CONSENSUS GUIDELINE FOR USE OF GLUCARPIDASE IN PATIENTS WITH HIGH-DOSE METHOTREXATE INDUCED ACUTE KIDNEY INJURY AND DELAYED METHOTREXATE CLEARANCE

Consensus guidelines established by an expert panel

Ramsey LB, Balis FM, O'Brien MM, et al. *Oncologist*. 2018;23:52-61.

> "The goal of this task force was to identify the population of patients who would benefit from glucarpidase rescue by more precisely defining the absolute MTX concentrations that put patients at risk for severe or life-threatening toxicities at specific time points after the start of the HDMTX infusion based on reported experience with HDMTX infusions."

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

Predicting early which patients will need glucarpidase is imperative.

On the importance of anticipating and identifying AKI:

- Approximately 2%–12% of adults treated with HDMTX develop nephrotoxicity (page 2)
- Serum creatinine is a suboptimal biomarker of AKI, as creatinine rise may lag significantly from the time of the renal insult. Elevated plasma MTX concentration may indicate HDMTX-induced AKI prior to a significant change in creatinine (page 2)

Please see the enclosed article for the quotes referenced.

Abbreviations: BL, baseline; Cr, serum creatinine; HDMTX, high-dose methotrexate; LV, leucovorin (folinic acid, citrovorum factor, 5-methyltetrahydrofolate); MTX, methotrexate; [MTX], plasma methotrexate concentration

On optimizing supportive care and rescue therapy:

- The purpose of alkalinization of the urine and fluid hydration is to maximize the solubility of MTX in urine. These measures do not enhance MTX clearance, which is largely dependent on glomerular filtration at high plasma MTX concentrations (page 4)
- LV rescue is less effective at high MTX concentrations, especially when the MTX concentration exceeds 10 µm for 48 hours or longer (page 4)
- Leucovorin is a storage vitamin, and excessive rescue could thus interfere with the MTX efficacy at the next HDMTX course (page 8)
- Glucarpidase rapidly metabolizes circulating MTX and reduces plasma MTX concentrations by > 95% within 15 minutes of administration (page 5)

To see if your patient is clearing MTX as expected, visit MTXPK.org.

This free, independently developed clinical decision-making tool provides patient-specific expected and actual elimination curves, along with serum creatinine trends and time to attain threshold levels for discharge planning.

Indication and Limitations of Use

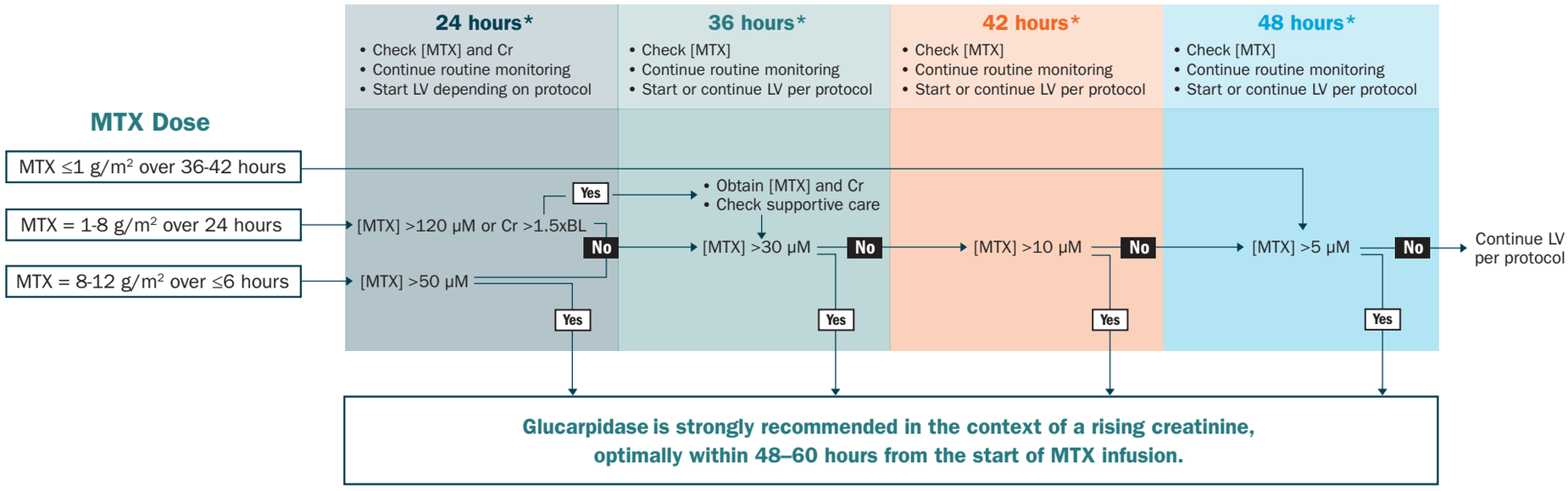
- Voraxaze® is a carboxypeptidase indicated to reduce toxic plasma methotrexate concentration (greater than 1 micromole per liter) in adult and pediatric patients with delayed methotrexate clearance (plasma methotrexate concentrations greater than 2 standard deviations of the mean methotrexate excretion 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

Please see enclosed full Prescribing Information and Important Safety Information on back cover.

See full article inserted in pocket

Administration of glucarpidase should optimally occur within 48–60 hours from the start of the HDMTX infusion, because life-threatening toxicities may not be preventable beyond this time point.

HDMTX Monitoring Guideline and Glucarpidase Treatment Algorithm



*Hours are indicated after infusion start. Provide adequate supportive care (urine pH >7, urine output >2.5 L/m² per day, emesis control).

Abbreviations: BL, baseline; Cr, serum creatinine; HDMTX, high-dose methotrexate; LV, leucovorin (folinic acid, citrovorum factor, 5-methyltetrahydrofolate); MTX, methotrexate; [MTX], plasma methotrexate concentration.

Adapted from Ramsey et al. 2018.

The expert panel was able to come to consensus, providing specific MTX concentrations above which glucarpidase is recommended. Implementation of the recommendations in this guideline may help reduce the incidence of life threatening HDMTX-induced toxicities.

Learn more at www.Voraxaze.com.

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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BTG

US-VRX-2000094 July 2020

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