Bedside treatment algorithm for safe administration of 24-hour high-dose methotrexate in adult acute lymphoblastic leukemia

Therapeutic drug monitoring (TDM) including within-cycle dose adjustment of high-dose methotrexate (HD-MTX), has been described in pediatric acute lymphoblastic leukemia (ALL),[1-3] but has, to our knowledge, not been previously reported for adults with ALL. We developed and implemented a bedside dosing algorithm that facilitated safe administration of HD-MTX achieving therapeutic plasma concentrations while reducing the risk of nephrotoxicity, over-rescue with folinic acid and prolonged hospitalization. HD-MTX remains an important component of therapy in the era of new treatments for ALL, owing to its proven efficacy and central nervous system (CNS) penetration. While generally well tolerated, the treatment is associated with significant inter- and intra-individual variability in drug excretion, resulting in challenges for safe and effective dosing. Plasma MTX concentration monitoring is routinely used to guide folinic acid rescue and to determine the need for glucarpidase in cases of delayed excretion or nephrotoxicity.

The aim of this study was to develop, implement and evaluate a bedside decision tool consisting of an algorithm for optimized HD-MTX administration in adult ALL. The algorithm was designed to enable safe and individualized administration of the drug to achieve target steady-state plasma concentrations (20-80 µM), with the possibility of within-cycle dose adjustment for high steady state concentrations.

We conducted a single-center study at Uppsala University Hospital including adult ALL patients aged 18-55 years treated according to Swedish national guidelines including pediatric protocols, mainly NOPHO ALL 2008,[4] with dose reductions for patients older than 45 years. HD-MTX was defined as 1.5-5 g/m^2 and, in most patients, was given with mercaptopurine and intrathecal therapy. HD-MTX was administered over 24 hours (h), with 10% of the dose given during the first hour. All patients received standard supportive care with intravenous hydration (≥3,000 mL/m^2), sodium bicarbonate for urine alkalization, and folinic

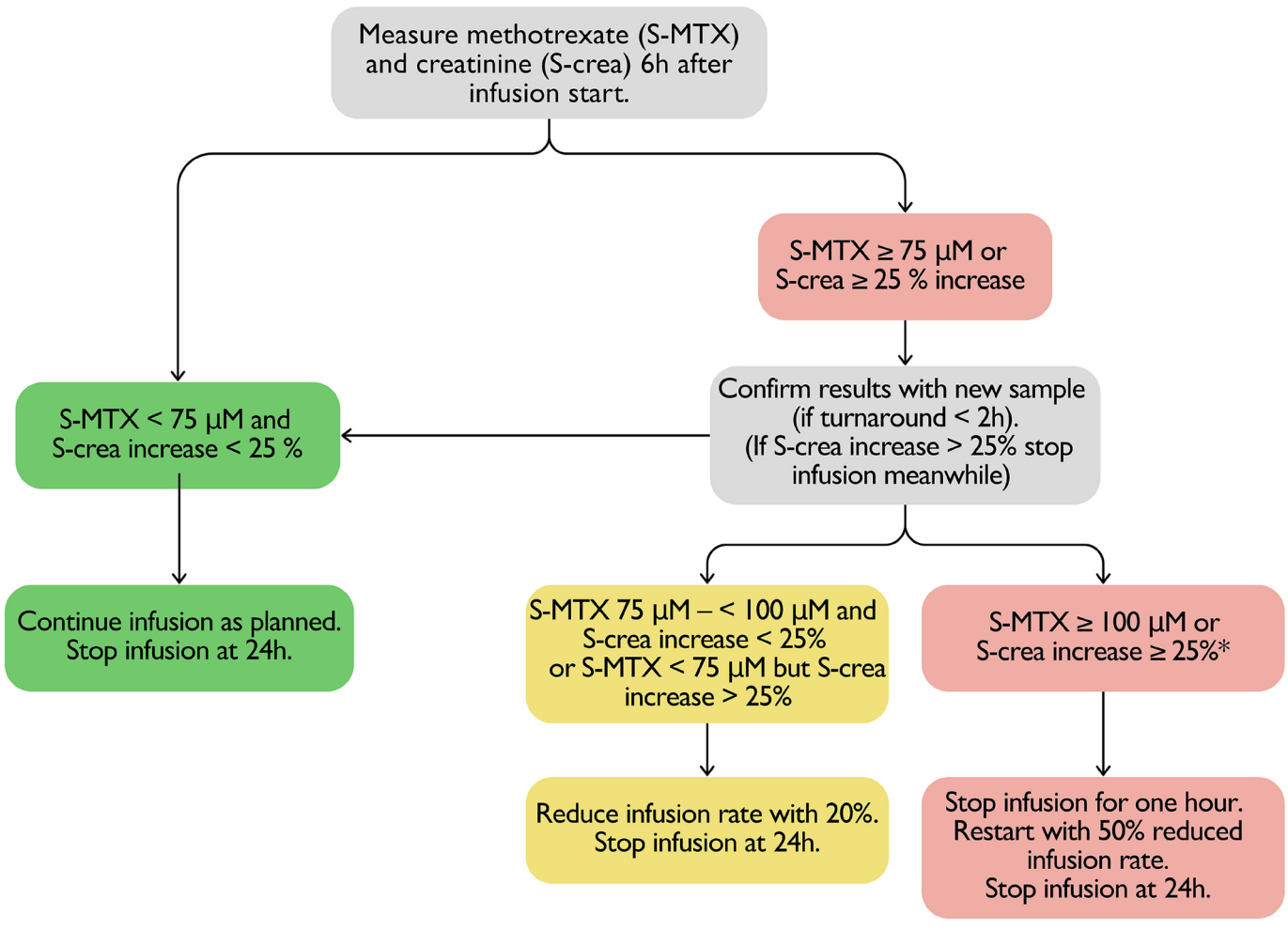


Figure 1. Schematic diagram of the dosing algorithm. Dosing algorithm for high-dose methotrexate (HD-MTX) in adult acute lymphoblastic leukemia. *If both S-MTX >100 µM and S-creatinine increase ≥25%, infusion could be stopped prematurely at the physician's discretion. The algorithm was used under the condition that urine production was >800 mL/4 hours (h) and urine pH ≥7.

acid rescue starting at 42 h.

In the first part of the study, from July 2015 to December 2018, data were collected from 17 patients receiving a total of 78 cycles of HD-MTX. Plasma MTX concentrations were measured 23 h after the start of infusion, at 36 h, and every 6 h thereafter until MTX-levels were <0.2 μM, and S-creatinine was measured starting at 36 h. From February 2017 to December 2018, extra samples for MTX and S-creatinine were collected at 2 and 6 h after the start of infusion, covering 27 of the 78 cycles included in the first part of the study. Although dose modifications based on samples at 2 and 6 h were not suggested, they were allowed at the treating physician's discretion.

These collected data were used to develop a bedside decision tool for dose reduction (Figure 1) in case of concentrations >75 μM at the 6-h sample. The tool was adapted from a previously published pediatric algorithm.[1-3] Steady state was generally not reached at 2 h but was typically attained at 6 h, and increased creatinine levels could not be detected at 2 h. Consequently, the 6-h time point was selected for use in the second part of the study.

In the second part, starting in March 2019, the algorithm (Figure 1) was introduced into clinical routine. Data were collected through December 2023, covering 23 adult ALL patients and a total of 106 HD-MTX cycles. To evaluate safety, the following were recorded: delayed excretion (defined as >1 μM at 42 h[2]), acute kidney injury (per KDIGO criteria[5]), total dose of folinic acid per treatment cycle, and glucarpidase administration. The time to MTX concentration <0.2 μM was used as a surrogate marker for hospital discharge. The decision tool permitted only dose reductions and was not intended to achieve higher plasma concentrations.

Categorical variables were compared using the χ^2 and Fisher's exact tests, means were compared using one-tailed *t* test, and $P<0.05$ was considered statistically significant. Statistical analyses were performed with MedCalc (www.medcalc.org). Ethical approvals were obtained for all parts of the study (EPN Dnr 2017/399, 2017-399-1B and 2020-06323). Informed consent was obtained from all patients providing extra samples before the algorithm was introduced into clinical routine, in accordance with the ethical approvals.

All patients who received a planned HD-MTX dose of 1.5-5 g/m² as a 24-h infusion were included in the comparison between non-TDM-guided treatment (Part 1) and the algorithm-guided treatment (Part 2). In total, 40 patients and 184 HD-MTX treatment cycles were evaluated. Use of the treatment algorithm resulted in no change in dosage in 69% of cycles (73/106), a recommended 20% reduction in 23% (25/106), and a 50% reduction in 8% (8/106). Dose reductions were more common in patients <46 years of age (treated according to protocols prescribing mainly 5g/m²). Reductions were recommended in 50% (28/56) of cycles: a 20% reduction in 38% (21/56) and a 50% reduction in 12% (7/56). A similar trend was seen when looking at patients with a prescribed dose ≥ 4 g/m², irrespective of patient age (*Online Supplementary Table S1*). Dose reductions were applied during the final 12-14 h of the infusion due to turnaround time for the 6-h samples and confirmatory samples (Figure 1). After algorithm implementation, there was a non-significant trend toward higher planned mean doses among patients aged <46 years (Table 1).

The target of MTX 20-80 μM was achieved at 23 h in 81% of algorithm-guided cycles, compared to 68% before implementing the decision tool. Values above target occurred in 17% and 29% of cycles, respectively, while 2% and 3%, respectively, were below target (prescribed dosage 1.5 g/m²), supporting the conclusion that the algorithm did not increase the risk of subtherapeutic concentrations (Figure 2). The safety evaluation showed that the incidence of delayed

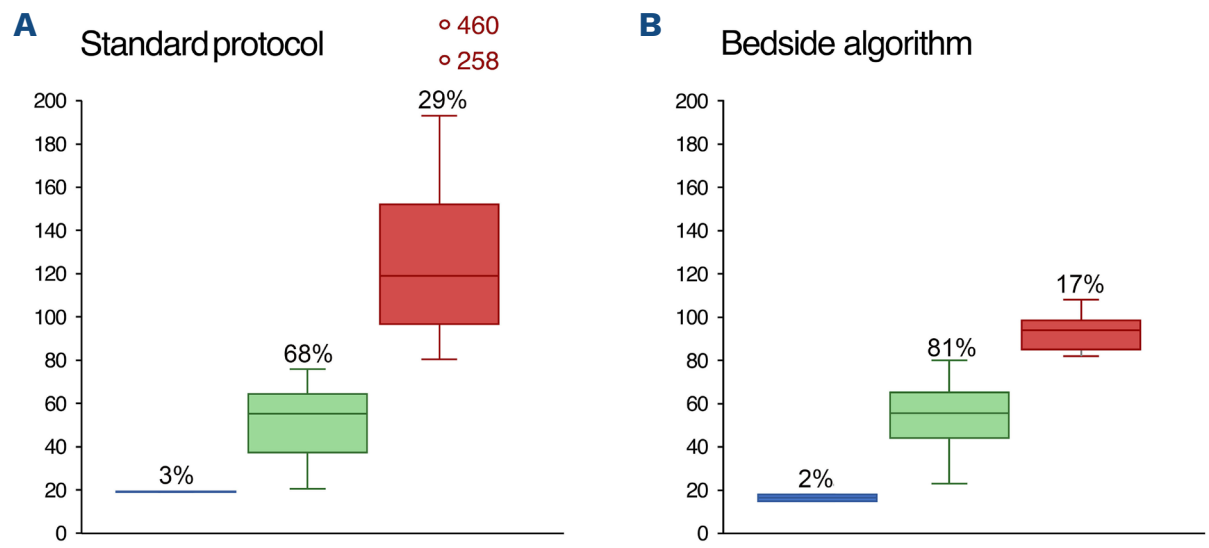


Figure 2. Box plots comparing target attainment in treatment cycles with and without the bedside algorithm. Box plots showing (A) standard and (B) bedside algorithm groups. Box plots represent treatment cycles with steady-state concentrations of methotrexate below (C_{23h} <20 μM; in blue), within (C_{23h} 20-80 μM; in green) and above (C_{23h} >80 μM; in red) target. There is a non-significant trend towards improved target attainment (81% *vs*. 68%) and fewer cycles above target (17% *vs*. 29%) (P=0.1, Fishers exact test). The standard group included two outliers with C_{23h} at 258 and 460 μM, respectively. Treatment cycles with C_{23h} <20 μM (2 cycles per group) used a low dose (1.5 g/m²) which was not further reduced by the algorithm.

excretion (MTX >1 μM at 42 h) and acute kidney injury was significantly lower in the algorithm-guided group compared with non-TDM-guided treatment (*P*< 0.01) (Table 1). The median time to MTX <0.2 μM was also significantly shorter in the algorithm group (*P*<0.01) after excluding one cycle in which the algorithm was not followed (Table 1, *Online Supplementary Figures S1, S2*). Despite use of the algorithm, 4% of cycles (4/106) exceeded 84 h to reach <0.2 μM, compared with 12% (9/78) with non-TDM-guided treatment (*Online Supplementary Figure S1*).

Inadequate urine alkalinization (pH <7), significant weight gain despite use of loop diuretics, and one case with concomitant omeprazole use were identified as possible contributing factors to delayed excretion.

By using this TDM-based bedside algorithm, we achieved safer HD-MTX administration with lower rates of renal toxicity, no use of glucarpidase, and shorter hospital stays. HD-MTX remains an important component in ALL treatment in the modern era, offering the advantage of reaching extramedullary compartments. The dose calculated per body surface area is typically given as a 24-h infusion, and pre-existing kidney failure may constitute a contraindication to treatment. In adult ALL, dosing recommendations vary between protocols and age groups, but the dose is seldom individualized within a treatment cycle to achieve a target concentration or area under the curve (AUC), as has been suggested for pediatric ALL.[6,7]

In this study of adult ALL patients, we selected a conservative upper threshold (>75 μM at 6 h) for dose reduction.[1] While pediatric studies have suggested target steady-state concentrations of >20 μM,[7] 65 μM,[8] or 50-80 μM,[2] a recent Chinese guideline for adult ALL proposed a range of 16-40 μM.[9] Information on optimal plasma concentrations for treating CNS disease in ALL remains limited across all age groups and might be further complicated by only moderate correlation between plasma and cerebrospinal fluid concentrations.[10,11]

A known complication of excessive folinic acid rescue is hypercalcemia, which can be fatal. Moreover, excessive folinic acid may reduce the efficacy of subsequent MTX cycles, and previous research has linked high folinic acid exposure to increased relapse risk.[12] In addition, for patients who develop kidney failure and delayed MTX excretion, further leukemia treatment may be compromised, both due

Table 1. Patient characteristics and main study outcomes related to safety.

Patient characteristics and outcomes	Non-TDM group 78 treatment cycles		Bedside algorithm 106 treatment cycles		*P*
	<46 y N=12 55 cycles	46–55 y N=5 23 cycles	<46 y N=15 56 cycles	46–55 y N=8 50 cycles	
Age, y, median (range)	25.0 (19.5-43.6)	48.6 (47.5-54.5)	31.1 (19.6-41.8)	50.6 (46.0-54.4)	0.6
Sex, male/female, N	8/4	2/3	8/7	4/4	NA
MTX-dose, g/m2, mean±SD (range) ¤Prescribed §Administered	3.8±1.1¤ (1.8-5.3) -	2.6±0.6¤ (1.8-4.6) -	4.3±0.9¤ (1.5-5.1) 4.0±0.8§ (1.3-5.1)	2.6±0.8¤ (1.5-4.7) 2.5±0.7§ (1.3-4.1)	<46 y 0.25 46-55 y 0.62
Delayed excretion, >1 μM at 42 h, % (fraction of cycles)	44 (34/78)		19 (20/106)		<0.01*
Acute kidney injury, all, % (fraction of cycles) Stage 1 Stage 2 Stage 3	18 (14/78) 14.1 (11/78) 2.6 (2/78) 1.3 (1/78)		4.7 (5/106) 3.8 (4/106) 0.9 (1/106) 0 (0/106)		<0.01*
Glucarpidase use, % (fraction of cycles)	2.6 (2/78)		0 (0/106)		NA
Time, h to MTX <0.2 μM, median (range), mean±SD	60 (42-216) 71±33		57 (42-204) 61±19 55 (42-132)# 60±13#		<0.05§ <0.01§
Folinic acid dose per cycle, mg, median (range), mean+SD All cycles Only cycles with delayed excretion	 133 (45-5,328) 421±1,000 276 (165-5,328) 845±1,415		 101 (47-2,710) 167±278 272 (141-2,710) 385±492		 <0.05 0.11

#Excluding one patient in whom the dose revision algorithm was not adhered to: algorithm recommended 50% reduction of infusion rate due to >25% increase in S-Crea at 6 hours (h). *X^2 test. §One-tailed *t* test. MTX: methotrexate; N: number; NA: not available; SD: standard deviation; TDM: therapeutic drug monitoring; y: year.

to treatment delays and because additional MTX cycles may be withheld.

Despite algorithm implementation, some patients still experienced delayed excretion. Monitoring urine alkalinization, vigilant urine pH adjustments, attention to concomitant medications and the presence of third-space fluid remains crucial. As a secondary observation, we noted a trend towards higher administered MTX doses after algorithm implementation. Previously, physicians occasionally reduced the MTX dose following a treatment course with delayed excretion. We hypothesize that the bedside algorithm provided confidence to maintain adequate dosing, with the knowledge that within-cycle adjustment could be made if needed.

In conclusion, implementation of a bedside MTX dosing algorithm facilitated safer administration of HD-MTX in adult ALL patients, achieving therapeutic plasma concentrations while reducing the risk of nephrotoxicity, over-rescue with folinic acid, and prolonged hospitalization. The main limitations of this study are the single-center design and predominantly Nordic population. The findings should, therefore, be interpreted within this context and confirmatory studies are necessary. With these precautions, the algorithm is applicable in routine care in similar populations of young patients, provided timely access to plasma MTX concentrations with turnaround times of less than two hours. Further research is needed to better define the optimal MTX target range in adult ALL and to refine dose individualization strategies.

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Contributions

A-KH is responsible for study concept, methodology, formal analysis, and writing, reviewing and editing the manuscript; JS and EBL are responsible for writing, reviewing and editing the manuscript; HH is responsible for study concept, methodology, and writing, reviewing and editing the manuscript. All authors have read and agreed to the final version of the manuscript for publication.

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Data-sharing statement

Original data are available from the corresponding author upon reasonable request.

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