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Title page

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Allopurinol increases DNA-thioguanine nucleotides during maintenance therapy in pediatric acute lymphoblastic leukemia

Authors

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Author Contributions

TE designed the study, obtained necessary approvals in Sweden and was the data manager of the study. RN was responsible for the approval of the study in Finland and was coordinating investigator in Finland. TE and JK extracted and analyzed data and wrote the manuscript. TE, JK, RN, JF, HV, LK and AC provided material and data. KS and MT were responsible for the thiopurine metabolite analyses. All authors reviewed and approved of the final version of the manuscript.

Running Title

Allopurinol increases DNA-TG in pediatric ALL

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Data Availability Statement

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

Trial registration

EudraCT Number: 2016-003409-33
Clinical Trials: NCT03022747

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Authors' disclosures

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Allopurinol can be used during ALL maintenance therapy (MT) to mitigate hepatotoxicity and enable adequate myelosuppression in patients with unfavorable, high-methylating 6-mercaptopurine (6MP) metabolism.[1] In this letter we report from a prospective, before-after trial on 51 pediatric ALL patients without prior signs of unfavorable 6MP metabolism, with data suggesting that allopurinol may enhance efficacy in ALL MT.

6MP is a prodrug that is metabolized in various ways, with thioguanine nucleotides (TGN) considered as the key intermediate metabolites mediating the antileukemic effect through incorporation in the DNA-strand.[2] Levels of DNA-incorporated TGN (DNA-TG) correlate more strongly with event-free survival (EFS) than erythrocyte levels of TGN (e-TGN).[2, 3] Methylated mercaptopurine metabolites (MeMP) are associated with liver toxicity, including transaminitis, nausea and hypoglycemia.[4] Allopurinol is sometimes used in ALL MT in patients with unfavorable, high-methylating 6MP metabolism,[1, 5] clinically characterized by hepatotoxicity and difficulty achieving targeted myelosuppression. In these patients, allopurinol reduces e-MeMP and increases e-TGN. In a prospective study we showed that addition of allopurinol to MT leads to higher e-TGN and lower e-MeMP even in patients without prior severe liver toxicity.[6] In the same study cohort, we now aimed to assess whether allopurinol could improve the efficacy of ALL MT by determining the effect on DNA-TG.

The Allopurinol study included 51 pediatric ALL patients from Sweden and Finland with thiopurine methyl transferase (TPMT) wild-type and without prior significant hepatotoxicity (Suppl. figure 1), treated according to NOPHO ALL-2008 based protocols. Patient characteristics and outcome are shown in suppl. table 1. The study was approved by the Ethics Committee (Dnr 913-16 in Sweden and EETTMK: 52 /2018 in Finland) and the Medical Products Agency of the participating countries (EudraCT-number 2016-003409-33 and NCT03022747).

The study comprised three phases: 12 weeks of standard MT followed by 12 weeks of MT with addition of allopurinol 50 mg/m² and finally 4 weeks of MT without allopurinol.[6] To prevent excessive myelosuppression, the 6MP dose was halved at the start of the allopurinol phase.[5] 6MP dose was thereafter titrated according to standard protocol guidelines.

6MP metabolites (e-TGN, e-MeMP and DNA-TG) were measured at nine predefined timepoints and analyzed at Bonkolab, Copenhagen.
For DNA-TG quantification 1−2 microgram DNA was purified from whole blood and thioguanine measured with ultra-performance liquid chromatography tandem mass spectrometry, as detailed by Jacobsen et al.[7]

A total of 375 DNA-TG measurements were analyzed, during the standard MT phase (n=166), during the allopurinol+MT phase (n=169) and 4 weeks after allopurinol was discontinued (n=40). Mean DNA-TG levels increased rapidly after addition of allopurinol and decreased when allopurinol was discontinued (Figure 1, Table 1). Intraindividual DNA-TG varied substantially, with mean coefficient of variation 32% during standard MT and 38% during the allopurinol phase. We therefore calculated each patient´s median DNA-TG for the different study phases and found a mean increase by 398 fmol/microgram DNA (paired analysis, 95% CI 257–539, p<0.001) when allopurinol was added, followed by a mean decrease by 543 (95% CI 393–692, p<0.001) when discontinued. Compared to historical data from the NOPHO ALL-2008 MT substudy (492 fmol/microgram DNA) and the TEAM-pilot study (530-764 fmol/microgram DNA),[8] the DNA-TG values were higher in our cohort even before adding allopurinol (748) and yet increased to 1251 when allopurinol was added (Table 2). The reason for the high baseline levels in our study is unclear but may partly be explained by the exclusion of patients with previous severe hepatotoxicity possibly indicating unfavorable 6MP metabolism.

As displayed in Figure 1 the increase in mean e-TGN was more rapid than for DNA-TG, reaching a plateau within 4 weeks after addition of allopurinol. In the same period e-MeMP showed a rapid and persistent decrease.

Since e-MeMP has been suggested to inhibit purine synthesis, thereby reducing guanine levels, which compete with TGN for DNA incorporation,[9, 10] there was initial concern that a substantial reduction in e-MeMP following addition of allopurinol might compromise DNA incorporation of TGN. We therefore calculated the DNA-TG/e-TGN ratio for each patient (Table 1). A low ratio would indicate a reduced DNA incorporation. Although we did see a slightly lower DNA-TG/e-TGN ratio the first weeks after addition of allopurinol, we believe that this merely reflects a natural delay caused by the time required for the metabolic process of integrating TGN into DNA,

rather than inhibition of DNA incorporation due to low e-MeMP. This is supported both by the gradually increasing ratio during the allopurinol phase, to the same levels as before allopurinol despite e-MeMP remaining low, and by the even higher ratio four weeks after truncation of allopurinol, caused by a more pronounced decrease in e-TGN compared to DNA-TG. The DNA-TG/e-TGN ratio was surprisingly high in our study, with mean 3.3 for the whole study period, which is approximately 50% higher than in the whole NOPHO ALL-2008 cohort.[8] The reason why the ratios are higher in our cohort is unclear, but the maintained high ratios indicate that allopurinol does not significantly inhibit the DNA incorporation of TGN, despite lower e-MeMP.

ALL MT treatment is traditionally targeted to a controlled myelosuppression, measured with WBC or ANC values.[11] NOPHO ALL-2008 used WBC for dose titration. As previously published,[6] the mean of all patients' median ANC within each phase declined from 1.6 to 1.3 $\times 10^9$/L (95% CI 1.4–1.8 vs 1.2–1.5, p=0.007) and WBC declined from 3.0 to 2.5 $\times 10^9$/L (95% CI 2.8–3.2 vs 2.3–2.7, p<0.001) when allopurinol was added, whereas the proportion of WBC analyses within the therapeutic target 1.5-3.0$\times 10^9$/L increased from 54% to 65% (95% CI 47–62% vs 58–72%, p=0.01, Table 1).

Despite lower mean ANC, the frequency of SAE (mainly febrile neutropenia) did not increase. This, however, must be interpreted cautiously due to the short intervention period. The total number of transfusions were low with no significant difference in the rate of transfusions between the study phases.

The mean administered 6MP dose, as reported in the patient diary, was 27 mg/m^2/day (95% CI 23–30) during the allopurinol phase, precisely half the reported dose during standard MT (54 mg/m^2/day; 95% CI 48–60). There were more treatment interruptions during the allopurinol phase, affecting 26 patients (34 events) during the allopurinol phase compared to 13 patients (p=0.03) (20 events, p<0.01) during standard MT phase. The number of days with therapy on hold was also higher with allopurinol, 200 out of 4158 (4.8%) patient-days, compared to 92/4284 (2.1%) without (p<0.01).

Treatment interruptions due to myelosuppression were most common during the first six weeks on allopurinol (20 of the 34 events). This may reflect that the 50% dose reduction of 6MP when commencing allopurinol is arbitrary and some

patients need to reduce their 6MP dose more than 50% when starting on allopurinol. The 12 weeks with allopurinol was not long enough to determine if the number of treatment interruptions would decrease with time.

As previously reported,[6] mean ALT decreased gradually from 184 IU/L week 13 (before allopurinol) to 99 IU/L week 25 (p=0.018, Table 1) after 12 weeks of allopurinol, indicating reduced hepatotoxicity.

DNA-TG has been correlated to reduced relapse rate in several studies and meta-analyses,[3, 12] with adjusted hazard ratio (aHR) as low as 0.72 per 100 fmol/microgram increase in DNA-TG in patients MRD-positive at the end of induction (95% CI 0.57−0.91).[12] The 398 fmol/microgram DNA mean increase in DNA-TG achieved in our study suggests that allopurinol could substantially improve EFS.

Compared to the TEAM strategy,[8] aiming to enhance MT efficacy by adding incremental doses of 6-thioguanine, the allopurinol study achieved higher DNA-TG levels and a greater increase. Rather than adding another cytotoxic agent, this strategy modulates thiopurine metabolism, allowing a 50% reduction of the 6MP dose. The approach is also simpler, using a fixed allopurinol dose and standard titration rules for 6MP and MTX.

In a recent retrospective report allopurinol was shown to be an independent prognostic factor for improved EFS in patients who received allopurinol during maintenance therapy compared to those who did not (adjusted hazard ratio = 0.29; 95% CI 0.10–0.80).[13] In that study by Mo et al., allopurinol was administered to patients with laboratory signs of hepatotoxicity during MT. Despite methodological weaknesses, including selection bias and immortal time bias, the findings raise the possibility of an association between allopurinol use and improved outcome.

In this transformative era for ALL therapy, where intense chemotherapy phases are being replaced by targeted antibodies with reduced toxicity,[14] we still believe that MT will remain essential for achieving long-term cure. Allopurinol add-on therapy may both improve tolerability and contribute to an increased efficacy of MT. Our previously published results, with reduced laboratory signs of liver toxicity, decreased e-MeMP and no increase in SAE frequency, suggest that allopurinol add-on treatment is safe and may reduce toxicity, whereas increased e-TGN and better

controlled WBC and ANC points towards enhanced treatment efficacy.[11] The increase in DNA-TG levels reported here, provides further evidence suggesting that allopurinol may lead to a more effective leukemia treatment. This should be evaluated in a future randomized study with endpoints including EFS and quality-of-life measures.

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Table 1. 6MP metabolite levels, hematologic parameters and ALT across all study weeks

	Std MT				MT + allopurinol				Std MT
Study week	w1	w5	w9	w13	w17	w19	w21	w25	w29
DNA-TG									
Mean	735	980	798	963	1216	1233	1301	1288	713
(95% CI)	(521–987)	(818–1261)	(676–1121)	(718–1143)	(921–1707)	(927–1364)	(1082–1795)	(1143–1678)	(510–833)
e-TGN									
Mean	254	282	251	280	485	447	462	440	185
(95% CI)	(209–300)	(247–318)	(217–285)	(235–325)	(424–546)	(383–511)	(383–541)	(379–501)	(161–210)
DNA-TG/ e-TGN - ratio									
Mean	3.2	3.7	3.3	3.6	2.9	3.1	3.5	3.3	3.8
(95% CI)	(2.7–3.7)	(3.2–4.2)	(2.9–3.8)	(3.1–4.2)	(2.1–3.6)	(2.5–3.6)	(2.7–4.3)	(2.7–3.9)	(3.3–4.3)
p-value compared to w13	-	-	-	-	0.04	0.05	0.76	0.27	-
e-MeMP									
Mean	6993	9830	9753	9481	3395	2459	2230	2791	3459
(95% CI)	(4904–9082)	(7718–11943)	(7726–11780)	(7346–11616)	(2397–4393)	(1634–3283)	(1455–3005)	(1868–3714)	(2324–4595)
WBC									
Mean	3.3	3.2	2.7	3.7	2.3	2.4	2.7	2.5	3.7
(95% CI)	(3.0–3.6)	(2.7–3.6)	(2.5–3.0)	(2.7–4.7)	(2.0–2.7)	(2.2–2.7)	(2.4–3.1)	(2.2–2.7)	(3.1–4.3)
1.5–3.0 n/tot (%)	18/48 (38%)	25/49 (51%)	32/48 (67%)	28/49 (57%)	34/45 (76%)	31/49 (63%)	30/47 (64%)	33/45 (73%)	19/45 (42%)
ANC									
Mean	1.8	1.8	1.4	1.9	1.2	1.2	1.5	1.3	2.2
(95% CI)	(1.6–2.1)	(1.4–2.1)	(1.2–1.6)	(1.5–2.3)	(0.9–1.5)	(1.0–1.4)	(1.2–1.8)	(1.1–1.5)	(1.6–2.8)
ALT									
Mean	130	125	170	184	132	129	112	99	110
(95% CI)	(86–175)	(82–167)	(101–240)	(124–245)	(96–169)	(80–177)	(65–160)	(56–141)	(79–140)

Allopurinol was administered throughout study weeks 13–24. Samples collected weeks 17–25 are considered being influenced by allopurinol.

Std MT: Standard maintenance therapy
$1.5–3.0 \times 10^9$/L is target level of white blood cells (WBC) during maintenance therapy in the NOPHO ALL-2008 protocol.
n: number of patients with WBC within target $1.5–3.0 \times 10^9$/L
tot: total number of patients with available WBC data for the corresponding week

Units of measure:
DNA incorporated thioguanine nucleotides (DNA-TG): fmol/microgram DNA
Thioguanine nucleotides in erythrocytes (e-TGN): nmol/mmol Hb
DNA-TG/e-TGN-ratio: (fmol/microgram)/(nmol/mmol)
Methylmercaptopurine nucleotides in erythrocytes (e-MeMP): nmol/mmol Hb
White blood cells (WBC): $\times 10^9$/L
Absolute neutrophil count (ANC): $\times 10^9$/L
Alanine aminotransferase (ALT): IU/L. 60 IU = 1 µkat

Table 2. Mean of patients' median values, in comparison with the TEAM pilot study and the NOPHO ALL-2008 maintenance therapy substudy[8]

	Allopurinol study		TEAM pilot study		NOPHO ALL-2008
	std MT	MT+AP	std MT	MT+TG	MT substudy
DNA-TG fmol/mikrog DNA					
Mean	847	1251	530	764	492
(95% CI)	(728–966)	(1095–1407)	(157–1279)	(273–1402)	(21–1104)
e-TGN nmol/mmol Hb					
Mean	264	458	240	721	231
(95% CI)	(231–297)	(404–512)	(100–485)	(339–1396)	(8–608)
e-MeMP nmol/mmol Hb					
Mean	8878	2366	8462	5931	12032*
(95% CI)	(7169–10587)	(1741–2990)	(177–21520)	(142–14385)	(4577–17383)*
WBC $\times 10^9$/L					
Mean	3.1	2.5	3.1	3.2	2.9
(95% CI)	(2.8–3.2)	(2.3–2.7)	(1.9–5.7)	(2.2–5.5)	(1.7–4.0)
Values within target 1.5–3.0	54%	65%	–	–	–
ANC $\times 10^9$/L					
Mean	1.6	1.3	1.8	1.9	1.6
(95% CI)	(1.4–1.8)	(1.2–1.5)	(0.7–3.7)	(1.0–3.7)	(0.5–2.7)
ALT IU/L					
Mean	136	101	139	118	–
(95% CI)	(97–175)	(77–125)	(26–373)	(20–265)	–
6MP dose mg/m^2/day					
Mean	54	27	53	45	–
(95% CI)	(48–60)	(23–30)	(6–121)	(7–79)	–

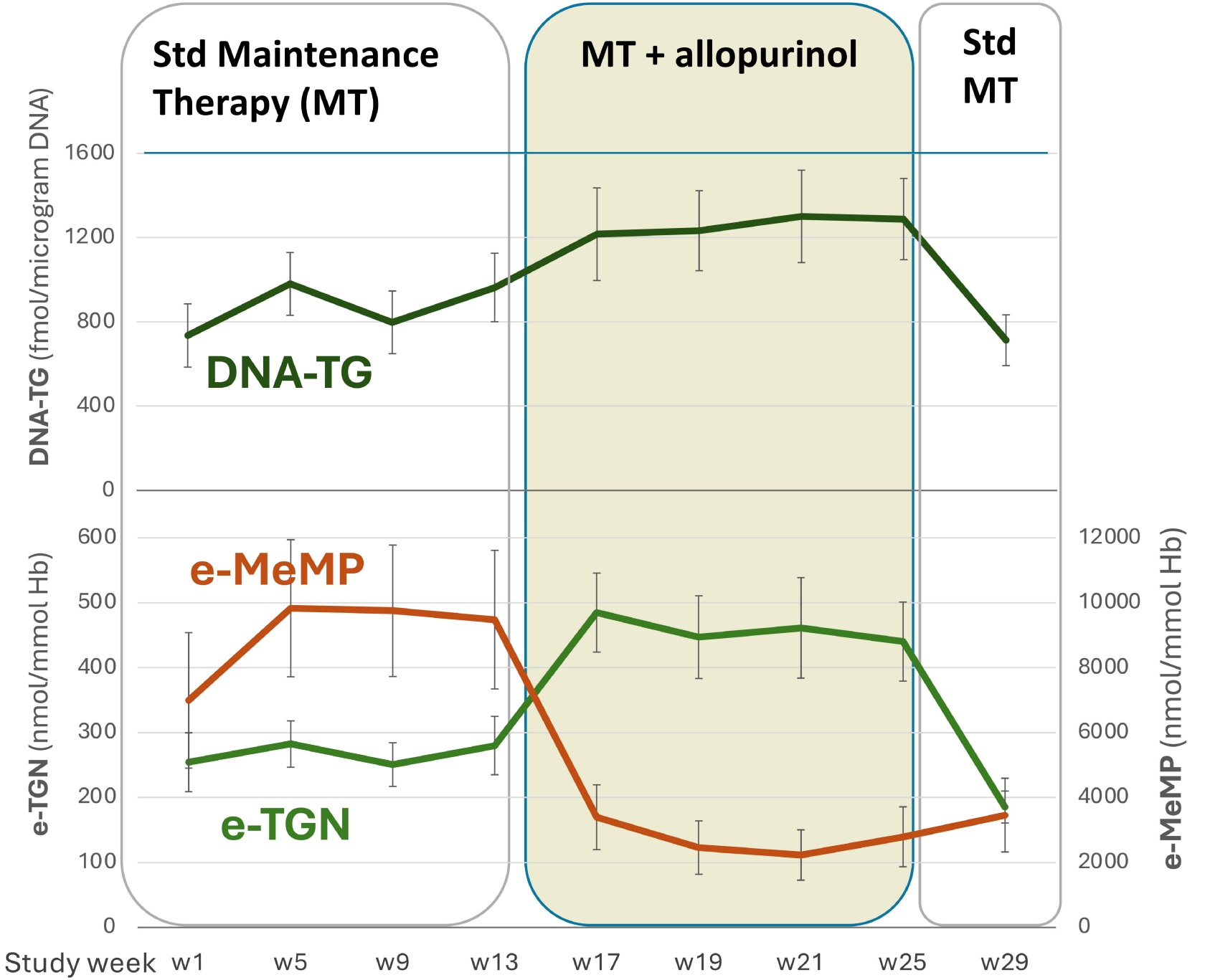
Std MT: Standard maintenance therapy
MT+AP: Maintenance therapy with addition of allopurinol
TEAM: Thiopurine Enhanced ALL Maintenance therapy
MT+TG: Maintenance therapy with addition of thioguanine
NOPHO: The Nordic Society of Paediatric Haematology and Oncology
DNA-TG: DNA incorporated thioguanine nucleotides
e-TGN: thioguanine nucleotides in erythrocytes
e-MeMP: methylmercaptopurine nucleotides in erythrocytes
WBC: white blood cells
ANC: absolute neutrophil count
ALT: alanine aminotransferase
6MP: 6-mercaptopurine

*median of the patients' medians and interquartile range (see TEAM-pilot)[8]

Figure 1. 6-mercaptopurine metabolite levels, means and 95% confidence intervals (error bars) across the different study phases.

Weeks 1–12: Standard maintenance therapy (Std MT) with 6-mercaptopurine and methotrexate.
Weeks 13–24: Maintenance therapy (MT) with addition of allopurinol. 6-mercaptopurine dose reduced by 50% to prevent excessive myelosuppression.
Weeks 25-29: Standard maintenance therapy (Std MT) without allopurinol.
Weeks 17-25 are considered being influenced by allopurinol as samples were collected at the start of the corresponding study week.

DNA-TG: DNA incorporated thioguanine nucleotides
e-TGN: thioguanine nucleotides in erythrocytes
e-MeMP: methylmercaptopurine nucleotides in erythrocytes


Std Maintenance Therapy (MT)
MT + allopurinol
Std MT
DNA-TG (fmol/microgram DNA)
1600
1200
800
400
0
DNA-TG
e-TGN (nmol/mmol Hb)
600
500
400
300
200
100
0
e-MeMP
e-TGN
12000
10000
8000
6000
4000
2000
0
e-MeMP (nmol/mmol Hb)
Study week
w1
w5
w9
w13
w17
w19
w21
w25
w29

SUPPLEMENTARY FILES

Letter to the Editor

Allopurinol increases DNA-thioguanine nucleotides during maintenance therapy in pediatric acute lymphoblastic leukemia

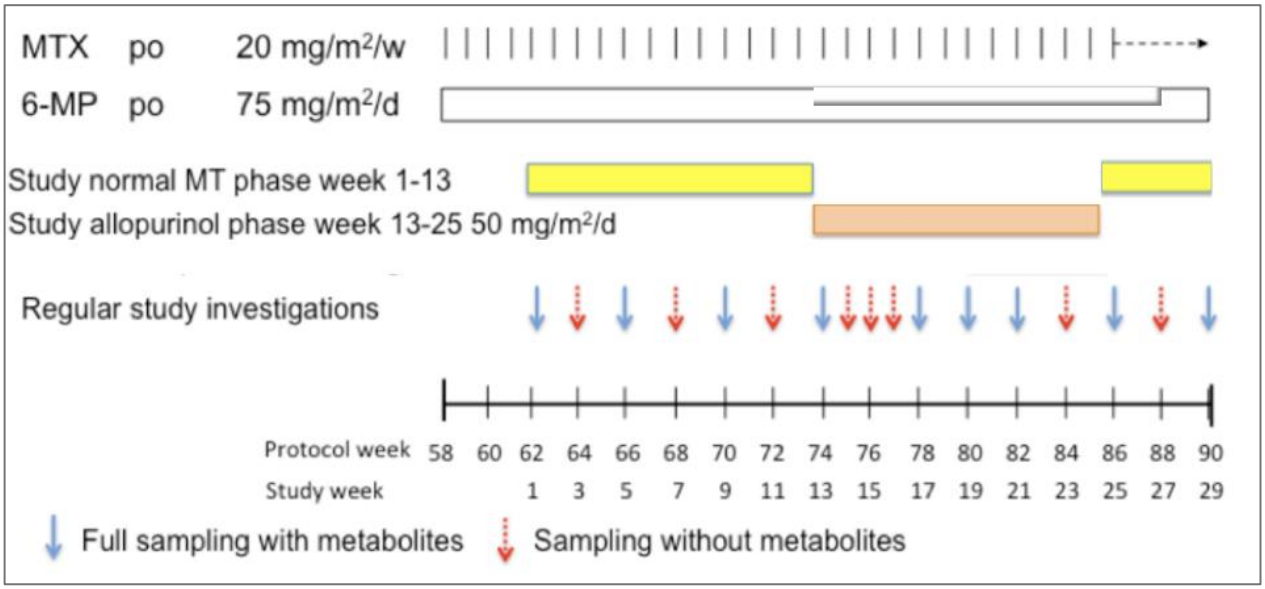
Supplementary table 1. Patient characteristics and outcome

	n	(%)	median	min-max
Age at diagnosis (years)			4	0–15
WBC at diagnosis (x10^9/L)			8.0	0.8–265
Sex				
Female	24	(47)		
Male	27	(53)		
Immunophenotype				
Pre-B	46	(90)		
T	5	(10)		
NCI risk group				
Low risk	38	(75)		
High risk	13	(25)		
Protocol risk group				
NOPHO ALL-2008				
Standard risk	33	(65)		
Intermediate risk	17	(33)		
NOPHO ALL 2014-Infant				
Standard risk	-	-		
Intermediate risk	1	(2)		
Outcome				
Relaps	3	(6)		
Second Malignant Neoplasm	1	(2)		

Characteristics of the 51 patients that commenced the allopurinol study.
Protocol risk group stratification is based on immunophenotype and minimal residual disease (MRD). Patients with PreB and MRD < 0.1% day 29 are stratified to standard risk. The distributions of sex, age, immunophenotype and risk group are consistent with the entire NOPHO ALL-2008 population.
(From our previous publication DOI:10.3324/haematol.2023.284390)

After a median follow-up of 67 months from diagnosis (interquartile range 56–77), three patients experienced bone marrow relapse at 2, 8 and 33 months, respectively, after end of therapy. An additional patient was diagnosed with Hodgkin lymphoma 15 months after completing ALL treatment.

Supplementary figure 1. Overview of the Allopurinol study



The study comprised three phases: 12 weeks of standard maintenance therapy (MT) followed by 12 weeks of MT with addition of allopurinol 50 mg/m^2 and finally 4 weeks of MT without allopurinol. There was an option to increase allopurinol to 100 mg/m^2 after 6 weeks if erythrocyte level of thioguanine nucleotides (e-TGN) was below 200 nmol/mmol Hb, which only applied to 4 patients. To prevent excessive myelosuppression, the 6-mercaptopurine (6MP) dose was halved at the start of the allopurinol phase. 6MP dose was thereafter titrated according to standard protocol guidelines.

Standard MT in the NOPHO ALL 2008 protocol consisted of daily 6MP 75 mg/m^2 and weekly methotrexate (MTX) 20 mg/m^2. Intermediate risk patients also received intrathecal MTX every 8 weeks. Oral 6MP and MTX doses were titrated to reach target white blood cell count (WBC) 1.5–3.0 ×10^9/L with 20% dose increment of both 6MP and MTX if WBC was above target for > 2 weeks and 50% dose reduction if below target. MT was withheld if WBC < 1.0 ×10^9/L or platelets < 50 ×109/L and restarted at 75% of the previous dose when WBC > 1.5 ×10^9/L.