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

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SUPPLEMENTARY FILES

Letter to the Editor

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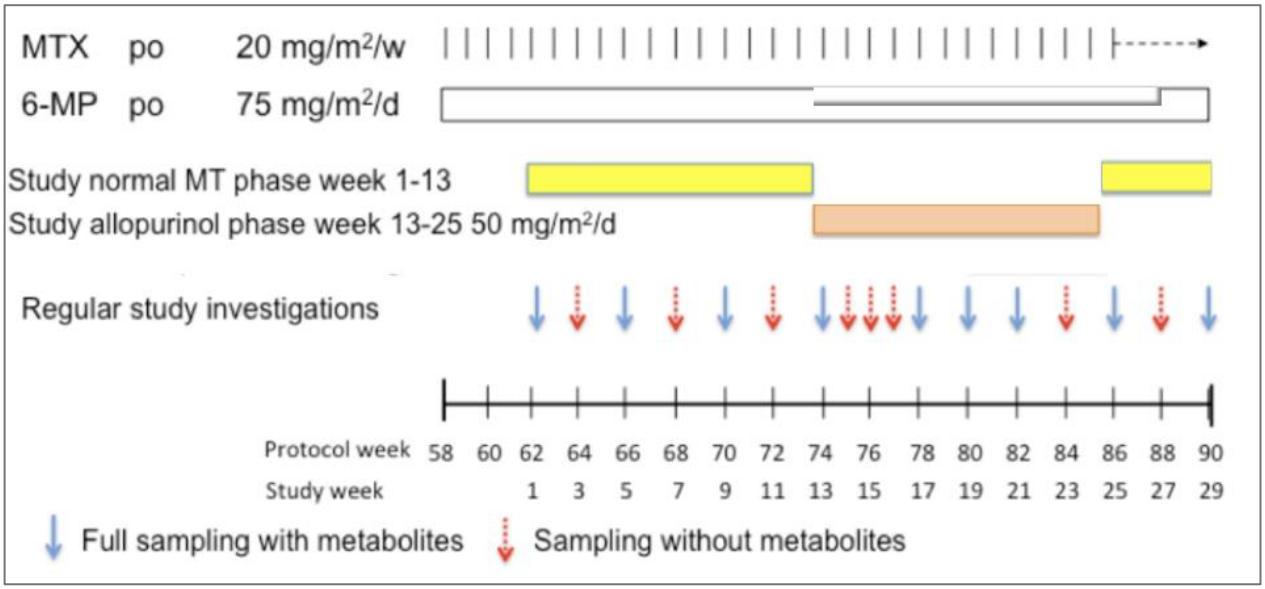
After a median follow-up of 67 months from diagnosis (interquartile range 56–77), three patients experienced bone marrow relapse at 2, 8 and 33 months, respectively, after end of therapy. An additional patient was diagnosed with Hodgkin lymphoma 15 months after completing ALL treatment.

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.