Severe acute renal failure following high-dose methotrexate therapy in adults with haematological malignancies: a significant number result from unrecognized co-administration of several drugs

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Introduction

High-dose methotrexate (HDMTX, >1 g/m²) administered as an intravenous (i.v.) infusion is an important component in the treatment regimen for a variety of cancers [1]. HDMTX-associated severe acute renal failure (ARF) is an infrequent but serious complication because MTX is predominantly excreted in the urine. Data from a number of studies performed in the 1970s showed that a sustained elevation of serum MTX concentrations at 24 h (≥5 µmol/L), 48 h (≥1 µmol/L) and 72 h (≥0.1 µmol/L) after the start of the MTX infusion is considered to be toxic. The usual serum MTX level 48 h after HDMTX is <0.1 µmol/L. In the era of optimal supported care the incidence of grade 3–4 ARF after HDMTX has decreased from 10% to 0.6% in solid-cancer patients [2]. However, to our knowledge, the current incidence of HDMTX-associated severe ARF is unknown in adult haematological patients. As the doses of MTX used are generally smaller compared with those received by solid-cancer patients (e.g. patients with osteosarcoma receive a MTX dose >8 g/m²), the risk of severe ARF is perhaps lower.

According to large case series, the reason why an individual patient comes down with ARF after HDMTX and modern supported care remains unexplained in the majority of cases [1,3]. Nevertheless, the analysis of potential risk factors was not the main target in these studies; for this reason, these data should be carefully managed. To further define the incidence, predisposing factors and outcome of severe ARF occurring after HDMTX therapy in adults with haematological malignancies, we retrospectively reviewed the clinical data of all patients with haematological malignancies treated with HDMTX at our institution between January 2002 and July 2007.

Methods

Patients

All consecutive patients above 18 years of age developing HDMTX-induced severe ARF were retrospectively analysed. The diagnosis was based on markedly elevated serum MTX levels (>10 µmol/L at 48 h after HDMTX) and severe ARF (grade 3–4 increases in serum creatinine, according to WHO criteria). Patients with rapidly progressing underlying disease, a known renal failure and pregnant or lactating women were excluded.

Study design and patient monitoring

Data were collected retrospectively by patient chart review and/or follow-up during hospitalization. Analysis of laboratory data included serial evaluation of serum creatinine levels, MTX levels and haematological parameters. Plasma for MTX determination was obtained 24 h post-MTX infusion, and then once daily until recovery of kidney function and decrease of MTX serum levels to <0.1 µmol/L. In addition, samples for MTX determination were obtained immediately before and 30 min following the dose of carboxypeptidase G2 (CPDG2). MTX was quantified using a fluorescence polarization immunoassay (FPIA) [3]. Haematologic and extra-haematologic toxicities were scored according to the WHO criteria. The study complied with all provisions of the Declaration of Helsinki and was conducted in accordance with Good Clinical Practice rules. The protocol was approved by the Institutional Ethical Committee.

Analysis of risk factors

The following predisposing factors were analysed: pre-existing renal impairment; urinary pH <7 prior, during and
after the administration of HDMTX; hypovolaemia; exposure to nephrotoxic agents, existence of a third compartment (e.g. pleural effusion); presence of the methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism and use of drugs known to alter the clearance of MTX. Concomitant therapy was also reviewed. The Naranjo criteria were used for the determination of causality for suspected adverse drug reactions [4].

Treatment strategies

During the 5-year study period, we have used pre-treatment alkaline hydration and postinfusion-guided leucovorin (LV) rescue initiated at 24–36 h after beginning of HDMTX (first administration 60 mg i.v., then 30 mg q6h until the serum MTX level becomes <0.1 µmol/L). Our treatment protocol for the patient who develops markedly elevated serum MTX levels and severe ARF is shown in Table 1.

Results

Incidence and clinical findings

A total of 158 courses of HDMTX (in 31 patients) were administered in our institution. During the study period, two cases (6.4%) of HDMTX-induced severe ARF occurred.

Patient 1. A 58-year-old male with primary cerebral lymphoma received chemotherapy with HDMTX cycles (2.5 g/m² over 3 h) according to the DeAngelis protocol [5]. The first course was delivered without problems, and the patient had eliminated MTX without delay. During the 3 h following the second course of HDMTX, the patient developed fever (38.5°C) and piperacillin–tazobactam (4 g/500 mg q6h) was initiated as empirical therapy. The next day (Day 2), the serum creatinine level had unexpectedly increased from 60 to 210 µmol/L. At this point, the plasma MTX level was 93 µmol/L. ARF was diagnosed and treated according to our treatment protocol for this condition (Table 1). CPDG2 is an investigational recombinant bacterial enzyme that hydrolyzes MTX to the inactive metabolite 2,4-diamino-5'-methylpteroyl acid (DAMPA). The bolus injection of CPDG2 (a dose of 50 U/kg) resulted in a rapid 95–99% reduction of serum levels of MTX in patients with renal failure after HDMTX [1,2]. Due to its molecular size, CPDG2 is restricted to the extracellular compartment, and the intracellular MTX concentration is initially unaffected by its use. For this reason, rescue with LV must be continued following the CPDG2 administration. On Day 3 the serum MTX level was very high at 40 µmol/L and CPDG2 was promptly administered. The response was excellent, the MTX level falling to 4.75 µmol/L within 1 h. Concomitantly, a charcoal haemoperfusion (ChH) programme also seemed effective (Figure 1A). However, cytotoxic MTX concentrations were sustained for 26 days and were only abated by the improvement of renal function. The patient developed grade 4 myelosuppression (nadir Day 8 after HDMTX), and grade 3 mucositis. He died 30 days after HDMTX due to septic complications. Concurrent medications, aside from piperacillin–tazobactam, did not differ between the two cycles of HDMTX.

Patient 2. A 39-year-old man with precursor B-lineage acute lymphoblastic leukaemia received chemotherapy according to PETHEMA ALL-AR-03 trial [6]. He was taking gemfibrozil, a cholesterol-lowering agent, for >1 year. Following the achievement of complete remission, the patient received the first cycle of early intensification chemotherapy that included 3 g/m² HDMTX. Twenty-four hours post-MTX infusion, creatinine and MTX levels were unexpectedly 166 and 24 µmol/L, respectively. Creatine kinase level and renal ultrasound were normal. With the diagnoses of ARF and impaired clearance of MTX, our treatment approach for this complication was initiated (Table 1). CPDG2 was administered at 152 h after HDMTX and the plasma MTX concentration decreased from 10.8 µmol/L to 3.7 µmol/L within 1 h. Serum MTX and creatinine levels were decreased to <0.02 µmol/L and 80 µmol/L, respectively, 16 days after HDMTX (Figure 1B). The patient developed grade 2 mucositis. Evidence of other MTX toxicity, such as myelosuppression or elevation of transaminase concentrations, was not observed. The patient fully recovered and no further complications occurred.

Risk factors

Initially, our two patients showed markedly increased MTX concentrations without apparent risk factors. However, when both cases were reviewed in retrospect, a potential drug interaction between HDMTX and either piperacillin–tazobactam (patient 1) or gemfibrozil (patient 2) were found. Use of the Naranjo probability scale registered causality as probable in both patients.

Table 1. Treatment protocol for patients with markedly elevated serum MTX concentration and severe renal failure at our institution

<table>
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<tr>
<th>Supported therapy</th>
<th>Hyperhydration: 4 500 ml/m²/day (alternating isotonic saline with glucose 5%)</th>
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<tr>
<td>Alkalization: 100 ml sodium bicarbonate 8.4% i.v. q4h, and oral sodium</td>
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<tr>
<td>Bicarbonate if urinary pH &lt;7</td>
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<tr>
<td>Furomide 20 mg/12 h i.v. from Day 3 to Day 15</td>
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<td>Checking for risk factors, especially concomitant drug treatments</td>
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<tr>
<th>Intracellular rescue with LV</th>
<th>High-dose LV*: 1 200 mg q24h as a continuous intravenous infusion for 5–6 days and then tapered based on plasma MTX levels</th>
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<tr>
<td>LV mouth washes with swallowing 30 mg q6h from Day 2 to Day 15</td>
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<tr>
<td>Extracellular rescue</td>
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<tr>
<td>CPDG2a: 50 U/kg as a single dose at Days 3–4 (as soon as available)</td>
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<td>ChH indicates charcoal haemoperfusion; CPDG2, recombinant carboxypeptidase G2; LV, leucovorin</td>
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*LV administration had to be stopped 4 h prior to carboxypeptidase G2 (CPDG2) and readministered 1 h following enzyme injection.

a After reconstitution of CPDG2 in normal saline, a single dose of 50 U/kg was administered i.v. over 5 min. CPDG2 was obtained on a compassionate use protocol.

(µmol/L)
Discussion

In the era of optimal supported care, HDMTX-induced severe ARF continues to cause high morbidity, mortality and resource utilization [3]. Multiple factors may influence the development of severe ARF following HDMTX therapy [1,2]. Our data suggest that a significant number of HDMTX-associated nephropathy in haematological cancer patients might result from potential drug–drug interaction between HDMTX and several agents. As far as we know, no other study has demonstrated the highly frequent role of drug interactions in the pathogenesis of HDMTX-induced ARF. In agreement with our study, a survey of the recent medical literature (Medline, from 1997 to July 2007) including 15 haematological patients described in 13 case reports highlights that a significant number (40%) of published cases with HDMTX-induced ARF result from co-administration of several drugs [5,7–16].

Fig. 1. Serum methotrexate and creatinine concentrations throughout the treatment course in patient 1 (A) and patient 2 (B).
Many agents are known to prolong MTX elimination, including probenecid, salicylates, non-steroidal anti-inflammatory drugs (NSAIDs) and weak organic acids. Penicillin is known to abolish tubular secretion of MTX in monkeys and reduce human organic anion transporter-mediated MTX elimination in an in vitro mouse model. Piperacillin was shown to reduce renal MTX clearance in rabbits. The weak organic acid and penicillin derivates, tazobactam, are also eliminated by glomerular filtration and tubular secretion. The influence of concomitant administration of piperacillin on the pharmacokinetic parameters of MTX and 7-hydroxymethotrexate (7-OH-MTX) was studied in rabbits. We propose that the interaction between MTX and piperacillin is mainly due to the reduced clearance of MTX combined with a slight increase in the formation clearance of the metabolite.

In our first case, piperacillin–tazobactam treatment was started 3 h after the initiation of HDMTX, and discontinued after six doses since a potential interaction between both drugs was suspected. A literature search found two prior reports of ARF following the co-administration of MTX and piperacillin–tazobactam [9,16]. In both cases, the MTX and creatinine levels returned to baseline with standard supported measures. Since penicillins inhibit the renal excretion of MTX, the product guide for MTX states that ‘if possible, avoid the concurrent use of MTX and a variety of penicillins, including piperacillin, amoxicillin, mezlocillin and oral penicillin’. Given the widespread use of HDMTX and piperacillin–tazobactam, clinicians should exercise caution and ensure careful monitoring of MTX and creatinine levels when they are administered concomitantly to avoid MTX toxicity. On the other hand, the interaction between HDMTX and ceftazidime has not been described; therefore, ceftazidime may be the appropriate antibiotic to be used with HDMTX if broad-spectrum coverage is required [9]. Our second case had been taking gemfibrozil for >1 year without renal complications. Gemfibrozil monotherapy of hyperlipidaemia may predispose to rhabdomyolysis and ARF. Strenuous exercise may contribute to rhabdomyolysis, and hypovolaemia may be a factor in the development of renal failure. A causality assessment using the Naranjo probability scale revealed that an adverse drug event due to gemfibrozil was possible.

To our knowledge, this is the first report linking ARF to the concomitant use of gemfibrozil and HDMTX. Since 70% of gemfibrozil is excreted in the urine, it is possible to suggest that the interaction between gemfibrozil and HDMTX may be secondary to competition between both drugs for renal tubular secretion.

The incidence of HDMTX-associated severe ARF seen in our series was higher than that reported in solid-cancer patients, occurring in 6.4% of patients. These differences are probably due to the more frequent adverse association of concomitant drugs used close to the time of HDMTX infusion in haematological patients.

There is no consensus about the optimal therapy for patients who had markedly high MTX levels and severe ARF. Adding high-dose LV alone is uncertain to promote a significant improvement in this life-threatening setting. Because of this concern, the application of both, intracellular (high doses of LV) and extracellular rescue therapy (CPDG2 and dialysis-based methods of drug removal) seems to be recommended [2,3,17].

Furthermore, cessation of concomitant drugs that could interfere with MTX metabolism is also mandatory. In our patients, we combined all these rescue therapies. CPDG2 was well tolerated and highly effective with a rapid 65.7–88.2% reduction in serum MTX concentrations. Concomitantly, daily ChH resulted in a median decrease in serum MTX level of 41% (range, 28–65%).

In conclusion, the incidence of HDMTX-induced severe ARF in adults with haematological malignancies may be considerably higher than that observed in other cancer patients. Our data and previously published case reports suggest that a significant number of HDMTX-associated nephropathy might result from potential drug–drug interaction between HDMTX and several agents. Clinicians should be aware of the potential pharmacokinetic interaction between HDMTX and either piperacillin–tazobactam or gemfibrozil. CPDG2 appears to be the treatment of choice when rapid elimination of MTX is indicated.

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Conflict of interest statement. None declared.

References

6. Ribera J, Oriol A, Morgades M et al. Treatment of high-risk (HR) Philadelphia chromosome-negative (Ph-) adult acute lymphoblastic leukemia (ALL) according to classical risk factors and minimal residual disease (MRD). Interim results of the PETHEMA ALL–AR-03 trial. ASH Meeting, Orlando, 2006; Abstract no. 1872


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