Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

# Glucarpidase Rescue After High-Dose Methotrexate in Osteosarcoma: A Case Report

**Rui Resende Bastos**

rui.bastos@ulssm.min-saude.pt

Unidade Local de Saúde Santa Maria

**Pedro Carrilho**

Unidade Local de Saúde Santa Maria

**Cecília de Melo Alvim**

Unidade Local de Saúde Santa Maria

**Tiago Sepúlveda Santos**

Unidade Local de Saúde Santa Maria

---

**Case Report**

**Keywords:** Osteosarcoma, high-dose methotrexate, glucarpidase, acute kidney injury, case report, methotrexate toxicity

**Posted Date:** November 1st, 2026

**DOI:** https://doi.org/10.21203/rs.3.rs-11217866/v1

**License:** This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

**Additional Declarations:** No competing interests reported.

---

## Abstract

# Background

Osteosarcoma is a rare primary malignant bone tumor for which high-dose methotrexate remains an important component of chemotherapy in selected patients. Acute kidney injury with markedly delayed methotrexate clearance is an uncommon but potentially life-threatening complication.

# Case presentation

We report the clinical course and management of high-dose methotrexate–induced acute kidney injury requiring glucarpidase rescue in a 23-year-old white woman with localized osteosarcoma of the right distal femur. She received her first cycle of high-dose methotrexate (20 g over 4 hours) as part of neoadjuvant chemotherapy. Baseline serum creatinine was 0.50 mg/dL. Despite intravenous hydration, urinary alkalinization, and leucovorin rescue, she developed non-oliguric acute kidney injury within 24 hours, with serum creatinine increasing to 2.32 mg/dL and plasma methotrexate concentration reaching 148 μmol/L. At 48 hours, methotrexate concentration remained elevated at 25 μmol/L, with persistent renal dysfunction. Glucarpidase 5,000 U was administered intravenously, and leucovorin rescue was intensified. Methotrexate concentrations subsequently declined progressively, while renal function gradually recovered. The clinical course was complicated by grade 3 anemia requiring red blood cell transfusion, transient hypokalemia, and volume overload. The patient was discharged 11 days after high-dose methotrexate administration with preserved urine output and improving renal function. Serum creatinine decreased to 1.28 mg/dL two weeks after discharge and to 0.63 mg/dL one month later. Further high-dose methotrexate was discontinued, and neoadjuvant chemotherapy was continued with cisplatin and doxorubicin.

# Conclusions

This case describes a serious complication of high-dose methotrexate treatment in a patient with a rare bone malignancy. It highlights the importance of close biochemical monitoring, early recognition of delayed methotrexate clearance, and timely glucarpidase administration in patients who develop acute kidney injury despite appropriate supportive measures.

## BACKGROUND

Osteosarcoma is a rare primary malignant bone tumor, accounting for less than 1% of all cancers diagnosed annually in the United States [1]. Surgery combined with perioperative multiagent chemotherapy remains the cornerstone of treatment for localized osteosarcoma.

Current clinical guidelines recommend either cisplatin plus doxorubicin or the MAP regimen (high-dose methotrexate, cisplatin, and doxorubicin) as first-line treatment options, with MAP generally preferred for patients younger than 40 years with good performance status [2]. High-dose methotrexate (HDMTX) is commonly defined as doses exceeding 500 mg/m² administered over 2–36 hours, which may cause clinically significant toxicities, most commonly acute kidney injury (AKI), myelosuppression, hepatotoxicity, and mucositis [3]. Although the incidence of HDMTX-associated acute kidney injury is higher among patients with lymphoma, it occurs in approximately 1.5% of treatment cycles in patients with sarcoma [4]. AKI is primarily caused by precipitation of methotrexate and its metabolites within the renal tubules, resulting in crystal nephropathy. Delayed methotrexate clearance results in prolonged exposure to toxic plasma concentrations, increasing the risk of myelosuppression, mucositis, hepatotoxicity, and further renal injury [5]. Despite standard preventive measures, including intravenous hydration, urinary alkalinization, and leucovorin rescue, delayed methotrexate clearance and clinically significant toxicity may still occur.

## CASE PRESENTATION

A 23-year-old white woman with localized osteosarcoma of the right distal femur, diagnosed in December 2025, was admitted for routine monitoring after receiving her first cycle of high-dose methotrexate (20 g administered over 4 hours) as part of neoadjuvant chemotherapy with HDMTX, doxorubicin, and cisplatin. Baseline renal function was normal, with a serum creatinine of 0.50 mg/dL.

Following HDMTX administration, standard supportive measures, including intravenous hydration, urinary alkalinization, and leucovorin rescue, were instituted.

Within 24 hours after completion of the HDMTX infusion, the patient developed non-oliguric acute kidney injury, with serum creatinine increasing to 2.32 mg/dL and a methotrexate concentration of 148 µmol/L. At 48 hours, plasma methotrexate concentration remained markedly elevated at 25 µmol/L, while serum creatinine persisted at 2.30 mg/dL, indicating delayed methotrexate clearance despite aggressive supportive therapy. Consequently, glucarpidase (5,000 U intravenously) was administered approximately 48 hours after completion of the methotrexate infusion, and leucovorin rescue was intensified.

Following glucarpidase administration, methotrexate elimination remained prolonged, although plasma methotrexate concentrations progressively declined thereafter (Figure 1). Peak serum creatinine reached 2.37 mg/dL at 96 hours, followed by gradual recovery of renal function. During hospitalization, the patient developed grade 3 anemia (hemoglobin nadir 6.9 g/dL), requiring transfusion of one unit of packed red blood cells, as well as transient hypokalemia that resolved with potassium supplementation. Because of volume overload while maintaining aggressive hydration, nephrology consultation was obtained, and furosemide therapy was initiated.

The patient was discharged 11 days after HDMTX administration with preserved urine output, improving renal function (serum creatinine 1.80 mg/dL), and resolving methotrexate toxicity. At follow-up two weeks after discharge, serum creatinine had decreased to 1.28 mg/dL and methotrexate concentration

to 0.14 μmol/L. One month later, renal function had nearly returned to baseline, with a serum creatinine of 0.63 mg/dL. Given the episode of severe HDMTX-induced acute kidney injury despite glucarpidase rescue, further HDMTX administration was permanently discontinued, and neoadjuvant chemotherapy was continued with cisplatin and doxorubicin alone.

# DISCUSSION AND CONCLUSIONS

Glucarpidase is a recombinant bacterial carboxypeptidase that rapidly hydrolyses extracellular methotrexate into the inactive metabolites DAMPA (4-deoxy-4-amino-N10-methylpteroic acid) and glutamate, providing an alternative nonrenal elimination pathway [6]. It was approved in January 2012 for the treatment of toxic plasma methotrexate concentrations in patients with delayed renal clearance of methotrexate due to impaired renal function [7]. Widemann et al. subsequently demonstrated the efficacy of glucarpidase in a pooled analysis of four multicenter, single-arm studies involving patients with HDMTX-induced acute kidney injury, demonstrating rapid and sustained reductions in plasma methotrexate concentrations together with recovery of renal function in most patients [5].

Our patient developed severe HDMTX-induced acute kidney injury with delayed methotrexate clearance despite standard supportive measures, including aggressive intravenous hydration, urinary alkalinization, and leucovorin rescue. No concomitant nephrotoxic medications or other recognized risk factors for methotrexate-associated nephrotoxicity were identified. Forty-eight hours after completion of the HDMTX infusion, plasma methotrexate concentration remained markedly elevated (25 μmol/L), while serum creatinine had increased from 0.50 to 2.30 mg/dL, thereby fulfilling consensus criteria for glucarpidase administration. Hemodialysis was not indicated due to the absence of urgent criteria. Following glucarpidase administration, methotrexate concentrations progressively declined, accompanied by gradual recovery of renal function, which had nearly returned to baseline one month later.

These findings are consistent with recent evidence. In a multicenter retrospective cohort study using a target trial emulation framework, Gupta et al. demonstrated that glucarpidase administration was associated with significantly higher adjusted odds of kidney recovery at hospital discharge compared with supportive care alone (adjusted OR, 2.70; 95% CI, 1.69–4.31) [8]. Early recognition of delayed methotrexate clearance is essential because glucarpidase is most effective when administered promptly after the diagnosis of HDMTX-induced acute kidney injury. Careful monitoring of serum methotrexate concentrations, renal function, urine output, and urinary pH is therefore critical to identify patients who may benefit from glucarpidase rescue before severe or irreversible toxicity develops. Although our report describes a single patient, the favorable clinical course observed after glucarpidase administration is consistent with these contemporary data, and the detailed longitudinal documentation of methotrexate levels and renal function strengthens the clinical description of treatment response.

# Abbreviations

**AKI:** Acute kidney injury

**CI:** Confidence interval

**DAMPA:** 4-Deoxy-4-amino-N10-methylpteroic acid

**HDMTX:** High-dose methotrexate

**MAP:** High-dose methotrexate, doxorubicin, and cisplatin

**OR:** Odds ratio

# Declarations

### Ethics approval and consent to participate

The publication of this case report was reviewed and approved by the Ethics Committee of the Centro Académico de Medicina de Lisboa (CAML), Lisbon, Portugal (reference no. 342/26).

### Consent for publication

Written informed consent was obtained from the patient for publication of this case report and the accompanying clinical data and images. A copy of the signed consent form is available for review by the Editor-in-Chief of the *Journal of Medical Case Reports* upon request.

### Availability of data and materials

All data generated or analysed during this case report are included in this published article. Additional information may be available from the corresponding author on reasonable request, subject to patient confidentiality.

### Competing interests

The authors declare that they have no competing interests.

### Funding

The article processing charge was funded by SERB Pharmaceuticals. The funder had no role in the clinical management of the patient, data collection, data analysis or interpretation, manuscript preparation, or the decision to submit the manuscript for publication.

### Authors' contributions

RRB and PC collected and analysed the clinical data and were major contributors to writing the manuscript. CMA and TSS were involved in the clinical management of the patient and critically revised the manuscript. All authors read and approved the final manuscript.

**Acknowledgements**

The authors have no acknowledgements to declare.

**Authors' information**

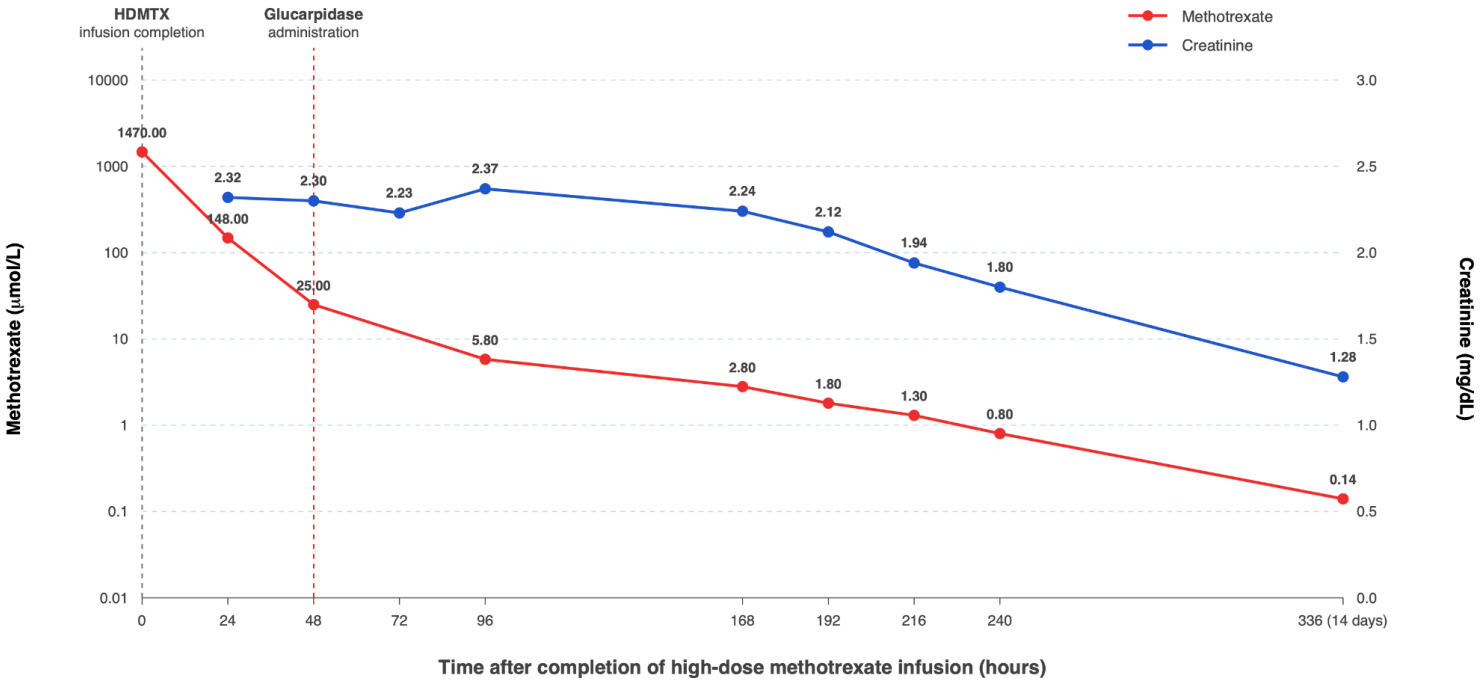
RRB is a Medical Oncology Resident at Unidade Local de Saúde Santa Maria, Lisbon, Portugal. PC is a General Training Resident at Unidade Local de Saúde Santa Maria, Lisbon, Portugal. CMA is a Consultant Medical Oncologist and Coordinator of the Soft Tissue and Bone Sarcoma Reference Centre at Unidade Local de Saúde Santa Maria, Lisbon, Portugal. TSS is a Consultant in Internal Medicine at Unidade Local de Saúde Santa Maria, Lisbon, Portugal.

# References

**REFERENCES**:

1. American Cancer Society. Key statistics for osteosarcoma. 2025. https://www.cancer.org/cancer/types/osteosarcoma/key-statistics.html. Accessed 13 Jul 2026.
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Bone Cancer. Version 2.2026. https://www.nccn.org/professionals/physician_gls/pdf/bone.pdf. Accessed 13 Jul 2026.
3. Howard SC, McCormick J, Pui CH, Buddington RK, Harvey RD. Preventing and managing toxicities of high-dose methotrexate. Oncologist. 2016;21:1471–82. doi:10.1634/theoncologist.2015-016480.
4. May J, Carson KR, Butler S, Liu W, Bartlett NL, Wagner-Johnston ND. High incidence of methotrexate associated renal toxicity in patients with lymphoma: a retrospective analysis. Leuk Lymphoma. 2014;55:1345–9. doi:10.3109/10428194.2013.840780.
5. Widemann BC, Schwartz S, Jayaprakash N, Christensen R, Pui CH, Chauhan N, et al. Efficacy of glucarpidase (carboxypeptidase G2) in patients with acute kidney injury after high-dose methotrexate therapy. Pharmacotherapy. 2014;34:427–39. doi:10.1002/phar.1360.
6. Ramsey LB, Balis FM, O'Brien MM, Schmiegelow K, Pauley JL, Bleyer A, et al. Consensus guideline for use of glucarpidase in patients with high-dose methotrexate-induced acute kidney injury and delayed methotrexate clearance. Oncologist. 2018;23:52–61. doi:10.1634/theoncologist.2017-0243.
7. Voraxaze (glucarpidase) [package insert]. West Conshohocken, PA: BTG International Inc.; 2012.
8. Gupta S, Kaunfer SA, Chen KL, Dias JA, Vijayan A, Rajasekaran A, et al. Glucarpidase for treatment of high-dose methotrexate toxicity. Blood. 2025;145:1858–69. doi:10.1182/blood.2024026211.

# Figures




## Figure 1

Temporal evolution of plasma methotrexate concentration and serum creatinine following high-dose methotrexate administration. Glucarpidase was administered approximately 48 hours after completion of the methotrexate infusion. Plasma methotrexate concentrations declined markedly following glucarpidase administration, consistent with its expected rapid enzymatic degradation of circulating methotrexate, while renal function recovered more gradually. Post-glucarpidase methotrexate concentrations should be interpreted with caution because DAMPA may interfere with conventional methotrexate immunoassays and overestimate the true methotrexate concentration.