

Hyper-alkalinization without hyper-hydration for the prevention of high-dose methotrexate acute nephrotoxicity in patients with osteosarcoma

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Abstract

Purpose To evaluate the reliability and renal safety of an original schedule of high-dose methotrexate (HDMTX) administration with hyper-alkalinization, and without hyper-hydration.

Methods Patients with osteosarcoma received HDMTX (8–12 g/m²) as a 4-h infusion. Hypertonic 8.4% sodium bicarbonate was infused prior to HDMTX, then once daily for 3 days. Methotrexate serum concentrations were measured at hour 4 (C_{max}), hour 24, hour 48, and hour 72. Urinary pH was measured on each miction. Serum creatinine was assessed on days 1, 3, and 8.

Results Twenty-six patients (median age: 18 years, range: 15–25) received a total of 344 cycles of HDMTX, including 16 patients treated in an outpatient basis. Urinary pH

remained constantly higher than 7.5 in all patients. Grade 1 creatininemia toxicity was observed in 31 cycles (9%), and grade 2 creatinine toxicity was observed in one patient. No episode of acute severe nephrotoxicity was observed. No significant worsening was observed in serum creatinine and calculated creatinine clearance from baseline to the end of therapy ($P = 0.74$). The main extra-renal toxicity was alkalization-related hypokalemia from H48. No re-hospitalization was required.

Conclusion Hyper-alkalinization appears an efficient and reliable method to prevent the acute renal toxicity of HDMTX and allows its safe administration in the outpatient setting.

Keywords Pharmacokinetics · High-dose methotrexate · Nephrotoxicity · Outpatient · Osteosarcoma · Sarcoma

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Introduction

Osteosarcoma (OS) is a rare malignant tumor that mainly afflicts children and young adults. Prior to the introduction of systemic chemotherapy, approximately 80–90% of patients died despite early radical surgery [1]. Neoadjuvant chemotherapy dramatically improved the disease-free survival and overall survival for patients with OS and is considered the gold standard treatment modality [2, 3].

The most effective drugs in OS are as follows: cisplatin, doxorubicin, ifosfamide, and high-dose methotrexate (HDMTX) [4, 5]. These drugs are always administered sequentially, because HDMTX-induced nephrotoxicity makes its administration with cisplatin or ifosfamide at high risk. The standard administration of HDMTX includes hyper-hydration, typically: 2.5–3.5 l/m²/24 h (beginning 12 h before HDMTX infusion, for 36–48 h).

Close monitoring of urinary pH is mandatory, with administration sodium bicarbonate before and after the infusion (45–50 mEq per liter of IV fluids), in order to maintain alkaline urinary pH [6]. However, this standard protocol shows several limitations. First, hyper-hydration may obscure the ability to reach the threshold peak [7, 8], and AUC (area under the concentration vs. time curve) [9] required to ensure the efficacy of HDMTX in OS. Hence, hyper-hydration rapidly decreases the plasma-to-tissue concentration gradient of methotrexate (MTX) and might reduce its anti-tumoral effect [10, 11]. Secondly, the *a posteriori* administration of oral or IV sodium bicarbonate does not reverse the renal damage caused by HDMTX in all cases, and a sizeable proportion of patients develop progressive renal function impairment after HDMTX-based chemotherapy [12]. Thirdly, Sand et al. [13] showed that maintaining an alkaline urinary pH was more important than maintaining high urinary flow to obtain optimal HDMTX clearance. Finally, a close fortnightly monitoring of urinary pH requires careful nursing care, as well as the cooperation of patients that may be difficult to obtain.

In view of these limitations, a strong and preventive—instead of *a posteriori*—urine alkalinization would be a coherent approach in view of the pathogenesis of HDMTX-induced acute nephrotoxicity. Indeed, HDMTX-induced nephrotoxicity is mainly mediated by the precipitation of MTX and its metabolites in the renal tubules [14]. The solubility of MTX and its metabolites is closely related to urinary pH (Table 1) [15].

As a consequence, we hypothesized the following: (1) an aggressive strategy of preventive urine alkalinization could prevent HDMTX-induced acute nephrotoxicity; (2) renal safety provided by hyper-alkalinization could allow withdrawing the commonly used hyper-hydration following HDMTX infusion and therefore provide optimal peak and AUC; and (3) this simplified, patient-friendly method of administration could facilitate nursing care and allow the outpatient administration of HDMTX.

The present study aimed to demonstrate the reliability and renal safety of a new schedule of HDMTX administration with hyper-alkalinization, and without hyper-hydration.

Table 1 Solubility of MTX and its metabolites (mg/ml) [15]

pH	MTX	7-OH MTX	DAMPA
5.0	0.39	0.13	0.05
6.0	1.55	0.37	0.10
7.0	9.04	1.55	0.85

MTX methotrexate, 7-OH MTX 7-hydroxy methotrexate, DAMPA 2,4-diamino-N₁₀-methyl pterico acid

Patients and methods

From 2001 to 2007, 26 patients with newly diagnosed, high-grade OS were treated in our institution using a specific hyper-alkalinization protocol for HDMTX administration, as described below. The first ten patients were treated in the inpatient setting. Given the good tolerability of this regimen, the 16 following patients were treated in the outpatient setting. The study was approved by the local ethics committee, and informed consent was obtained from each patient or guardian. The medical records of each patient were prospectively entered in a computed database. Patients had received no previous anticancer therapy and had a normal baseline renal function. They had no concomitant disease potentially leading to acute renal dysfunction.

Treatment protocol

Patients received pre-operative chemotherapy for 8 weeks, followed by 2 weeks off treatment before radical excision surgery was performed. HDMTX was given as a single agent (8–12 g/m²) on day 1, then on days 8 and 15. In addition, patients received ifosfamide (5 g/m², four courses), cisplatin (100 mg/m², one course) and doxorubicin (60 mg/m², two courses) given sequentially, as previously described [16–18]. Anti-emetic prophylaxis included anti-5HT₃ and corticosteroids at standard doses. From 2006, anti-NK1 (aprepitant) was added to this regimen. Within 6 weeks after surgery, patients received adjuvant chemotherapy based on the same regimen in good responders to pre-operative chemotherapy.

Administration of HDMTX

Patients received 500 ml of 8.4% sodium bicarbonate (500 mEq, B Braun Medical, Boulogne-Billancourt, France) over 1 h before HDMTX infusion (day 1), then on days 2, 3, and 4. From day 1 to day 4, patients also received 4 g (53.6 mEq) of KCl daily IV supplementation. The dose of HDMTX was 8 g/m² (four patients) or 12 g/m² (22 patients). HDMTX dose was diluted in 500 ml of 0.9% NaCl and infused over a 4-h period. HDMTX was not followed by forced hydration, and the IV route was stopped for the following 20 h. Leucovorin rescue was introduced 24 h after start of HDMTX infusion (20 h after completion of the 4-h infusion) [6]. Dose of folinic acid was subsequently adjusted as a function of serum methotrexate levels, as previously described (Table 2) [12, 15]. On day 4, leucovorin was discontinued, and patients were discharged once serum methotrexate levels reached ≤0.1 mM/l. Patients received the instruction to maintain oral hydration >2l per 24 h for three consecutive days upon discharge.

Table 2 Leucovorin rescue according to methotrexate levels 48 h after the start of HDMTX infusion [15]

MTX concentration (mol/l)	Leucovorin dose (mg/m ² q6 h × 8)
5×10^{-7}	15
1×10^{-6}	100
2×10^{-6}	200
MTX methotrexate	

Sample and pharmacokinetics analysis

Urinary pH was measured on each miction for 3 days following HDMTX infusion. Serum creatinine was measured on days 1, 3, and 8. Methotrexatemia was measured at H0, H4 ($C_{\max}$), H24, H48, and H72. HDMTX pharmacokinetic parameters were estimated using the software package Thermo Kinetica 4.4 (Inna Phase Corp., USA) and assuming a non-compartmental analysis (NCA).

Analysis of toxicity

Creatinine clearance was calculated according to the Cockcroft and Gault formula [19]. The degree of nephrotoxicity and other adverse events were graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 2.0. In addition to short-term toxicities, we investigated whether this method of administration of HDMTX induced progressive renal dysfunction, defined as a significant increase of serum creatinine or decrease in calculated creatinine clearance, from baseline to the end of treatment.

Statistical analysis

Student's *t* test was used to analyze changes of serum creatinine and calculated creatinine clearance from baseline to the end of treatment. Calculations were performed with NCSS 2007 software (NCSS, Kaysville, UT, USA).

Results

Patients characteristics are summarized in Table 3. Among the 26 patients (9 females, 17 males), the primary tumor site was axial in 4 patients (15%), and limbs in 22 patients (85%). Three patients (11.5%) had synchronous lung metastases. The median age was 18 years (range: 15–25). A total of 344 cycles, including the pre-operative and post-operative treatments, were evaluable for toxicity and for HDMTX pharmacokinetics (Table 4).

Table 3 Patients characteristics (*n* = 26)

Characteristics	Results
Median age (range)	18 (15–25)
Gender, <i>n</i> (%)	
Male	17 (65)
Female	9 (35)
Primary site, <i>n</i> (%)	
Axial	4 (15)
Limbs	22 (85)
Median no. of cycles received (range)	11 (2–16)
Baseline SCr (μmol/l), mean (±SD)	68.5 (±21.5)
EOT SCr (μmol/l), mean (±SD)	69.7 (±17.5)
Baseline CrCl (ml/min), median (range)	88 (72–159)
EOT CrCl (ml/min), median (range)	92 (70–152)

EOT end of treatment, *SCr* serum creatinine, *CrCl* creatinine clearance, *SD* standard deviation

Renal safety of HDMTX given with hyper-alkalinization and without hyper-hydration

Urinary pH remained constantly higher than 7.5 in all patients. In 31 cycles (9%) of HDMTX, reversible creatininemia elevation (grade 1, <1.5 ULN) was noticed. Grade 2 creatinine elevation was observed in one patient. No episode of acute severe nephrotoxicity was observed. Regarding progressive renal dysfunction, no significant worsening was observed in serum creatinine and calculated creatinine clearance from baseline to the end of therapy ($P = 0.74$) (Table 1). No patient required the administration of carboxypeptidase.

Extra-renal toxicity

Toxicity included manageable grade 1–2 nausea and emesis in all patients, and grade 2 transaminase elevation in 42% of patients. Grade 3 neutropenia occurred in 65% of patients, and febrile neutropenia in one patient. Grade 1–2 mucositis occurred in 26% of patients.

The main acute toxicity was grade 3 hypokalemia, which occurred in five patients. Because hypokalemia was not associated with serum creatinine elevation, it was supposed to be secondary to hyper-alkalinization. Hence, hypokalemia was easily managed with IV or oral KCl supplementation from H24. No grade 4 toxicity occurred.

Although the activity of this regimen was not the endpoint of the study, we observed pathological tumor necrosis rates following pre-operative chemotherapy within the expected range with HDMTX-based regimens [7–10] (median: 95%, range: 15–100%).

Table 4 HDMTX pharmacokinetic parameters ($n = 26$)

Dose	n	Mean $C_{\max}$ ($\mu\text{mol/l}$)	Mean C_{H24} ($\mu\text{mol/l}$)	Mean C_{H48} ($\mu\text{mol/l}$)	Median AUC ($\mu\text{mol/l h}$)
HDMTX 8 g/m ²	4	1,088 (± 277.4)	12.57 (± 2.14)	0.48 (± 0.31)	4,414 (3,317–4,955)
HDMTX 12 g/m ²	22	1,266.9 (± 295.8)	25.48 (± 1.67)	1.82 (± 0.25)	5,217 (3,966–6,118)

Discussion

In the previously described chemotherapy protocols in patients with OS, HDMTX was always administered sequentially with other active drugs (cisplatin and ifosfamide) because of its threatening nephrotoxicity. Such neoadjuvant protocols were scheduled over more than 10 weeks, thus lowering chemotherapy dose intensity, in spite of the theoretical knowledge that dose-intensive treatments warrant a better efficacy in chemosensitive tumors [8, 20]. Hence, the optimal neoadjuvant chemotherapy regimen in OS remains to define, and better ways to increase dose-intensity with acceptable toxicity could possibly improve results.

The aim of this study was to optimize HDMTX administration by avoiding its nephrotoxicity with aggressive hyper-alkalinization and to assess the impact of the lack of forced hydration on the pharmacokinetics of HDMTX. There was an obvious intra-patient and inter-patient variability in HDMTX serum concentrations, as previously described in the literature [21, 22]. We demonstrated that the administration of HDMTX with hyper-alkalinization and without forced hydration is a safe and reliable method to prevent nephrotoxicity: over 344 cycles, no acute renal dysfunction was noticed. Urinary pH remained stable and >7.5 , avoiding precipitation of MTX and its metabolites in the renal tubules. In previous studies, the overall incidence of significant acute nephrotoxicity was close to 1.8% [14], whereas another case series reported 30% of patients had a doubling of the baseline serum creatinine [12]. Acute nephrotoxicity was seen in 4% of patients in the present case series of 344 cycles, a proportion that favorably compares with previously published data.

Besides, the lack of forced hydration did not significantly altered HDMTX pharmacokinetics. The threshold peak (700–1,000 $\mu\text{mol/l}$) [9] recommended to ensure the efficacy of HDMTX in OS were easily reached.

Outpatient administration requires following for safety: (1) alkalinization (e.g., method reported in this paper, sodium bicarbonate in daily IV fluids), (2) reliable patients (able to return for bag changes and laboratory exams), and (3) facility and staff willing to see patients for laboratory exams, IV fluid questions and that troubleshoot clearance problems on a daily basis.

Finally, the renal safety provided by this method allows the administration of HDMTX in the outpatient setting, which became a standard in our institution following the completion of this study.

Beyond the renal safety provided by this method, we suggest that it might also allow the concomitant administration of HDMTX and other active drugs, for instance ifosfamide. Indeed, increasing the dose intensity of neoadjuvant chemotherapy is a coherent approach in an effort to increase the proportion of patients with a high degree of necrosis in the primary tumor at the time of definitive surgery [7]. The degree of necrosis in the primary tumor predicts subsequent event-free survival (EFS) [23]. Previously published studies established the efficacy of neoadjuvant chemotherapy [24, 25], but never demonstrated the superiority of intensified neoadjuvant chemotherapy. For instance, a recent phase III study [26] compared two chemotherapy regimens associating doxorubicin and cisplatin, using two different dose intensities. The dose-intensive regimen was associated with an improved rate of good ($>90\%$ necrosis) histologic responses: 36 versus 50% ($P = 0.003$). Oddly enough, this improvement in histologic response rate did not result in improved progression-free survival or overall survival. To date, no randomized trial assessed the potential benefit of increasing the dose intensity of HDMTX and ifosfamide. We assume that our new schedule of administration of HDMTX could be a helpful tool for further studies aiming to evaluate the efficacy of a dose-intense regimen based on the association of HDMTX and ifosfamide in patients with OS.

Conclusions

We demonstrated that hyper-alkalinization is an efficient and reliable method to prevent the acute renal toxicity of HDMTX in patients with OS. Moreover, this method allows the safe administration of HDMTX in the outpatient setting. Further studies will determine whether this method allows the concomitant administration of HDMTX and other active drugs, which might provide a way to increase the dose intensity of each active agent by increasing dose density.

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