 |
| Lymphoma | 11 | 4 | 15 |
| % within lymphoma | 73.3% | 26.7% | 100% |
| % within all patients | 10.8% | 3.9% | 3.9% |
| Total | 60 | 42 (100%) | 102 (100%) |

occurs in 60%- 80% of patients that treated with high dose MTX and generally resolved in one to two weeks later. Rarely high dose MTX could lead to rise in bilirubine.(14) Also hepatic fibrosis (with a second risk for hepatocelluar carcinoma) reported rarely.(15) In over all our groups didn't see any studies on very high dose MTX (> 8-10 gr/m2) in Iranian population and was very little in literature review.

## Patients and methods

In this prospective study all patients with Osteogenic sarcoma, Ewing sarcoma and lymphoma that candidate for high dose MTX entered. The dose MTX was 8-10 gr/$m^2$/cycle. Leucovorin rescue used after MTX therapy. Inclusion criteria were: Neutrophil>1500 for ALL and 2500 for sarcom patients, Platelet>100000, normal renal function and normal liver function. Exclusion criteria were: Leukopenia, thrombocytopenia, alchol abuse, pregnancy, hepatitis, HBSAg+, HBCAb+, HCV+ or abnormal liver function test or liver involvement secondary to primary disease. The patients didn't receive any other drugs with liver effect. Patients examed prior to start the treatment protocol and befor and after of every cycle of high dose MTX. Liver toxicities defined to every abdominal pain due to liver enlargement, every rising in aminotranferases, blirubin and alkaline phosphatase.

After performing a good IV line, maintenance fluid therapy and Kytril 3 mg, 30 minutes befor initiation of MTX therapy ordered. The treatment protocol was: MTX 8-10 gr/$m^2$/cycle in 500$^{cc}$ NS/4h and then Leucovorin rescue 30mg/6h for at least 20 doses. The patients with lymphoma received 2- 4 cycles (mean= 2.3 course /case) and oteogenic sarcoma and Ewing sarcoma 2- 5 cycles (mean= 2.7 course/case. Total dose in lymphoma patients were 20-36 gr/$m^2$ and in sarcoma patients were 27-50 gr/m2. Pre MTX therapy in all patients were: maintenance IV fluid therapy + 1000 cc NS/day + 1 vial bicarbonate.

## Results

In this prospective study 102 cases enrolled, 58.8% male (60 cases), 1.2% female,(42) mean age was 19.5 years (5-80). 23 cases were in childhood period (12/male and 11/female), 71 cases were 15-30 years (43/male, 28/female), and 8 cases more than 31 years old (5/male, 3/female) respectively (Table- 1). All patients were 102, 72 cases were osteogenic sarcoma (38/male, 34/female) 15 cases Ewing sarcoma (11/male, 4/female) and 15 cases were lymphoma (11/male, 4/female) respectively. Total courses of MTX therapy were 273 (mean: 2.67/case). In Osteogenic sarcoma, Ewing sarcoma and Lymphoma were (Table- 2): 204, 34, 35 courses. The major toxicities other than liver were: Nausea and vomiting 32%, allopecia 12%, rash 3%, steomatitis 5%, anorexia 15%, and cytopenia 10% respectively. Assessment of liver toxicity was the goal of our study, revealed: abdominal pain due to hepatomegally was not detected, rising in bilirubin and alkaline phosphatase were not and all of them had normal prothrombine time. But the abnormality in liver function tests such as AST, ALT detected in our patients as below: this toxicity was in 23 cases (46.9%) 11/men (18.3%) and 12/female (28.6%) respectively. The maximum toxicity was grade 2 toxicity according to NCI criteria. All of them resolved spontaneously without any specific management and treatment except watch and wait. The maximum grade of all toxicities were grade 2 toxicity according to NCI criteria (16) and resolved in the end of treatment. In follow up duration (at least 6 months) we didn't see any permanent abnormality or liver dysfunction.

## Discussion

High dose methotrexate defined to: usage of MTX more than 1000 mg/m2,(4) and in new report is usage of MTX more than 500 mg/$m^2$.(17) The studies about liver toxicity were not lot of but some studies revealed: One of these studies reported, rising in liver function in 80% of their cases and all were transient and reversible.(18) This abnormality

in another study was 60% and same to that study was transient.(19) Outryve and his groups reported, grade 2 histologic liver toxicity in a case report.(20) The study of Evan M,(21) and co worker on 10 cases with acute lymphoblastic leukemia treated with intensive dose of MTX, nine of 10 had abnormality in liver function tests and 9 had rising in AST and ALT, 7 had rise in LDH, and 2 cases had rise in bilirubin. 3 patients had hepatomegally and 1 case developed prolongation in prothrombine time. The other Study of Mashhadi,(13) in south east of Iran: in this study patients with choriocarcinoma and acute lymphoblastic leukemia received 500mg/$m^2$ and 1500 mg/$m^2$ respectively enrolled and evaluated for over all toxicity due to this dosage of MTX. Results showed, neusea and vomiting (28%), hepatomegally (0%), rising in AST and ALT in 15% but all was less than 2 times of upper limit of normal and grade 2 toxicity (>2 times of upper limit of normal) was not reported, headache 20%. But in recent study with very high dose methotrexate (8-10 gr/$m^2$/course) and total dose in lymphoma patients were 20-36 gr/$m^2$ and in sarcoma patients were 27-50 gr/$m^2$. Our evaluation focused on liver toxicity and showed: The major toxicities other than liver were: Nausea and vomiting 32%, allopecia 12%, rash 3%, steomatitis 5%, anorexia 15%, and cytopenia 10% respectively. Assessment of liver toxicity was the goal of our study, revealed: abdominal pain due to hepatomegally was not detected, rising in bilirubin and alkaline phosphatase were not and all of them had normal prothrombine time. But the abnormality in liver function tests such as AST, ALT detected in our patients as below: this toxicity was in 23 cases (46.9%) 11/men (18.3%) and 12/female (28.6%) respectively. The maximum toxicity was grade 2 toxicity according to NCI criteria.

## Conclusion

Our study revealed, liver toxicity due to very high dose methotrexate therapy limited to abnormal AST and ALT. All of these toxicity returned to normal in 2-3 weeks ofter cessation of treatment.

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