# Glucarpidase for Treatment of High-Dose Methotrexate Toxicity

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## Introduction

- High-dose methotrexate (HD-MTX) is one of the most effective treatment options for numerous malignancies but results in high rates of AKI, neutropenia, and hepatotoxicity
- Glucarpidase is a recombinant bacterial enzyme that cleaves MTX, but evidence supporting its use for clinical MTX toxicity is scarce
- Accurate assessment of glucarpidase's improvement of clinical outcomes in adults with MTX-AKI can help clinicians weigh risks and benefits of glucarpidase administration and standardize its use across centers
- Prior studies that investigated glucarpidase's ability to rescue HD-MTX toxicity were limited by small sample size, heterogeneous population, absence of key data on confounders, and lack of control group

**We estimated the effect of treatment with glucarpidase on clinical outcomes, including mortality, using data from patients with MTX-associated AKI (MTX-AKI) obtained from 28 cancer centers across the US**

## Methods and Materials

**Study design**

Target trial emulation of adults with MTX-AKI who received or did not receive glucarpidase at 28 cancer centers across the US from 2000 to 2022

Exclusion criteria: ESKD or moribund condition (likely to die within 48 hours) at the time of MTX initiation

**Primary Outcome**

Kidney recovery at hospital discharge, defined as survival to hospital discharge without KRT-dependence and with SCr <1.5-fold baseline

**Statistical analyses**

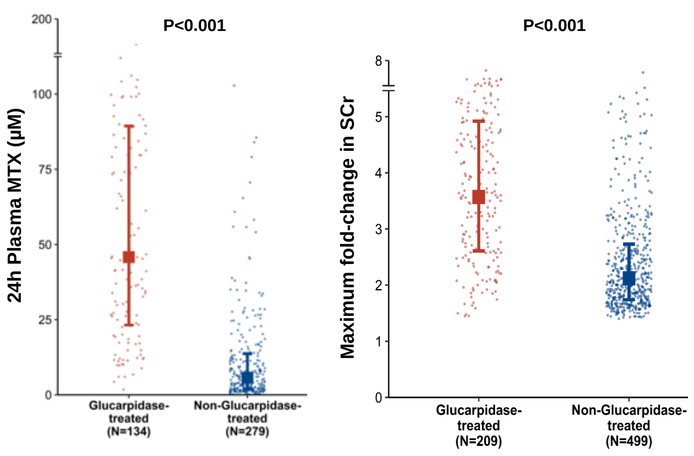
- Primary outcome: odds of kidney recovery at hospital discharge among patients who received glucarpidase in the first 96 hours following MTX initiation versus those who did not
- Seven prespecified sensitivity analyses and four subgroup analyses
- Secondary outcomes: mortality and time to kidney recovery, assessed using adjusted Kaplan-Meier estimates and a multivariable Cox model

## Results

### Table 1: Baseline characteristics

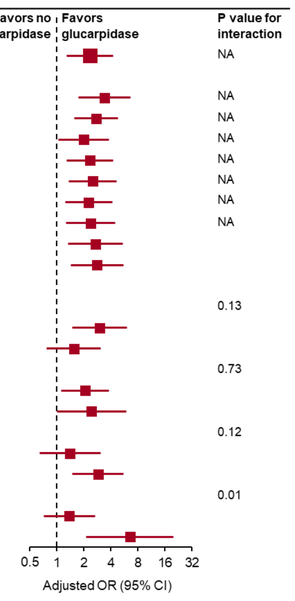
| Characteristic | Treated with glucarpidase (N=209) | Not treated with glucarpidase (N=499) |
|---|---|---|
| **Demographics & coexisting conditions** | | |
| Age (yrs) – median (IQR) | 64 (51–71) | 64 (55–71) |
| Male sex | 148 (70.8) | 347 (69.5) |
| White Race | 176 (84.2) | 421 (84.4) |
| BMI (kg/m$^2$) – median (IQR) | 30 (27–36) | 28 (24–32) |
| Hypertension | 134 (64.1) | 263 (52.7) |
| Diabetes mellitus | 54 (25.8) | 84 (16.8) |
| COPD | 15 (7.2) | 21 (4.2) |
| Congestive heart failure | 9 (4.3) | 24 (4.8) |
| Coronary artery disease | 28 (13.4) | 51 (10.2) |
| Chronic liver disease | 4 (1.9) | 4 (0.8) |
| **Malignancy category** | | |
| Primary CNS lymphoma | 61 (29.2) | 206 (41.3) |
| Acute lymphoblastic leukemia | 36 (17.2) | 41 (8.2) |
| Other lymphoma or leukemia | 105 (50.2) | 236 (47.3) |
| Osteosarcoma/other solid tumor | 7 (3.3) | 16 (3.2) |
| **MTX infusion** | | |
| Duration of infusion (hours) | | |
| Median (IQR) | 4.1 (3.0–5.6) | 4.2 (4.0–5.2) |
| <12 | 172 (82.3) | 444 (89.0) |
| 24-42 | 37 (17.7) | 55 (11.0) |
| Dose (g/m$^2$) – median (IQR) | 3.5 (3.0–5.3) | 3.5 (3.5–5.2) |
| **Other chemotherapy** | | |
| Within 30d prior to MTX initiation | 137 (65.6) | 259 (51.9) |
| Within 4d following MTX initiation | 75 (35.9) | 170 (34.1) |
| **Concomitant treatments** | | |
| Nephrotoxic medications | 115 (55.0) | 203 (40.7) |
| IV fluids (L) on day 0 – median (IQR) | 3.0 (1.6–3.6) | 2.1 (1.1–3.5) |
| IV fluids (L) on day 1 – median (IQR) | 3.6 (3.0–4.5) | 3.5 (2.9–4.0) |
| Leucovorin dose (mg) – median (IQR) | 200 (25–610) | 75 (25–200) |
| **Baseline labs – median (IQR)** | | |
| WBC count (K/mm$^3$) | 7.1 (4.9–10.1) | 7.0 (4.7–9.8) |
| Absolute neutrophil count (per mm$^3$) | 4603 (2866–7166) | 4900 (2943–7198) |
| Hemoglobin (g/dl) | 10.3 (8.9–11.6) | 11.0 (9.5–12.5) |
| Platelet count (K/mm$^3$) | 196 (147–275) | 202 (148–272) |
| Albumin (g/dL) | 3.5 (3.1–3.9) | 3.6 (3.2–3.9) |
| LDH (U/L) | 253 (202–325) | 216 (179–280) |
| ALT (U/L) | 26 (17–41) | 23 (15–40) |
| SCr (mg/dl) | 0.8 (0.7–1.0) | 0.8 (0.7–1.0) |
| eGFR (mL/min/1.73m$^2$) | 94 (80–105) | 95 (81–105) |
| Urine pH | 7.5 (7.0–8.0) | 8.0 (7.0–8.0) |
| **24h MTX level (μM) – median (IQR)** | 46 (24–91) | 7 (2–18) |
| **Initial AKI characteristics** | | |
| AKI stage | | |
| Stage 1 | 18 (8.6) | 216 (43.3) |
| Stage 2 | 53 (25.4) | 179 (35.9) |
| Stage 3 | 138 (66.0) | 104 (20.8) |
| Max fold-change in SCr – median (IQR) | 3.7 (2.6–4.9) | 2.1 (1.7–2.7) |
| Oliguria | 14 (6.7) | 8 (1.6) |

### Figure 1: Plasma MTX Levels at 24h and Initial Severity of AKI in Glucarpidase-Treated vs. Non-Glucarpidase-Treated Patients




### Figure 2: Kidney Recovery in Glucarpidase-Treated versus Non-Glucarpidase-Treated Patients

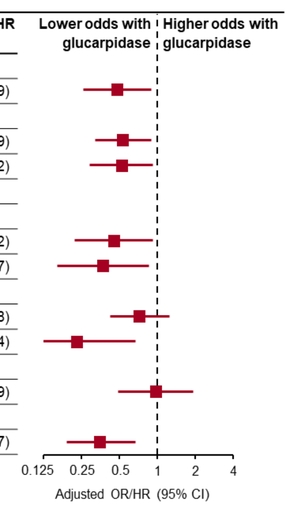
| | No. Events/ No. Patients (%) | Adjusted OR (95% CI)* | P value for interaction |
|---|---|---|---|
| Primary analysis | 183/708 (25.8) | 2.34 (1.28–4.27) | NA |
| Sensitivity analyses | | | |
| 1. Glucarpidase in first 60h | 183/708 (25.8) | 3.39 (1.73–6.66) | NA |
| 2. IPTW | 144/565 (25.5) | 2.72 (1.55–4.83) | NA |
| 3. Multiple imputation | 183/708 (25.8) | 1.98 (1.03–3.79) | NA |
| 4. Adjusted for site[a] | 183/708 (25.8) | 2.34 (1.28–4.27) | NA |
| 5. Adjusted for site[b] | 183/708 (25.8) | 2.51 (1.36–4.62) | NA |
| 6. Adjusted for IVF and leucovorin[c] | 183/708 (25.8) | 2.26 (1.23–4.16) | NA |
| 7. Limited to 2012 or later | 176/665 (26.5) | 2.37 (1.27–4.44) | NA |
| 8. Limited to MTX infusion <12h | 165/618 (26.7) | 2.70 (1.34–5.43) | NA |
| 9. Limited to glucarpidase ≥50 U/kg | 170/632 (26.9) | 2.81 (1.42–5.57) | NA |
| Subgroups | | | |
| Age, years | | | 0.13 |
| <65 | 93/368 (25.3) | 2.99 (1.48–6.05) | |
| ≥65 | 90/340 (26.5) | 1.54 (0.77–3.08) | |
| Sex | | | 0.73 |
| Male | 125/495 (25.3) | 2.06 (1.12–3.78) | |
| Female | 58/213 (27.2) | 2.43 (1.00–5.92) | |
| Baseline eGFR, ml/min/1.73m$^2$ | | | 0.12 |
| <90 | 84/267 (31.5) | 1.40 (0.64–3.09) | |
| ≥90 | 99/441 (22.4) | 2.87 (1.48–5.57) | |
| Maximum initial severity of AKI | | | 0.01 |
| Stage 1 or 2 | 158/466 (33.9) | 1.37 (0.71–2.67) | |
| Stage 3 | 25/242 (10.3) | 6.52 (2.12–20.03) | |




The odds ratios (ORs) in the Forest plot for the primary and sensitivity analyses are adjusted for demographics (age, sex, race), body mass index, comorbidities (hypertension, diabetes mellitus, congestive heart failure, chronic obstructive pulmonary disease, coronary artery disease, chronic liver disease), baseline laboratory data (eGFR, WBC count, hemoglobin, serum albumin, lactate dehydrogenase, urine pH), malignancy type, MTX treatment data (dose, infusion duration, volume of IV fluids on days 0 and 1, leucovorin dose on days 0 and 1), receipt of other nephrotoxins, 24-hour plasma MTX levels, and maximum fold-change in serum creatinine and oliguria in the first 4 days following MTX initiation. The ORs in the Forest plot for the subgroup analyses are adjusted for age, sex, race, hypertension, diabetes mellitus, body mass index, baseline laboratory data (eGFR, white blood cell count, and serum albumin), malignancy type, MTX infusion duration, CNS prophylaxis vs. treatment, nephrotoxic medications, 24-hour plasma MTX levels, and maximum fold-change in serum creatinine and oliguria in the first 4 days following MTX initiation. [a]Further adjusted for site as a random effect. [b]Further adjusted for site according to likelihood of prescribing glucarpidase. [c]Further adjusted for IV fluids and leucovorin dose on days 2 to 4 after MTX initiation.

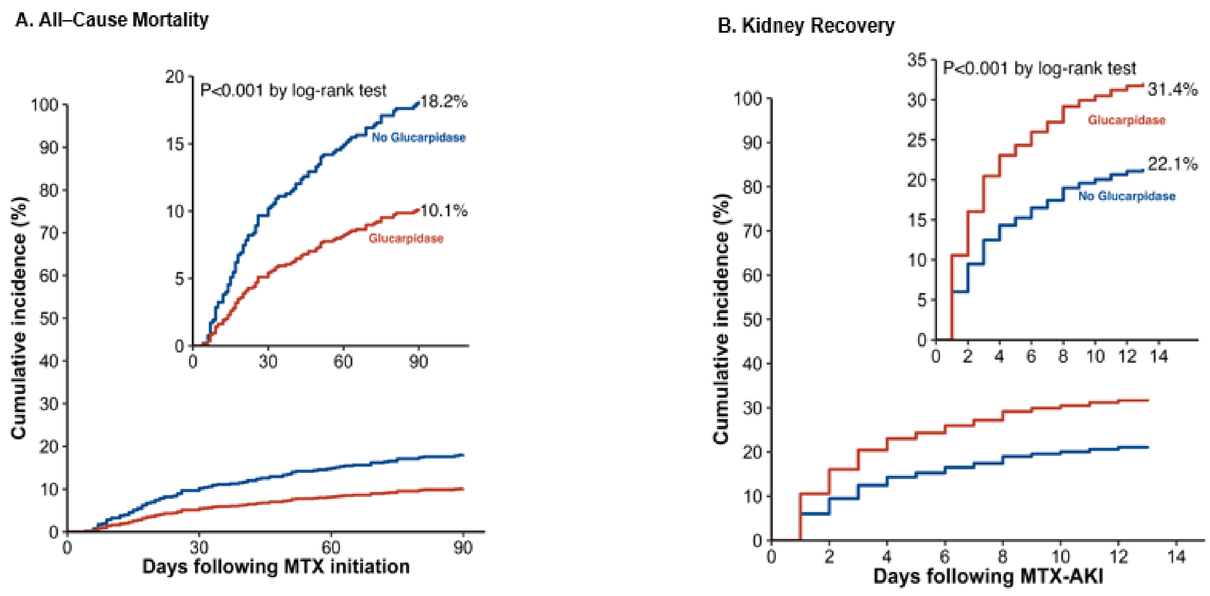
### Figure 4: Mortality and Renal and Extrarenal Outcomes in Glucarpidase- vs. Non-Glucarpidase-Treated Patients

| Outcome | No. Events/ No. Patients (%) | Adjusted OR/HR (95% CI)* |
|---|---|---|
| Death | | |
| All–cause mortality | 99/708 (14.0) | 0.48 (0.26–0.89) |
| Renal Outcomes | | |
| Time to kidney recovery (first 14 days) | 155/706 (22.0) | 0.53 (0.32–0.89) |
| Persistent kidney impairment or death at day 90 | 166/583 (28.5) | 0.52 (0.29–0.92) |
| Extrarenal Outcomes assessed on day 7 | | |
| Neutropenia | | |
| Grade ≥2 (ANC <1500/mm$^3$) | 98/648 (15.1) | 0.45 (0.22–0.92) |
| Grade ≥3 (ANC <1000/mm$^3$) | 63/680 (9.3) | 0.37 (0.16–0.87) |
| Transaminitis | | |
| Grade ≥1 (ALT ≥ULN)[a] | 163/479 (34.0) | 0.74 (0.43–1.28) |
| Grade ≥2 (ALT ≥3x ULN)[b] | 46/479 (9.6) | 0.25 (0.09–0.74) |
| Mucositis | | |
| Any grade | 74/707 (10.5) | 0.96 (0.49–1.89) |
| MTX Rechallenge | | |
| Within 30 days following index MTX infusion | 212/662 (32.0) | 0.35 (0.19–0.67) |




The odds ratios (ORs) and hazard ratios (HRs) in the Forest plot are adjusted for age, sex, race, hypertension, diabetes mellitus, body mass index, baseline laboratory data (eGFR, white blood cell count, and serum albumin), malignancy type, MTX infusion duration, CNS prophylaxis vs. treatment, nephrotoxic medications, 24-hour plasma MTX levels, and maximum fold-change in serum creatinine and oliguria in the first 4 days following MTX initiation. Abbreviations: ALT, alanine aminotransferase; ANC, absolute neutrophil count; ULN, upper limit of normal. [a]Grade ≥1 transaminitis also includes a ≥1.5-fold increase in ALT compared to baseline if the baseline was abnormal. [b]Grade ≥2 transaminitis also includes a >3-fold increase in ALT compared to baseline if the baseline was abnormal.

### Figure 3: Mortality and Kidney Recovery in Glucarpidase- vs. Non-Glucarpidase-Treated Patients




## Conclusions

- Adults with MTX-AKI treated with glucarpidase had a higher odds of kidney recovery, faster time to kidney recovery, and lower mortality compared to those not treated with glucarpidase
- These data suggest that patients who develop MTX-AKI early and those with more severe AKI may benefit the most from glucarpidase
- Glucarpidase-treated patients had higher 24-hour plasma MTX concentrations and greater severity of AKI compared to non-glucarpidase-treated patients, suggesting the demonstrated benefit of glucarpidase may be an underestimate
- RCTs are needed to confirm the efficacy of glucarpidase and to establish the full spectrum of populations that may benefit from it

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