The Oncologist
The official journal of the Society for Translational Oncology

Supplemental Tables for:
Consensus Guideline for Use of Glucarpidase in Patients with High-Dose Methotrexate Induced Acute Kidney Injury and Delayed Methotrexate Clearance
Laura B. Ramsey et al.

Table S1. Methotrexate levels in pediatric patients at specified times after the start of the HDMTX infusion.

	3g/m² 3h infusion			1-3g/m² 24h infusion			4g/m² 24h infusion			5g/m² 24h infusion			>8-9g/m² 4h infusion			10-14g/m² 4h infusion		
	N	Mean conc.	>2 SD	N	Mean conc.	>2 SD	N	Mean conc.	>2 SD	N	Mean conc.	>2 SD	N	Mean conc.	>2 SD	N	Mean conc.	>2 SD
24h	[b]87	[b]1.17	[b]3.95	[b]43	[b]26.9	[b]81.6	[b]42	[b]57.8	[b]103.0	[a]784 [b]395	[a]109 [b]75.4	[a]206 [b]152.8	[b]73	[b]5.47	[b]29.7	[b]269	[b]8.6	[b]60.1
36h										[a]790	[a]2.9	[a]11.9						
42h										[a]784 [b]400	[a]1.4 [b]0.99	[a]6.9 [b]3.7						
48h	[b]89	[b]0.17	[b]0.69	[b]40	[b]0.38	[b]1.78	[b]42	[b]0.48	[b]2.12	[a]776 [b]406	[a]0.8 [b]0.49	[a]4.4 [b]2.23	[b]73	[b]0.28	[b]0.85	[b]267	[b]0.38	[b]2.1
60h										[a]562	[a]0.46	[a]1.9						
72h	[b]35	[b]0.11	[b]0.41	[b]8	[b]0.11	[b]0.30	[b]21	[b]0.16	[b]0.75	[a]237 [b]207	[a]0.50 [b]0.14	[a]2.0 [b]0.63	[b]56	[b]0.12	[b]0.34	[b]249	[b]0.11	[b]0.46

Pediatric MTX pharmacokinetic data adapted from [a]NOPHO ALL-2008 data[1, 2] and [b]Cincinnati Children's Hospital Medical Center unpublished data. Other resources of pediatric methotrexate pharmacokinetic data available include St. Jude Children's Research Hospital data[3] (http://mtx.stjude.org) and Children's Oncology Group data[4]. N, number of subjects analyzed at each dose and time point. Conc, concentration tested by immunoassay. SD, standard deviation. >2SD, the MTX concentration that is equal to the 97.7th percentile, which is 2 standard deviations above the mean.

Table S2. Methotrexate levels in adult patients at 24, 48 and 72h after the start of the HDMTX infusion.

	1-2g/m2			>2-3g/m2			>3-4g/m2			>4-6g/m2			>6g/m2		
	N	Mean conc.	>2SD	N	Mean conc.	>2SD	N	Mean conc.	>2SD	N	Mean conc.	>2SD	N	Mean conc.	>2 SD
24h	18	4.14	19.7	46	11.39	42.17	313	7.61	62.95	41	3.67	20.09	65	8.59	50.39
48h	18	0.24	0.76	47	0.62	1.6368	320	0.77	6.71	42	0.62	6.62	65	1.31	13.27
72h	17	0.11	0.43	38	0.30	1.48	265	0.40	4.6	28	0.09	0.23	56	0.40	3.1

Adult MTX pharmacokinetic data adapted from May et al after a 3-4 hour MTX infusion.[5] N, number of subjects analyzed at each dose and time point. Conc, concentration tested by immunoassay. SD, standard deviation. >2SD, the MTX level that is equal to the mean plus 2 standard deviations.

The Oncologist
The official journal of the Society for Translational Oncology

Supplemental Tables for:
Consensus Guideline for Use of Glucarpidase in Patients with High-Dose Methotrexate Induced Acute Kidney Injury and Delayed Methotrexate Clearance
Laura B. Ramsey et al.

Table S3. Standard Supportive Care Measures for HDMTX Therapy

	Measure	Rationale	Recommendation	Ref
Prior to HDMTX	Urine alkalinization	To maintain solubility of MTX in renal tubules	Increase urine pH to ≥7 and specific gravity ≤1.010 prior start of the MTX infusion	[6]
	Prehydration	To maintain solubility of MTX in renal tubules	Start hydration at least 4 h prior to start of the MTX infusion	[6]
During HDMTX Infusion	Urine alkalinization	To maintain solubility of MTX in renal tubules	Maintain urine pH above 7 and specific gravity ≤1.010	[6]
	Hyperhydration	To maintain solubility of MTX in renal tubules	Maintain continuous i.v. hyperhydration without interruption (≥2.5L/m^2 body surface area in 24 h)	[6]
	Restrict co-medications	To avoid kidney injury and delayed MTX elimination	Evaluate comedications and avoid those with an adverse MTX interaction	[7-10]
After HDMTX	Urine alkalinization	To maintain solubility of MTX in renal tubules	Maintain urine pH above 7 until MTX concentration is <10 µM	[6]
	Hyperhydration	To maintain solubility of MTX in renal tubules	Maintain continuous i.v. hyperhydration without interruption (≥2.5L/m^2 body surface area in 24 h) until MTX concentration is <10 µM	[6]
	Monitor plasma MTX concentrations	To recognize delayed MTX elimination and to guide leucovorin dosing	Monitor plasma MTX concentrations at least from the end of the MTX infusion until MTX concentrations are below threshold according to treatment protocols (commonly <0.1 µM).	[11]
	Monitor serum creatinine	To recognize early kidney injury	Compare serum creatinine to baseline	
	Leucovorin rescue	To prevent MTX toxicity	Leucovorin rescue is imperative and doses should be adapted to MTX concentrations according to treatment protocols	[11-13]

The Oncologist
The official journal of the Society for Translational Oncology

References

1 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 Chemotherapy and Pharmacology 2003;51:311-320.
2 Svahn T, Mellgren K, Harila-Saari A, et al. Delayed elimination of high-dose methotrexate and use of carboxypeptidase g2 in pediatric patients during treatment for acute lymphoblastic leukemia. Pediatr Blood Cancer 2016
3 Ramsey LB, Bruun GH, Yang W, et al. Rare versus common variants in pharmacogenetics: Slco1b1 variation and methotrexate disposition. Genome Research 2012;22:1-8.
4 Ramsey LB, Panetta JC, Smith C, et al. Genome-wide study of methotrexate clearance replicates SLCO1B1. Blood 2013;121:898-904.
5 May J, Carson KR, Butler S, et al. High incidence of methotrexate associated renal toxicity in patients with lymphoma: A retrospective analysis. Leukemia & Lymphoma 2014;55:1345-1349.
6 Sasaki K, Tanaka J, Fujimoto T. Theoretically required urinary flow during high-dose methotrexate infusion. Cancer Chemother Pharmacol 1984;13:9-13.
7 Ronchera CL, Hernandez T, Peris JE, et al. Pharmacokinetic interaction between high-dose methotrexate and amoxycillin. Ther Drug Monit 1993;15:375-379.
8 Thyss A, Milano G, Kubar J, et al. Clinical and pharmacokinetic evidence of a life-threatening interaction between methotrexate and ketoprofen. Lancet 1986;1:256-258.
9 de Miguel D, García-Suárez J, Martín Y, et al. Severe acute renal failure following high-dose methotrexate therapy in adults with haematological malignancies: A significant number result from unrecognized co-administration of several drugs. Nephrology Dialysis Transplantation 2008;23:3762-3766.
10 Troger U, Stotzel B, Martens-Lobenhoffer J, et al. Drug points: Severe myalgia from an interaction between treatments with pantoprazole and methotrexate. BMJ 2002;324:1497.
11 Messmann R and Allegra C. Antifolates: Lippincott Williams & Wilkins, PA, USA, 2001, 139-184.
12 Skärby TC, 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;20:1955-1962.
13 Cohen IJ. Progression of osteosarcoma after high-dose methotrexate: Over-rescue by folinic acid. Pediatr Hematol Oncol 2003;20:579-581.