High-dose methotrexate complicated by acute tubular necrosis: a case report

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High-dose methotrexate (HDMTX) forms the basis for the majority of chemotherapy regimens for primary CNS lymphoma. Several toxicities are encountered with HDMTX, of most concern is acute nephrotoxicity. This case report illustrates several aspects of HDMTX-related renal injury.

Methotrexate (MTX) is a folate antagonist used for the treatment of primary central nervous system lymphoma (PCNSL). High-dose MTX (HDMTX) serves as the platform for essentially all chemotherapy used for treatment of PCNSL. Dosing of MTX varies by regimen; however doses of 3 to 8 gm/m^2 are commonly used and necessitate forced intravenous hydration, urinary alkalinization followed by leucovorin (folinic acid) rescue to mitigate side effects [1–3]. Serum MTX levels are monitored at 24, 48 and 72 h or until the MTX level is less than 0.10 µm/l. Although myelosuppression, mucositis, hepatitis and acute renal insufficiency are among the reported risks, MTX is usually well tolerated. Leucovorin rescue mitigates the risk of myelosuppression, mucositis and hepatic injury however has no effect renal toxicity. Renal failure due to HDMTX is due to intrarenal MTX concentrations of excreted drug exceeding the solubility in the renal tubule leading to crystal nephropathy. To mitigate MTX renal toxicity, MTX dosing is based on a measured creatinine clearance and administered with hyperhydration and urinary alkalinization (urine pH >7.). We report on a patient with severe and prolonged renal insufficiency due to acute tubular necrosis (ATN) following HDMTX cycle number one given at 8 gm/m^2 despite a normal pretreatment creatinineclearance and maintenance of urinary alkalinization.

Case report

A 58-year old nondiabetic male with 1 year history of subacute visual loss in his left eye presented for treatment. Left eye vitrectomy revealed atypical lymphocytes and B cell monoclonal proliferation consistent with lymphoma. Staging for PCNSL including magnetic resonance imaging (MRI) of brain and spine and cerebrospinal fluid (CSF) cytology, all were unremarkable. Baseline laboratory tests were normal (serum creatinine 1 mg/dl, creatine clearance 105 ml/min) aside from serum glucose of 127 mg/dl (due to concomitant dexamethasone use as the patient had no history of diabetes). Concurrent medications include pantoprazole and scopolamine eye drops for vitrectomy-related glaucoma. No nephrotoxic drugs including intravenous iodinated contrast were given throughout the hospital course. The patient was admitted to hospital for first cycle of high-dose methotrexate. As per protocol, after 5 h of intravenous hydration and documented alkalinization of the urine (pH exceeded 7), the patient received MTX 8 gm/m^2 (total dose = 16 gm) over 4 h. Starting 24 h after the start of the infusion, MTX serum levels were drawn (**Figure 1**). Due to elevated 24 h serum MTX level (>10µm/l), leucovorin dose was adjusted to 100 mg/m^2 intravenously every 6 h [3,4].

On day 3, early evidence of renal insufficiency presented as demonstrated by a marked increase in serum creatinine. Bilateral kidney ultrasound performed on day 6 demonstrated no evidence of nephrolithiasis or hydronephrosis. Urine analysis on three occasions was normal and revealed no evidence of crystals. A 24 h measured creatinine clearance collected on day 8 revealed a glomerular filtration rate of 18 ml/min. Throughout hospitalization, urinary pH remained within 7.5–8.5 and urine output remained greater than 2 L/day. The patient continued receiving intravenous leucovorin and urinary alkalinization until discharge (hospital day 12). Renal biopsy demonstrated patchy acute tubular necrosis (hospital day 10). Because of slow recovery of renal function, HDMTX cycle number two was delayed until ten weeks following cycle number one. At that time, renal function had improved however serum creatinine remained elevated (1.5 mg/dl) and the

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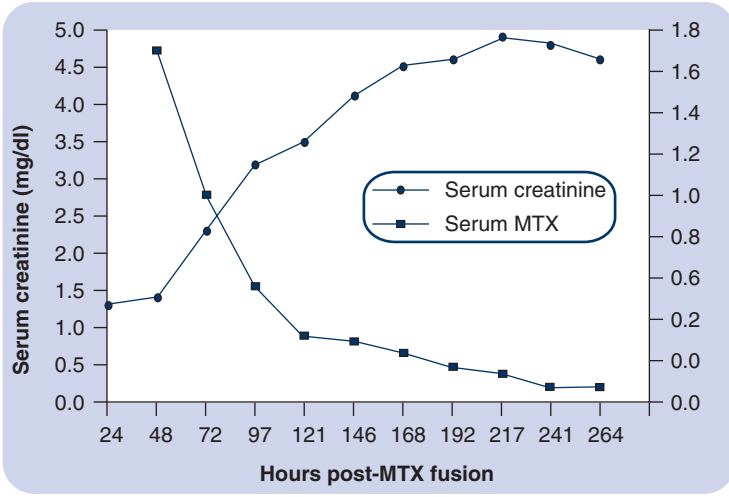
Figure 1. Serum MTX and creatinine for cycle 1.



MTX: Methotrexate.

creatinine clearance had deteriorated (84 ml/min) relative to pretreatment values. Other than establishing a new baseline serum creatinine and clearance, there was no evidence of toxicity from HDMTX cycle number one.

The patient has continued to receive full-dose MTX (completed eight cycles of MTX, each cycle given at 8 gm/m^2) without evidence of nephrotoxicity. Consolidative orbital radiotherapy (36 Gy in 24 fractions) was administered at the conclusion of HDMTX. At last follow-up, 12 months since completion of all PCNSL-directed therapy, the patient is clinically and radiographically in complete remission.

Discussion

Following infusion, MTX quickly distributes to tissues and brain with a distribution halflife of 0.75 h. Elimination is via renal glomerular filtration and active tubular excretion with a small percentage of hepatic metabolism. Elimination halflife increases with dose, displaying nonlinear pharmacokinetics, but is approximately 8–15 h when high doses are employed [4].

Nephrotoxicity of MTX due to urinary crystallization in the presence of acidic pH has been well-described [4–6]. Methotrexate, however, has rarely been demonstrated to cause ATN notwithstanding urine alkalinization [5,6]. Acute tubular necrosis is caused by prolonged renal hypoperfusion or direct toxicity due to a pharmacologic agent, in this case HDMTX. Nephrotoxic ATN is evidenced by intrarenal vasoconstriction, direct tubule toxicity and/or tubule obstruction. Prompt treatment of ATN secondary to MTX toxicity is crucial as it is reversible in almost all cases. The primary treatment goal is introduction of a loop diuretic in order to flush the renal tubules. Supportive care includes hydration and urinary alkalinization. In rare instances, despite adequate hydration and urinary alkalization, renal function deteriorates causing decreased MTX elimination. In certain instances, carboxypeptidase G2 or thymidine may be considered. The recurrence risk of methotrexate-induced nephrotoxicity is unknown but believed to be low [7]. One study reported all patients who received additional methotrexate infusions after recovering from a nephrotoxic cycle of methotrexate tolerated the cycles well without recurrence of nephrotoxicity [7].

Future MTX cycles should only be given after renal function has returned to baseline by monitoring the patient's creatinine clearance and serum creatinine [7,8]. Following recovery of renal function, subsequent cycles may be administered at full dose, although exact recommendations are meager. Leucovorin doses should be modified only in response to methotrexate levels. Leucovorin doses exceeding current practice guidelines provide no clinical benefit [7].

Expert commentary

Nephrotoxic ATN secondary to MTX is rare (as contrasted with mild renal insufficiency commonly seen with HDMTX exposure). However, once the patient recovers from the initial renal insult, retreatment with HDMTX is both reasonable and safe. Nephrotoxic ATN is unlikely with subsequent HDMTX cycles.

Highlights

- High-dose methotrexate may be nephrotoxic .
- Nephrotoxic occurence is idiosyncratic.
- Prior episodes of nephrotoxicity does not predict for recurrence.

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