Low Prevalence of High-dose Methotrexate Nephropathy in Patients With Malignancy

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Introduction. Methotrexate is an antifolate medication frequently used in the treatment of malignant and nonmalignant diseases. The usage of high-dose methotrexate was limited to patients with osteosarcoma, Ewing sarcoma, lymphoma, and acute lymphoblastic leukemia. One of the major side effects of high-dose methotrexate is nephropathy. The aim of present study was to determine the renal side effects of high-dose methotrexate in patients with malignancies.
Materials and Methods. In a study of 102 patients with osteosarcoma (n = 72), Ewing sarcoma (n = 15), and lymphoma (n = 15), treated with high-dose methotrexate, clinical and laboratory data including kidney function tests were recorded at baseline and during follow-up visits. The mean duration of follow-up was 6 months.
Results. The mean age of the patients was 19.5 years (range, 5 to 80 years). The total courses of methotrexate therapy were 273 (median, 2.67 per patient). The mean creatinine level was 0.82 mg/dL. Of the 102 patients, 3 (2.9%) developed acute kidney injury with an at risk phase. Another patient (1.0%) developed acute kidney injury and its phase was injury according to the RIFLE criteria. None of the cases were failed and acute kidney injury was alleviated in all of the affected patients.
Conclusions. Our data revealed a low prevalence of acute kidney injury with high-dose methotrexate therapy. In addition, these toxicities were limited to the first and second phases of the RIFLE classification, all of which resolved spontaneously.

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INTRODUCTION

Methotrexate is an antifolate medication used in the treatment of malignant and nonmalignant diseases.[1-3] Administration of methotrexate at a dose higher than 1 g/m^2 is generally referred to as "high-dose methotrexate therapy.[4]" One of the most important toxicities due to high-dose methotrexate is kidney failure.[5,6] Causes of kidney function impairment due to high-dose methotrexate have not been elucidated although precipitation of methotrexate or its metabolites in renal tubules or direct tubular effects may be the culprit.[7] Other factors such as abnormality in preglomerular resistance and direct damage to glomeruli are also considered.[6,8-10]

Good hydration and alkalinization significantly reduce methotrexate nephrotoxicity.[11] Acute kidney failure, which is the most common high-dose methotrexate renal toxicity, seen in 2% to 10% of patients receiving methotrexate,[12,13] is usually reversible with complete recovery, and treatment could be continued without dose reduction.[14] A number of past studies have reported prevalence of methotrexate nephrotoxicity, but there is substantial

controversy. The aim of the present study was to determine the prevalence of high-dose methotrexate nephrotoxicity in patients with various malignancies in a medical center in Zahedan, Iran.

MATERIALS AND METHODS

In a prospective longitudinal study from 2007 to 2009, a total of 102 patients with osteosarcoma, Ewing sarcoma, and lymphoma were followed up during their treatment with high-dose methotrexate. The study was approved by regional ethical committee. The inclusion criteria were a neutrophil count greater than 2.5×10^9/L, a platelet count greater than 100×10^9/L, normal kidney function (evaluated by urinalysis and serum electrolytes, creatinine, and blood urea nitrogen), and normal liver and heart function. Patients with alcohol abuse, pregnancy, hepatitis, and heart disease, and those at risk of kidney dysfunction (such as infection and aminoglycoside therapy) were excluded.

Complete blood count, blood urea nitrogen; serum creatinine, calcium, sodium, potassium, and uric acid; and urinalysis were measured before the start of treatment. The patients were assessed for toxicity before and 1 week after each cycle of treatment. Methotrexate therapy was administered every 21 days for osteogenic and Ewing sarcoma and every 2 weeks for lymphoma. Other drugs administered were vincristine and doxorubicin, which do not have any major renal toxicity. After establishing an appropriate intravenous line, maintenance fluid therapy and granisetron, 3 mg, were initiated 30 minutes before initiation of methotrexate therapy. The dose of methotrexate was 8 g/m^2 to 10 g/m^2 per cycle (for adult and pediatric patients, respectively), which was infused in 500 mL of isotonic saline within 4 hours. Leucovorin rescue was administered after methotrexate therapy (30 mg per 6 hours for at least 20 doses). Pre–high-dose methotrexate therapies were maintenance intravenous fluid therapy in 1000 mL of isotonic saline within 2 hours plus 1 vial of bicarbonate.

All of the patients had a urine pH equal or higher than 7 and then started therapy. After 1 week and then before each cycle of methotrexate therapy, baseline electrolytes measurement and urnialysis were repeated. In children, glomerular filtration rate (GFR) was estimated as 0.41 × height/serum creatinine, and in adults, it was calculated according to the Cockroft-Gault formula. In case of any abnormality in urine output or a rise in serum creatinine level, other specific and sensitive methods were used for measurement of kidney injury, and the risk, injury, and failure (RIFLE) criteria were applied to determine the grade and phase of kidney injury.[15,16]

RESULTS

A total of 102 eligible patients were enrolled, of whom 60 (58.8%) were males and 42 (41.2%) were females. The mean age of the patients was 19.5 years old (range, 5 to 80 years). Twenty-three patients were in children aged younger than 15 years (12 males and 11 females), 71 were 15 to 30 years old (43 males and 28 females), and 8 were older than 30 years old (5 males and 3 females). Seventy-two patients had osteosarcoma (38 males and 34 females), 15 had Ewing sarcoma (11 males and 4 females), and 15 had lymphoma (11 males and 4 females). Table 1 summarizes demographic and clinical baseline data of the patients.

The total courses of methotrexate therapy were 273 (mean, 2.67 courses per patient). Patients with osteosarcoma, Ewing sarcoma, and lymphoma received 204, 34, and 35 courses, respectively. All of the patients received at least 2 courses of high-dose methotrexate. Prior to treatment, all of the patients had normal kidney function tests, including blood urea nitrogen and serum creatinine level and urinalysis. After the first course, only 1 patient developed elevated creatinine, and in the second course, 2 other patients experienced a rise in creatinine level (Table 2). All of the

Table 1. Baseline Characteristics of Patients*

Characteristic	Value
Number of patients	102
Mean age, y	19.5 (5 to 80)
Gender	
Male	60 (58.8)
Female	42 (41.2)
Primary disease	
Osteogenic sarcoma	72 (70.6)
Ewing sarcoma	15 (14.7)
Lymphoma	15 (14.7)
Methotrexate	
Total cycles	273
Mean cycles per patient	2.67
Baseline creatinine, mg/dL	0.82
Mean body mass index, kg/m^2	17.8 (10 to 32)

*Values in parentheses are ranges for reports of mean values and percentages for categorical data.

Table 2. Changes in Serum Creatinine Level

Cycle	Number of Patients		Injury Phase	Serum Creatinine, mg/dL	
	Total	Acute Kidney Injury		Baseline	Follow-up
First	102	1	1	0.7	1.4
Second	102	2	1	0.8 and 1.0	1.3 and 1.5
Third	48	1	2	1.3	2.6
Fourth	15	0	…	…	…
Fifth	15	0	…	…	…

patients, according to the RIFLE criteria, were at-risk groups. These patients had a normal urine output, but they had a rising in creatinine level and the calculated GFR showed a risk phase of kidney injury. Forty-eight patients received a third course of methotrexate, and among whom 1 patient developed abnormal creatinine level. The nephrotoxicity, according to the RIFLE criteria, was within the injury group. This patient had a normal urine output. Fifteen patients received a fourth course and 6 received a fifth course of methotrexate therapy, and none of them developed a rising of creatinine compared to the pretreatment levels. At the end of the study, 4.9% of all of the patients had developed a rising in creatinine level (2.94% with phase 1 kidney injury and 1.0% with phase 2 kidney injury). Failure, loss, or end-stage renal disease phases of acute kidney injury were not detected (Table 2). All of the patients with abnormal creatinine levels were in the adult group.

All toxicities resolved spontaneously during the follow-up. No electrolyte imbalance, proteinuria, and glucosuria were detected in this cohort of patients.

DISCUSSION

Classically, high-dose methotrexate has been defined as administration of methotrexate more than 1000 mg/m^2, although the use of methotrexate more than 500 mg/m^2 may also be considered as high-dose methotrexate.[4,17] Results of the present study showed a low prevalence of renal toxicity due to high-dose methotrexate, and all toxicities were limited to phase 1 and 2 kidney injury.

Different studies reported various frequencies of methotrexate nephropathy. In one study, nephrotoxicity was reported in 91% of 23 patients (defined as any elevation of serum creatinine from grade 1 to 4),[14] but another study in sarcoma patients showed nephrotoxicity in only 1.8%.[7] The former study by Green and coworkers evaluated 23 patients (12 males and 11 females) with a median age of 72 years old with primary central nervous system lymphoma. Rising of creatinine level more than 15% occurred in 91% of patients in the first cycle of treatment.[14] Fifteen patients experienced grade 2, 3 had grade 3, and 3 had grade 4 nephrotoxicity. Total courses of high-dose methotrexate administration were 161 cycles, of which 122 cycles (76%) were associated with rising in creatinine level when compared to the baseline. All male patients experienced rising in creatinine level in at least 1 course of the treatment. In 4-month follow-up, 18 patients had permanent kidney injury and creatinine level was the same as that at the end of high-dose methotrexate therapy.[14] In contrast, Hempel and coworkers did not find any significant kidney dysfunction. In this study, transient decrease in GFR occurred, but all spontaneously recovered without medication.[18] Gronroos and coworkers evaluated kidney function in a long-term follow-up of 30 patients who received high-dose methotrexate.[21] Thirty-nine percent of the patients had normal GFR at the end of the treatment, 50% had moderate decrease in GFR (90 mL/min/1.73 m^2 to 114 mL/min/1.73 m^2), and 11% had a more significant decrease in GFR (< 90 mL/min/1.73 m^2). Twenty-nine percent of the patients developed significant albuminuria. Serum electrolytes such as potassium and sodium were in normal range without any abnormality and glycosuria was not detected. In another study, de Miguel and coworkers[20] enrolled 31 patients with a total of 158 courses of high-dose methotrexate. The dose of methotrexate was 2 g/m^2 to 3 g/m^2 per cycle and 6.4% of the patients developed acute kidney failure with serious complications which needed specific management.

Our previous study showed no kidney dysfunction in patients with choriocarcinoma and acute lymphoblastic leukemia who received 500 mg/m^2 to 1500 mg/m^2 of methotrexate per

cycle, and toxicities were limited to nonrenal side effects.[17] In this study on 98 patients with acute lymphoblastic leukemia and choriocarcinoma, the maximum dose of methotrexate was 1500 mg/m^2 in leukemic patients for a single course and 500 mg/m^2 in choriocarcinoma patients (dosage of methotrexate was much lower than that in the present study), and toxicities were other than kidney injury and the major toxicity was limited to liver damage.[17]

In contrast to studies conducted by Green and colleagues[14] and Gronroos and coworkers,[19] in this large-scale study we found a low prevalence of methotrexate nephrotoxicity (about 4%) which may be due to variation in susceptibility to drug side effects in different populations. Gronroos and coworkers' study[19] showed not only a high prevalence of methotrexate nephrotoxicity but also higher-grade kidney dysfunction plus proteinuria. However, Widemann and associates[7] also reported a low prevalence of methotrexate nephrotoxicity, but with higher grades than our study. Although our study showed a lower incidence of kidney dysfunction and reversible abnormality, we observed different results with some other drugs.[21,22] This finding revealed the lower susceptibility of our patients to drug toxicities and adverse effect.

Another interesting finding in our study was the kidney injury independent of dose and cycle, as all of the patients in every cycle had complete renal recovery prior to next cycle, and in the following cycle, they did not have any evidence of kidney injury. Finally, the injuries were not linked with gender.

The limitations of our study were the wide range of age, different disease settings, and different courses of treatment protocols. Another possible cause of bias is that we did not have many candidates for high-dose methotrexate therapy during the period of this study.

CONCLUSIONS

Our study revealed not only a low prevalence of renal toxicity due to very high-dose methotrexate therapy, but also toxicities which were only limited to the early phase of acute kidney injury. We observed toxicity episodes in the initial courses of treatment, usually occurred in the first or second course of methotrexate therapy, which were non-dose dependent.

CONFLICT OF INTEREST

None declared.

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