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

Case Study 1:
HDMTX-Induced AKI in Osteosarcoma

HARBORSIDE
Medical Education

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Case Study 1
HDMTX-Induced AKI in Osteosarcoma

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.

Osteosarcoma and HDMTX

- Primary cancer of bone, often high grade with lung metastasis
- More common among children and young adults
- Predisposition to distal femur, proximal tibia, and proximal humerus
- HDMTX is part of first-line combination chemotherapy for children and active adjuvant therapy for adults
- HDMTX-induced AKI occurs in ~1.8% of patients with osteosarcoma treated on clinical trials, with a 4.4% mortality rate[1]

1. Widemann BC, et al. *Cancer.* 2004;100(10):2222-32.

Identifiable Risk Factors

- Baseline chronic kidney disease and/or extensive comorbidities
- Pretreatment volume depletion
- Pre-therapy acidic urine
  - Alkalinization increases MTX solubility 10x with a pH increase from 6 to 7
- Drug interactions
  - Probenecid, salicylates, sulfisoxazole, penicillins, and nonsteroidal anti-inflammatory agents
- Heavy neoadjuvant or palliative pretreatment

Pretreatment Strategies

- Proper pre-treatment counseling/chemotherapy education
- Oral hydration
- Urine testing and sodium bicarbonate
- Leucovorin doses at home, starting 24 hours after initiating MTX
- Timely lab draws (peak and subsequent)
- Warning symptoms: fever, chills, nausea, vomiting

Case Study

- 31-year-old female patient presenting with right proximal tibia pain and blastic lesion with periosteal signs on x-ray
- Diagnosed with localized fibroblastic osteosarcoma
- Neoadjuvant systemic therapy initiated:
  - Doxorubicin 75 mg/m^2 IV continuous infusion over 72 hours
  - Cisplatin 120 mg/m^2 over 4 hours IV
  - Four cycles with planned aggressive IV fluids 250 mL/hr

Case Study

- Response assessment every 2 cycles with repeat PET/CT scan with IV contrast noting positive response
- Undergoes radical resection and endoprosthetic reconstruction with negative margins and 70% necrosis
- Adjuvant treatment strategy: HDMTX alternating with single-agent high-dose ifosfamide

Case Study

- Creatinine
  - Pre-treatment baseline: 0.4-0.5 mg/dL
  - Post-treatment: 0.85 mg/dL
- HDMTX prep includes pre-therapy counseling
- Proceeds with HDMTX 10 mg/m^2 IV over 4 hours
- MTX peak: 1726.54 µM with associated fatigue
- MTX 24 hours: 263.76 µM
- Experiences lethargy and worsening altered mental status

Identifying Emerging Toxicity

- Expected MTX level after 24 hours: <50 μM[1]
- Employ a team approach: triage nurse, advanced practice provider, attending physician, and pharmacist
- Combine interpretation of laboratory and clinical assessment to make rapid decisions

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

Case Study

- Patient instructed to report to emergency department
- Pharmacist alerted to initiate approval for glucarpidase
- Total time for treatment decisions: <5 minutes

Emergent Rescue Interventions

- Alkaline fluids: 125 mL/hr increasing to 200 mL/hr
- Leucovorin: 100 mg every 6 hours
- Glucarpidase: 50 units/kg

- When initiating rescue interventions, remember:
  - Leucovorin: less effective for high MTX concentrations
  - Glucarpidase: rapid metabolism of >95% within 15 minutes
  - Dialysis-based methods relatively ineffective at reducing plasma MTX concentrations

Glucarpidase

- Ensure your institution stocks glucarpidase or has a plan to access it rapidly
- Administration should occur within 48-60 hours after HDMTX initiation
  - Life-threatening toxicities may not be preventable beyond this point

Interpreting Lab Values

- MTX level
  - Considering starting glucarpidase if at:
    - 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 + creatinine increase
- Creatinine
  - Creatinine clearance may lag an unexpected identified high MTX level
  - >50% from baseline 24-36 hours from start = 0.99 specificity of delayed MTX clearance

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

Case Study

- Sodium acetate: 125 mL/hr, increased to 200 mL/hr
- Leucovorin: 100 mg every 6 hours
- Glucarpidase: 3000 units IV (50 unit/kg)
- Labs
  - Creatinine peak = 1.05 mg/dL
  - AST/ALT = normal limits
  - MTX clearance of <0.1 on day 9

Toxicities of Delayed MTX Clearance

- Worsened renal function
- Exacerbations of non-renal adverse events:
  - Myelosuppression
  - Mucositis
  - Dermatologic toxicity
  - Hepatotoxicity
- Expedited treatment allows for optimal MTX clearance and resolution of symptoms and baseline creatinine

Case Study

- Discharged on day 5
  - Resolving oral ulcers
  - Decreasing creatinine level
  - MTX level = 0.14
- New post-HDMTX injury baseline creatinine = 0.71
- Further HDMTX cycles administered inpatient with close monitoring without delayed clearance noted

Summary of Key Points

- Provide pretreatment counseling on urine testing, leucovorin doses, lab draws, alkaline IV fluid use, and warning symptoms of AKI.
- Risk factors for HDMTX-induced AKI include baseline chronic kidney disease, extensive comorbidities, pretreatment volume depletion, acidic urine, and identifiable drug interactions.
- Working as a team to monitor patients for delayed HDMTX clearance and emergent intervention is critical to timely treatment decision making.
- In addition to using consensus guidelines:
  - Correlate inappropriately high levels of MTX to clinical findings and lab anomalies
  - Monitor patients until <0.1 MTX clearance