HOUSTON Methodist LEADING MEDICINE

High Dose Methotrexate and Leucovorin Rescue Clinical Guidance Document

Background

- High-dose methotrexate (MTX): Any dose of MTX ≥ 500 mg/m^2.
- Indication for use: High dose MTX is typically used in the treatment of acute leukemias, central nervous system lymphomas, and osteosarcomas.

Hydration and Urinary Alkalinization

Indication	• Maintenance of adequate hydration and urine output is essential for appropriate and rapid clearance of MTX. • MTX may precipitate in an acidic environment and has a low solubility in urine. As such, patients must be adequately hydrated, and the urine pH must be ≥ 7 prior to MTX infusion initiation.[1] ○ Methotrexate and its metabolites, including 7-OH-methotrexate and 4-deoxy-4-amino-N-10-methylpteroic acid (DAMPA), are poorly soluble at an acidic pH.[1]
Dose	Initiate the continuous infusion of one of the following alkalinizing IV hydrations agents at 125-150 mL/h. • Sodium bicarbonate 100-150 mEq per liter in dextrose 5% water or sterile water • Sodium acetate 150 mEq per liter in dextrose 5% water or sterile water • Sodium bicarbonate po 650 mg/m2 every 6 hours with lactated ringer (LR) at 125-150 mL/hour • Sodium bicarbonate 1 mEq/kg in 50 mL D5W infused over 30 minutes every 4-6 hours
Considerations	• It is recommended to administer at least 2.5 – 3.5 liters/m^2 of intravenous (IV) fluid hydration per day starting 4 to 12 hours prior to anticipated MTX infusion initiation with a goal urine output of ≥150 mL/h. • Consider using oral sodium bicarbonate to achieve urinary alkalinization in patients receiving rituximab given the IV incompatibility between sodium bicarbonate IV solution and rituximab. • It is important to continue to maintain urine pH ≥ 7 until MTX systemically cleared (MTX level ≤0.1 µmol/L or at the discretion of treating MD).

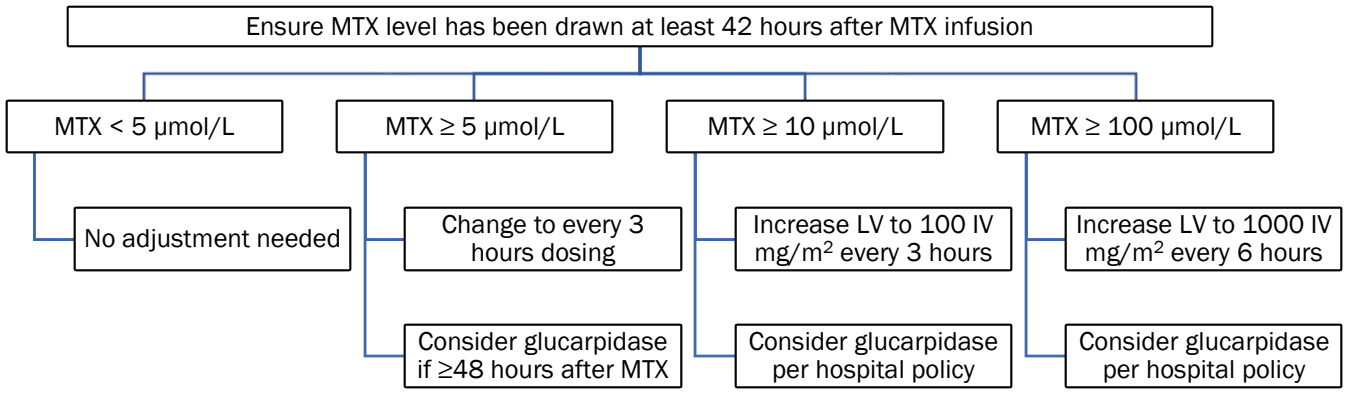
Monitoring

Leucovorin Rescue

A. Leucovorin (LV) is a reduced form of folic acid and an essential coenzyme for nucleic acid synthesis. It can be used to "rescue" cells from methotrexate toxicity.
B. LV does not increase clearance of MTX.

MTX Monitoring

A. The timing of the first MTX level is dependent on the protocol (Appendix B). Typically, the first level should be drawn 24 hours after completion of MTX infusion and continue every 24 hours until MTX clearance (≤0.1 µmol/L or at the discretion of treating MD).
B. MTX levels can be obtained earlier as clinically indicated for any rapid changes in renal function or to facilitate early discharge.
C. Adjust LV based on MTX levels and/or signs of renal toxicity using the following guideline adopted from Howard et al. 2016.[1]



Delayed MTX Clearance

General recommendations for management of delayed MTX clearance

A. Ensure urine alkalinization (pH >7)
B. Optimize hydration
C. Assess extravascular fluid collections
D. Assess potential drug-drug interactions
E. Follow the algorithm outlined above for increased LV administration

Risk factors for delayed MTX clearance

A. Urine pH < 7
B. Less than 3L/m^2 of IV fluid hydration per 24 hours
C. Use of concomitant nephrotoxins (See Appendix A for specific examples)
D. Pre-existing hepatic or renal dysfunction
E. Presence of third space fluid collection

Appendix A: Management of Pertinent Drug Interactions

Drug	Effect	Mechanism	Management
Baricitinib	↑ baricitinib toxicity	Methotrexate may enhance immunosuppressive effects of baricitinib	Avoid concomitant use
Ciprofloxacin	↑ methotrexate toxicity	↓ clearance of methotrexate	Avoid within 24 hours and until MTX clearance
Cisplatin and other nephrotoxic agents	↑ methotrexate toxicity	Synergistic effects; cisplatin also ↓ clearance of methotrexate	Avoid concomitant use or use with caution; monitor levels
Levetiracetam	↑ methotrexate toxicity	↓ clearance of methotrexate	Consider alternative therapy
NSAIDs / COX-2 inhibitors	↑ methotrexate effect	Inhibit renal clearance and tubular secretion of methotrexate	Avoid NSAIDs at least 48 hours prior to MTX and continue to hold until MTX clearance
Penicillins	↑ methotrexate effect	Inhibit renal clearance and tubular secretion of methotrexate	Avoid combination but if taken, hold until MTX clearance
Phenytoin	↑ methotrexate toxicity	Displacement and ↑ bioavailability	Avoid combination but if taken, hold until MTX clearance
Proton Pump Inhibitors	↑ methotrexate effect	Inhibits renal elimination of methotrexate or its metabolite	Avoid combination but if taken, hold until MTX clearance Switch to famotidine until MTX clearance if clinically indicated
Salicylates	↑ methotrexate toxicity	↓ clearance of methotrexate; competes with MTX for tubular secretion	Avoid concomitant use; hold ASA prior to MTX infusion and until clearance
Sulfonamides / Bactrim	↑ methotrexate toxicity	Displacement, ↑ bioavailability, ↓ clearance of methotrexate, and synergistic anti-folate activity	Avoid within 48 hours and until MTX clearance
Sulfonylureas	↑ methotrexate toxicity	Displacement and ↑ bioavailability	Avoid combination but if taken, hold until MTX clearance
Tetracycline	↑ methotrexate toxicity	Displacement and ↑ bioavailability	Avoid combination but if taken, hold until MTX clearance
Thiazide diuretics	Prolonged leukopenia	Unknown	Consider alternative therapy
Azathioprine / Mercaptopurine	↑ thiopurine effect	↓ thiopurine metabolism	Thiopurine dose adjustment is required

Appendix B: High Dose Methotrexate Literature

AUTHOR/ YEAR	MTX DOSE	MTX INFUSION DURATION	LEUCOVORIN RESCUE DOSE	START OF LEUCOVORIN[A]
Acute lymphoblastic leukemia				
Takeuchi 2002	100 mg/m^2 bolus, then 500 mg/m^2 as a 4-hour infusion	4 hours	15 mg every 6 hours for 8 doses	28 hours
Linker 2002	220 mg/m^2 bolus, then 60 mg/m^2 per hr x 36 hours	36 hours	50 mg/m^2 IV every 6 hours for 3 doses, then orally until serum MTX < 0.05 µM	36 hours

Han 2001; Hill 2004	8 g/m^2 (age ≤ 4) 6 g/m^2 (age > 4)	10% bolus, remainder over 23 hours	15 mg/m^2 every 3 hours, then every 6 hours when serum MTX < 2 x 10^6 µM	36 hours
Pui 2004	2 g/m^2	2 hours	10 mg/m^2 every 6 hours	44 hours
Asselin 2011	5 g/m^2 (0.5 g/m^2 bolus over 30 minutes, then 4.5 g/m^2 over 23.5 hours)	24 hours	75 mg/m^2 then 15 mg/m^2 every 6 hours until serum MTX ≤ 0.1 µM	36 hours
Central nervous system Lymphoma				
Ferreri 2009; Joerger 2010	3.5 g/m^2 (0.5 g/m^2 in 15 minutes, then 3 g/m^2 as a 3- hour infusion)	3 hours, 15 minutes	15 mg/m^2 every 6 hours for 12 cycles or until serum MTX levels are undetectable	24 hours
Batchelor 2003	8 g/m^2	4	Pharmacokinetically guided until serum methotrexate < 1 x 10^6 µM	24
Wright 2015	2-5 g/m^2	24	15 mg/m^2 every 6 hours for 5 doses	24
Osteosarcoma				
Souhami 1997	8 g/m^2 (≥ 12 years old) 12 g/m^2 (< 12 years old)	Not specified	12 mg/m^2 IV or 15 mg/m^2 orally every 6 hours for 10 doses	24 hours
Fuchs 1998	12 g/m^2 (maximum 20 g)	Not specified	15 mg/m^2 every 6 hours for 12 doses	Not specified
Bacci 2001	12 g/m^2 (escalate to 14 g/m^2 if 6-hr serum MTX < 1 µM/L)	6 hours	15 mg every 6 hours for 11 doses	24 hours
Goorin 2003	12 g/m^2	4 hours	15 mg every 6 hours for 10 doses	24 hours
Ferreri 2005	12 g/m^2	4 hours	8 mg/m^2 every 6 hours for 11 doses	24 hours
Holmboe 2012	Mean dose, 12 g/m^2 (range, 8-16 g/m^2)	4 hours	Standard dosing until serum MTX ≤ 0.2 µM	24 hours

[A]After start of MTX

Glucarpidase administration

- Glucarpidase is indicated for the treatment of toxic plasma methotrexate concentrations (>1 µM/L) in patients with delayed methotrexate clearance due to impaired renal function.
- Consensus guidelines suggest that optimal glucarpidase administration is within 48 to 60 hours from the start of the high-dose methotrexate infusion (beyond this point, life-threatening toxicities may not be preventable).
- Please refer to "PROCEDURE SYSTEM RXCLIN 163: Pharmacy Consult to Manage Glucarpidase" for more information.

References

1. Howard SC, McCormick J, Pui CH, Buddington RK, Harvey RD. Preventing and Managing Toxicities of High-Dose Methotrexate. *Oncologist*. 2016;21(12):1471-1482. doi:10.1634/theoncologist.2015-0164
2. Takeuchi J, Kyo T, Naito K, et al. Induction therapy by frequent administration of doxorubicin with four other drugs, followed by intensive consolidation and maintenance therapy for adult acute lymphoblastic leukemia: the JALSG-ALL93 study. *Leukemia*. 2002;16:1259-1266.
3. Linker C, Damon L, Ries C, Navarro W. Intensified and shortened cyclical chemotherapy for adult acute lymphoblastic leukemia. *J Clin Oncol*. 2002;20:2464-2471.
4. Hann I, Vora A, Harrison G, et al. Determinants of outcome after intensified therapy of childhood lymphoblastic leukaemia: results from Medical Research Council United Kingdom acute lymphoblastic leukaemia XI protocol. *Br J Haematol*. 2001;113:103-114.
5. Hill FG, Richards S, Gibson B, et al. Successful treatment without cranial radiotherapy of children receiving intensified chemotherapy for acute lymphoblastic leukaemia: results of the risk-stratified randomized central nervous system treatment trial MRC UKALL XI (ISRC TN 16757172). *Br J Haematol*. 2004;124:33-46.
6. Pui CH, Sandlund JT, Pei D, et al. Improved outcome for children with acute lymphoblastic leukemia: results of Total Therapy Study XIIIB at St Jude Children's Research Hospital. *Blood*. 2004;104:2690-2696.
7. Joerger M, Huitema AD, Krahenbuhl S, et al. Methotrexate area under the curve is an important outcome predictor in patients with primary CNS lymphoma: a pharmacokinetic-pharmacodynamic analysis from the IELSG no. 20 trial. *Br J Cancer*. 2010;102:673-677.
8. Souhami RL, Craft AW, Van der Eijken JW, et al. Randomised trial of two regimens of chemotherapy in operable osteosarcoma: a study of the European Osteosarcoma Intergroup. *Lancet*. 1997;350:911-917.
9. Fuchs N, Bielack SS, Epler D, et al. Long-term results of the co-operative German-Austrian-Swiss osteosarcoma study group's protocol COSS-86 of intensive multidrug chemotherapy and surgery for osteosarcoma of the limbs. *Ann Oncol*. 1998;9:893-899.

10. Bacci G, Briccoli A, Ferrari S, et al. Neoadjuvant chemotherapy for osteosarcoma of the extremity: long-term results of the Rizzoli's 4th protocol. *Eur J Cancer*. 2001;37:2030-2039.
11. Goorin AM, Schwartzentruber DJ, Devidas M, et al. Presurgical chemotherapy compared with immediate surgery and adjuvant chemotherapy for nonmetastatic osteosarcoma: Pediatric Oncology Group Study POG-8651. *J Clin Oncol*. 2003;21:1574-1580.
12. Ferrari S, Smeland S, Mercuri M, et al. Neoadjuvant chemotherapy with high-dose Ifosfamide, high-dose methotrexate, cisplatin, and doxorubicin for patients with localized osteosarcoma of the extremity: a joint study by the Italian and Scandinavian Sarcoma Groups. *J Clin Oncol*. 2005;23:8845-8852.
13. Holmboe L, Andersen AM, Morkrid L, et al. High dose methotrexate chemotherapy: pharmacokinetics, folate and toxicity in osteosarcoma patients. *Br J Haematol*. 2012;73:106-114.
14. Asselin BL, Devidas M, Wang C, et al. Effectiveness of high-dose methotrexate in T-cell lymphoblastic leukemia and advanced-stage lymphoblastic lymphoma: a randomized study by the Children's Oncology Group (POG 9404). *Blood*. 2011;118:874-883.
15. Ferreri AJ, Reni M, Foppoli M, et al. High-dose cytarabine plus high-dose methotrexate versus high-dose methotrexate alone in patients with primary CNS lymphoma: a randomised phase 2 trial. *Lancet*. 2009;374:1512-1520