ORIGINAL ARTICLE

The effects of high dose methotrexate in patients with neoplastic diseases: a prospective study

MA Mashhadi*

Department of Internal Medicine, Hematology and Oncology Research Center, Zahedan University of Medical Sciences, Zahedan, Iran

Abstract

Background: Methotrexate (MTX) is one of the most widely used anti-cancer agents. The administration of a high-dose methotrexate (HD-MTX) can be safely administered to patients with normal renal function, using alkalinization, hydration, and pharmacokinetically guided leucovorin (LV) rescue. The aim of this study was to determine the side effects of HD-MTX in patients with for neoplastic diseases.

Methods: In a prospective study on all admitted patients in Hematology and Oncology Ward, receiving MTX for chemotherapy and without any other underlying disease, after full physical examination and performing necessary paraclinical exams (Na, K, Ca, BUN, Cr, Uric acid, SGOT, SGPT, bilirubin and ECG), the information form was filled for all at admission and in follow up visits to be used in a final assessment. Renal and hepatic function was assessed at the beginning of chemotherapy and systematically during subsequent cycles on the basis of available laboratory methods. The follow up included liver and renal function and other necessary laboratory tests.

Results: There were 98 cases, 48 of whom suffered from acute lymphoblastic leukemia and received high dose MTX (at least 2.5 gr) and 50 with choriocarcinoma received at least 800 mg per cycle. 31 cases were male and 67 female. The mean age was 26.4 years. The most common side effects were nausea and vomiting in 28 cases (28%). Hepatotoxicity (a rise in alanine aminotransferase > two to three times of the upper limit of normal) was not observed in any patient. Nephrotoxicity (at least 30% increase in BUN or creatinine or 30% rise in creatinine clearance) was not observed. In 8 patients, a rise in alanine aminotransferase less than two times the upper limit of normal was noticed. All these minor abnormalities were resolved in closed follow ups. None developed bone marrow suppression, serum electrolyte imbalance, and severe allergic reactions.

Conclusion: Our study revealed that MTX side effects in southern Iran were minimal and toxicity was absent at the end of treatment. The side effects of MTX should be revised in different populations with different genetic and HLA profile.

Keywords: Methotrexate; Hepathotoxicity; Side effects

Introduction

Methotrexate (MTX) is an important drug used in the management of malignancies and connective tissue disorders, such as rheumatoid arthritis. MTX is an inhibitor of dihydrofolate reductase, a critical enzyme in maintaining the intracellular folate pool in its reduced form as tetrahydrofolate, which is important for the synthesis of purine nucleotides and some amino acids.[1] Renal impairment and age are generally considered risk factors for developing MTX toxicity, but studies have shown conflicting results.[2] Gastrointestinal (GI) side effects also often occur during MTX treatment.[3] A rise in the liver enzymes, in particular the transaminases, occurs frequently during MTX treatment.[3,4] Dose, obesity, alcohol, and lack of folate supplementation are considered to be associated with hepatotoxicity.[5,6] Overall toxicity scores, including both hepatotoxicity and GI side effects have also been reduced by the addition of folic acid.[7-9]

***Correspondence:** Mohammad Ali Mashhadi, MD, Assistant Professor of Department of Internal Medicine, Hematology and Oncology Research Center, Zahedan University of Medical Sciences, Zahedan, Iran. **Tel:** +98-915-3411445, e-**mail:**dralimashhadi@yahoo.com
Received: December 12, 2007 Accepted: March 9, 2008

High-dose methotrexate (HD-MTX) with leucovorin (LV) rescue is used in the treatment of osteosarcoma, lymphoma and leukaemia. This treatment is usually given as a prolonged infusion, the duration of which can range from 4 to 48 hours. HD-MTX is usually well tolerated, patients are adequately hydrated and the urinary pH is kept above 7. Alkalization of the urine increases MTX excretion and reduces the risk of precipitation within the renal tubules, which can lead to acute renal failure.[10] The primary toxicities of HD-MTX infusions are myelosuppression and gastrointestinal mucositis. Mucositis precedes myelosuppression and its onset is usually 3–7 days after treatment. Myelosuppresssion and mucositis are usually resolved by about day 14. Other toxicities include acute and chronic hepatitis, self-limiting pneumonitis and central nervous system disturbances.[11] The aim of this study was to determine the side effects in patients treated with HD-MTX for neoplastic diseases.

Materials and Methods

In a prospective study, we evaluated MTX side effects in all admitted patients in Hematology and Oncology Ward who were candidate for MTX treatment during 2003–2006. Every patient treated with MTX with a dose more than 1000 mg in a therapeutic protocol was included in the study. Patients with liver and every other organ involvement or with a confirmed dysfunction were excluded. In addition, if the patients had any abnormality that might compromise the evaluation of toxicity, they were excluded from the study. The patients were assessed during admission and in the follow ups for any side effects. We evaluated and examined the patients for hepatotoxicity (a rise in alanine aminotransferase > two to three times the upper limit of normal, which according to the protocol rules, was a reason for MTX withdrawal). The 10 most commonly reported adverse side effects were nausea, dizziness, headache, rash, fatigue/malaise, abdominal pain, stomatitis, cough, alopecia, and diarrhea. The information about the patients was recorded in data sheets for final assessment. Baseline laboratory tests, complete blood cell count, urinalysis, serum electrolytes, blood urea nitrogen, creatinine, uric acid, liver enzymes and bilirubin tests were done for all patients.

The inclusion criteria were requiring a high dose MTX (without prior treatment), receipt of a written informed consent, age ≥ 10 years, absolute neutrophil count > 1500, platlet > 100000, normal renal and liver function test and creatinine clearance > 50 ml/min. The Exclusion criteria for the use of high dose MTX were prior administration of MTX, a creatinine clearance < 50 ml/min (Cockroft formula), liver disorders, leucopenia, thrombocytopenia, alcohol abuse, treatment with folic or folinic acid, pregnancy, and karnofsky status < 50. Hepatic function was reassessed each week before the subsequent cycle of the therapy. The patients were examined in all visits and were asked for muscle cramps, seizures and loss of taste to detect neurotoxicity.

After preparing a certain IV-line, all the patients received maintenance fluid replacement. Other pretreatment medications were Kytril and metoclopramide (10 mg) intravenously, 30 minutes before initiation of chemotherapy.

In choriocarcinoma, every cycle consists of 100 mg/m^2 MTX+IV push and then 200 mg/m^2 MTX+1000 ml NS in 12 hours and after 16 hrs, Leukovorine 30 mg/6 h (repeated every 2 weeks for at least 5 cycles). In acute lemphoblastic leukemia, single dose of MTX contained 1.5 gr/m^2 (at least 2.5 gr) MTX+500 ml NS in 6 hours and after 16 hrs Leukoverine, 30 mg/6 h. In both groups, the administration of MTX was at least 2500 mg (in acute lymphoblastic leukemia, 2500 mg stat and in choriocharcinoma, 500 mg every 2 weeks).

If hepatotoxicity (3 times rise in serum liver function test) was detected in the follow-up laboratory exams, the subsequent course of treatment was stopped till normal renal tests were achieved. Chemotherapy was continued in cases not showing hepatotoxicity and substantial neurotoxicity. Finally, the data were analyzed with SPSS Version 10 software. A p value of < 0.05 was considered significant. The data analysis was performed, using Chi Square and Fisher Exact tests.

Results

98 patients (31 males and 67 females) were enrolled. The patients were 10-55 years old (mean age=26.4 years), and were treated for solid tumors and hematological malignancies according to the applicable chemotherapy protocols. 48 cases (31 males and 17 females) had acute lymphoblastic leukemia, and 50 female cases had choriocarcinoma. No hepatotoxicity was noticed (a rise in alanine aminotransferase > three

times the upper limit of normal). In 15 patients (7 cases with ALL and 8 with choriocarcinoma), a rise in alanine aminotransferase less than two times the upper limit of normal was detected. The most common complications were nausea and vomiting observed in 28 cases (28%). 20 cases (21%) complained of headache. The maximum duration of these complications was 48 hours. Vaginal bleeding and fever were detected in a 24-year-old woman with ALL-L2 and a total dose of 2.5 gr. This patient complained of hyperuricemia, proteinuria, upper extremity DVT, rash and abdominal pain. Stomatitis, GI bleeding, vomiting and pleuretic chest pain were detected in a 27-year-old woman with choriocarcinoma, but they were resolved with mere supportive care. None of the patients showed bone marrow suppression (leucopenia, thrombocytopenia and anemia), serum electrolyte imbalance, seizure, and severe allergic reactions. The results are summarized in the Table 1. Most of these symptoms appeared with the first or at most second pulse of MTX. The onset of symptoms was reported within 12 hours of taking MTX and continued for up to 1-2 days. Most of the patients had taken conventional anti-emetics and H_2 blockers for MTX related GI symptoms in the past with little or no benefit. All of these side effects were, according to WHO grading, less than grade 2 except thrombocytopenia that was grade 2 and 3 of toxicity. The patients were checked in the follow up closely and all of these toxicities were resolved spontaneously. The elevation of transaminases or creatinine was not observed, but nausea (grade 1 and 2) was found in 28% of patients and grade 1–2 mucositis in one patient. No acute HDMTX-related neurotoxicity was observed. On the follow-up, all patients resolved their toxicities without any specific medications.

Discussion

In our study, 98 patients with ALL and choriocarcinoma underwent chemotherapy with MTX and did not manifest any hepatotoxicity or any other significant toxicity. In our patients, side effects such as flu-like syndrome were not yet reported. One study on 411 patients receiving MTX showed that next to folate supplementation, a higher BMI is related to hepatotoxicity. Prior GI disorders and a younger age are related to the occurrence of diarrhea. MTX withdrawal is related to the absence of folate supplementation, prior GI disorders, BMI, and female sex. The side effects of MTX in this population included nausea in 37%, headache and dizziness in 24%, malaise and fatigue in 20%, abdominal pain in 19 %, stomatitis in 17 %, cough in 17 % and diarrhea in 10 %.[10] In this study, hepatotoxicity occurred in 26 %, which contradicts what was found in our study. The review of literature showed that the overall toxicity was mild to moderate which is in accordance with the data in our study. The first study consisted of 25 patients, of

Table 1: Prevalence of MTX side-effects in admitted patients in hematology & oncology ward in comparison with other studies.

MTX side effects	Prevalence according to other studies	Prevalence in our study	
		Number	%
Nausea and Vomiting	Common	28	28
Headache	Common	20	21
Dizziness	Common	5	5
Alopecia	Common	10	11
Hepatotoxicity	Common	0	0
Rash	Common	2	2
Stomatitis	Less common	1	1.1
Proritus	Less common	2	2
Anorexia	Less common	15	16
Bleeding	Less common	2	2
Flu-like syndrome	Less common	5	5
Chest pain	Less common	3	3
Abdominal pain	Less common	6	6
Diarrhea	Rare	2	2
Thromboemboli	Rare	1	1
Eosinophilia	Rare	1	1

whom 3 suffered from mucositis, 2 from DVT, one from PTE and one from renal failure. Agranulocytosis and thrombocytopenia were observed in one patient.[11] Another study was done on 45 patients of whom 12 had grade 2-3 unspecified toxicity.[12] In another study on 34 patients, the dose reduction was observed in 37% of the cases. Grade 3 mucositis was seen in 2% and real failure in 1%.[13] In another study by WHO, grade 3-4 toxicity was seen in 11% of the patients, and one patient died from septicemia secondary to grade 4 neutropenia according to WHO grading.[12] In a unique multicenter study, grades 3-4 toxicity were observed in < 10 % of patients.[14] The results of the present study, although a single center study, revealed that the side effect in southern Iran is very minimal and the major treatment related toxicity according to WHO grading was minimal and should be revised in different populations. Our data showed an association between a lower age and diarrhea. In accordance with the study of Anderson et al., the efficacy of MTX was higher in a man which is in accordance with the finding in our study. The risk of developing severe hepatotoxicity or other toxicities after MTX treatment is controversial. Therefore, systematic monitoring of the patients' hepatic function and of the other organs is necessary after the completion of chemotherapy. MTX has the potential to produce both mild and severe side effects. Our study revealed that these side effects in southern Iran were minimal and toxicity was absent or completely resolved in the end of treatment. Side effects of MTX should be revised in different populations with different genetic and HLA profiles.

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