GLUCARPIDASE FOR TREATMENT OF HIGH-DOSE METHOTREXATE TOXICITY

Gupta, et al. *Blood* 2025

AIM OF THE STUDY

Evaluate the effect of treatment with glucarpidase on clinical outcomes, including kidney recovery, neutropenia, hepatotoxicity, mucositis, and mortality, using data from patients with MTX-associated AKI obtained from a large number of cancer centers across the United States.

SUMMARY OF DATA

Data from 708 patients with HDMTX-induced AKI across 28 US cancer centers showed that the 209 patients treated with glucarpidase had:

- 2.70-fold higher adjusted odds of kidney recovery at hospital discharge (95% CI, 1.69-4.31) compared to those not treated with glucarpidase
- Faster time to kidney recovery (aHR, 1.88, 95% CI, 1.18-3.33) in the first 14 days compared to those not treated with glucarpidase
- A lower likelihood of Grade ≥2 neutropenia (aOR, 0.50 [95% CI, 0.28-0.91]) and Grade ≥2 transaminitis at Day 7 (aOR, 0.31 [95% CI, 0.13-0.77]) compared to those not treated with glucarpidase

aHR, adjusted hazard ratio; AKI, acute kidney injury; aOR, adjusted odds ratio; CI, confidence interval; HDMTX, high-dose methotrexate; MTX, methotrexate.

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

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

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

Please see Important Safety Information throughout and scan or click the QR code on the last page for full Prescribing Information.

STUDY DESIGN

A retrospective analysis of data from patients treated at 28 cancer centers across the US from 2000 to 2022, comparing a group of patients who received glucarpidase with a group of patients who did not receive glucarpidase.

Primary outcome:

- Kidney recovery at hospital discharge
  Defined as a composite of survival to hospital discharge without KRT dependence and with SCr <1.5-fold baseline

Secondary outcomes:

- Time to kidney recovery in the first 14 days
- Incidence and severity of neutropenia, transaminitis, and mucositis
- MTX rechallenge within 30 days following the index MTX infusion
- Persistent kidney impairment or death at Day 90
- Time to death assessed within the first 90 days

Inclusion criteria:

- ≥18 years of age
- High-dose IV MTX (≥1 g/m^2, infusion duration of either <12 or 24 [±4] hours)
- Developed MTX-AKI defined as a ≥1.5-fold increase in SCr within 4 days after initiation of MTX compared to the baseline value

Exclusion criteria:

- End-stage kidney disease
- Moribund (likely to die within 2 days) at the time of MTX initiation

RESULTS

708 patients

209 patients
(29.5%)
treated with glucarpidase

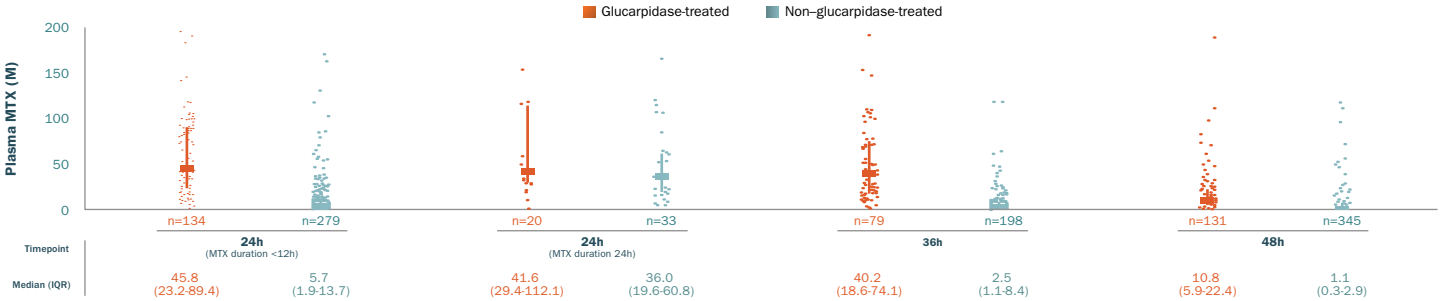
499 patients
(70.5%)
NOT treated with glucarpidase

Initial AKI Stages	Stage 1 SCr 1.5-1.9 x baseline, or ≥0.3 mg/dL	Stage 2 SCr 2.0-2.9 x baseline	Stage 3 SCr 3.0 x baseline, or ≥4.0 mg/dL
Patients treated with glucarpidase	18 (8.6%)	53 (25.4%)	138 (66.0%)
Patients not treated with glucarpidase	216 (43.3%)	179 (35.9%)	104 (20.8%)

In patients treated with glucarpidase, glucarpidase was administered at a median of **54 hours** following initiation of MTX; no patient received glucarpidase beyond 96 hours.

The median dose of glucarpidase was **50 U/kg**.

Plasma MTX levels



More than half of glucarpidase-treated patients had a 24-hour MTX level <50 µM

AKI, acute kidney injury; IQR, interquartile range; IV, intravenous; KRT, kidney replacement therapy; MTX, methotrexate; SCr, serum creatinine.

Important Safety Information (continued)
Warnings and Precautions

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.

RESULTS (continued)

Higher odds of kidney recovery was observed in patients treated with glucarpidase

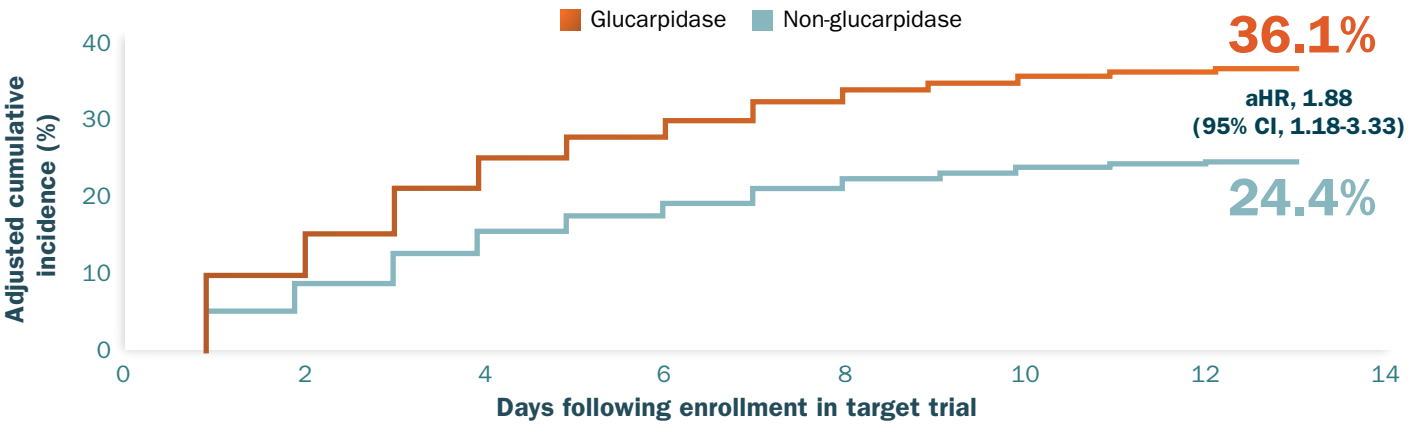
2.70 OR
(95% CI, 1.69-4.31)

Adjusted OR of kidney recovery in patients treated with glucarpidase

Additional studies are needed to establish whether patients with MTX levels that are more modestly supratherapeutic may also benefit from glucarpidase.

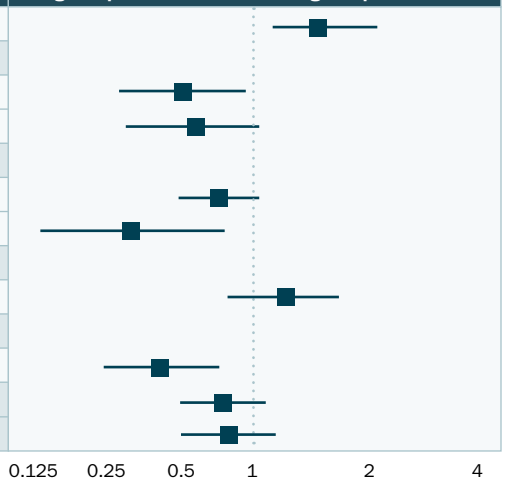
Glucarpidase-associated adverse events included nausea (n=12; 5.7%), diarrhea (n=1; 0.5%), and paresthesia (n=1; 0.5%)

Patients treated with glucarpidase had a faster time to kidney recovery



Lower odds for neutropenia and transaminitis with glucarpidase

Outcome	No. Events/No. Patients (%)	aOR/aHR* (95% CI)
Time to kidney recovery*	390/1645 (23.7)	1.88 (1.18-3.33)
Neutropenia on Day 7		
Grade ≥2 (ANC <1500/mm^3)	266/1502 (17.7)	0.50 (0.28-0.91)
Grade ≥3 (ANC <1000/mm^3)	169/1573 (10.7)	0.56 (0.29-1.06)
Transaminitis on Day 7		
Grade ≥1 (ALT ≥ULN)†	389/1167 (33.3)	0.72 (0.47-1.10)
Grade ≥2 (ALT ≥3x ULN)‡	113/1167 (9.7)	0.31 (0.13-0.77)
Mucositis on Day 7		
Any Grade	177/1644 (10.8)	1.34 (0.80-2.26)
MTX rechallenge		
Within 30 days following index MTX infusion	466/1645 (28.3)	0.41 (0.24-0.72)
Persistent kidney impairment or death at Day 90	388/1349 (32.0)	0.74 (0.49-1.11)
Time to death*	232/1645 (14.1)	0.76 (0.49-1.18)



*Time to kidney recovery and time to death are shown as HRs. All other outcomes are shown as ORs.
†Grade ≥1 transaminitis also includes a ≥1.5-fold increase in ALT compared to baseline if the baseline was abnormal.
‡Grade ≥2 transaminitis also includes a >3-fold increase in ALT compared to baseline if the baseline was abnormal.
aHR, adjusted hazard ratio; ALT, alanine aminotransferase; ANC, absolute neutrophil count; aOR, adjusted odds ratio; CI, confidence interval; MTX, methotrexate; ULN, upper limit of normal.

Important Safety Information (continued)
Warnings and Precautions

Monitoring Methotrexate Concentration/Interference With Assay

- Measurement of methotrexate concentrations within 48 hours of Voraxaze® administration using immunoassays results in an overestimation of the methotrexate concentration

CONCLUSION AND DISCUSSION

In summary, this study observed a higher adjusted odds of kidney recovery in patients with MTX-associated AKI that were treated with glucarpidase compared to those not treated with glucarpidase, and the association was consistent across multiple sensitivity analyses.

These findings have interesting implications for clinical practice and the design of future studies. They highlight the need to re-examine existing algorithms that rely on arbitrarily defined cutoffs for recommending glucarpidase and instead develop a more evidence-based approach. Consensus guidelines from 2018 recommend glucarpidase for patients receiving MTX infusions (8-12 g/m^2) over ≤6 hours only if they have a rising SCr and their 24-hour plasma MTX levels are >50 µM, but in the current study, more than half of the glucarpidase-treated patients had a 24-hour MTX level <50 µM.

Data for these findings are from the following participating cancer centers: Brigham and Women's Hospital/Dana-Farber Cancer Center, Duke University, Indiana University School of Medicine, Johns Hopkins University School of Medicine, Massachusetts General Hospital, Mayo Clinic, MD Anderson Cancer Center, Memorial Sloan Kettering Cancer Center, Moffitt Cancer Center, Ochsner Health, Ohio State University, Stanford Health Care, Thomas Jefferson University, University Hospitals Cleveland Medical Center, University of Alabama Birmingham, University of California (Los Angeles), University of California (San Francisco), University of Colorado, University of Florida (Gainesville), University of Kentucky, University of Miami, University of Pennsylvania, University of Pittsburgh Medical Center, University of Virginia, University of Washington, Vanderbilt University Medical Center, Washington University, Yale University.

AKI, acute kidney injury; MTX, methotrexate; SCr, serum creatinine.

Use MTXPK.org to monitor whether your patient is clearing MTX as expected and to help determine if Voraxaze® (glucarpidase) is indicated

Visit **Voraxaze.com**

Visit **MTXPK.org**

Reference: Gupta S, Kaunfer SA, Chen KL, et al. Glucarpidase for treatment of high-dose methotrexate toxicity. *Blood*. 2025;145(17):1858-1869.

Important Safety Information (continued)

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

To report suspected adverse reactions, contact SERB Pharmaceuticals at 1-877-3784 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

SERB Pharmaceuticals

US-VRX-2500045/May 2025

Full Prescribing Information

Please see Important Safety Information throughout and scan or click the QR code above for full Prescribing Information.