Advances in Managing Acute Kidney Injury: Improving Outcomes for Patients Treated With High-Dose Methotrexate

Case Study 2:
HDMTX-Induced AKI in CNS Lymphoma

HARBORSIDE
Medical Education

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Case Study 2

HDMTX-Induced AKI in Central Nervous System Lymphoma

Learning objectives:

- Plan strategies to monitor patients treated with high-dose methotrexate (HDMTX) for development of acute kidney injury (AKI)
- Identify patient and disease characteristics that trigger treatment with glucarpidase
- Formulate plans to treat AKI caused by HDMTX safely and effectively based on best available evidence and recent guidelines

HDMTX-Induced AKI

- HDMTX is used in several regimens for patients with solid tumors and hematologic malignancies.
- Delayed MTX clearance can lead to significant morbidity and mortality.
- AKI develops in up to 12% of patients after treatment with HDMTX, with a 6% mortality rate.[1,2]

1. Howard SC, et al. *Oncologist.* 2016;21:1471-82.
2. Ramsey LB, et al. *Oncologist.* 2018;23:52-61.

CNS Lymphoma and HDMTX

- Highly aggressive non-Hodgkin lymphoma confined to the central nervous system (CNS), including the brain, spine, cerebrospinal fluid, and eyes
- Typically responds to both chemotherapy and radiation
- Inferior survival compared with non-CNS lymphomas
- Improved prognosis with the introduction of HDMTX
  - Results after treatment are durable in half of patients
  - Therapy can be associated with late neurotoxicity
- Poor prognosis for patients that failed first-line therapy

Case Study

- 58-year-old female patient with a 2-month history of gait imbalance and worsening one-sided weakness
- MRI imaging reveals homogenous brain mass
- Biopsy reveals diffuse large B-cell lymphoma, CD20+, Ki67 75%
- Negative for other systemic involvement
- Baseline labs = normal limits; no pleural effusions
- Current medications: pantoprazole, scopolamine eye drops, dexamethasone

HDMTX Contraindications and Drug Interactions

- Contraindications
  - Third-space fluid (pleural effusions or ascites)
  - Elevated baseline serum creatinine
  - Hepatic failure
  - Impaired bone marrow function
  - Impaired urinary output
- Drug interactions
  - Trimethoprim, sulfamethoxazole
  - Proton pump inhibitors
  - Nonsteroidal anti-inflammatory drugs
  - Penicillins
  - Salicylates
  - Probenecid

Case Study

- Undergoes first cycle of rituximab, HDMTX, vincristine, and procarbazine
- Baseline serum creatinine level and creatinine clearance are normal
- Glucose level elevated secondary to dexamethasone
- Five hours of IV hydration and alkalinization of urine (pH >7)
- Patient receives MTX 3.5 g/m^2 over 24 hours and leucovorin rescue

MTX Therapy Precautions

- Alkalinization of the urine = >7 pH
- Increased solubility of MTX when pH increases from 5 to 7
  - MTX and its metabolites have up to a 20-fold increase in solubility
  - Renal tubular precipitation = pH <5.7
  - Keep urine pH >7.0 to allow MTX levels to decrease to <0.1 μM
- Adequate hydration promotes diuresis and prevents intratubular precipitation of MTX
- Recommended: IV fluids of at least 2.5-3.5 L/m^2/day starting 4-12 hours before HDMTX infusion

Case Study

- 36 hours post-infusion
  - MTX serum concentration = 41 μM
  - Serum creatinine rises to 3 mg/dL
    - 1.8 mg above the upper limit of normal = renal dysfunction
- Glucarpidase administered (50 units/kg)
- 42 hours post-infusion
  - MTX serum concentration = 21 μM

Mechanism of Action

- Methotrexate
  - Antifolate antimetabolite
  - High dose = 500 mg/m^2 infused over 2-36 hours
- Leucovorin
  - Folinic acid that works to restore cellular metabolism after HDMTX administration
  - For MTX plasma concentrations >5 µM, multiply MTX level by patient weight (kg) for dose[1]
  - Does not reduce MTX plasma levels
  - Administration later than 48 hours after starting HDMTX significantly increases risk of morbidity[2]

1. Ramsey LB, et al. *Oncologist.* 2018;23:52-61.
2. Bertino JR. *Semin Oncol.* 1977;4:203-16.

Glucarpidase

- Extracellularly converts MTX to glutamate and 4-deoxy-4-amino-N 10-methylpteroic acid (DAMPA)
- Works in tandem with leucovorin
- Potential side effects
  - Paresthesia
  - Flushing
  - Nausea/vomiting
  - Hypotension
  - Pruritus
  - Fever
  - Headache

Treatment Considerations

- Leucovorin and glucarpidase
  - Do not administer simultaneously; glucarpidase inactivates leucovorin
  - Wait at least 2 hours after leucovorin administration to administer glucarpidase
- Check plasma MTX levels at 24, 48, and 72 hours after starting the MTX infusion, at a minimum
- Serum MTX levels should be followed until the plasma level is <0.1 μM

Glucarpidase Administration

- Indication: serum creatinine significantly elevated relative to baseline
- Guidelines for administering glucarpidase based on MTX plasma concentration[1]
  - 24 hours: >120 µM (1-8 g/m^2 MTX) or >50 µM (8-12 g/m^2 MTX)
  - 36 hours: >30 µM
  - 42 hours: >10 µM
  - 48 hours: >5 µM
- Glucarpidase administration should occur within 48-60 hours from the start of HDMTX infusion
- Ensure your institution stocks glucarpidase or has a plan to access it rapidly

1. Ramsey LB, et al. *Oncologist.* 2018;23:52-61.

Glucarpidase Alternatives

- High-dose leucovorin alone
  - Associated with treatment failure[1,2]
  - Can interfere with efficacy of subsequent HDMTX treatment cycles[3]
- Hemodialysis
  - Patients experience rebound effect of MTX when dialysis stops
  - Multiple rounds across ~5.6 days to clear MTX[4]
  - Side effects: myocardial infarction, stroke, intradialytic hypotension

1. Cohen IJ, et al. *Pediatr Hematol Oncol.* 2003;20:579-81.
2. Skärby TC, et al. *Leukemia.* 2006;20:1955-62.
3. Sterba J, et al. *Clin Chem.* 2006;52:692-700.
4. Wall SM, et al. *Am J Kidney Dis.* 1996;28:846-54.

Glucarpidase, Hospital Stay, and Mortality

- Average length of hospital stay among patients with CNS lymphoma and HDMTX-induced AKI[1]
  - Treated with glucarpidase: 14.7 days
  - Treated with dialysis but not glucarpidase: 40.7 days
  - Treated with/without dialysis but not glucarpidase: 21.9 days
- Lower mortality, inpatient mortality, and 90-day mortality rates with glucarpidase[1]
- Clinically important 99% or greater sustained reduction of serum MTX levels and noninvasive rescue from MTX toxicity among renally impaired patients who received glucarpidase[2]

1. Demiralp B, et al. *Clinicoecon Outcomes Res.* 2019;11:129-44.
2. Widemann BC, et al. *Pharmacotherapy.* 2014;34:427-39.

Case Study

- Fully improved renal function after rapid identification of HDMTX-induced AKI and administration of glucarpidase within guideline-recommended time frame

Post-Glucarpidase Considerations

- Restart leucovorin rescue 2 hours after glucarpidase administration and continue for at least 48 hours
- Monitor patients until MTX plasma levels decrease to ≤0.1 µM
- >1 glucarpidase administration within 48 hours may decrease the efficacy of HDMTX

Ramsey LB, et al. *Oncologist.* 2018;23:52-61.

Summary of Key Points

- Be aware of contraindications to HDMTX, including third-space fluids, baseline elevated serum creatinine, and drug-drug interactions, and check hepatic, renal, and bone marrow function prior to initiating therapy.
- Adequate hydration, leucovorin, and glucarpidase reduce incidence of HDMTX-induced AKI.
- Understand mechanisms of action and relationships of MTX, leucovorin, and glucarpidase.
- Wait at least 2 hours after leucovorin administration prior to giving glucarpidase, and ensure glucarpidase administration occurs before 48-60 hours from start of HDMTX infusion.
- Glucarpidase is associated with improved outcomes, decreased mortality, and decreased length of hospital stay.