High-Dose Methotrexate, Leucovorin and Glucarpidase Dosing, Administration, and Monitoring – Adult/Pediatric – Inpatient Clinical Practice Guideline

Note: Active Table of Contents – Click to follow link

EXECUTIVE SUMMARY ................................................................................................ 3
SCOPE............................................................................................................................ 4
METHODOLOGY ............................................................................................................ 5
DEFINITIONS: ................................................................................................................ 6
INTRODUCTION ............................................................................................................. 6
RECOMMENDATIONS ................................................................................................... 7
UW HEALTH IMPLEMENTATION................................................................................ 13
REFERENCES .............................................................................................................. 14
Contact for Content:
Name: Sara Shull, PharmD, MBA, BCPS
Phone Number: (608) 262-1817
Email Address: ssmith-shull@uwhealth.org

Contact for Changes:
Name: Philip Trapskin, PharmD, BCPS
Phone Number: (608) 263-1308
Email Address: ptrapskin@uwhealth.org

Guideline Author:
Mike Fallon, PharmD, BCOP - Pharmacy
Erin McCreary, PharmD – Pharmacy

Coordinating Team Members:
Mary Mably, RPh, BCOP – Pharmacy
Mike Reed, RPh, BCOP – Pharmacy

Review Individuals/Bodies:
Kenneth DeSantes, MD – Pediatric Hematology/Oncology
Christopher Fletcher, MD – Adult Hematology/Oncology

Committee Approvals/Dates:
Pharmacy Oncology Service Line: December 2015
Chemotherapy Review Council: January 2016
Pharmacy & Therapeutics Committee (Last Periodic Review: September 2015)
  • Interim revisions: January 2016, September 2016

Release Date: September 2016 | Next Review Date: September 2018
**Executive Summary**  
**Guideline Overview**
These guidelines provide recommendations for the prevention, monitoring, and treatment of methotrexate toxicity in adult and pediatric patients receiving high-dose methotrexate therapy.

**Key Practice Recommendations**
1. Prevention of toxicity for patients receiving high-dose methotrexate should include hyperhydration, urine alkalization, pharmacokinetically guided leucovorin rescue, and monitoring for drug interactions.\(^1\text{-}^{11}\) (Class 1, Level of Evidence A)
2. Monitoring of toxicity for patients receiving high-dose methotrexate should begin 24 hours after the start of the methotrexate infusion and include methotrexate blood concentration, serum creatinine, urine output, and urine pH.\(^1\text{-}^{2,11}\text{-}^{13}\) (Class 1, Level of Evidence B)
3. High-dose-methotrexate-induced nephrotoxicity treatment should include leucovorin dose-adjustment and may include glucarpidase.\(^1\text{-}^{11,14}\text{-}^{18}\) (Class 1, Level of Evidence C)

**Companion Documents**
1. Drug Concentration Monitoring Delegation Protocol
2. Renal Function-Based Dose Adjustment Delegation Protocol
3. Renal Function-Based Dose Adjustments – Adult – Inpatient/Ambulatory Clinical Practice Guideline
4. UWHC Guidelines for the Management of Extravasation of Chemotherapeutic Agents – Pediatric/Adult – Inpatient/Ambulatory Clinical Practice Guideline
5. Intravenous Administration of Formulary Medications – Adult – Inpatient/Ambulatory
6. Intravenous Administration of Formulary Medications – Neonatal/Pediatric – Inpatient/Ambulatory
7. Medications Defined as Chemotherapy at UWHC

**Pertinent UW Health Policies & Procedures**
1. [UWMF Policy 102.081: Methotrexate Injection](#)

**Patient Resources**
1. [Medication Fact Sheet: Methotrexate (pediatrics)](#)
2. [Medication Fact Sheet: Carboxypeptidase (Glucarpidase) (pediatrics)](#)
3. [Lexicomp: Methotrexate]
4. [Lexicomp: Glucarpidase]
5. [Lexicomp: Leucovorin]
Scope
Disease/Condition(s):
Hematologic and solid tumor malignancies requiring utilization of high-dose methotrexate

Clinical Specialty:
Bone Marrow Transplant, Hematology, Nursing, Oncology, Pediatrics, Pharmacy

Intended Users:
Advanced Practice Providers, Pharmacists, Physicians, Registered Nurses

Objectives:
To maximize outcomes and minimize toxicity associated with high-dose methotrexate regimens. In addition, this guideline aims to avoid inappropriate use of glucarpidase.

Target Population:
1. Adult and pediatric inpatients receiving high-dose methotrexate

Interventions and Practices Considered:
1. This guideline recommends appropriate use of enteral sodium bicarbonate, intravenous sodium bicarbonate, leucovorin, and glucarpidase as preventative supportive care for and the treatment of high-dose methotrexate toxicity.
2. This guideline provides recommendations for the appropriate monitoring of high-dose methotrexate treatment utilizing methotrexate blood concentration, serum creatinine, urine output, and urine pH.

Major Outcomes Considered:
1. Renal clearance of high-dose methotrexate to below detectable levels in the absence of toxicity
2. Prevention and resolution of toxic reactions to methotrexate (i.e. myelosuppression, oral mucositis, acute kidney injury, acute hepatic dysfunction, and acute dermatitis)

Guideline Metrics:
1. Adherence to guideline of recommendations
2. Incidence and severity of methotrexate toxicities as identified through voluntary reporting and retrospective chart review
Methodology

Methods used to analyze the Evidence:
Review of the following:
1. Standard drug databases including AHFS Drug Information, Lexi-Comp On-line, Drug Facts and Comparison and Micromedex;
2. FDA package inserts using Drugs@FDA website;
3. Existing UW Health Clinical Practice Guidelines; PubMed database and Google scholar with the keywords: leucovorin, methotrexate, high-dose methotrexate, methotrexate monitoring, glucarpidase, carboxypeptidase-G2

Methods Used to Formulate the Recommendations:
Review of standard drug databases, pertinent guidelines and literature with treatment effect size and estimate of certainty of the treatment effect established according to the rating scheme (see below)

Rolling Scheme for the Strength of the Recommendations:
A modified Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system developed by the American Heart Association and the American College of Cardiology Foundation has been used to assess the Quality and Strength of the evidence in this Clinical Practice Guideline.19

Figure 1: American Heart Association Grades of Recommendation19

Method of Guideline Validation:
Clinical experts from key clinical areas reviewed the final guideline.
**Definitions:**
1. High-dose methotrexate: any dose of methotrexate ≥ 500 mg/m$^2$.
2. Creatinine clearance (CrCl): measure of the rate in which creatinine, a byproduct of protein metabolism, is cleared from the blood by the kidneys.
3. Below detection methotrexate blood concentration: Laboratory result ≤ 0.05 µM/L (for additional information see [UW Health Lab Test Directory](#)).

**Introduction**
Methotrexate is one of the most widely used anti-cancer agents and has application where immunosuppression is required (rheumatoid arthritis, psoriasis and after bone marrow transplant). Methotrexate blood concentration monitoring is useful because both drug concentration and exposure time have been correlated with toxicity. The severity of toxicity is directly proportional to the duration at which the extracellular concentration remains above the critical threshold. The critical threshold varies from organ to organ. The most common toxic reactions to methotrexate are myelosuppression, oral mucositis, acute kidney injury, acute hepatic dysfunction, and acute dermatitis. Intestinal mucositis, diarrhea, vomiting, vaginal mucositis, conjunctivitis, vasculitis, immunosuppression, and acute neurotoxicity may also occur. High-doses of methotrexate (>500 mg/m$^2$) are used for a wide variety of hematologic and solid tumor malignancies. High-dose methotrexate is considered lethal unless appropriately reversed by leucovorin rescue in a timely manner.

The etiology of methotrexate-induced nephrotoxicity is mediated by the precipitation of methotrexate and its metabolites in the renal tubules. Because methotrexate is primarily excreted via the kidneys, elimination of the drug becomes problematic once nephrotoxicity has occurred.

Current recommendations for the prevention of methotrexate nephrotoxicity are routine monitoring of creatinine and methotrexate blood concentration, dose-adjusted leucovorin rescue, aggressive hydration, and urine alkalinization. The utilization of these prophylactic strategies has decreased the incidence of severe and life-threatening toxicities from 10% to less than 1%. However, nephrotoxicity potentially leading to death still occurs in a fraction of patients, especially in adult patients with poor performance status.

Glucarpidase (Voraxaze®) is a recombinant carboxypeptidase enzyme that degrades folic acid and methotrexate into inactive metabolites. Thus, it provides an alternate non-renal pathway for methotrexate elimination in patients with renal dysfunction during high-dose methotrexate treatment. It is FDA approved for the treatment of toxic methotrexate blood concentrations in patients with delayed methotrexate clearance due to impaired renal function. Glucarpidase has no impact on intracellular concentrations of methotrexate or on reversing methotrexate-induced renal toxicity. Protection of cells from intracellular methotrexate still requires the administration of high-dose leucovorin.
Recommendations

1. Prevention of toxicity for patients receiving high-dose methotrexate

1.1 Patients should receive adequate hydration per specific chemotherapy protocol (Class I, Level B)^1,2,6,11,20,22

1.1.1 A minimum of four hours of pre-hydration is reasonable. (Class IIa, Level C)^6,22,23

1.1.2 It is reasonable to titrate pre-hydration to maintain urine output at ≥ 100 mL/hr until methotrexate blood concentration is below detection (Class IIa, Level C)^1

1.1.3 It is recommended that patients receive 2.5-3.5 L/m^2 per 24 hours of fluid, starting 12 hours before the start of the MTX infusion and continuing for 24 to 48 hours. (Class IIa, Level C)^11

1.2 Urine alkalization with a goal urine pH ≥ 7 should be achieved prior to initiation of high-dose methotrexate and continued until methotrexate blood concentration is below detection (Class 1, Level A)^1,20,22,24

1.2.1 Medications or fluids that may acidify the urine (e.g. folic acid, vitamin C, normal saline, cranberry juice, soda etc.) should be avoided. (Class I, Level B)^1,2,13,20

1.2.2 Adult patients

1.2.2.1 Prior to admission for high-dose methotrexate it may be useful for patients to take oral sodium bicarbonate to support rapid urinary alkalization (Class IIb, Level B)^3

1.2.2.1.1 It is reasonable to consider instructing patients to take ½ tsp baking soda by mouth every 4-6 hours for 5 doses, starting the day before high-dose methotrexate treatment is initiated. (Class IIb, Level C)^3,5,25

1.2.2.2 Intravenous maintenance fluids should be sterile water or dextrose 5% solution with 100 mEq of sodium bicarbonate per liter. (Class I, Level B)^1,20,23

1.2.2.3 If urine pH is less than 7 while on appropriate intravenous fluids, a sodium bicarbonate IV 50mEq bolus is indicated as often as every 2 hours. (Class I, Level B)^1,20

1.2.3 Pediatric patients

1.2.3.1 Sodium bicarbonate 1 mEq/mL intravenously may be infused at a rate of 0.15 mEq/kg/hr, titrated up by 2 mEq/hr or down by 1 mEq/hr to keep urine pH between 7 and 8. (Class IIb, Level C)^3

1.2.3.2 Maintenance fluids of dextrose 5% or sodium chloride 0.45% should be infused at a rate of 125 mL/m^2/hr until the methotrexate blood concentration is below detection. (Class I, Level B)^1,20

1.3 Specific protocols should be followed to guide starting time, dose, and frequency of leucovorin rescue following high-dose methotrexate administration (Class I, Level B)^1,20

1.3.1 Adult patients

1.3.1.1 Leucovorin should be started 24 hours following the initiation of therapy. (Class 1, Level B)^1,2,4,12,20,26,27

1.3.1.2 An initial intravenous dose of 50 mg/m^2 may be considered to ensure adequate and rapid absorption (Class IIb, Level C)^1,8,11

1.3.1.2.1 It is reasonable for subsequent doses of leucovorin to be 15 mg/m^2 intravenously until the methotrexate blood concentration is ≤ 0.5 µM/L
in patients without increased risk factors for methotrexate toxicity (Class IIb, Level C)\textsuperscript{1,20}

1.3.1.2.2 It is reasonable for 15 mg leucovorin to be given orally every 6 hours once the methotrexate blood concentration is ≤ 0.5 µM/L and continued until the methotrexate blood concentration is undetectable (≤ 0.05 µM/L) in patients without increased risk factors for methotrexate toxicity. (Class IIb, Level C)\textsuperscript{1,20}

1.3.1.2.3 Adult patients can be considered for discharge when the methotrexate blood concentration is ≤ 0.1 µM/L but is not yet undetectable. It is reasonable to discharge patients with a prescription for 15 mg oral leucovorin tablets to be taken every 6 hours along with ½ tsp baking soda every 6 hours until a follow-up methotrexate blood concentration is confirmed to be ≤ 0.05 µM/L. (Class IIb, Level C)\textsuperscript{1,20}

1.3.1.2.3.1 A follow-up methotrexate blood concentration should be drawn no later than 48 hours after discharge.

1.3.1.3 Intravenous route should be used for doses of leucovorin greater than 25 mg and for patients at risk of decreased oral absorption (Class 1, Level B)\textsuperscript{9,20}

1.3.2 Pediatric patients

1.3.2.1 Individual protocols should be followed for dosing of leucovorin (Class 1, Level B)\textsuperscript{4}

1.4 Drug-drug interactions with methotrexate have potential to initiate or worsen toxicity and should be avoided (Class I, Level B)\textsuperscript{2-6}

1.4.1 Medications that displace methotrexate from binding sites on plasma proteins, resulting in increased methotrexate blood concentrations (e.g. sulfonamides, salicylates, phenytoin, and tetracycline), should be avoided. (Class I, Level B)\textsuperscript{3-6}

1.4.2 Medications that reduce renal tubular transport as a result of decreased urine pH (increased acidity), resulting in increased methotrexate blood concentrations (e.g. folic acid, salicylates, ascorbic acid, multiple vitamins containing vitamin C), should be avoided. (Class I, Level B)\textsuperscript{3-6}

1.4.3 Medications that compete for P-glycoprotein transport, CYP450 metabolism, or renal excretion of methotrexate, resulting in increased methotrexate blood concentrations and toxicities (e.g. non-steroidal anti-inflammatory drugs [NSAIDs], penicillins, probenecid, gemfibrozil, cyclosporine, ciprofloxacin, amiodarone, doxycycline, simvastatin) should be avoided. (Class I, Level B)\textsuperscript{3-6,11,28}

1.4.4 Concomitant use of proton pump inhibitors, such as omeprazole, esomeprazole, and pantoprazole, with methotrexate (primarily at high doses), should be avoided, as they may elevate and prolong blood concentrations of methotrexate and/or its metabolite hydroxymethotrexate (Class I, Level A)\textsuperscript{3,5}

1.5 Patients with third-space fluids such as pleural effusions, significant edema, or ascites, may have altered volume of distribution and extended terminal half-life of methotrexate, causing delayed elimination of the drug that is not likely correctable with hemodialysis. For this reason, it is reasonable to examine patients to identify potential sites of third-spacing prior to administration of high-dose methotrexate and to consider holding treatment in those patients with significant third-spacing present (Class IIa, Level B)\textsuperscript{3,6,11,29}
1.5.1 It is reasonable to evaluate patients with weight gain ≥ 2 kg from admission for third-spacing and fluid retention and consider these patients at risk for delayed methotrexate clearance.

1.5.2 Use of furosemide within 48 hours of the initiation of high-dose methotrexate can delay methotrexate clearance. It is reasonable to consider furosemide use within 48 hours of high-dose methotrexate for patients with signs and symptoms of fluid overload where the benefit of use outweighs the risk.

1.5.2.1 It is not appropriate to utilize furosemide within 48 hours of high-dose methotrexate initiation to increase urine output in the absence of symptoms.

2. Monitoring of toxicity for patients receiving high-dose methotrexate

2.1 Patients with pleural effusions, pericardial effusions, ascites, edema, urine output < 500 mL/day, weight gain ≥ 2 kg from admission, diarrhea, vomiting, pre-existing renal dysfunction, urinary tract obstruction, and significant changes in serum creatinine and/or calculated creatinine clearance during treatment with high-dose methotrexate are at increased risk for toxicity (Class I, Level A)\(^{1,8,10-12,22}\).

2.2 Methotrexate blood concentration and serum creatinine should be monitored 24 hours after the start of the methotrexate infusion and then at least once daily until elimination to below detection. (Class I, Level C)\(^{20}\)

2.2.1 It is reasonable to monitor methotrexate blood concentration and serum creatinine at 36-hours of treatment in patients with increased risk factors for methotrexate toxicity (Table 1).

2.3 It is reasonable to measure urine output continuously and document output at least every 8 hours. (Class IIa, Level C)\(^{1}\)

2.4 To assess for alkalosis, it is reasonable to monitor urine pH and respiratory rate every 8 hours and serum bicarbonate daily. (Class IIa, Level C)\(^{2}\)

3. Treatment of high-dose-methotrexate-induced nephrotoxicity or delayed clearance

3.1 Leucovorin dosing should be evaluated for potential adjustment starting 24 hours after start of methotrexate (Class I, Level B)\(^{1,20}\)

3.1.1 It may be reasonable to adjust leucovorin dose to 100 mg/m\(^2\) IV every 6 hours if serum creatinine increases ≥50% from baseline or to 100 mg/m\(^2\) IV every 3 hours if serum creatinine increases ≥100% from baseline. (Class IIb, Level C)\(^{9}\)

3.1.2 If methotrexate blood concentration is ≥50 µmol/L at 24 hours, it may be reasonable to increase leucovorin dose to 100 mg/m\(^2\) IV every 3 hours. (Class IIb, Level C)\(^{4}\)

3.1.3 The dosing algorithm in Table 1 should be used to guide leucovorin dose adjustments. (Class I, Level B)\(^{1,10,20}\).
**Table 1: Leucovorin Dosing Algorithm**

1. This table may only be utilized to consider dose adjustments in adult inpatients.

<table>
<thead>
<tr>
<th>24-hour Concentration</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10 µM/L</td>
<td>No change; Draw next AM concentration</td>
</tr>
<tr>
<td>&lt; 20 µM/L for Hyper-CVAD*</td>
<td></td>
</tr>
<tr>
<td>≥ 10 µM/L and/or SCr ≥ 125% baseline</td>
<td>Increase fluids to 175 mL/hr</td>
</tr>
<tr>
<td>≥ 20 µM/L for Hyper-CVAD*</td>
<td>Adjust leucovorin to 30mg/m2 IV Q6H</td>
</tr>
<tr>
<td>Draw 36 hour concentration</td>
<td></td>
</tr>
<tr>
<td>≥ 10 µM/L and/or SCr ≥ 150% baseline</td>
<td>Increase fluids to 200 mL/hr</td>
</tr>
<tr>
<td>≥ 20 µM/L for Hyper-CVAD*</td>
<td>Adjust leucovorin to 100mg/m2 IV Q6H</td>
</tr>
<tr>
<td>Draw 36 hour concentration</td>
<td></td>
</tr>
<tr>
<td>&gt; 50 µM/L and/or SCr ≥ 200% baseline</td>
<td>Increase fluids to 200 mL/hr</td>
</tr>
<tr>
<td>≥ 20 µM/L for Hyper-CVAD*</td>
<td>Adjust leucovorin to 100mg/m2 IV Q3H</td>
</tr>
<tr>
<td>Draw 36 hour concentration</td>
<td>Consider glucarpidase use**</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Conditional 36-hour Concentration</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 3 µM/L</td>
<td>Increase fluids to 200mL/hr if not already there</td>
</tr>
<tr>
<td></td>
<td>Increase leucovorin to 30 mg/m2 IV Q6H</td>
</tr>
<tr>
<td>≥ 10 µM/L and/or SCr ≥ 125% baseline</td>
<td>Increase fluids to 200mL/hr if not already there</td>
</tr>
<tr>
<td></td>
<td>Increase leucovorin to 100mg/m2 IV Q6H</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>42-48 hour “next AM” Concentration</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 0.5 µM/L</td>
<td>Transition to PO leucovorin</td>
</tr>
<tr>
<td>0.51 – 1 µM/L</td>
<td>No change; Draw next AM concentration</td>
</tr>
<tr>
<td>1.01-5 µM/L and/or SCr ≥ 125% baseline</td>
<td>Increase fluids to 200mL/hr if not already there</td>
</tr>
<tr>
<td></td>
<td>Increase leucovorin to 30 mg/m2 IV Q6H</td>
</tr>
<tr>
<td>5.01 – 9.99 µM/L and/or SCr ≥ 150% baseline</td>
<td>Increase fluids to 200mL/hr if not already there</td>
</tr>
<tr>
<td></td>
<td>Increase leucovorin to 30 mg/m2 IV Q3H</td>
</tr>
<tr>
<td></td>
<td>Consider glucarpidase use**</td>
</tr>
<tr>
<td>10-49.99 µM/L and/or SCr ≥ 200% baseline</td>
<td>Increase fluids to 200mL/hr if not already there</td>
</tr>
<tr>
<td></td>
<td>Increase leucovorin to 100mg/m2 Q3H</td>
</tr>
<tr>
<td></td>
<td>Consider glucarpidase use**</td>
</tr>
<tr>
<td>≥ 50 µM/L</td>
<td>Increase fluids to 200mL/hr if not already there</td>
</tr>
<tr>
<td></td>
<td>Increase leucovorin to 1000 mg/m2 Q6H</td>
</tr>
<tr>
<td></td>
<td>Consider glucarpidase use**</td>
</tr>
</tbody>
</table>

*For HyperCVAD, increase the fluids immediately per the algorithm if 24 hour concentration or SCr is elevated. Increase the leucovorin dose per the algorithm as well, but do not start these changes until hour 36. If the escalation requires 100 mg/m2 dosing, discontinue the 50 mg/m2 leucovorin bolus order and start with 100 mg/m2 at hour 36.

### 3.2 Treatment with glucarpidase

#### 3.2.1 To be eligible for glucarpidase treatment patients should meet BOTH the methotrexate concentration outlined in Table 2 AND have evidence of impaired renal function (CrCl < 60 mL/min OR SCr ≥ 150% baseline). (Class I, Level A)\(^\text{15,17,21,33}\)

#### 3.2.1.1 Glucarpidase should not be given if the methotrexate blood concentration is ≤ 1 µM/L. (Class I, Level A)\(^\text{15,17,21,33}\)

---

Copyright © 2016 University of Wisconsin Hospitals and Clinics Authority
Contact: CCKM@uwhealth.org
Last Revised: 09/2016
3.2.1.2 It is reasonable to consider toxicities other than renal dysfunction (e.g. central nervous system, mucositis) in the use of glucarpidase. (Class IIa, Level A)\textsuperscript{7,9}

Table 2: Methotrexate concentration eligibility criteria for glucarpidase administration. \textsuperscript{7, 9}

<table>
<thead>
<tr>
<th>[MTX] (µM/L) at 24 hours</th>
<th>[MTX] (µM/L) at 42 hours</th>
<th>[MTX] (µM/L) at 48 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>&gt;5</td>
<td>&gt;3</td>
</tr>
</tbody>
</table>

Note: Methotrexate concentrations [MTX] are measured from the START of the infusion.

3.2.2 Leucovorin rescue dosing should be monitored closely with glucarpidase administration (Class 1, Level A)\textsuperscript{17,21}

3.2.2.1 Glucarpidase has no impact on intracellular concentrations of methotrexate. Leucovorin should still be administered to protect cells from intracellular methotrexate, which will be released into the vascular space following glucarpidase administration. (Class I, Level A)\textsuperscript{7,9,15,17,33}

3.2.2.2 To allow glucarpidase to optimally metabolize methotrexate rather than leucovorin, which is also metabolized by glucarpidase, leucovorin should not be administered within 2 hours before or 2 hours after a dose of glucarpidase. (Class I, Level A)\textsuperscript{15,17,21}

3.2.2.3 Starting 2 hours after glucarpidase injection, the SAME dose of leucovorin as given prior to glucarpidase should be administered for at least 48 hours following the dose (Class I, Level A)\textsuperscript{15,17,21}

3.2.2.4 Beyond 48 hours after administration of glucarpidase, leucovorin doses should be adjusted based on methotrexate concentrations per Table 1. (Class 1, Level A)\textsuperscript{15,17,21}

3.2.2.5 It is reasonable to continue leucovorin for a minimum of 3 days after methotrexate blood concentration is first undetectable. (Class IIa, Level C)\textsuperscript{17,21}

3.2.3 Glucarpidase dosing

3.2.3.1 A dose of 50 units/kg IV is recommended (Class 1, Level A)\textsuperscript{15,17,21}

3.2.3.1.1 It may be reasonable to round glucarpidase doses to the nearest 1000 unit vial size. (Class IIb, Level C)\textsuperscript{7}

3.2.3.2 Glucarpidase should be administered intravenously as a bolus injection over 5 minutes (Class I, Level A)\textsuperscript{7}

3.2.3.3 Second and third doses of glucarpidase are NOT recommended, as they have not shown clinical benefit and may increase risk of immunogenicity. (Class III, Level A)\textsuperscript{15,17}

3.2.4 Monitoring patients following glucarpidase administration

3.2.4.1 Methotrexate blood concentration should be monitored daily until below detection, as for 48 hours after a glucarpidase dose, methotrexate blood concentration will be artificially elevated. This is due to the fact that glucarpidase metabolizes methotrexate into an inactive metabolite (4-deoxy-4-amino-N10-methylpterio acid), which is detected, along with active methotrexate, in the immunoassay; thus, accurate methotrexate blood concentration can only be obtained ≥48 hours after glucarpidase administration. (Class 1, Level A)\textsuperscript{7, 9}
3.2.4.2 Urine output should be monitored at least every 8 hours until stable, then every 24 hours. (Class I, level A)

3.2.4.3 Following glucarpidase administration SCr is likely to continue to gradually rise for three days prior to declining; thus serum creatinine should be monitored every 12 hours until stable, then every 24 hours. (Class 1, Level A)$^{17,21}$

3.2.5 Dialysis-based methods have not been shown to reduce methotrexate toxicity and are not recommended (Class III, Level B)$^{1,11,29}$
**UW Health Implementation**

**Benefits/Harms of Implementation**

This guideline is intended to provide a resource for making decisions regarding the prevention, monitoring, and treatment of methotrexate toxicity in adult and pediatric patients receiving high-dose methotrexate therapy. Use of the guideline is expected to improve the safety and efficiency of the high-dose methotrexate treatment process.

**Qualifying Statements:**

1. This guideline must be used in conjunction with clinical evaluation, and adjustments must be made to account for the individual patient. Factors to consider include age, body weight, drug interactions, renal insufficiency, hepatic insufficiency, and other concurrent disease states.

**Potential Benefits:**

1. Delineate appropriate supportive care and monitoring for patients receiving high-dose methotrexate
2. Standardize starting and escalation dosing of leucovorin rescue following administration of high-dose methotrexate
3. Define criteria and dosing of glucarpidase in patients experiencing high-dose methotrexate toxicity

**Potential Harms:**

1. Patients must be monitored for laboratory and clinical signs and symptoms of metabolic alkalosis. Iatrogenic metabolic alkalosis can be seen by monitoring CO$_2$ (serum CO$_2$ > 34), anion gap and pH on serum chemistry. Clinically, metabolic alkalosis results in changes in mental status, muscle spasms, and decreased respiratory drive that can be life threatening (respiratory rate >30 is a sign that the patient may not be able to compensate for increased CO$_2$).
2. Serious allergic reactions, including anaphylaxis, are possible with glucarpidase administration
3. Development of anti-glucarpidase antibodies is possible following administration of a single dose of glucarpidase

**Implementation Strategy**

1. This guideline will be housed on U-Connect in a dedicated folder for clinical practice guidelines.
2. Pharmacists will be educated about the guideline at staff and team meetings.
3. Nurses and physicians will be educated about the guideline and through in-service education sessions.

**Implementation Tools/Plan**

1. Health link will be used to implement the clinical practice guideline. Beacon treatment plans containing high-dose methotrexate will be updated and maintained to reflect recommendations in this guideline.
2. A standardized pharmacokinetic monitoring note will be utilized by clinical pharmacists to ensure recommendations are followed.
3. The dose button for glucarpidase will be locked at 50 units/kg.
4. Evaluation of guideline: A retrospective medication-use evaluation of high-dose methotrexate and each dose of glucarpidase will be completed to assess utility of the guideline. A prospective evaluation will occur for one year from guideline approval to assess the safety and efficacy of leucovorin dose-adjustments.
Disclaimer
CPGs are described to assist clinicians by providing a framework for the evaluation and treatment of patients. This Clinical Practice Guideline outlines the preferred evidence-based approach for most patients. It is not intended to replace a clinician’s judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.

References


