EARLY WARNING SIGNS OF HIGH DOSE METHOTREXATE (HDMTX) INDUCED ACUTE KIDNEY INJURY (AKI)

An Oncologic Emergency

Patients who survive an AKI episode have:[1]

- Double the risk of death
- Triple the risk of end stage renal disease
- Ten times the risk of developing incident or progressive chronic kidney disease

The rate of cardiovascular events in AKI patients is as high as 22% and mortality related to cardiovascular events is 33% in patients with AKI.[2]

Early warning signs

Treatment with glucarpidase is recommended in the case of high MTX concentrations and rising creatinine.

Renal tissue damage from MTX precedes the decline in renal function observed by:[3]

- Decreased urine output
- Positive fluid balance
- Weight change
- Plasma MTX concentrations above the expected MTX level
- Increased serum creatinine, which is a lagging indicator

Consensus Guidelines

An expert panel was convened to provide specific, expert consensus guidelines for the use of glucarpidase in patients who develop HDMTX induced nephrotoxicity and delayed methotrexate excretion. The guideline provides recommendations to identify the population of patients who would benefit from glucarpidase rescue by more precisely defining the absolute methotrexate concentrations associated with risk for severe or life-threatening toxicity at several time points after the start of an HDMTX infusion.[4]

MTX Monitoring Tool

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.

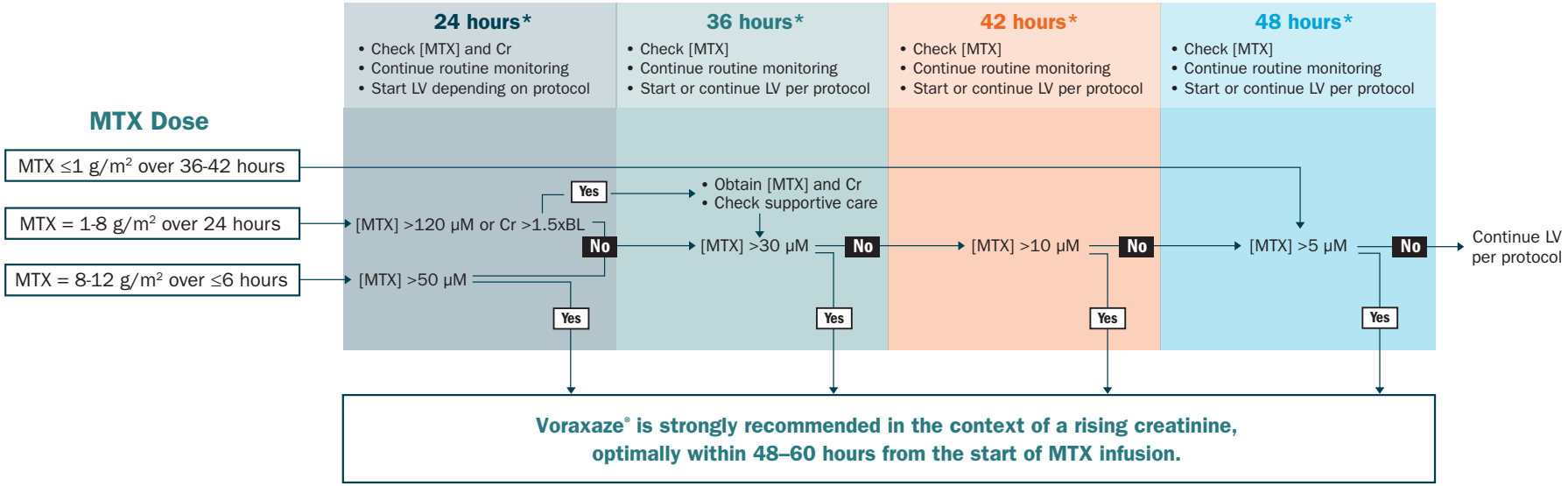
Administration of glucarpidase should optimally occur within 48–60 hours from the start of the HDMTX infusion, because life-threatening toxicities may not be preventable beyond this time point.[4]

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 Important Safety Information and accompanying full Prescribing Information.

HDMTX Monitoring Guideline and Voraxaze® 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 p. 7 fig 5

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

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

Please see accompanying full Prescribing Information.

24-hour Medical Information: 1-877-377-3784
Customer Service: 1-844-293-0007

References

1. Silver SA, Siew ED. *Adv Chronic Kidney Dis.* 2017;24: 246-25 **2.** Demiralp B et al. *ClinicoEconomics and Outcomes Research* 2019;11:129-144. **3.** Howard SC, et al. *Oncologist.* 2016;21(12):1471-1482. **4.** Ramsey LB, et al. *Oncologist*. 2018;23(1):52-61.