Monitoring Your Patients for High-Dose Methotrexate (HDMTX)-Induced Acute Kidney Injury

Know the Signs

HDMTX-Induced Acute Kidney Injury (AKI) Leads to Delayed Methotrexate (MTX) Clearance, Resulting in Prolonged, Elevated Plasma MTX Concentrations[1,2]

- HDMTX-induced renal toxicity results from the precipitation of MTX in the renal tubules in the setting of[2,3]:
  - Low urinary pH (<7)[2,4]
  - Decreased urinary flow rates
  - High urinary MTX concentrations

Patients Experiencing AKI Are at Risk for Severe Clinical Consequences[5]

Patients who survive an AKI episode have[5]:

2x Risk of death

3x Risk of end-stage renal disease

10x Risk of developing incident or progressive chronic kidney disease

Read on to learn about the risk factors and warning signs of HDMTX-induced renal toxicity

HDMTX-Induced AKI Can Lead to Potentially Irreversible Life-Threatening Systemic Toxicity and Organ Damage[1,2,4,6,7]

Mucositis

Myelosuppression

Hepatoxicity

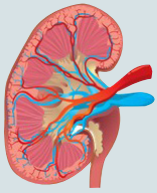
Pulmonary toxicity

Up to 12% of Patients Who Receive HDMTX Will Experience Delayed MTX Clearance Due to AKI[2,6,8,9]

Risk factors for HDMTX-induced AKI include[4]:

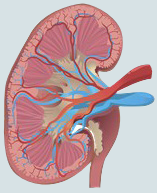
- Volume depletion
- Acidic urine (pH <7)
- Chronic kidney disease
- AKI during prior MTX courses
- Concomitant use of nephrotoxic medications
- Hypoalbuminemia

Progressive Grades of Renal Toxicity per National Cancer Institute[10,11]



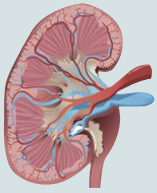
Healthy Renal Function

- SCr within the normal range:
  - 0.7 to 1.2 mg/dL (males)
  - 0.5 to 1.0 mg/dL (females)



NCI CTCAE Grade 1

- SCr: >ULN to 1.5x ULN



NCI CTCAE Grade 2

- SCr: >1.5 to 3.0x BL *or* >1.5 to 3.0x ULN

BL, baseline; BSA, body surface area; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; SCr, serum creatinine; ULN, upper limit of normal.

An Elevated Plasma MTX Level Is Often the First Sign of HDMTX-Induced AKI and May Precede Other Signs, Such as[1,6]

- Decreased urine output
- Positive fluid balance
- Weight change
- Increased SCr

In a Study of Over 600 Adult Lymphoma Patients Receiving HDMTX, MTX Concentrations >1.28 µM at 48 Hours Led to[12]:

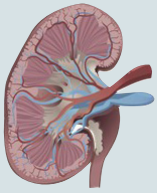
5x higher risk of AKI

5x higher ICU admissions

3.4 days longer hospital LOS

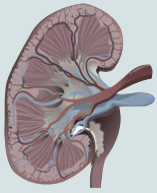
4x higher 30-day mortality rates

*From a retrospective analysis of 642 patients with lymphoma who received 2804 cycles of HDMTX between Jan 2002 – Dec 2018. Median age was 66 years and primary endpoints included nephrotoxicity, ICU admission, hospital LOS, and 30-day mortality after HDMTX. ICU, intensive care unit; LOS, length of stay.



NCI CTCAE Grade 3

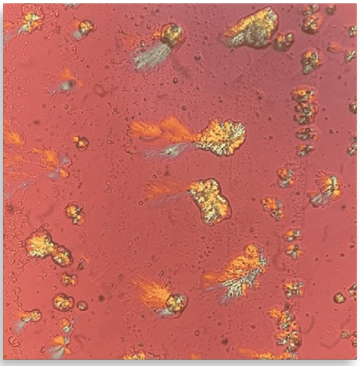
- SCr: >3.0x BL *or* >3.0 to 6.0x ULN
- Urine output:
  - Adults: oliguria (<80 mL in 8 hours)
  - Children: <500 mL/1.73 m^2 BSA/day
  - Infants: <0.5 mL/kg/hour for 24 hours



NCI CTCAE Grade 4

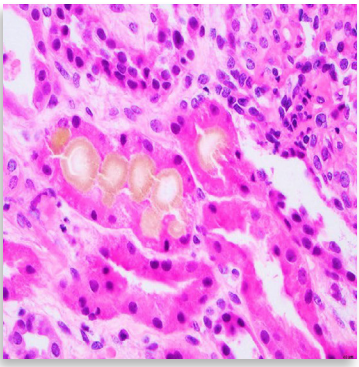
- SCr: >6.0x ULN
- Urine output:
  - Adults: anuria (<240 mL in 24 hours)
  - Children/Infants: no urine output for 12 hours

Precipitation of MTX in Renal Tubules Underlies the Development of HDMTX-Induced AKI[2,13]



Methotrexate crystals in urine with positive birefringence under polarized light[13]

Image source: Sami et al. *Cureus*. 2022;14(6):e26052.



Intratubular ring-shaped brown-tinged methotrexate crystals in kidney biopsy findings[4]

Figure reprinted with permission from Dasgupta AD, et al. *J Nephrol*. 2023.

Delayed MTX Clearance Due to AKI Is an Oncologic Emergency[1,6,7]

- Identify and treat delayed MTX clearance early to diminish risk for severe toxicity or death[6,7,14]

Visit MTXPK.org to see if your patient is clearing MTX as expected[15]

Access to see a comprehensive list of risk factors for delayed MTX clearance

References: 1. Howard SC et al. *Oncologist*. 2016;21(12):1471-1482. **2.** Widemann BC et al. *Oncologist*. 2006;11(6):694-703. **3.** Amitai I et al. *Hematol Oncol*. 2020;38(4):584-588. **4.** Dasgupta AD, et al. *J Nephrol*. 2023. doi:10.1007/s40620-023-01567-2 **5.** Silver SA, Siew ED. *Adv Chronic Kidney Dis*. 2017;24:246-252. **6.** Ramsey LB et al. *Oncologist*. 2018;23(1):52-61. **7.** Widemann BC et al. *J Clin Oncol*. 2010;28:3979-3986. **8.** Widemann BC et al. *Cancer*. 2004;100(10):2222-2232. **9.** Bacci G et al. *Acta Oncologica*. 1998;37(1):41-48. **10.** Blood tests: normal values. Merck Manual. Updated September 2022. Accessed May 31, 2023. https://www.merckmanuals.com/professional/resources/normal-laboratory-values/blood-tests-normal-values#top **11.** National Cancer Institute, US Department of Health and Human Services. *Common Terminology Criteria for Adverse Events (CTCAE). Version 5.0*. Published November 27, 2017. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf **12.** O'Donoghue DF et al. *JCO Oncol Pract*. 2022;1:1-7. **13.** Sami et al. *Cureus*. 2022;14(6):e26052. **14.** Ward S et al. *Clin Toxicol*. 2013;51(7):575-724. Abstract 7. **15.** Taylor ZL et al. *Clin Pharmacol Ther*. 2020;108(3):635-643.

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