Treating With High-Dose Methotrexate (HDMTX)

ROADMAP FOR SUCCESSFUL MANAGEMENT OF DELAYED MTX CLEARANCE

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

Provide supportive measures to protect against HDMTX-induced AKI, which could lead to delayed MTX clearance – an oncologic emergency.[1-4]

- Discontinue medications that may interfere with MTX clearance (e.g., NSAIDs, PPIs).[1]
- Initiate vigorous hydration and monitor fluids before and during infusion (approximately 90% of MTX is eliminated by the kidneys).[1,2]
- Ensure sufficient urine alkalinization (pH ≥7) before start of infusion.[1,3]
- Monitor MTX levels and renal function (i.e., SCr levels) post infusion.[1,3]

Note: Leucovorin rescue is essential when administering HDMTX, but it does not clear MTX from the body.[1]

Factors that might increase risk of delayed MTX clearance[1,5]:

- BMI ≥25 kg/m^2
- Renal insufficiency prior to HDMTX (i.e., CrCl <60 mL/min)
- Prior toxicity with HDMTX
- Adult and elderly patients, as many as 60% of whom may have some degree of renal dysfunction
- Volume depletion, third spacing, polyuria

In a study of 43 adult patients receiving HDMTX, 4 (9%) did not exhibit ANY risk factors and still experienced delayed MTX clearance.[5]

Check for early warning signs of delayed MTX clearance[1,3]:

- Decreased urine output
- Positive fluid balance
- Weight change
- Plasma MTX concentrations higher than expected
- Increased serum creatinine, a lagging indicator

Note: The following MTX levels in patients receiving HDMTX are predictive for the development of toxicity: >10 µM at 24 hours (in patients receiving doses 8 g/m^2 over 4 hours) and >1 µM at 48 hours.[2]

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

Leucovorin is less effective in the presence of high circulating MTX concentrations, particularly those exceeding 10 µM for at least 48 hours.[3]

Identify and treat delayed MTX clearance early.

Use MTXPK.org[6,*]

Monitor whether your patient is clearing MTX as expected

Anticipate and detect delayed clearance early

Enter your patient's lab values and plot a trend line for MTX clearance

Determine when treatment with Voraxaze® is indicated[6,7]

Follow Consensus Guidelines[3]

Identify MTX concentrations known to confer risk of severe or life-threatening toxicity

If your patient's MTX level is:

- **>50 µM at 24 h[†]** (for doses 8-12 g/m^2 over ≤6 h)[‡]
- **>30 µM at 36 h[†]** (for doses >1 g/m^2)
- **>10 µM at 42 h[†]** (for doses >1 g/m^2)
- **>5 µM at 48 h[†]** (for all doses of HDMTX)

Voraxaze is strongly recommended in the context of rising creatinine, optimally within 48-60 h from the start of HDMTX infusion

*The MTXPK.org tool is validated in adult and pediatric patients based on >40,000 MTX concentration levels in 1315 patients.[6,8]

† From start of HDMTX infusion.[3]

‡ For MTX doses of 1-8 g/m^2 over 24 hours, if MTX concentration is >120 µM or SCr is greater than 1.5x baseline, continue supportive care and check MTX concentration at 36 hours.[3]

Delayed MTX clearance due to AKI is an oncologic emergency.[1,3,4]

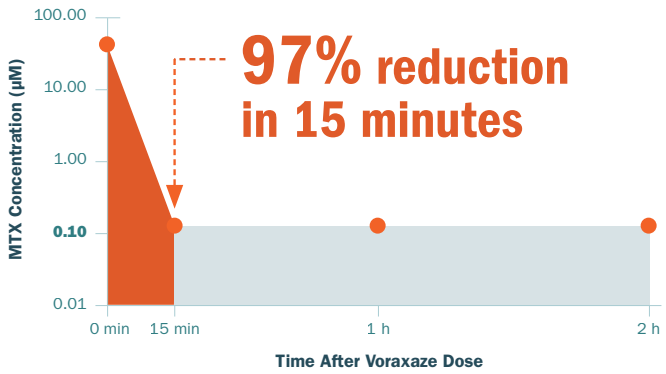
See next page for the solution »

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

Please see additional Important Safety Information on next page and Prescribing Information.

Resolve the oncologic emergency of delayed MTX clearance due to AKI with Voraxaze.[1,4,7]

- MTX concentrations were reduced by ≥97% within 15 minutes in 100% of patients (N=22) and were maintained at a >95% reduction for up to 8 days in 91% (20/22).[7]



Rapid reduction of MTX levels with Voraxaze may[1,4,9,10]:

- Help prevent life-threatening toxicity and death
- Facilitate renal recovery
- Allow patients to resume HDMTX therapy or receive other chemotherapy
- Decrease length of stay in the ICU and hospital

Early treatment with Voraxaze reduces length of stay in the hospital and ICU.[9]

- 54% fewer days in hospital when treated within 3 days vs after 3 days following admission (10 days vs 21.7 days; *P*=0.002)
- 91% fewer days in ICU when treated within 3 days vs after 3 days following admission (0.8 days vs 8.9 days; *P*=0.020)

References: **1.** Howard S et al. *Oncologist.* 2016;21(12):1471-1482. **2.** Widemann BC et al. *Oncologist.* 2006;11:694-703. **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.** Schwartz S et al. *Oncologist.* 2007;12:1299-1308. **6.** Taylor ZL et al. *Clin Pharmacol Ther.* 2020;108(3):635-643. **7.** Voraxaze® [prescribing information]. BTG International Inc.; 2019. **8.** Data on file at Cincinnati Children's Hospital Medical Center. **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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Administer Voraxaze within 48-60 hours from the start of the HDMTX infusion, because life-threatening toxicities may not be preventable after this time.[3]

Administer as a single bolus IV injection of 50 U/kg over 5 minutes.[7]

- Do not give leucovorin within 2 hours before or after the Voraxaze dose.
- For the first 48 hours, keep leucovorin at the same dosage as given before Voraxaze.
  - Voraxaze can interfere with immunoassay measurements of MTX for up to 48 hours post administration; use a chromatographic method to measure MTX concentrations for the first 48 hours after Voraxaze administration.
- Beyond 48 hours, determine leucovorin dosage based on the measured MTX concentration.

After Voraxaze administration, continue supportive measures and monitor.

- Therapy with leucovorin should be continued until the MTX concentration has been maintained below the leucovorin treatment threshold for a minimum of 3 days.[7]
- Prompt and effective treatment with Voraxaze may permit patients to receive other chemotherapy or resume HDMTX therapy when additional courses are indicated.[1,10]

Abbreviations: AKI, acute kidney injury; BMI, body mass index; CrCl, creatinine clearance; ICU, intensive care unit; IV, intravenous; MTX, methotrexate; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; SCr, serum creatinine.

Important Safety Information

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

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