Expert Review of Anticancer Therapy

ISSN: 1473-7140 (Print) 1744-8328 (Online) Journal homepage: www.tandfonline.com/journals/iery20

A nephrology perspective on the clinical impact and management of delayed high-dose methotrexate elimination

María José Soler, Laura Cosmai, Lui Forni, Jolanta Małyszko, Rukshana Shroff, Ben Sprangers & Corinne Isnard Bagnis

To cite this article: María José Soler, Laura Cosmai, Lui Forni, Jolanta Małyszko, Rukshana Shroff, Ben Sprangers & Corinne Isnard Bagnis (27 May 2026): A nephrology perspective on the clinical impact and management of delayed high-dose methotrexate elimination, Expert Review of Anticancer Therapy, DOI: 10.1080/14737140.2026.2677940

To link to this article: https://doi.org/10.1080/14737140.2026.2677940

Published online: 27 May 2026.

EXPERT REVIEW OF ANTICANCER THERAPY
https://doi.org/10.1080/14737140.2026.2677940

Taylor & Francis
by informa

REVIEW

OPEN ACCESS Check for updates

A nephrology perspective on the clinical impact and management of delayed high-dose methotrexate elimination

María José Soler[a,b,c], Laura Cosmai[d], Lui Forni[e,f], Jolanta Małyszko[g], Rukshana Shroff[h,i], Ben Sprangers[j,k] and Corinne Isnard Bagnis[l,m]

[a]Nephrology Department, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Research, Barcelona, Spain; [b]Centro de Referencia en Enfermedad, Glomerular Compleja del Sistema Nacional de Salud de España (CSUR), Barcelona, Spain; [c]RICORS2040 (Kidney Disease), Barcelona, Spain; [d]Nephrology and Dialysis Unit, ASST Fatebenefratelli Sacco, Milan, Italy; [e]Department of Critical Care, Royal Surrey Hospital Foundation Trust, Guildford, UK; [f]School of Medicine, University of Surrey, Guildford, UK; [g]Department of Nephrology, Dialysis and Internal Medicine, Medical University of Warsaw, Warsaw, Poland; [h]Great Ormond Street Hospital NHS Foundation Trust, London, UK; [i]University College London Great Ormond Street Institute of Child Health, London, UK; [j]Department of Nephrology, Ziekenhuis Oost-Limburg, Genk, Belgium; [k]Department of Immunology and Infection, Biomedical Research Institute, UHasselt, Diepenbeek, Belgium; [l]Département de Néphrologie, APHP Sorbonne Université, Paris, France; [m]Groupe de Recherche Interdisciplinaire Francophone en Onco-Néphrologie (GRIFON), Paris, France

ABSTRACT

Introduction: Delayed methotrexate elimination (DME) is observed in ~15% of treatment cycles in patients with cancer receiving high-dose methotrexate (HDMTX). Given the strong association between DME and nephrotoxicity, oncologists might benefit from the input of a nephrologist/medical oncologist with a focus on nephrology when assessing and planning treatment for patients requiring HDMTX.

Areas covered: Identifying patients who are at risk of DME and related acute kidney injury (AKI), and developing a bespoke assessment and monitoring plan (with a focus on kidney assessment and monitoring), may help to reduce the risk of complications and enable the continuation of HDMTX treatment, hopefully optimizing long-term survival outcomes.

Expert opinion: In this perspective article, based on a search of PubMed literature and expert opinion, we explore the definition and causes of DME and AKI, and the impact of these on patients receiving HDMTX, and examine the key risk factors and early indicators of DME and AKI. A pathway with a nephrology focus is suggested for the assessment, monitoring, and treatment of patients with or at risk of DME.

ARTICLE HISTORY
Received 10 November 2025
Accepted 18 May 2026

KEYWORDS
Acute kidney injury; creatinine; glucarpidase; leucovorin; methotrexate; nephrology; toxicity

1. Introduction

Delayed methotrexate elimination (DME) is observed in ~15% of treatment cycles in patients with cancer receiving high-dose methotrexate (HDMTX) [1]. Given DME can lead to potentially life-threatening nephrotoxicity [1–3], the management of DME and related acute kidney injury (AKI) is important. It is imperative to understand the causes and risk factors of DME, and its impact on outcomes in the kidneys and other organ systems, subsequent oncology treatment, and survival. Once patients with or at risk of DME/AKI are identified, planning is required to optimize their cancer treatment pathway and reduce the likelihood of persistent and/or worsening toxicity.

This article looks at these topics in light of publication of European consensus guidelines on DME management in 2024 and the recent European Union (EU) approval of glucarpidase to reduce toxic methotrexate levels in adults and children with DME or at risk of methotrexate toxicity [1,4]. The content is based on a search of literature in PubMed (search terms including methotrexate, high-dose and kidney) up until May 2025 supplemented by our expert opinion and clinical experience.

2. Definition, causes, and impact of DME and AKI

Methotrexate is an antifolate chemotherapeutic agent that is often used at high doses (usually ≥500 mg/m^2, administered intravenously over several hours) to treat various hematologic malignancies and solid tumors [1–3]. An important toxicity associated with HDMTX is AKI [1–3]; this generally occurs within the first few days and is defined through an increase in plasma creatinine (typically ≥1.5-fold increase within 4 days) with concomitant decrease in glomerular filtration rate (GFR) [1,2]. Other toxicities associated with HDMTX and DME include multi-organ failure (Figure 1) [1,3,5,6].

Given that methotrexate is predominantly cleared via the kidneys [2], AKI can result in DME, defined as a plasma methotrexate concentration ≥10 µmol/L at 24 hours (for short infusions), ≥1 µmol/L at 42/48 hours, or ≥0.3 µmol/L at 72 hours post infusion [1]. Therefore, DME prolongs exposure to high, toxic concentrations of methotrexate and its metabolites, thereby increasing the risk of further toxicity [1–3]. Mechanisms underlying DME/AKI include crystal precipitation of methotrexate and its metabolites in kidney tubules, reduced perfusion from afferent arteriolar vasoconstriction, and direct tubular toxicity (Figure 1) [2,3,6].

CONTACT Corinne Isnard Bagnis corinne.bagnis@aphp.fr Department of Nephrology AP-HP, Pitié-Salpêtrière University Hospital, 48 Boulevard de l'Hôpital, Paris 75013, France

Article highlights

- DME can complicate high-dose methotrexate treatment.
- DME can result in kidney and other organ damage if not managed appropriately.
- It is crucial to identify patients at risk of renal injury.
- At-risk patients may benefit from tailored management.
- Onco-nephrology specialists have a key role in the management of these patients.

Because DME can exacerbate AKI, which then may lead to further DME, managing HDMTX-induced DME is critical to prevent further toxicity and facilitate appropriate completion of anticancer treatment. Most cases of DME and AKI are reversible if treated quickly [2].

However, if methotrexate concentration is not lowered in a timely fashion then kidney damage may result (nephron loss and progression to acute/chronic kidney disease [CKD]) as well as damage to other organ systems, inadequate anticancer treatment (with the risk of affecting long-term outcomes), and potentially death [2,3].

2.1. Indicators

Although DME is defined by plasma methotrexate concentration, a potential early indicator of DME is an increase in plasma creatinine concentration 24–36 hours after HDMTX infusion (Figure 1) [1]. While often considered a lagging marker of kidney damage (i.e. with substantial kidney damage preceding significant increases in creatinine), there is evidence suggesting that increases in creatinine levels can develop well within 24 hours of methotrexate infusion [11,12]. A decrease in urinary output (oliguria) [1,3,7], a positive fluid balance, and weight gain may be further indicators of DME/AKI [1,3]. Damage- or stress- associated biomarkers of tubular injury (e.g. NGAL, KIM1, TIMP2, IGFBP7) may predict HDMTX-induced AKI, although their clinical role requires further validation [7,8,13].

2.2. Risk factors

Key risk factors for DME/AKI include pre-existing kidney dysfunction (any grade), volume depletion and concomitant use of other potential nephrotoxins (Table 1). Other important risk factors are indicated in Figure 1 [1–3,14,15]. When assessing the risk of DME/AKI, these factors should be considered in the context of the anticipated plasma methotrexate concentration based on the administered dose [1].

3. Assessment and monitoring

Initial assessment and serial monitoring of plasma methotrexate concentration and kidney function are essential for patients receiving HDMTX [1,2]. However, more intensive monitoring may be required for patients with known risk factors for DME, such as baseline kidney dysfunction [3], or infants who demonstrate high variability in methotrexate elimination [16]. A tailored health assessment framework for the kidneys, developed with nephrologist input, may be helpful prior to HDMTX treatment. Differentiating between AKI, other acute kidney diseases and disorders, and CKD is an important aspect of the kidney assessment; point-of-care ultrasound, other imaging (e.g. magnetic resonance imaging or computed tomography [CT]), and additional blood and urine tests may be useful in this regard. The assessment should also review concomitant medications (e.g. antihypertensives, other cardiovascular medications, and antidiabetic treatments) for nephrotoxic potential (or indeed, renoprotective effects) and risk of drug–drug interactions.

As a minimum, plasma creatinine concentration and/or GFR (to assess kidney function) and methotrexate concentration (to assess DME, ideally using high-performance liquid chromatography) should be measured at least every 24 hours after HDMTX infusion until methotrexate concentration is acceptable (nontoxic) and any impairment in kidney function recovers [1,17]. International Consensus Guidelines for Anticancer Drug Dosing in Kidney Dysfunction (ADDIKD) recommend direct measurement of GFR (via clearance of exogenous markers) to assess kidney function in patients due to receive HDMTX [17,18]. When GFR cannot be directly measured, estimated GFR (eGFR) (typically calculated using the CKD Epidemiology Collaboration [$eGFR_{CKD\text{-}EPI}$] equation [2021], based on creatinine and/or cystatin C measurements) is, in our opinion, acceptable. Alongside these measurements, regular monitoring of clinical signs/symptoms, weight changes, fluid balance, and urine output help to identify early AKI after HDMTX treatment. Urine pH measurement can assess whether alkalization has been effectively achieved prior to administering HDMTX [3].

MTXPK.org is a useful, free tool to help monitor the pharmacokinetics of methotrexate, including in patients with DME, and guide the need for interventions [19].

4. Treatment planning

A proactive plan with regular review that considers all risk factors is needed to ensure HDMTX treatment success. Patients with risk factors of DME may require a reduced dose, particularly those with moderate-to-severe kidney impairment, prior HDMTX-associated toxicity, or poor performance status [1,3,17]; however, the risk of DME must be balanced with the risk of inadequate anticancer treatment. Temporary discontinuation of potentially nephrotoxic medications that may impact methotrexate elimination should be considered (Table 1) [1–3,17].

Supportive measures to prevent DME/AKI are required before, during, and/or after HDMTX treatment, particularly forced diuresis (dextrose/saline at a flow rate ≥2.5 L/m^2/24 hours), urine alkalization (sodium bicarbonate supplementation of hydration fluid to achieve urine pH ≥7), and drainage of third-space effusions (Table 2) [1,17]. These measures dilute methotrexate in the urine, maintain urinary output and fluid balance, and prevent methotrexate crystallization in kidney tubules [1,3]. Patients with rapid weight gain suggestive of positive fluid balance, other signs of fluid retention, or kidney dysfunction may require loop diuretics to maintain urine production and prevent fluid overload (and associated complications), while patients with suboptimal urine alkalization may require acetazolamide (a diuretic that, unlike loop diuretics, is not associated with urine acidification) (Table 2) [1].

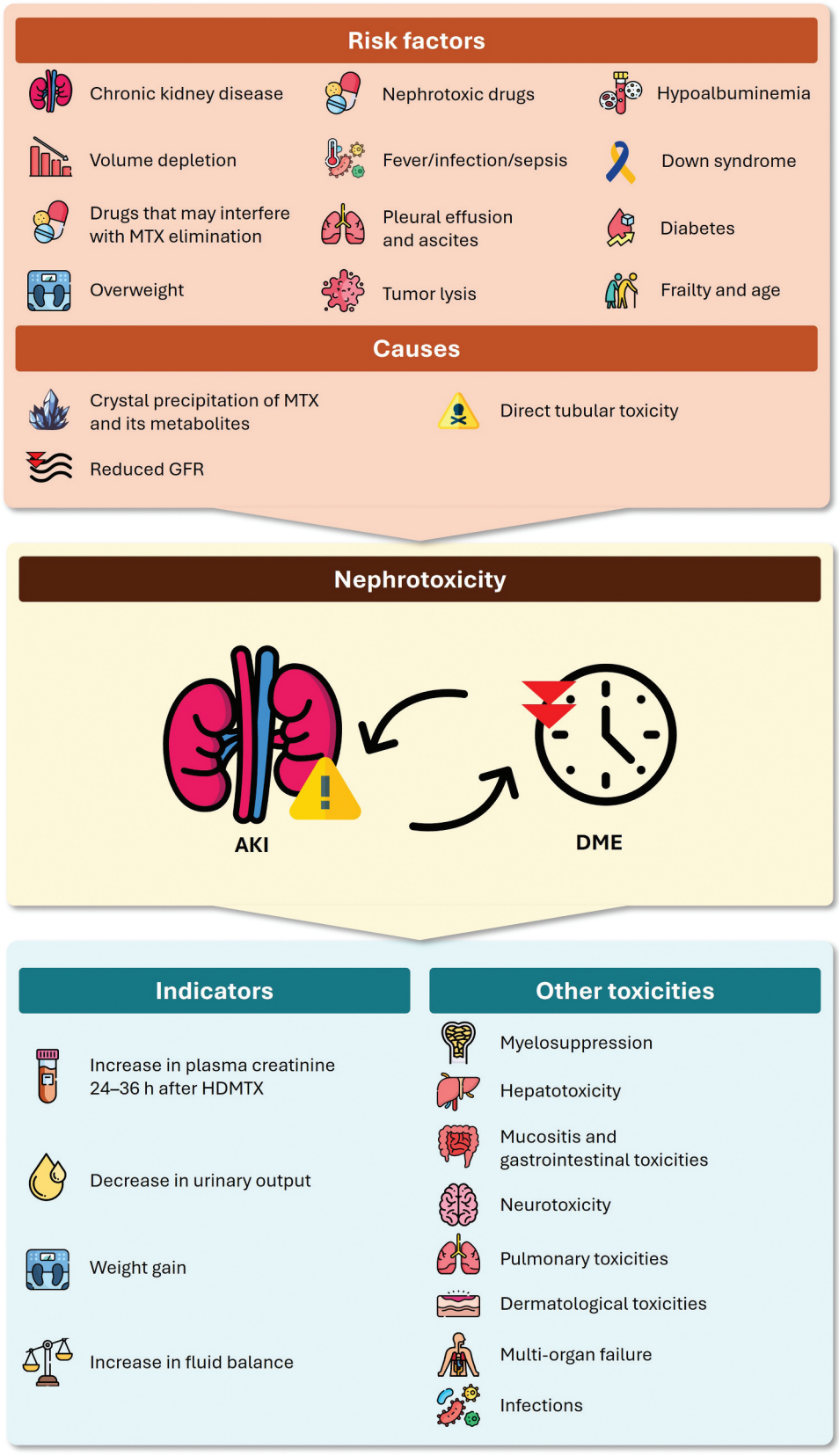

Figure 1. Risk factors and indicators associated with DME and/or AKI [1–3,5–10].

Abbreviations: AKI, acute kidney injury; DME, delayed methotrexate elimination; GFR, glomerular filtration rate; h, hours; (HD) MTX, (high-dose) methotrexate.

Table 1. Potentially nephrotoxic medications that may impact methotrexate elimination [1–3,14].

Potentially nephrotoxic medications that may impact methotrexate elimination
Major risk: use with caution or avoid
• Iodine-containing contrast media [1,3]
• Proton pump inhibitors [1–3,14]
Moderate risk: monitor
• Antiepileptic: levetiracetam [3]
• Non-steroidal anti-inflammatory drugs and acetylsalicylic acid (aspirin) [1,3,14]
• Probenecid and weak organic acids (e.g. pyrazoles) [1,3]
• Some antibiotics: beta-lactams, sulfonamides, and vancomycin [1,3,14]
Tyrosine kinase inhibitors and other nephrotoxic anticancer drugs [1]

Table 2. Supportive measures and leucovorin rescue for patients receiving HDMTX [1–3,17,20].

Supportive measures required before, during, and after HDMTX
Pre HDMTX
• Adjust initial HDMTX dose according to kidney function
• Consider temporarily withdrawing any potentially nephrotoxic medications that might impact methotrexate elimination
• Start hyperhydration with dextrose/saline at a flow rate ≥2.5 L/m^2/24 h
• Ensure urine alkalization with sodium bicarbonate supplementation of the hydration fluid to achieve urine pH ≥7
• Drain all third-space effusions
• Consider loop diuretics for patients with rapid weight gain, other signs of fluid retention, or kidney dysfunction
• Consider acetazolamide in patients with suboptimal urine alkalization
During HDMTX
• Continue all instigated supportive measures, maintaining urinary output at >100 mL/m^2/h and urine pH ≥7
• Try to avoid weight gain
Post HDMTX
• Continue with all instigated supportive measures
• Administer leucovorin (see local prescribing information for dosage information), usually 24–36 h after methotrexate, with further doses given at least every 6 h thereafter (with the dose adjusted according to plasma methotrexate concentration) until methotrexate is cleared to nontoxic levels
• If patient shows signs of DME, optimize their supportive measures (including intensified hydration) and quickly implement emergency treatment to rapidly lower methotrexate concentration, ideally glucarpidase (or, if not available, higher-dose leucovorin)
• Extracorporeal treatments may be considered in limited circumstances (e.g. when there is a large plasma methotrexate burden, anuria, or electrolyte imbalances) or when glucarpidase is unavailable, but should generally be avoided*, with glucarpidase generally outperforming extracorporeal methods

*Although these techniques can be used to lower plasma methotrexate concentration, extracorporeal treatments, such as hemodialysis, have little effect on intracellular methotrexate stores or the duration of methotrexate toxicity, and remove leucovorin from the blood.
Abbreviations: DME, delayed methotrexate elimination; h, hours; HDMTX, high-dose methotrexate.

Following HDMTX infusion, leucovorin (folinic acid) rescue is used to reduce the risk of DME-related complications (Table 2) [1,2,17,21]. Leucovorin, given to replenish depleted intracellular folate and reduce methotrexate toxicity, is usually administered 24–36 hours after methotrexate infusion. Further doses of leucovorin are given at least every 6 hours thereafter (with the dose adjusted according to plasma methotrexate concentration) until methotrexate is cleared to nontoxic levels. However, if given within 24 hours of HDMTX, leucovorin can interfere with its anticancer activity [1] by competing for cellular uptake [2].

When patients develop DME, this should be managed not only by optimizing supportive measures [1] but also with additional interventions, such as higher-dose leucovorin and, when appropriate, glucarpidase [1,2]. Extracorporeal treatments may be considered in some circumstances (e.g. when there is a large plasma methotrexate burden or if glucarpidase is unavailable) [1,20]; however, these are not recommended over glucarpidase [20], which typically outperforms methods such as hemodialysis (Table 2) [5,20].

The recombinant bacterial carboxypeptidase enzyme glucarpidase may be considered for patients with DME or at risk of methotrexate toxicity [2,4]. Glucarpidase acts by metabolizing methotrexate into two nontoxic, inactive metabolites, glutamate and 2,4-diamino-N10-methylpteroic acid (DAMPA), which are excreted in the urine or undergo further metabolism in the liver [1,2,4,6]. Safety and efficacy data show that glucarpidase is an effective and well-tolerated treatment to rapidly reduce plasma methotrexate concentration in both adults and children with DME [1,2,4,22–28]. Glucarpidase is recommended when plasma methotrexate concentration is >2 standard deviations above the mean expected elimination curve (based on the time and dose at which methotrexate was administered) or above prespecified threshold concentrations at designated post-infusion timepoints [1]. Across the EU, glucarpidase, at a single intravenous 50 units/kg bolus dose, is indicated to reduce toxic plasma methotrexate concentrations in adults and children (aged ≥28 days) with DME [4]. Administration of glucarpidase within 60 hours, but ideally within 48 hours, of HDMTX infusion or suspected toxicity is recommended in consensus guidelines and in the Summary of Product Characteristics [1,2,4].

A single dose of glucarpidase results in >95% median reduction in plasma methotrexate concentration within 15 minutes of administration and, for most patients, a sustained reduction lasting for several days [2,4,22–25]. This reduction in methotrexate concentration is often accompanied by an improvement and/or normalization in creatinine concentration over the following days [4,23,24]. Subsequent doses of glucarpidase appear to have little additional benefit in reducing methotrexate concentration [22,27,28]. Methotrexate concentration may rebound (likely to be clinically irrelevant [1]) >48 hours after glucarpidase treatment due to release from tissue stores); therefore, monitoring and leucovorin treatment are important in these cases [2]. Timely glucarpidase administration not only demonstrates a clinically important, sustained reduction in methotrexate concentration [4], but also reduces the length of hospital stay [29], decreases mortality [29], improves the odds of and time to renal recovery [30], and permits methotrexate rechallenge [31].

The empiric administration of glucarpidase at doses (1,000–2,000 units) below the standard, recommended dose of 50 units/kg has been investigated in patients receiving HDMTX as treatment for central nervous system lymphoma [32,33]. While routine planned, low-dose glucarpidase use was found to be feasible, use of lower than recommended doses of glucarpidase is not approved and may carry the risk of undertreatment and potential rebound effects.

Leucovorin should not be given within a 2-hour window either side of glucarpidase administration to avoid drug–drug interactions [1,2,4]. An increased leucovorin dose may be considered if glucarpidase is not available; however, there are concerns that high leucovorin doses may negatively impact the effectiveness of HDMTX [1,34,35].

HDMTX retreatment may be important to optimize long-term cancer outcomes and improve survival; however, its feasibility depends on recovery from prior complications and the risk of further DME and toxicity. Following a decrease in plasma methotrexate concentration and kidney recovery, careful planning may enable retreatment through GFR assessment versus a planned methotrexate dose. Avoiding extracorporeal treatments, such as hemodialysis, should be a key objective [20], as hemodialysis is associated with methotrexate rebound effects and an increased risk of infection and bleeding [1]. Hemodialysis is also less effective than glucarpidase at rapidly lowering methotrexate concentration and has little impact on methotrexate toxicity [20].

5. Conclusions

Given the association between methotrexate and nephrotoxicity, oncologists might benefit from input from a nephrologist or medical oncologist with a focus on nephrology when assessing and planning treatment for patients requiring HDMTX. Although it is helpful for all patients treated with HDMTX, nephrologist input might be particularly beneficial for children and patients at high risk of HDMTX DME to avoid progression to CKD. Identifying patients at risk of AKI and developing an assessment, monitoring, and treatment plan based on guidelines may help reduce the risk of complications and enable continuation of HDMTX.

6. Expert opinion

Although tailored management can be used in attempts to mitigate the risk of renal injury in patients treated with HDMTX, further research is needed to improve kidney outcomes. There are several pressing areas here. For example, the best method of differentiating between AKI and CKD as a cause of DME remains to be established. This will potentially include use of novel biomarkers. More knowledge is required to help determine early diagnostic tools and markers of DME other than creatinine concentration, especially damage markers and other measures of renal function. As previously mentioned, although damage- or stress- associated biomarkers of tubular injury such as NGAL, KIM1, TIMP2, and IGFBP7 may predict HDMTX-induced AKI, their clinical role requires further validation [7,8].

It will also be valuable to identify additional reliable risk factors for DME/AKI, including pharmacogenetic/pharmacogenomic markers (e.g. specific genetic polymorphisms). A recent systematic review found that methotrexate metabolism and clearance in pediatric patients with acute lymphoblastic leukemia may be influenced by several genes, including *SLCO1B1*, *ABCB1*, *ABCC2*, and *MTHFR*, with *SLCO1B1* variants having substantial and consistent effects on clearance [36].

Benefits will be accrued by improving the accuracy of kidney assessment, especially GFR assessment, validating clearance of new exogenous markers for directly measured GFR. Despite the utility of iohexol for measuring GFR, a range of different protocols are used in different centers, and there is a need for standardization [37]. The potential of real-time, point-of-care GFR measurement via fluorescent marker and transdermal detection methodology has been demonstrated but remains to be fully realized [38]. In addition, incorporation of CT-derived muscle mass measurements into eGFR equations could create more personalized estimates to account for differences in muscle mass. The development and validation of such an approach has recently been described, demonstrating its value in patients with atypical muscle mass who may already have received CT scans as part of their medical follow-up [39].

Attention should also focus on utilizing eGFR equations developed specifically for certain populations, thereby taking into account relevant population-specific characteristics that may confound estimation via standard formulae, e.g. use of the modified Schwartz ('bedside') equation in children [40], to avoid overestimating GFR in young patients, or the Chronic Kidney Disease in Children under 25 years old (CKiD U25) equations [41], covering adolescence and young adulthood, developed to be complementary to the modified Schwartz equation, allowing for use of cystatin C as well as serum creatinine. In the elderly, changes in muscle mass and renal physiology can also confound GFR estimation based on a single creatinine measurement and equations incorporating cystatin C may provide more reliable estimates [42].

Further knowledge in areas such as those described above will help to develop standardized protocols for kidney assessment/monitoring to guide use of HDMTX, especially in children for whom data are lacking. Ultimately, this should enable more precise tailoring of treatment to optimize use of HDMTX in all patients with cancer for whom this agent may provide therapeutic benefit.

Author contributions

All authors were involved in Conceptualization and Writing – review & editing. All authors have read and agreed to the published version of the manuscript.

Funding

This work was supported by SERB Specialty Pharmaceuticals. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Declaration of interests

MJ Soler reports personal fees from AstraZeneca, Bayer, Boehringer Ingelheim, Esteve, Fresenius, GE Healthcare, ICU, Janssen, Lilly, Novo Nordisk, Pfizer, Travere Therapeutics, and Vifor, and grants and personal fees from Boehringer Ingelheim and SERB. L Forni reports research support from Baxter, SphingoTec and Vantive, and personal fees from Baxter and Vantive. C Isnard Bagnis reports personal fees from AstraZeneca, Boehringer Ingelheim and SERB. Authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Acknowledgments

Medical writing support (including development of a draft outline and subsequent drafts in consultation with the authors, assembling tables and figures, collating author comments, copyediting, fact checking and referencing) was provided by Hannah Mace, MPharmacol, CMPP (Aspire Scientific Ltd, Manchester, UK) and funded by SERB Specialty Pharmaceuticals.

ORCID

Corinne Isnard Bagnis http://orcid.org/0000-0002-1048-6636

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Bielack S, Soussain C, Fox C, et al. A European consensus recommendation on the management of delayed methotrexate elimination: supportive measures, leucovorin rescue and glucarpidase treatment. J Cancer Res Clin Oncol. 2024;150(10):441. doi: 10.1007/s00432-024-05945-6
   - •• **Recent paper presenting the consensus of a group of European experts on management of DME.**
2. Ramsey L, Balis F, O'Brien M, 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(1):52–61. doi: 10.1634/theoncologist.2017-0243
   - •• **US consensus guideline on the use of glucarpidase to manage DME and HDMTX-associated AKI.**
3. Howard SC, McCormick J, Pui CH, et al. Preventing and managing toxicities of high-dose methotrexate. Oncologist. 2016;21(12):1471–1482. doi: 10.1634/theoncologist.2015-0164
   - • **Overview of strategies for prevention and treatment of HDMTX toxicity.**
4. Protherics Medicines Development Ltd. Voraxaze (glucarpidase): summary of product characteristics. 2024.
5. Gros L, Roldán A, Cabero-Martínez A, et al. Incidence and management of patients with methotrexate delayed elimination in the clinical practice: a Delphi study. J Oncol Pharm Pract. 2023;29(4):794–801. doi: 10.1177/10781552221079568
6. Kielbowski K, Rosik J, Bakinowska E, et al. The use of glucarpidase as a rescue therapy for high dose methotrexate toxicity - a review of pharmacological and clinical data. Expert Opin Drug Metab Toxicol. 2023;19(11):741–750. doi: 10.1080/17425255.2023.2272593
7. De Chiara L, Lugli G, Villa G, et al. Molecular mechanisms and biomarkers associated with chemotherapy-induced AKI. Int J Mol Sci. 2022;23(5):2638. doi: 10.3390/ijms23052638
8. Fox E, Busch C, DeBernardo A, et al. A pharmacologically-based approach to high dose methotrexate administration to investigate nephrotoxicity and acute kidney injury biomarkers in children and adolescents with newly diagnosed osteosarcoma. Cancer Chemother Pharmacol. 2021;87(6):807–815. doi: 10.1007/s00280-021-04248-8
9. Lin WY, Tsai CK, Yeh CM, et al. Identifying risk factors for methotrexate-induced acute kidney injury despite full prevention in patients with primary central nervous system lymphoma. Toxicol Appl Pharmacol. 2025;502:117436. doi: 10.1016/j.taap.2025.117436
10. Ylinen E, Jahnukainen K, Saarinen-Pihkala UM, et al. Assessment of renal function during high-dose methotrexate treatment in children with acute lymphoblastic leukemia. Pediatr Blood Cancer. 2014;61(12):2199–2202. doi: 10.1002/pbc.25137
11. Buddington RK, Wong T, Buddington KK, et al. Early clinical indicators of acute kidney injury caused by administering high-dose methotrexate therapy to juvenile pigs. Front Nephrol. 2023;3:1193494. doi: 10.3389/fneph.2023.1193494
12. Skärby T, Jönsson P, Hjorth L, et al. High-dose methotrexate: on the relationship of methotrexate elimination time vs renal function and serum methotrexate levels in 1164 courses in 264 Swedish children with acute lymphoblastic leukaemia (ALL). Cancer Chemother Pharmacol. 2003;51(4):311–320. doi: 10.1007/s00280-002-0552-1
13. Barreto JN, Kashani KB, Mara KC, et al. A prospective evaluation of novel renal biomarkers in patients with lymphoma receiving high-dose methotrexate. Kidney Int Rep. 2022;7(7):1690–1693. doi: 10.1016/j.ekir.2022.03.013
14. Rattu MA, Shah N, Lee JM, et al. Glucarpidase (voraxaze), a carboxypeptidase enzyme for methotrexate toxicity. P T. 2013;38(12):732–744.
15. Schwartz S, Martus P, Ludwig W-D, et al. Toxicity and risk factors contributing to delayed methotrexate (MTX) elimination in adult/elderly patients (pts) treated with high-dose methotrexate therapy (HDMTX), a 2-year, single center survey. Blood. 2006;108(11):2439. doi: 10.1182/blood.V108.11.2439.2439
16. Beechinor RJ, Thompson PA, Hwang MF, et al. The population pharmacokinetics of high-dose methotrexate in infants with acute lymphoblastic leukemia highlight the need for bedside individualized dose adjustment: a report from the Children's Oncology Group. Clin Pharmacokinet. 2019;58(7):899–910. doi: 10.1007/s40262-018-00734-0
17. Sandhu G, Adattini J, Armstrong Gordon E, et al. Integrating International Consensus Guidelines for Anticancer Drug Dosing in Kidney Dysfunction (ADDIKD) into everyday practice. EClinicalMedicine. 2025;82:103161. doi: 10.1016/j.eclinm.2025.103161
18. Sandhu G, Adattini J, Armstrong Gordon E, et al. Aligning kidney function assessment in patients with cancer to global practices in internal medicine. EClinicalMedicine. 2025;82:103102. doi: 10.1016/j.eclinm.2025.103102
19. Taylor Z, Mizuno T, Punt N, et al. MTXPK.Org: a clinical decision support tool evaluating high-dose methotrexate pharmacokinetics to inform post-infusion care and use of glucarpidase. Clin Pharmacol Ther. 2020;108(3):635–643. doi: 10.1002/cpt.1957
   - • **Development of the MTXPK.org tool to support clinical decision making in the use of glucarpidase.**

20. Ghannoum M, Roberts DM, Goldfarb DS, et al. Extracorporeal treatment for methotrexate poisoning: systematic review and recommendations from the EXTRIP workgroup. Clin J Am Soc Nephrol. 2022;17(4):602–622. doi: 10.2215/cjn.08030621
21. Jiang R, Mei S, Zhao Z. Leucovorin (folinic acid) rescue for high-dose methotrexate: a review. J Clin Pharm Ther. 2022;47(9):1452–1460. doi: 10.1111/jcpt.13739
22. Buchen S, Ngampolo D, Melton R, et al. Carboxypeptidase G2 rescue in patients with methotrexate intoxication and renal failure. Br J Cancer. 2005;92(3):480–487. doi: 10.1038/sj.bjc.6602337
23. Janeway K, Gros L, Schwartz S, et al. A pooled subgroup analysis of glucarpidase treatment in 86 pediatric, adolescent, and young adult patients receiving high-dose methotrexate therapy in open-label trials. Pediatr Blood Cancer. 2023;70(9):e30506. doi: 10.1002/pbc.30506
24. Schwartz S, Borner K, Müller K, et al. Glucarpidase (carboxypeptidase G2) intervention in adult and elderly cancer patients with renal dysfunction and delayed methotrexate elimination after high-dose methotrexate therapy. Oncologist. 2007;12(11):1299–1308. doi: 10.1634/theoncologist.12-11-1299
25. Widemann B, Balis F, Kempf-Bielack B, et al. High-dose methotrexate-induced nephrotoxicity in patients with osteosarcoma. Cancer. 2004;100(10):2222–2232. doi: 10.1002/cncr.20255
26. Widemann B, Schwartz S, Jayaprakash N, et al. Efficacy of glucarpidase (carboxypeptidase G2) in patients with acute kidney injury after high-dose methotrexate therapy. Pharmacotherapy. 2014;34(5):427–439. doi: 10.1002/phar.1360
27. Widemann B, Balis F, Kim A, et al. Glucarpidase, leucovorin, and thymidine for high-dose methotrexate-induced renal dysfunction: clinical and pharmacologic factors affecting outcome. J Clin Oncol. 2010;28(25):3979–3986. doi: 10.1200/JCO.2009.25.4540
28. Widemann B, Balis F, Murphy R, et al. Carboxypeptidase-G2, thymidine, and leucovorin rescue in cancer patients with methotrexate-induced renal dysfunction. J Clin Oncol. 1997;15(5):2125–2134. doi: 10.1200/JCO.1997.15.5.2125
29. Demiralp B, Koenig L, Kala J, et al. Length of stay, mortality, and readmissions among Medicare cancer patients treated with glucarpidase and conventional care: a retrospective study. Clinicoecon Outcomes Res. 2019;11:129–144. doi: 10.2147/CEOR.S188786
30. Gupta S, Kaunfer S, Chen K, et al. Glucarpidase for treatment of high-dose methotrexate toxicity. Blood. 2025;145(17):1858–1869. doi: 10.1182/blood.2024026211
•• **Study assessing the effects of glucarpidase administration to improve renal and extrarenal outcomes in patients with HDMTX-associated AKI.**
31. Truong HL, Barreto JN, Mara KC, et al. Rechallenge with high-dose methotrexate after treatment with glucarpidase in adult patients with lymphoma. JCO Oncol Pract. 2024;20(6):797–807. doi: 10.1200/OP.23.00628
32. Schaff LR, Lobbous M, Carlow D, et al. Routine use of low-dose glucarpidase following high-dose methotrexate in adult patients with CNS lymphoma: an open-label, multi-center phase I study. BMC Cancer. 2022;22(1):60. doi: 10.1186/s12885-021-09164-x
33. Schaff LR, Carlow D, Schofield R, et al. Low-dose planned glucarpidase allows safe outpatient high-dose methotrexate treatment for CNS lymphoma. JCO Oncol Pract. 2024;20(10):1384–1390. doi: 10.1200/op.24.00080
34. Skärby T, Anderson H, Heldrup J, et al. High leucovorin doses during high-dose methotrexate treatment may reduce the cure rate in childhood acute lymphoblastic leukemia. Leukemia. 2006;20(11):1955–1962. doi: 10.1038/sj.leu.2404404
35. Haran A, Even-Zohar N, Haran M, et al. Impact of folinic acid dosing on efficacy and toxicity of high-dose methotrexate in central nervous system lymphoma. Clin Lymphoma Myeloma Leuk. 2024;24(3):187–93.e1. doi: 10.1016/j.clml.2023.10.012
36. Rahmayanti SU, Amalia R, Rusdiana T. Systematic review: genetic polymorphisms in the pharmacokinetics of high-dose methotrexate in pediatric acute lymphoblastic leukemia patients. Cancer Chemother Pharmacol. 2024;94(2):141–155. doi: 10.1007/s00280-024-04694-0
37. Mohamed AAA, Bökenkamp A, Cavalier E, et al. Diverse protocols for measuring glomerular filtration rate using iohexol clearance. Nephrol Dial Transpl. 2024;39(6):1037–1039. doi: 10.1093/ndt/gfae006
38. Delanaye P, Glassock RJ. A difficult path to point-of-care measurement of glomerular filtration rate. Nat Rev Nephrol. 2025;21(5):285–286. doi: 10.1038/s41581-025-00947-0
39. Stehlé T, Ouamri Y, Morel A, et al. Development and validation of a new equation based on plasma creatinine and muscle mass assessed by CT scan to estimate glomerular filtration rate: a cross-sectional study. Clin Kidney J. 2023;16(8):1265–1277. doi: 10.1093/ckj/sfad012
40. Schwartz GJ, Muñoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol. 2009;20(3):629–637. doi: 10.1681/asn.2008030287
41. Pierce CB, Muñoz A, Ng DK, et al. Age- and sex-dependent clinical equations to estimate glomerular filtration rates in children and young adults with chronic kidney disease. Kidney Int. 2021;99(4):948–956. doi: 10.1016/j.kint.2020.10.047
42. Raman M, Middleton RJ, Kalra PA, et al. Estimating renal function in old people: an in-depth review. Int Urol Nephrol. 2017;49(11):1979–1988. doi: 10.1007/s11255-017-1682-z