Understanding and Managing Methotrexate Nephrotoxicity

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Hemoperfusion • Thymidine • High-dose chemotherapy • Rescue agents

LEARNING OBJECTIVES
After completing this course, the reader will be able to:
1. Discuss the pharmacology of methotrexate.
2. Describe the current incidence and presentation of high-dose methotrexate-induced renal dysfunction.
3. Discuss conventional and investigational treatment approaches to high-dose methotrexate-induced renal dysfunction.

ABSTRACT
Methotrexate (MTX) is one of the most widely used anticancer agents, and administration of high-dose methotrexate (HDMTX) followed by leucovorin (LV) rescue is an important component in the treatment of a variety of childhood and adult cancers. HDMTX can be safely administered to patients with normal renal function by the use of alkalization, hydration, and pharmaco-kinetically guided LV rescue. Despite these measures, HDMTX-induced renal dysfunction continues to occur in approximately 1.8% of patients with osteosarcoma treated on clinical trials. Prompt recognition and treatment of MTX-induced renal dysfunction are essential to prevent potentially life-threatening MTX-associated toxicities, especially myelosuppression, mucositis, and dermatitis. In addition to conventional treatment approaches, dialysis-based methods have been used to remove MTX with limited effectiveness. More recently carboxypeptidase-G2 (CPDG2), a recombinant bacterial enzyme that rapidly hydrolyzes MTX to inactive metabolites, has become available for the treatment of HDMTX-induced renal dysfunction. CPDG2 administration has been well tolerated and resulted in consistent and rapid reductions in plasma MTX concentrations by a median of 98.7% (range, 84%–99.5%). The early administration of CPDG2 in addition to LV may be beneficial for patients with MTX-induced renal dysfunction and significantly elevated plasma MTX concentrations.

INTRODUCTION
Methotrexate (MTX), a classical antifolate, is one of the most widely used and studied anticancer agents [1–4]. Unlike other anticancer agents, MTX can be safely administered over a wide dose range, ranging from 20 mg/m² per week in maintenance chemotherapy for acute lymphoblastic leukemia and treatment of nononcologic diseases including rheumatoid arthritis or psoriasis [4–6], and when combined with leucovorin (LV) rescue, to doses of 1,000–33,000 mg/m² [7]. The latter, termed high-dose...
Methotrexate (HDMTX) is usually administered as a prolonged i.v. infusion and is an important component in the treatment regimens for a variety of cancers, including acute lymphoblastic leukemia, lymphoma, osteosarcoma, breast cancer, and head and neck cancer [3, 8–11]. HDMTX can be safely administered to patients with normal renal function by vigorously hydrating and alkalinizing the patient to enhance the solubility of MTX in urine and through the use of pharmacokinetically guided LV rescue to prevent potentially lethal MTX toxicity [2, 12].

Despite these preventive measures, MTX-induced nephrotoxicity continues to occur, albeit infrequently. As MTX is primarily cleared by renal excretion, MTX-induced renal dysfunction may lead to delayed elimination of MTX, and the resulting sustained, elevated plasma MTX concentration may lead to ineffective rescue by LV and a marked enhancement of MTX’s other toxicities [3, 9, 13–15].

Since the introduction of HDMTX with LV rescue more than 25 years ago by Djerassi et al. [16], our ability to safely administer this regimen to patients has improved, and there have been a number of advances in the treatment of HDMTX-induced renal dysfunction over the past 20 years. This report reviews the etiology, incidence, presentation, and treatment of HDMTX-induced renal dysfunction.

Methotrexate Pharmacology

Knowledge of MTX’s mechanism of action and metabolism are important for understanding MTX-associated toxicities and treatment. MTX enters the cell via the reduced folate carrier and undergoes polyglutamation catalyzed by folylpolyglutamate synthetase. Once polyglutamated, MTX is retained in cells for prolonged periods of time. Methotrexate and its polyglutamates block de novo nucleotide synthesis primarily by depleting cells of reduced tetrahydrofolate cofactors through inhibition of dihydrofolate reductase (DHFR) (Fig. 1) [17]. MTX polyglutamates and dihydrofolates that accumulate as a result of DHFR inhibition also inhibit thymidylate synthase and other enzymes involved in the purine biosynthetic pathway [18, 19].

Similar to other antimetabolites, critical determinants of MTX cytotoxicity are not only drug concentration but also duration of exposure. High concentrations of MTX may be well tolerated for brief periods of time, whereas prolonged exposure to low concentrations can result in life-threatening toxicity. The type of toxicity observed with MTX is also a function of this concentration–time dependence. Exposure to millimolar concentrations of MTX for minutes to hours may lead to acute renal, central nervous system, and liver toxicity; exposure to MTX concentrations as low as 0.01 and 0.005 μM for >24 hours may result in bone marrow and gastrointestinal epithelial toxicity, respectively [20].

Following administration of HDMTX, two metabolites, 7-hydroxy-methotrexate (7-OH-MTX) and 2,4-diamino-N10-methylpteroylglutamic acid (DAMPA), are observed in plasma. Within 12–24 hours of the start of a HDMTX infusion, the plasma concentration of 7-OH-MTX, formed by the action of the enzyme aldehyde oxidase, exceeds the concentration of MTX [21, 22]. Intracellular polyglutamation of 7-OH-MTX results in prolonged retention and enhanced cytotoxicity [23]. DAMPA, a minor, inactive [24–26] metabolite of MTX, accounting for <5% of the total dose of drug that is excreted in urine [24], is presumably formed from MTX that is excreted into the intestinal tract, hydrolyzed by bacterial carboxypeptidases, and then reabsorbed.

Pathogenesis of MTX-Induced Renal Dysfunction

The etiology of MTX-induced renal dysfunction is believed to be mediated by the precipitation of MTX and its metabolites in the renal tubules [21, 22, 27] or via a direct toxic effect of MTX on the renal tubules [17]. More than 90% of MTX is cleared by the kidneys [13]. MTX is poorly soluble at acidic pH, and its metabolites, 7-OH-MTX and DAMPA, are six- to tenfold less soluble than MTX, respectively [21, 24]. An increase in the urine pH from 6.0 to 7.0 results in a five- to eightfold greater solubility of MTX and its metabolites, a finding that underlies the recommendation of i.v. hydration (2.5–3.5 liters of fluid per m² per 24 hours, beginning 12 hours before MTX infusion and continuing for 24–48 hours) and urine alkalinization (40–50 mEq sodium bicarbonate per liter of i.v. fluid) prior to, during, and after the administration of HDMTX.

Shorter durations of HDMTX infusions with resultant higher plasma and urinary MTX concentrations may carry an increased risk for renal dysfunction.

Several drugs have been associated with increased toxicity when coadministered with MTX. The most significant interactions involve agents that interfere with MTX excretion, primarily by competing for renal tubular secretion, such as probenecid, salicylates, sulfisoxazole, penicillins, and nonsteroidal anti-inflammatory agents [28–31].

MTX-induced renal dysfunction results in sustained, elevated plasma MTX concentrations, which in turn may lead to ineffective rescue by LV and a marked enhancement of MTX’s other toxicities, especially myelosuppression, mucositis, hepatitis, and dermatitis [2, 3, 9, 14, 15].

Vomiting and diarrhea during or shortly after the administration of MTX have been observed in patients who developed MTX toxicity [32, 33], but the majority of patients with renal dysfunction are initially asymptomatic, and most present with nonoliguric renal dysfunction [14, 32, 34]. An abrupt rise in serum creatinine during or shortly
after MTX infusion indicates the development of renal dysfunction and can result in significantly elevated plasma MTX concentrations. Although the risk for MTX toxicity is dependent upon the dose and schedule of administration, plasma MTX concentrations should be ≤1.0 μM at 42 hours after the start of the HDMTX infusion, and plasma MTX concentrations ≥10 μM at this time point are associated with a high risk for the development of toxicities [2, 32, 33]. In the absence of early diagnosis based on urine output, serum creatinine, and plasma MTX determination, coupled with intervention that includes pharmacokinetically guided increase in LV rescue, patients present following a delay of several days with severe mucositis, profound bone marrow suppression, and less commonly, dermatitis. Rescue attempts with even very high doses of LV at this symptomatic stage have a small likelihood of relieving MTX toxicities. Significantly elevated liver function tests have been associated with HDMTX administration but do not appear to be associated with the development of renal failure.

**INCIDENCE**

In the 1970s, prior to routine monitoring of plasma MTX concentrations and pharmacokinetically guided adjustment of LV, the mortality associated with HDTMX infusions ranged between 4.6% and 6% [35–37]. Data from a number of studies performed in the 1970s found that elevated plasma MTX concentrations were predictive for the development of renal toxicities (Table 1). These studies demonstrated that: (a) sustained elevation of plasma MTX concentrations at 24 hours (>5–10 μM), 48 hours (>1.0 μM), and 72 hours (>0.1 μM) after administration of MTX are predictive for the development of toxicity; (b) in the absence of elevated plasma MTX concentrations, the risk for the development of MTX-associated toxicities is minimal; (c) in most circumstances, the development of MTX-associated toxicities can be ameliorated or prevented when patients with elevated plasma MTX concentrations receive pharmacokinetically guided doses of LV rescue. These studies resulted in uniform institution of aggressive hydration, alkalinization, and pharmacokinetically guided LV. Nomograms guiding the duration and degree of rescue with LV based upon plasma MTX concentrations as a function of time of drug administration were developed and are being used in ongoing clinical trials that administer HDMTX (Fig. 2) [38].

Reports of significant morbidity and mortality secondary to HDMTX-induced renal dysfunction, however, continue to appear in the literature [15, 32, 39–41].

With the advent of new therapeutic strategies, we recently reassessed the current incidence of HDMTX-induced renal dysfunction in patients with osteosarcoma, a population that usually is treated with HDMTX administered as a short i.v.

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**Figure 1. Folate pathway.** Sites of action of methotrexate (MTX) and of the rescue agents leucovorin and thymidine. MTX primarily inhibits dihydrofolate reductase (DHFR). This results in the depletion of reduced folates (FH₄), which are required for deoxythymidine monophosphate (dTMP) synthesis from deoxyuridine monophosphate (dUMP), and in accumulation of dihydrofolates (FH₂), which inhibit purine synthesis. The MTX rescue agent leucovorin restores the reduced folate pool after conversion to its active metabolite 5-methyltetrahydrofolate (5-CH₃-FH₄). Thymidine is directly converted to thymidine monophosphate by the enzyme thymidine kinase (TK), thereby circumventing blockade of the de novo pathway by MTX.
infusion separate from cycles that contain other cytotoxic drugs. Our review of the recent literature after 1980, a time during which hydration and alkalinization were administered routinely as part of HDMTX administration, and of clinical trials estimated the incidence of renal dysfunction following HDMTX to be 1.8%. Of 3,887 patients, 68 developed grade ≥2 (World Health Organization criteria) nephrotoxicity. The mortality among patients who developed renal dysfunction was 4.4% [42]. Of note, this estimate only included patients entered in clinical trials, who likely receive optimal supportive care. The incidence of HDMTX-induced renal dysfunction in all patients receiving HDMTX may be higher outside clinical trials and in older patients, as the likelihood of reduced renal function resulting from physiological aging processes and acquisition of comorbidities increases with age. No comparable overview in adult/elderly patients (e.g., patients with primary central nervous system lymphoma) exists, but some available data indicate that the incidence of HDMTX-related nephrotoxicity may be considerably higher in this subgroup of patients [43].

**Table 1. Plasma methotrexate concentrations indicating a high risk for the development of methotrexate (MTX)-associated toxicities**

<table>
<thead>
<tr>
<th>Methotrexate</th>
<th>Leucovorin</th>
<th>No. of patients/MTX cycles</th>
<th>Defined toxic MTX concentration</th>
<th>No. of toxic concentration/toxicity</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–15 g/m² over 20 hrs or 1 g/m² as bolus</td>
<td>40 mg/m² at hr 24, then 25 mg/m² q6h × 12 doses</td>
<td>52/?</td>
<td>≥0.9 μM at 48 hrs</td>
<td>≥0.5 μM at 72 hrs</td>
<td>?</td>
</tr>
<tr>
<td>2 g/m² as bolus or over 20 hrs</td>
<td>40 mg/m² at hr 24, then 256 mg/m² q6h × 12</td>
<td>?/40</td>
<td>&gt;0.1 μM at 72 hrs</td>
<td></td>
<td>7/8</td>
</tr>
<tr>
<td>50–250 mg/kg over 6 hrs</td>
<td>15 mg/m² q6h × 8, start 2 hrs post-MTX (augmented for some pts with MTX &gt;0.9 μM at 48 hrs)</td>
<td>78/395</td>
<td>≥0.9 μM at 48 hrs</td>
<td></td>
<td>12/5</td>
</tr>
<tr>
<td>8 g/m² over 4 hrs</td>
<td>9–15 mg q6h × 12 starting 2 hrs post-MTX</td>
<td>?</td>
<td>&gt;10 μM at 24 hrs</td>
<td>74/24</td>
<td></td>
</tr>
<tr>
<td>50–300 mg/kg over 4 hrs</td>
<td>40 mg/m² 4 hrs post-MTX then 15 mg q6h × 11 (augmented for all pts with MTX &gt;10 μM at 24 hrs)</td>
<td>134/496</td>
<td>&gt;10 μM at 24 hrs</td>
<td>83/12</td>
<td></td>
</tr>
<tr>
<td>725–15,000 mg/m² over 6 hrs</td>
<td>5–90 mg/m² q3h × 8 starting 3 hrs post-MTX then 12 mg/m² q6h × 8 (augmented for all pts with 24-hr MTX &gt;5 μM)</td>
<td>?/114</td>
<td>&gt;5 μM at 24 hrs and MTX t1/2 &gt;3.5 hrs</td>
<td>5/1</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: hr, hour; pts, patients; q3h, every 3 hours; q6h, every 6 hours; t1/2, half-life.

Conventional Treatment Approaches

The cornerstones of preventing HDMTX toxicity—alkalinization, maintaining urine output, monitoring serum creatinine and plasma MTX concentrations, and pharmacokinetically guided LV rescue—are also the cornerstones of management of the patient who develops early signs of renal dysfunction. Renal dysfunction, recognized by a rise in serum creatinine and elevated plasma MTX concentrations, should be initially addressed by promptly increasing the LV dose or schedule based on the time-dependent concentration of MTX (Fig. 2) [2]. Similar to MTX, LV (5-formyltetrahydrofolate) enters the cell via the reduced folate carrier and is converted to its active metabolite 5-methyltetrahydrofolate (5-mTHF) (Fig. 1). The reversal of MTX by LV is competitive, with relatively higher concentrations of LV required as the MTX concentration increases [2, 4]. Hydration and alkalinization should be continued or increased, provided that adequate urine output can be maintained. Other supportive care measures include administering antibiotics, management of fluid and electrolytes, and transfusion of blood products as necessary.

The concern that patients remain at risk for severe MTX toxicity as long as elevated concentrations of MTX persist in the circulation is reflected in the scientific literature, in which methods that attempt to address the underlying problem of impaired MTX elimination have been reported. We reviewed 30 publications published in 1980–2002 on the use and efficacy of dialysis-based methods of MTX removal in 49 patients with HDMTX-induced renal dysfunction [42]. The most frequently used single methods were hemodialysis (n = 10), high-flux hemodialysis (n = 9), and charcoal hemoperfusion or charcoal hemofiltration (n = 7), and 16 patients were treated with multiple modalities. Peritoneal dialysis alone resulted in a minimal decrease in plasma MTX concentrations [44, 45]. The use of other single-modality methods of MTX removal resulted in a median decrease in plasma MTX concentration of 52% (range,
In humans, the half-life of Thd is approximately 10 minutes, and thus this investigational drug needs to be administered as a continuous i.v. infusion in order to maintain effective plasma concentrations [59]. Thd has been used in 16 patients with MTX-induced renal dysfunction as a rescue agent in combination with LV [14, 58]. Severe toxicity was observed in only three patients, in whom Thd was initiated 5, 12, and 13 days after the start of MTX infusion. The development of Thd as an investigational agent by the National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) was recently discontinued, and thus Thd is currently not available for investigational use.

The carboxypeptidase-G class of enzymes hydrolyze the terminal glutamate from naturally occurring folates and folate analogs, such as MTX [60]. Carboxypeptidase-G rapidly converts MTX to the inactive metabolites DAMPA and glutamic acid, thus providing an alternate route of elimination to renal excretion. In the 1970s carboxypeptidase-G1, extracted from *Pseudomonas stutzeri* [61, 62], effectively lowered plasma MTX concentrations in a small number of patients with brain tumors who had been treated with HDMTX [63, 64]. The bacterial source of CPDG1, however, was lost, and no additional patients were treated [65].

Subsequently, carboxypeptidase-G2 (CPDG2, glucarpidase), a recombinant form of the bacterial enzyme CPDG2, cloned from *Pseudomonas* strain RS-16, has become available and is being developed by CTEP and by Protherics Inc. (Brentwood, TN). It hydrolyzes the glutamate residue from naturally occurring and synthetic folate analogues [66, 67]. When administered to patients with HDMTX-induced renal dysfunction, CPDG2 metabolizes circulating MTX to the inactive metabolite DAMPA (Fig. 3), thus providing an alternate route of elimination to renal excretion. In 21 patients with MTX-induced renal dysfunction treated on a compassionate-use protocol of the NCI, CPDG2 lowered plasma MTX concentrations within 15 minutes of administration by >98% [34, 68]. This group of patients received Thd in addition to CPDG2, because of the concern that CPDG2 could hydrolyze both LV and its active metabolite, 5-mTHF. CPDG2 and Thd rescue were well tolerated in these patients, and MTX-related toxicities were mild to moderate.

To assess the role of Thd in these patients, this study was subsequently amended to restrict Thd administration to patients with prolonged (>96 hours) exposure to MTX or with severe toxicity at study entry. MTX-associated toxicities and outcome were compared in 44 patients who did and 56 patients who did not receive Thd. That study demonstrated that CPDG2 and LV rescue without Thd effectively rescued patients with HDMTX-induced renal dysfunction, provided CPDG2 was administered within 96 hours of the start of the MTX infusion [69].

The efficacy in rapidly lowering plasma MTX concentrations was confirmed in a European study [70], in which LV and CPDG₂ were administered to 82 patients with HDMTX-induced renal dysfunction. CPDG₂ was administered at a median of 52 hours (range, 25–178 hours) following the start of the MTX infusion and resulted in a 97% (range, 73%–99%) reduction in plasma MTX concentrations. While CPDG₂ preferentially hydrolyzes MTX (Kₘ of 8 μM), it can also hydrolyze LV (Kₘ of 120 μM) and its active metabolite 5-mTHF (Kₘ of 35 μM). The effect of CPDG₂ on MTX, LV, and 5-mTHF plasma concentrations was assessed in 11 patients using reverse-phase high-performance liquid chromatography [71]. Although LV concentrations were maintained following CPDG₂ administration, LV was likely in the form of the inactive d-isomer. The active metabolite of LV, 5-mTHF, was indeed a substrate for CPDG₂ and was effectively hydrolyzed. These findings formed the basis for the recommendation to continue with the administration of high doses of LV (250 mg/m² every 6 hours) for 48 hours after CPDG₂ to allow for restoration of the intracellular reduced folate pool. Hempel et al. [72] recently evaluated the effect of CPDG₂ on the inactive d-isomer and the active l-isomer of LV in vitro, and demonstrated that the active l-isomer was degraded much faster than the d-isomer.

After systemic CPDG₂ administration, DAMPA plasma concentrations are similar to pre-CPDG₂ MTX concentrations. Persistently high concentrations of the poorly water soluble DAMPA could theoretically lead to further renal toxicity by precipitation in the renal tubules. To evaluate whether DAMPA could contribute to a delay in renal recovery, we studied 20 patients who received CPDG₂ and Thd for MTX-induced renal dysfunction. In this population, serum creatinine returned to normal values at a median of 22 days after administration of MTX [34]. This time period is similar to the time to renal recovery seen in patients with HDMTX-induced renal dysfunction and a comparable degree of renal injury who were treated with conventional dialysis-based methods [42]. CPDG₂ administration, therefore, does not appear to impact negatively upon the recovery of renal function.

Interestingly, following administration of CPDG₂ for MTX-induced renal dysfunction, plasma DAMPA concentrations decline more rapidly than MTX concentrations, suggesting a nonrenal elimination of DAMPA [34]. In a nonhuman primate study of DAMPA metabolism, DAMPA was found to be metabolized to hydroxy-DAMPA, DAMPA-glucuronide, and hydroxy-DAMPA-glucuronide [25]. These metabolites were also identified in patients who received CPDG₂ for MTX-induced renal toxicity.
Metabolism of DAMPA thus likely underlies the more rapid elimination of DAMPA relative to MTX in patients with MTX-induced renal dysfunction treated with CPDG₂ [25].

**CURRENT CONTROVERSIES**

**Is Current Supportive Treatment of HDMTX-Induced Renal Failure Adequate?**

Although the use of alkalization and hydration with HDMTX greatly diminishes the risk for significant nephrotoxicity, we have estimated that approximately 1.8% of patients treated with HDMTX on clinical studies with optional supportive care still develop renal dysfunction that may prove life threatening. With supportive treatment only, patients remain at risk for severe toxicity as long as elevated concentrations of MTX persist in the circulation. High concentrations of LV may be inadequate in this situation. This clinical observation is supported by laboratory studies that demonstrated that reversal of MTX by LV is competitive, with relatively higher concentrations of LV required as the MTX concentration increases. When concentrations of MTX reached 100 μM, even tenfold higher LV concentrations (1,000 μM) were unable to protect bone marrow cells from toxicity [73].

In a recent single-institution retrospective review, administration of high doses of LV within 24–48 hours of HDMTX administration rescued 13 patients with HDMTX-induced renal dysfunction [74]. A significant proportion of the 13 patients developed neutropenia (n = 8) (absolute neutrophil count [ANC] <1,000/μl), thrombocytopenia (n = 7) (platelet count <100,000/μl), and mucositis (n = 6). The authors concluded that treatment with high doses of LV administered within 24–48 hours after the start of the MTX infusion is sufficient therapy in patients with MTX-induced renal dysfunction. Based on a lower median MTX plasma concentration at 48 hours (16.3 μM) and a lower median peak serum creatinine concentration (2.0 mg/dl), compared with 20 patients who received CPDG₂ as a rescue agent (median MTX concentration at 46 hours, 201 μM; median peak serum creatinine, 3.7 mg/dl) [34], the patients reported by Flombaum and Meyers [74] may have suffered from less severe MTX-associated nephrotoxicity. Close monitoring and the ability to intervene early at this single institution likely contributed to the relative success of this approach, although it must be recognized that, despite this early intervention, significant toxicities occurred.

The development of renal dysfunction following MTX administration remains a significant management challenge. The multitude of dialysis-based methods directed at lowering plasma MTX concentrations following development of nephrotoxicity attests to the difficulty encountered by clinicians caring for such patients. The dialysis-based methods are relatively inefficient at reducing plasma MTX concentrations, and sole reliance on administering elevated doses of LV is not sufficient treatment for many patients. More effective management strategies could result in better outcomes for these patients.

**Risk Versus Benefits of CPDG₂**

Current treatment for patients who develop HDMTX-induced renal dysfunction relies on high doses of LV to reduce the risk for toxicity, and with markedly elevated plasma MTX concentrations, the use of a dialysis-based methods of drug removal is often attempted. These charcoal hemodialysis/filtration-based methods must be continuously applied, or repeated on a daily basis in order to reduce plasma MTX concentrations to a range in which standard doses of oral LV can be administered. The risks associated with charcoal hemodialysis/filtration-based methods include the risks associated with the insertion of vascular access devices, the risk for bleeding secondary to heparinization and thrombocytopenia, and the risks associated with multiple transfusions of blood products.

The benefits of CPDG₂ administration include a >98% decrease in plasma MTX concentration within minutes of enzyme administration. Patients can then be safely managed with LV rescue alone. Early administration of CPDG₂ may diminish the risk for serious to life-threatening MTX toxicity. Furthermore, patients avoid the risks associated with charcoal hemodialysis/filtration-based methods of MTX removal, which may not be readily available outside of major medical centers.

The risks of CPDG₂ administration appear to be infrequent and minor in nature. Four of 21 patients treated with CPDG₂ described readily reversible side effects consisting of a feeling of warmth (n = 2), tingling in the fingers (n = 1), flushing (n = 2), shaking (n = 1), and head pressure (n = 1) [34], and only 2 of 82 patients in a European study of CPDG₂ for HDMTX-induced renal dysfunction described mild and completely reversible symptoms of flushing (n = 2) and shaking (n = 1) [70]. The theoretical risk for a worsening of renal function secondary to accumulation of the poorly water soluble MTX metabolite DAMPA has not been borne out, as the time to renal recovery is no different than that of historical controls treated with charcoal hemodialysis/filtration-based methods [42]. Even though CPDG₂ hydrolyzes MTX preferentially, 5-mTHF, the active metabolite of LV, is also hydrolyzed. Continuing to administer higher doses of LV for 48 hours after administration of CPDG₂ is therefore currently recommended and appears effective.
Recom mendations

The lack of early clinical symptoms predicting the development of renal dysfunction emphasizes the need for routine daily monitoring of plasma MTX concentrations and serum creatinine after the administration of HDMTX, until MTX has declined to levels allowing discontinuation of LV (<0.05 to 0.1 μM). After the diagnosis of renal dysfunction has been established, a prompt increase in LV based on plasma MTX concentrations is critical for successful management.

Patients who develop renal dysfunction and have plasma MTX concentrations ≤10 μM at 42–48 hours after the start of the MTX infusion can likely be successfully managed with LV administration and supportive care. Although very early institution of high-dose LV alone may be sufficient for patients with MTX concentrations >10 μM at 42–48 hours, CPDG2 offers a rapid means of decreasing plasma MTX concentrations by 1–2 logarithms within minutes of administration. The risks of CPDG2 toxicity appear minimal, but as with any foreign protein, anaphylactic reactions could theoretically occur. Continuation of high-dose LV for 48 hours following CPDG2 administration is advised to replete intracellular reduced folate pools. After that time, LV rescue should be modified based on the lowered plasma MTX concentrations. The most commonly used commercially available fluorescence polarization immunoassay and all immunoassays significantly overestimate plasma MTX concentrations after administration of CPDG2, because of the crossreactivity of DAMPA in these assays, and results obtained with these assays will not fully reflect the ability of CPDG2 to hydrolyze MTX [26]. As DAMPA is cleared more rapidly than MTX in patients with renal dysfunction, the accuracy of immunoassay results increases within a few days of CPDG2 administration.

For patients with HDMTX-induced renal dysfunction with sustained MTX concentrations >10 μM at 42–48 hours after the start of the MTX infusion, we would recommend that CPDG2 be administered in addition to LV. For patients with renal dysfunction and plasma MTX concentrations of 1–10 μM, administration of CPDG2 may be considered, but fewer data are available for this population. CPDG2 is an investigational drug that can be obtained on a compassionate-use protocol from CTEP at the following address: Pharmaceutical Management Branch, CTEP, NCI, Executive Plaza North, Room 7147, 9000 Rockville Pike, Bethesda, Maryland 20892-7422, USA. Telephone: 301-496-5725.

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Disclosures of Potential Conflicts of Interest

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