haematologica
Journal of the Ferrata Storti Foundation

From niche to blockbuster: a greater role for allopurinol in maintenance treatment of acute lymphoblastic leukemia

by Martin Stanulla

Received: April 16, 2024.
Accepted: April 29, 2024.

Citation: Martin Stanulla. From niche to blockbuster: a greater role for allopurinol in maintenance treatment of acute lymphoblastic leukemia.
Haematologica. 2024 May 9. doi: 10.3324/haematol.2024.285080 [Epub ahead of print]

Editorial

From niche to blockbuster: a greater role for allopurinol in maintenance treatment of acute lymphoblastic leukemia

Martin Stanulla

Pediatric Hematology and Oncology, Hannover Medical School, Hannover, Germany

Martin Stanulla, MD, MSc
Department of Pediatric Hematology and Oncology
Hannover Medical School
Carl-Neuberg-Str. 1
D-30625 Hannover, Germany
Tel.: +49-511-532-7879
Fax.: +49-511-532-9120
Email: stanulla.martin@mh-hannover.de

Running title: Allopurinol in pediatric ALL

Modern treatment strategies for pediatric acute lymphoblastic leukemia (ALL) are based on important therapeutic elements that are applied sequentially over two to three years and lead to a long-term survival of about 90% (1). Thiopurine drugs (6-mercaptopurine, MP; 6-thioguanine, TG) have played a role in the majority of these elements since the 1950s and are particularly prominent in the maintenance phase (2). MP is currently the thiopurine of choice for maintenance treatment (3).

In this issue of Haematologica, Källström and colleagues report on their study of the effect of allopurinol in pediatric thiopurine S-methyltransferase (*TPMT*) wild-type ALL patients who showed no signs of a shifted unfavorable metabolism of MP during maintenance therapy (4).

As a prodrug, MP is metabolized via three pathways by the enzymes hypoxanthine-guanine phosphoribosyltransferase (HGPRT), thiopurine S-methyltransferase (TPMT) and xanthine oxidase (XO), to form essentially 6-thioguanine nucleotides (TGN), 6-methylmercaptopurine (MMP), 6-methylmercaptopurine nucleotides (MMPN) and 6-thiouracil (TU) (Figure 1) (2,5). TGN are thought to be the major cytotoxic compounds resulting from the metabolism of MP, as they interfere with nucleic acid synthesis and induce cell cycle arrest and apoptosis (2,5). Methylated MP metabolites (MMP, MMPN) are generated by TPMT from MP and from 6-thioinosine monophosphate (TIMP) after MP is metabolized to TIMP by HGPRT. Genetic variation in *TPMT* affects enzyme activity, influencing TGN and methylated MP metabolite levels (5). Patients with low TPMT activity experience higher TGN levels and hematotoxicity but may respond better to treatment. Conversely, high TPMT activity results in lower TGN levels and increased methylated MP metabolites, potentially leading to liver toxicity and reduced therapeutic efficacy. However, TPMT is likely not the only explanation for a shift in metabolism in favor of methylated MP metabolites and the mechanisms behind this require further investigation.

The repeated observations of a prognostically favorable therapeutic effect of high TGN levels and low methylated MP metabolites have led to considerations on how to optimize their ratio. Dose escalation of MP is not expedient, as this was shown to lead to an unfavorable outcome, most likely due to a disproportionate increase in methylated MP metabolites (6). Monotherapy with TG is problematic due to increased liver toxicity and may also be disadvantageous due to lack of formation of methylated MP metabolites which, together with methotrexate, inhibit purine biosynthesis and promote incorporation of phosphorylated TGN into DNA and RNA (3). An interesting but not finally evaluated alternative may be a split dose approach with twice instead of once daily application of MP (7). A reasonable option originates from patients with inflammatory bowel disease (IBD). In IBD patients treated with azathioprine or MP who have an unfavorable ratio of TGN to methylated MP metabolites, the addition of the XO inhibitor allopurinol can lead to a reversal of the unfavorable metabolite ratio, resulting in increased therapeutic efficacy and less liver toxicity (8). Allopurinol may act through elevation of thioxanthine, an intermediate on the path of MP to TU, which was shown to inhibit TPMT. Analogous observations have also been described in ALL patients with unfavorable metabolite ratios, in whom the addition of allopurinol was able to restore adequate myelosuppressive maintenance therapy and reduce liver toxicity and hypoglycemia (9).

Källström and colleagues went one step further in their phase II study by administering allopurinol not only to ALL patients with unfavorable metabolic shift and significant liver toxicity, but to an unselected pediatric cohort of *TPMT* wild-type ALL patients. Eight centers in Sweden and Finland enrolled 51 standard- and intermediate-risk ALL patients, 48 of whom completed the study. Conventional maintenance therapy, MP dose-reduced maintenance therapy with adjunctive allopurinol, and finally again conventional maintenance therapy were given sequentially over a period of 28 weeks. No particular side effects were observed and treatment with allopurinol was well tolerated. The mean TGN levels measured in erythrocytes (e-TGN) increased significantly after addition of allopurinol (280 to 440 nmol/mmol

hemoglobin) and the primary endpoint of e-TGN > 200 nmol/mmol hemoglobin was reached in 91% of patients when on allopurinol compared to 67% on conventional maintenance.

Why are these results important? Higher TGN levels have been associated with a lower relapse risk in pediatric ALL (10). About 90% of ALL patients are *TPMT* wild-type, but only a small proportion of these patients (about 10%) have an unfavorably shifted metabolite ratio of TGN to methylated MP metabolites and develop signs of liver toxicity or hypoglycemia. Therefore, the approach of Källström and colleagues potentially changes the indication for administration of allopurinol from correcting an unfavorable metabolic situation and ensuring adequate therapy use for a smaller group of problematic patients to a broader therapy optimization strategy with the potential to improve the outcome for the majority of pediatric ALL patients.

Another current promising therapy optimization strategy for establishing an improved ratio of TGN and methylated MP metabolites is being tested in the TEAM (Thiopurine Enhanced ALL Maintenance) study which evaluates the addition of low-dose TG to MP/methotrexate-based maintenance therapy against standard maintenance (EudraCT: 2018-001795-38) (10).

Of course, the study of Källström and colleagues is only a beginning and, analogous to the TEAM study, the approach must be carefully evaluated in a randomized clinical trial with much larger numbers of patients. Such an expanded evaluation may answer important questions, such as the potential reduction of leukemia relapses, an associated optimal balance between TGN and methylated MP metabolites, or the identification of patient subgroups with particular benefit from the approach (e.g., patients MRD-positive after induction). Equally important would be a careful assessment of toxicity profiles including observations on rare thiopurine-associated toxicities, such as secondary malignant neoplasms, hepatic sinusoidal obstruction syndrome and others. Another important benefit of the study could be the initiation of further accompanying research in the field of maintenance

treatment of ALL, for example to clarify the hitherto incomplete understanding of the underlying mechanisms of the allopurinol effect.

Overall, the authors can be applauded for having taken an important first step with their study; we look forward to further steps and hope that these can ultimately contribute to improving the quality of treatment for our patients.

References

1. Inaba H, Mullighan CG. Pediatric acute lymphoblastic leukemia. Haematologica. 2020;105(11):2524-2539.

2. Elion GB. The purine path to chemotherapy. Science. 1989;244(4900):41-47.

3. Escherich G, Richards S, Stork LC, Vora AJ; Childhood Acute Lymphoblastic Leukaemia Collaborative Group (CALLCG). Meta-analysis of randomised trials comparing thiopurines in childhood acute lymphoblastic leukaemia. Leukemia. 2011;25(6):953-959.

4. Källström J, Riitta Niinimäki, Johan Fredlund, et al. Effects of allopurinol on 6-mercaptopurine metabolism in unselected patients with pediatric acute lymphoblastic leukemia: a prospective phase II study. Haematologica. xxx

5. Weinshilboum R. Thiopurine pharmacogenetics: clinical and molecular studies of thiopurine methyltransferase. Drug Metab Dispos. 2001;29(4 Pt 2):601-605.

6. Schmiegelow K, Björk O, Glomstein A, et al. Intensification of mercaptopurine/methotrexate maintenance chemotherapy may increase the risk of relapse for some children with acute lymphoblastic leukemia. J Clin Oncol. 2003;21(7):1332-1339.

7. Bell BA, Brockway GN, Shuster JJ, et al. A comparison of red blood cell thiopurine metabolites in children with acute lymphoblastic leukemia who received oral mercaptopurine twice daily or once daily: a Pediatric Oncology Group study (now The Children's Oncology Group). Pediatr Blood Cancer. 2004;43(2):105-109.

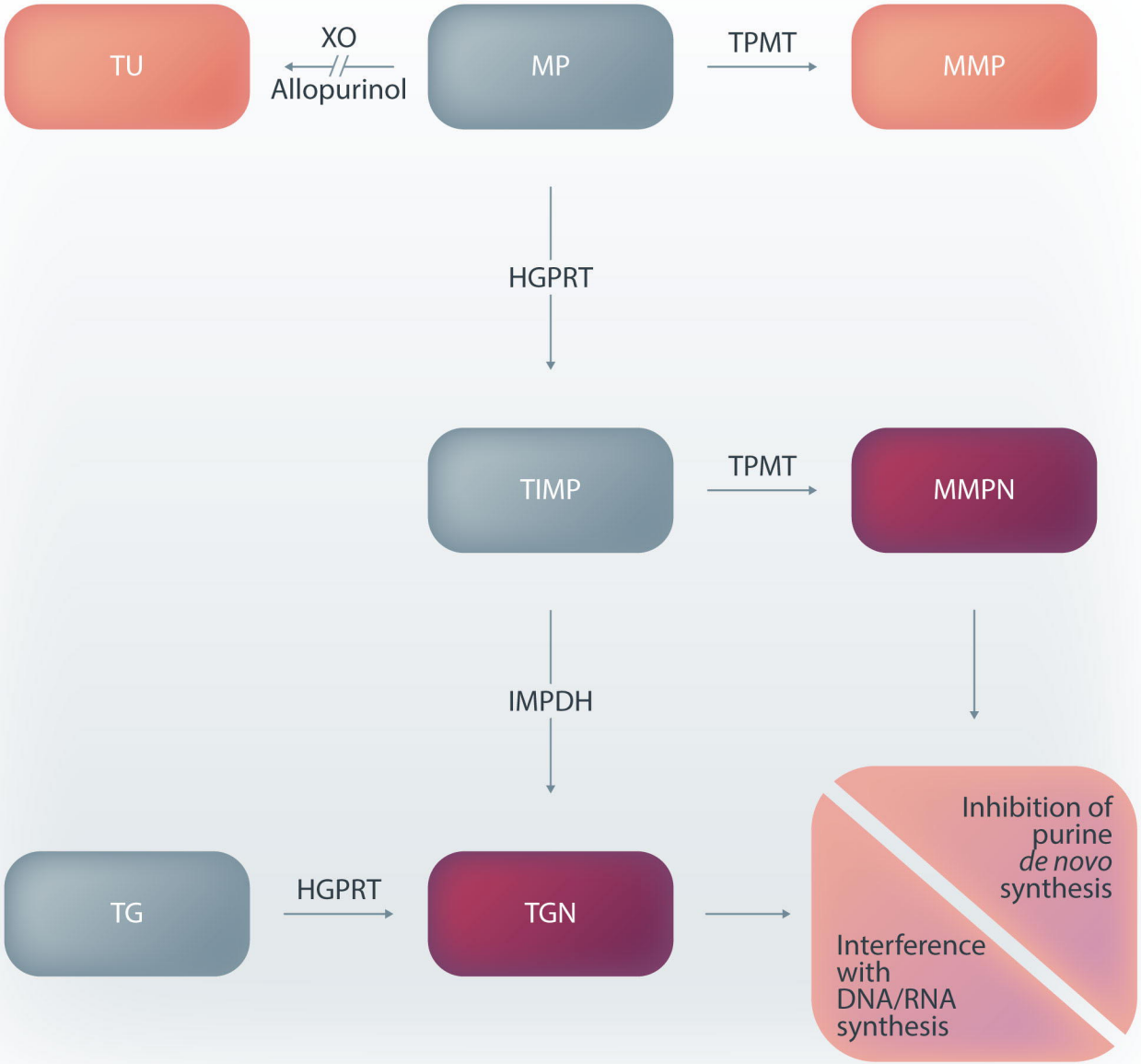
8. Turbayne AK, Sparrow MP. Low-Dose Azathioprine in Combination with Allopurinol: The Past, Present and Future of This Useful Duo. Dig Dis Sci. 2022;67(12):5382-5391.

9. Cohen G, Cooper S, Sison EA, Annesley C, Bhuiyan M, Brown P. Allopurinol use during pediatric acute lymphoblastic leukemia maintenance therapy safely corrects skewed 6-mercaptopurine metabolism, improving inadequate myelosuppression and reducing gastrointestinal toxicity. Pediatr Blood Cancer. 2020;67(11):e28360.

10. Larsen RH, Utke Rank C, Grell K, et al. Increments in DNA-thioguanine level during thiopurine-enhanced maintenance therapy of acute lymphoblastic leukemia. Haematologica. 2021;106(11):2824-2833.

Figure legend:

The prodrug 6-mercaptopurine (MP) is metabolized via three pathways by the enzymes hypoxanthine-guanine phosphoribosyltransferase (HGPRT), thiopurine S-methyltransferase (TPMT) and xanthine oxidase (XO), to essentially form 6-thioguanine nucleotides (TGN), 6-methylmercaptopurine (MMP), 6-methylmercaptopurine nucleotides (MMPN) and 6-thiouracil (TU). TGN are thought to be the major cytotoxic compounds resulting from the metabolism of MP, as they interfere with nucleic acid synthesis and induce cell cycle arrest and apoptosis (2). Methylated MP metabolites (MMP, MMPN) are generated by TPMT from MP and from 6-thioinosine monophosphate (TIMP) after MP is metabolized to TIMP by HGPRT. Methylated MP metabolites do positively correlate with adverse drug effects (e.g., liver toxicity, hypoglycemia) and, in addition, were shown to contribute to thiopurine toxicity by inhibiting purine biosynthesis (MMPN). TU is generally believed to be ineffective. Inosine-5-monophosphate dehydrogenase (IMPDH); 6-thioguanine (TG).


TU
XO
Allopurinol
MP
TPMT
MMP
HGPRT
TIMP
TPMT
MMPN
IMPDH
TG
HGPRT
TGN
Inhibition of purine *de novo* synthesis
Interference with DNA/RNA synthesis