Delayed Methotrexate (MTX) Clearance Can Occur in Any Patient Receiving High-Dose MTX (HDMTX)[1,2]

KNOW WHEN IT'S TIME TO ACT.

Delayed MTX clearance due to acute kidney injury (AKI) is an oncologic emergency, putting patients at risk for severe toxicity or death.[1,3,4] Timely treatment requires early recognition and action.

- Up to 12% of patients who receive HDMTX chemotherapy will experience delayed MTX clearance due to AKI.[5,6] In a study of 43 patients, 4 (9%) did not exhibit any risk factors and still experienced delayed MTX clearance.[2]

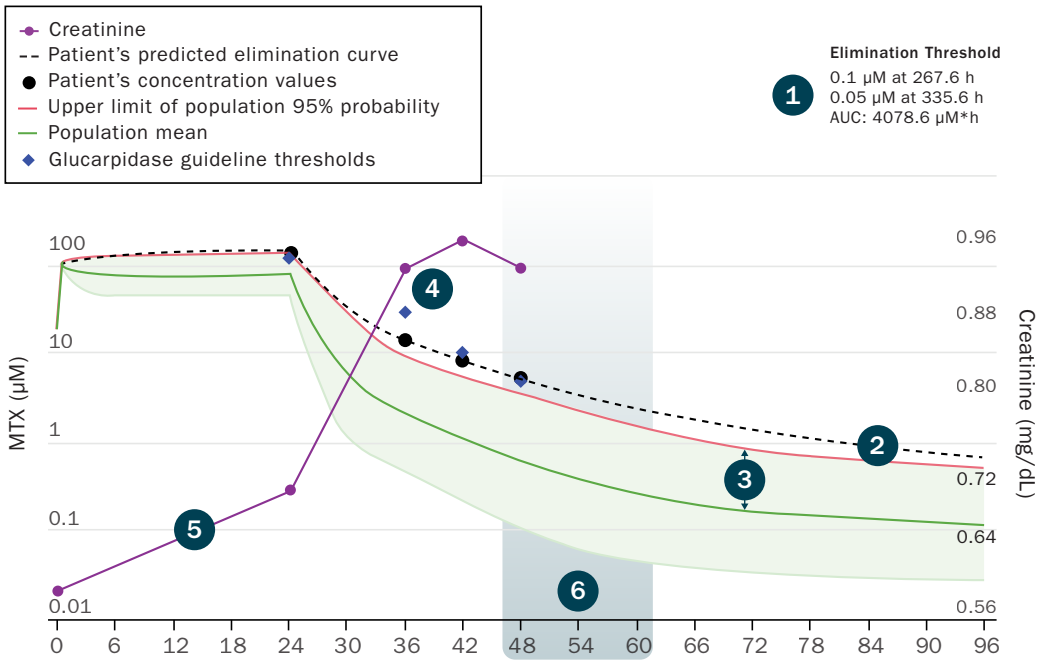
Delayed clearance of MTX increases risk for severe toxicities, including **nephrotoxicity**, **hepatotoxicity**, **neurotoxicity**, **mucositis**, and **myelosuppression**.[1,2]

MTXPK.org is a powerful tool that helps you monitor how well your patients are clearing MTX. You can get started with a single MTX and SCr lab value.[7]

1. Know when to expect your patient's MTX concentration to reach a level acceptable for discharge
2. Evaluate your patient's expected MTX clearance
3. Compare your patient's MTX clearance with the population mean and 2 SD above the mean
4. See how your patient's MTX levels compare with levels known to confer risk for serious MTX toxicity based on expert consensus guidelines
5. Evaluate serum creatinine (SCr) trend
6. Anticipate and diagnose delayed MTX clearance early, allowing you to act within the critical treatment window of 48-60 hours to lower circulating MTX levels and facilitate renal recovery[3]

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

Example Graphical Readout of an Actual Patient



Plasma and serum creatinine data based on an actual case of a 15-year-old patient with acute lymphoblastic leukemia (ALL). Methotrexate (MTX) levels obtained at 24, 36, 42, and 48 hours. The MTXPK.org tool has been validated for use with adult and pediatric patients based on over 40,000 MTX concentration levels in 1315 patients.[7] AUC, area under the concentration-time curve.

Consider using MTXPK.org in patients receiving HDMTX who have:

Presented for HDMTX treatment with risk factors for delayed MTX clearance[1,2]

- Renal insufficiency prior to HDMTX (i.e., CrCl <60 mL/min)
- Adult or elderly patients*
- Third spacing (i.e., pleural effusions, ascites, intracranial fluid)
- Body mass index ≥25 kg/m^2
- Volume depletion due to vomiting, diarrhea, or other factors
- Prior toxicity with HDMTX

Exhibited early warning signs of AKI[1,3]

- Decreased urine output
- Positive fluid balance
- Weight increase
- Plasma MTX concentrations above the expected MTX level
- Increase in SCr

*As many as 60% of adult cancer patients may have some degree of renal dysfunction.[1] CrCl, creatinine clearance.

MTXPK.org can be used to determine when Voraxaze is indicated for your patient[7,8]:

- ✓ MTX levels >2 SD above the mean MTX excretion curve
- ✓ MTX levels >1 µmol/L
- ✓ SCr trend line indicating impaired renal function

Voraxaze lowers MTX levels by ≥97% in 15 minutes.[8]

Prompt recognition of delayed MTX clearance and rapid reduction of MTX levels with Voraxaze may:

- Help prevent life-threatening toxicity and death[1,4,9]
- Facilitate renal recovery[1]
- Allow patients to resume HDMTX therapy or receive other chemotherapy[1,10]
- Decrease hospital and ICU length of stay[9]

Indication and Limitations of Use

- Voraxaze® is a carboxypeptidase indicated to reduce toxic plasma methotrexate concentration (greater than 1 micromole per liter) in adult and pediatric patients with delayed methotrexate clearance (plasma methotrexate concentrations greater than 2 standard deviations of the mean methotrexate excretion curve specific for the dose of methotrexate administered) due to impaired renal function
- Limitations of Use: Voraxaze® is not recommended for use in patients who exhibit the expected clearance and expected plasma methotrexate concentration. Reducing plasma methotrexate concentration in these patients may result in subtherapeutic exposure to methotrexate

Warnings and Precautions

Serious Hypersensitivity Reactions

- Serious hypersensitivity reactions, including anaphylactic reactions, may occur. Serious hypersensitivity reactions occurred in less than 1% of patients

Monitoring Methotrexate Concentration/Interference With Assay

- Methotrexate concentrations within 48 hours following Voraxaze® administration can only be reliably measured by a chromatographic method due to interference from metabolites. Measurement of methotrexate concentrations within 48 hours of Voraxaze® administration using immunoassays results in an overestimation of the methotrexate concentration

Adverse Reactions

- In clinical trials, the most common related adverse events (occurring in >1% of patients) were paresthesia, flushing, nausea and/or vomiting, hypotension and headache

Drug Interactions

- Voraxaze® can decrease leucovorin concentration, which may decrease the effect of leucovorin rescue unless leucovorin is dosed as recommended, and may also reduce the concentrations other folate analogs or folate analog metabolic inhibitors

Please see full Prescribing Information.

References: **1.** Howard S et al. *Oncologist*. 2016;21(12):1471-1482. **2.** Schwartz S et al. *Oncologist*. 2007;12:1299-1308. **3.** Ramsey LB et al. *Oncologist*. 2018;23(1):52-61. **4.** Widemann BC et al. *J Clin Oncol*. 2010;28(25):3979-3986. **5.** Bacci G et al. *Acta Oncol*. 1998;37(1):41-48. **6.** Widemann BC et al. *Cancer.* 2004;100(10):2222-2232. **7.** Taylor ZL et al. *Clin Pharmacol Ther.* 2020;108(3):635-643. **8.** Voraxaze®. Prescribing information. BTG International Inc.; 2019. **9.** Demiralp B et al. *Clinicoecon Outcomes Res*. 2019;11:129-144. **10.** Christensen AM et al. *Cancer.* 2012;118(17):4321-4330.

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VORAXAZE® (glucarpidase)
1000 units/vial for intravenous injection