Cancer Chemother Pharmacol (2009) 63:599–604
DOI 10.1007/s00280-008-0772-0

ORIGINAL ARTICLE

Renal dysfunction during and after high-dose methotrexate

Myke R. Green · Marc C. Chamberlain

Received: 18 February 2008 / Accepted: 8 May 2008 / Published online: 27 May 2008

Abstract
Purpose To evaluate renal dysfunction in adult patients encountered during and immediately after repeated administrations of high-dose methotrexate (HDMTX) for treatment of primary central nervous system lymphoma (PCNSL).
Methods In this single-center, retrospective, open label trial, 23 consecutive adult patients aged between 19 and 94 years diagnosed with PCNSL were given ≥4 consecutive cycles of HDMTX (8 gm/m^2/dose) every 14 days as per institution protocol. Serum creatinine and serum methotrexate levels were measured at 24, 48 and 72 h after beginning of HDMTX infusion.
Results Forty-eight percent of all patients (30% of all HDMTX cycles) experienced a ≥200% increase in baseline creatinine during treatment. Nine percent of patients met requirements for administration of carboxypeptidase-G_2 (glucarpidase) under compassionate use from National Cancer Institute. Thirty percent of patients at the conclusion of HDMTX therapy demonstrated a NCI Common Toxicity Criteria (CTC) grade 2 or higher increase in post-treatment serum creatinine compared to pre-treatment serum creatinine amongst whom ten patients (43%) had levels outside of the normal range.
Conclusion Renal dysfunction of CTC grade 2, 3 or 4 is common during treatment with HDMTX in the treatment of PCNSL, occurring in 40% of all cycles. Renal dysfunction persists at least 4 months following the conclusion of therapy in nearly 30% of patients. Male patients age greater than 50 years are at greatest risk of renal dysfunction.

Keywords Methotrexate · MTX · Renal dysfunction · Lymphoma · Creatinine

M. R. Green
Department of Pharmacy, Intermountain Healthcare Corporation, Salt Lake City, UT, USA

M. C. Chamberlain (✉)
Department of Neurology and Neurological Surgery, Seattle Cancer Care Alliance, University of Washington/Fred Hutchinson Cancer, Research Center,
895 Eastlake Avenue E, Mail-stop: G-6800,
PO Box 10923, Seattle, WA 98109-1023, USA
e-mail: chambemc@u.washington.edu

Introduction

Methotrexate given in doses ≥3.5 gm/m^2 (also termed high-dose methotrexate; HDMTX) is utilized for adjuvant therapy of osteosarcoma, for single-agent or as part of multi-agent treatment of primary central nervous system lymphomas (PCNSL), and in combination therapy of acute lymphoblastic leukemia as well as adult and pediatric non-Hodgkin lymphomas [1–3]. Much attention has been focused on the acute renal toxicity of HDMTX, but there is a paucity of data evaluating the spectrum of subacute to acute renal dysfunction encountered during therapy and after therapy [4].

High-dose methotrexate acts in a cell-cycle specific manner to disrupt protein and DNA synthesis via the inhibition of several enzymes in the folic acid cycle [1]. This causes DNA strand breakage and ineffective DNA repair due to intracellular purine depletion in rapidly-dividing cells, leading to apoptosis.

Acute renal failure (ARF) is the most common form of renal toxicity due to HDMTX and is seen in 2–10% of treatment cycles [4, 5]. The most commonly described pathophysiology of ARF is the precipitation of methotrexate and its metabolites in the acidic environment of the

urine. Other possible causes of ARF have been previously described [6]. High-dose methotrexate-induced ARF is almost universally reversible and, given adequate recovery time, rarely will patients require discontinuation of HDMTX or dose reductions upon future cycles. Maintenance of adequate urine flow and urinary alkalinization while receiving HDMTX is essential to prevent this adverse effect [1, 4, 7].

Progressive renal dysfunction, defined as steady increase in baseline serum creatinine, with each subsequent cycle of HDMTX has not been reported in the literature. We report our retrospective, single-center experience in 23 consecutive patients treated with greater than four consecutive cycles of HDMTX for the treatment of PCNSL.

Methods

Patients

Eligibility criteria for this retrospective case controlled series included patients with histologically confirmed PCNSL who received a minimum of four consecutive cycles of HDMTX and, in alternating weeks, rituximab. All patients received a similar HDMTX treatment protocol, including aggressive hydration to maintain urine output ≥200 mL/h and urinary pH >7 before administration of HDMTX and throughout the elimination phase until serum methotrexate levels decreased to ≤0.1 mM/L. Patients who did not receive a minimum of 4 cycles of HDMTX were not considered for inclusion. The most common reason for not receiving a minimum of 4 cycles of HDMTX was radiographic progression of disease.

High-dose methotrexate was administered at 8 g/m^2 per dose intravenously over 4 h every 2-weeks with a goal of administering of 8–10 cycles total. Before each cycle of HDMTX, calculated creatinine clearance was determined using most recent serum creatinine [8]. For patients with calculated creatinine clearance ≤50 mL/min, dose of HDMTX was decreased by 50% [9]. High-dose methotrexate was delayed for patients with calculated creatinine clearance ≤30 mL/min until improvement in serum creatinine was demonstrated.

In addition, all patients received intravenous folinic acid (10 mg/m^2 per dose) every 6 h beginning 20 h after completion of the HDMTX infusion per institution protocol. Dose of folinic acid was altered as a function of serum methotrexate levels obtained at 24, 48 and 72 h after beginning of HDMTX infusion [10]. Serum creatinine levels were obtained simultaneously with serum methotrexate levels. Additionally, serum creatinine and methotrexate levels were obtained >72 h after each dose of HDMTX at the physician's discretion. Intravenous hydration and leucovorin was discontinued and patients were discharged to home once serum methotrexate levels reached ≤0.1 mM/L. All patients were given instructions to maintain oral hydration >1.5 L/m^2 per 24 h for three consecutive days upon discharge. Depending on velocity of methotrexate elimination, some patients were given discharge folinic acid (leucovorin calcium 25 mg per os every 6 h for 3 days).

Patient characteristics at baseline

The baseline characteristics are summarized in Table 1. The majority of patients (78%) were age ≥50 years with a nearly equal distribution among each sex. The median serum creatinine at baseline for all patients is 0.8 mg/dL (range 0.3–1.3), whereas the median serum creatinine at baseline for males aged ≥50 years is 1 mg/dL (range 0.8–1.3) ($P = 0.86$).

Analysis of degree of renal dysfunction

The degree of renal dysfunction and adverse events were termed and categorized according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 3.0.

Table 1 Baseline characteristics of patients

Characteristics	Results	*P*
Total number of patients	23	–
Median (range) age (in years)	72 (19–94)	–
Patients <50/≥50 years of age (%)	5 (22)/18 (78)	0.04
Sex (%), male/female	12 (52)/11 (48)	NS
Total cycles of HDMTX given, all patients	161	–
Total cycles of HDMTX given, patients ≥50 years	124	–
Average (range) cycles of HDMTX per patient	7 (4–10)	–
Median (range) initial baseline SCr, all patients	0.8 mg/dL (0.3–1.3)	–
Median (range) initial baseline SCr, males aged ≥50 years	1 mg/dL (0.8–1.3)	–
Median initial baseline SCr, male/female (mg/dL)	1/0.8	NS

SCr serum creatinine

Statistical analysis

Analysis of change of baseline serum creatinine in relation to peak serum creatinine or "new baseline" serum creatinine achieved at end of treatment employed Student's *t* test. Analysis of change in serum creatinine at the start or within each cycle of HDMTX relative to baseline serum creatinine in each cohort utilized the exact binomial test.

Results

A total of 21 patients (91%) experienced an increase in serum creatinine by >15% during at least 1 cycle. Fifteen patients experienced a CTC grade 2 increase in serum creatinine, three were grade 3 and three were grade 4. Of the 161 cycles of HDMTX administered, 122 (76%) were associated with an increase in serum creatinine from baseline. All of the male patients experienced this event during at least one of the cycles of HDMTX, with male patients aged ≥50 years experiencing the most significant renal dysfunction during each cycle of HDMTX.

Serum creatinine at end-of-therapy

Eleven of the 12 male patients in this study established a "new baseline" serum creatinine at the end of therapy. This new baseline serum creatinine at end of therapy was CTC grade 2 in eight patients and grade 3 in three patients. In addition, these 11 male patients showed a progressive and consecutive increase in serum creatinine from cycle to cycle. This new baseline was a median of 0.4 mg/dL (range 0–0.7) greater than baseline, which translates to a clinically significant change in renal function in a disease which affects the elderly in a disproportionate manner. Female patients age ≥50 years also experienced an increase in serum creatinine from baseline, however, while it was statistically significant, it was not clinically significant as the median serum creatinine at end of therapy was 0.8 mg/dL (range 0.6–1.2) (Table 2).

The majority of our study cohort (17 patients, 74%) experienced a CTC grade 1 increase in serum creatinine at end of therapy of 10–49% relative to baseline (Table 3). Six patients (25%) experienced an increase in serum creatinine >50% from baseline. Of these six patients, CTC grade 2 increase in serum creatinine was noted in three patients, two patients experienced grade 3 and one patient experienced grade 4 increase in serum creatinine at end of therapy relative to baseline serum creatinine. Six of the seven patients who did not experience an increase in end of therapy serum creatinine were female.

Table 3 Effect of HDMTX on SCr from baseline to end of therapy

Characteristics	Results	*P*
Patients who experienced ≤10% increase in SCr	7 (30%)	NS
Patients who experienced 10–49% increase in SCr	10 (43%)	0.02
Patients who experienced ≥50% increase in SCr	6 (25%)	NS

Peak serum creatinine

The median (range) peak serum creatinine during HDMTX treatment for all patients in this study was 1.9 mg/dL (0.4–4.9), (CTC grade 2 increase in serum creatinine), which represents more than a doubling of serum creatinine from baseline. The effect was more blunted in females, but was especially pronounced in males aged ≥50 years, who experienced a greater than threefold increase (CTC grade 3) in peak serum creatinine. The median increase in serum creatinine, from baseline to peak, was 1 mg/dL (range 0.1–4) in all patients. Males aged ≥50 years experienced a median increase of 1.7 mg/dL (range 0.3–4), while females aged ≥50 years experienced a median increase of 0.7 mg/dL (range 0.1–1.6) (Table 4). The increase in serum creatinine caused elevated methotrexate levels necessitating a change in the treatment plan including increased dose or frequency of folinic acid administration or delaying discharge from hospital while monitoring renal function.

Intra-therapy change in serum creatinine

Only two of the 23 patients in this study did not experience a single episode of renal dysfunction. Both of these patients were female, one aged 19 and one aged 65 years. Fifteen patients in this study experienced at least one episode of an

Table 2 Characteristics of "new baseline" at end of therapy and increase in SCr from baseline to end of therapy (EOT)

Characteristics	Results (mg/dL)	*P*
Median (range) SCr, all patients	1.1 (0.3–1.8)	–
Median (range) SCr, males aged ≥50 years	1.4 (1–1.8)	–
Median (range) SCr, females aged ≥50 years	0.8 (0.6–1.2)	–
Median (range) increase, baseline to EOT, all patients	0.4 (0–0.7)	0.002
Median (range) increase, baseline to EOT, males aged ≥50 years	0.4 (0–0.7)	0.0004
Median (range) increase, baseline to EOT, females aged ≥50 years	0.2 (0 – 0.4)	0.01

Table 4 Characteristics of peak SCr and increase in SCr from baseline to peak

Characteristics	Results (mg/dL)	*P*
Median (range) SCr, all patients	1.9 (0.4–4.9)	
Median (range) peak SCr, males aged ≥50 years	2.6 (1.2–4.9)	
Median (range) peak SCr, females aged ≥50 years	1.4 (0.7–2.3)	
Median (range) increase, baseline to peak SCr, all patients	1.0 (0.1–4)	0.00008
Median (range) increase, baseline to peak SCr, males aged ≥50 years	1.7 (0.3–4)	0.00008
Median (range) increase, baseline to peak SCr, females aged ≥50 years	0.7 (0.1–1.6)	0.007

increase in serum creatinine by 50–200% from baseline (Table 5). Eleven patients (two females, nine males) experienced a CTC grade 3 or 4 increase in serum creatinine from baseline during any cycle. Of the 161 cycles of HDMTX administered in this study, 122 cycles (76%) were associated with an increase in serum creatinine from baseline. Sixty-three cycles (39%) were associated with an increase in serum creatinine from baseline of at least 50%. Fifteen cycles were associated with a >200% increase in serum creatinine from baseline. Seven of these cycles were CTC grade 2, five were grade 3 and three were grade 4. The second cycle was, on average, where an increase in serum creatinine was first detected. Notably, there were two patients (both male) who experienced such severe and profound renal dysfunction with elevated serum methotrexate levels that the administration of carboxypeptidase-G_2 (glucarpidase) via compassionate use protocol from National Cancer Institute was required.

Serum methotrexate levels

Analysis of the serum methotrexate levels reveals no consistent correlation with serum creatinine levels, except in males aged ≥50 years. In males younger than 50 years and female patients of any age, serum methotrexate measurements displayed no consistent trend or association with serum creatinine levels ($P = 0.72$). In six of the ten male patients age ≥50 years, the serum methotrexate levels obtained at hour 24, 48 and 72 following each dose of HDMTX increased proportionately with increases in serum creatinine ($P = 0.02$). In each of these six patients with elevated serum methotrexate levels, the time to obtain a serum methotrexate level <0.1 mM/L took progressively longer with each cycle of HDMTX, with an average of 21 h longer comparing first cycle to final cycle. In four of the male patients age ≥50 years, the serum methotrexate levels at hours 24 and 48 displayed correlation with progressively increasing serum creatinine levels ($P = 0.04$). However, analysis of serum methotrexate levels obtained 72 h after each dose of HDMTX did not display correlation with increasing serum creatinine levels ($P = 0.2$).

Serum creatinine 4 months after completion of HDMTX

Eighteen patients of the original cohort were evaluable 4 months after completion of HDMTX therapy (Table 6). These 18 patients evaluated at 4-months post-HDMTX did not receive any further therapy for PCNSL after the final administration of HDMTX and rituximab. The average serum creatinine at 4 months following completion of HDMTX therapy for all evaluable patients was unchanged from the average seen immediately upon completion of therapy indicating no improvement in renal dysfunction as a consequence of HDMTX treatment. The mean serum creatinine for males and females aged ≥50 years 4 months after was 1.3 mg/dL (range 1.1–1.9) and 1 mg/dL (range 0.4–1.2), respectively. For males aged ≥50 years, a slight decrease in baseline serum creatinine was present while

Table 5 Intra-therapy renal dysfunction

Characteristics	Results	*P*
Patients with grade 1 increase in SCr from baseline during any cycle	16 (70%)	0.004
Patients with grade 2 increase in SCr from baseline during any cycle	15 (65%)	0.004
Patients with grade 3/4 increase in SCr from baseline during any cycle	11 (48%)	0.001
Cycles with any increase in SCr, from baseline	122 (76%)	0.005
Cycles associated with grade 1 increase in SCr, from baseline	59 (37%)	0.0001
Cycles associated with grade 2 increase in SCr, from baseline	48 (30%)	0.002
Cycles associated with grade 3/4 increase in SCr, from baseline	15 (9%)	NS
Average (range) cycle where SCr aberration first detected	2 (1–6)	–

Patients who met NCI criteria for carboxypeptidase-G_2 administration 2 (9%)

NCI National Cancer Institute

Table 6 Characteristics of SCr 4 months after completion of HD-MTX ($n = 18$)

Characteristics	Results (mg/dL)
Mean (range) SCr, all patients	1.1 (0.4–1.8)
Mean (range) SCr, males aged ≥50 years	1.3 (1.1–1.9)
Mean (range) SCr, females aged ≥50 years	1 (0.4–1.2)

female patients aged ≥50 years demonstrated a slight increase in serum creatinine, though both findings failed to demonstrated statistical significance.

Discussion

This study is the first to quantify the adverse effects of HDMTX on renal function during and immediately following active treatment with HDMTX, as well as identify which patient populations are most affected. The incidence of renal dysfunction in this series is much higher than previously reported [4]. It is not clear why the incidence is higher in this study as median age and renal function are similar to other HDMTX trials in patients with PCNSL. One explanation may be the rarity of CTC grade 4 or greater change in creatinine, reported in this and other series [1, 4–6], resulting in underreporting of actual renal toxicity in prior studies. Careful evaluation of this patient series did not reveal obvious causes of renal dysfunction associated with HDMTX, such as fluctuations in urine pH, methotrexate crystallization or acute tubular necrosis. Furthermore, no drug–drug interactions or concomitant medications [1] were found in this cohort that could explain the high incidence of renal dysfunction.

It is important to recognize the clinical significance of increased serum creatinine caused by HDMTX. As PCNSL affects the elderly disproportionately, small changes to measured serum creatinine can produce profound effects upon glomerular filtration rate (GFR). This global change to GFR may affect the pharmacokinetics and pharmacodynamics of concomitant drugs in a patient population prone to polypharmacy [11]. Furthermore, patients with HDMTX-induced renal dysfunction may require drug holidays thereby preventing the application of dose intensity for the treatment of PCSNL. This study demonstrates that patients ≥50 years of age, the largest group of patients with PCNSL, are at greater risk for subacute and acute renal dysfunction. However, males ≥50 years of age are particularly sensitive to the adverse renal effects both during HDMTX therapy and after therapy for a minimum of 4 months. Noteworthy is that fact that in our series, males were more likely to experience a durable increase in serum creatinine.

While this study is small in scope and is a retrospective analysis, it provides valuable data in order to prospectively risk-stratify PCNSL patients with respect to renal toxicity planning to receive HDMTX. It also provides rationale for closer monitoring, both before and after beginning treatment with HDMTX, especially for patients who are at higher risk for renal dysfunction from HDMTX due to age and gender. The findings of this study may also serve to guide clinicians regarding potential changes needed in the treatment plan as patients receive sequential cycles of HDMTX.

Changes in serum creatinine due to repeated administration of HDMTX led to changes in management of these patients. In six of the ten male patients aged ≥50 years, the elimination phase of methotrexate was prolonged leading to persistently elevated serum methotrexate levels, which correlated with diminishing creatinine clearance. Clinical management of these patients included protracted inpatient hospitalizations to facilitate vigorous hydration and, in most cases, increased doses of intravenous leucovorin [10]. Due to a decrease in calculated creatinine clearance, four patients required 50% dose reductions in HDMTX dose beginning with the fifth cycle in three patients and the sixth cycle in one patient. Notably, patients who experienced renal dysfunction from repeated administration of HDMTX did not experience clinical toxicity, such as myelosuppression, hepatitis, mucositis or dermatitis associated with sustained elevated plasma methotrexate levels. The only recognized toxicity from HDMTX treatment in all patients included in this series is persistent renal dysfunction in select patients. Although it is beyond this scope of this manuscript, patients who required prolonged hospitalizations incurred increased treatment costs associated with administration of HDMTX.

Both patients who received carboxypeptidase-G_2 in this study on an emergency, compassionate use protocol developed acute nephrotoxicity and elevated serum methotrexate levels abruptly. The clinical use and monitoring of carboxypeptidase-G_2 has been well-described previously [1, 12]. Both patients required a protracted holiday from methotrexate, but were successfully re-challenged with HDMTX without repeat nephrotoxicity [6]. High-dose methotrexate re-challenge was attempted once recovery and stabilization of serum creatinine was demonstrated. The dose of HDMTX used for, and subsequent to, re-challenge in these two patients was based on most recent serum creatinine as previously described with a goal of administration of eight total HDMTX cycles.

Evaluation of 18 patients (78%), 4 months after the end of therapy reveals a durable increase in serum creatinine. While it is impossible to account for all variables that may have been encountered or the long term applicability of a finding noted 4 months after end of therapy, it appears

that the "new baseline" established upon completion of HDMTX therapy may be due to permanent renal damage.

Limitations to this study include the following: patient population of predominantly older patients with a single diagnosis, i.e. PCNSL, retrospective analysis of data, limited determination of etiology of renal dysfunction (beyond ruling out methotrexate crystallization and acute tubular necrosis as causative) and lack of follow-up beyond 4 months following conclusion of treatment. Despite these limitations, this study of 23 consecutive patients provides a robust cohort with which to draw several conclusions in order to prospectively stratify risk for patients with PCNSL receiving or planning to receive HDMTX. The first is that males aged $\geq$50 years receiving sequential courses of HDMTX are at higher risk for intra-therapy and post-therapy increases in serum creatinine. These increases in serum creatinine may necessitate changes in the treatment plan for patients receiving subsequent cycles of HDMTX. Clinicians should routinely obtain 24-h urine collection for measured or serum creatinine for creatinine clearance before, during and after a treatment course of HDMTX. Also, administration of HDMTX to males aged $\geq$50 years may require longer hospitalizations and/or more aggressive hydration and folinic acid administration to complete each cycle.

Acknowledgments Contribution: M.R.G. and M.C·C. designed the research, analyzed data, synthesized results, and wrote the manuscript and tables.

Conflict of interest statement The authors declare no competing financial interests.

References

1. Green MR, Chowdhary S, Lombardi KM, Chalmers LM, Chamberlain M (2006) Clinical utility and pharmacology of high-dose methotrexate in the treatment of primary CNS lymphoma. Expert Rev Neurother 6(5):635–652
2. Ferguson WS, Goorin AM (2001) Current treatment of osteosarcoma. Cancer Invest 19(3):292–315
3. Frei E III, Blum RH, Pitman SW, Kirkwood JM, Henderson IC, Skarin AT, Mayer RJ et al (1980) High dose methotrexate with leucovorin rescue. Rationale and spectrum of antitumor activity. Am J Med 68(3):370–376
4. Widemann BC, Adamson PC (2006) Understanding and managing methotrexate nephrotoxicity. Oncologist 11(6):694–703
5. Chan H, Evans WE, Pratt CB (1977) Recovery from toxicity associated with high-dose methotrexate: prognostic factors. Cancer Treat Rep 61:797–804
6. Green MR, Chowdhary SA, Chalmers LM, Lombardi KM, Chamberlain MC (2006) High-dose methotrexate complicated by acute tubular necrosis. Therapy 3(4):495–497
7. Proudfoot AT, Krenzelok EP, Vale JA (2004) Position paper on urine alkalinization. J Toxicol Clin Toxicol 42(1):1–26
8. Cockcroft DW, Gault MH (1976) Prediction of creatinine clearance from serum creatinine. Nephron 16(1):31–41
9. The NCCN Central Nervous System Cancers Clinical Practice Guidelines in Oncology (Version 1.2008). 2008 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed 29 April 2008
10. Bleyer WA (1989) New vistas for leucovorin in cancer chemotherapy. Cancer 63:995–1007
11. Rollason V, Vogt N (2003) Reduction of polypharmacy in the elderly: a systematic review of the role of the pharmacist. Drugs Aging 20(11):817–832
12. Widemann BC, Balis FM, Murphy RF, Sorensen JM, Montello MJ, O'Brien M, Adamson PC (1997) Carboxypeptidase-G2, thymidine, and leucovorin rescue in cancer patients with methotrexate-induced renal dysfunction. J Clin Oncol 15(5):2125–2134