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LETTER TO THE EDITORS

HIGH-DOSE 6-MERCAPTOPURINE INFUSIONS AND TUMOR LYSIS SYNDROME

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We treated five non-Hodgkin lymphoma patients (4–9 years) with one high-dose 6-mercaptopurine infusion (HD-6MP: 1300 mg/m^2 . 24 h) [1] within a therapeutic window at diagnosis. All patients received allopurinol (200 mg/m^2 . d) to prevent urate nephropathy.

The antimetabolite 6MP, an analogue of hypoxanthine, is converted intracellularly into thioIMP by hypoxanthine guanine phosphoribosyltransferase (HGPRT). ThioIMP is converted into thioguanine nucleotides and methylthioIMP (MetIMP). The latter metabolites exhibit cytotoxic effects [2, 3]. 6MP is catabolized by xanthine oxidase into thioxanthine and thiouric acid [2]. Xanthine oxidase is inhibited by allopurinol and its metabolite oxypurinol. 6MP is methylated direct into methyl-6MP. Methyl-6MP-riboside is produced by degradation of MetIMP or methylation of thioinosine.

We investigated the metabolism of HD-6MP in plasma and red blood cells (RBCs) before and at 4, 20, 24, 28 and 48 h after the start of HD-6MP. One patient at diagnosis had a tumor lysis syndrome (TLS), which is characterized by hyperuricaemia, hyperpotassaemia, hyperphosphataemia and hypoalcaemia. Just before start of HD-6MP serum uric acid and potassium levels had normalized and phosphate was 2.4 mM (normal 1.3–1.9 mM) and calcium 1.9 mM (2.2–2.6 mM) in this patient.

Although there were large interpatient variations in concentrations of 6MP and its metabolites (Table 1), the patient with TLS can be clearly distinguished from the others: 6MP and its metabolites in plasma except methyl-6MP-riboside were much higher and the MetIMP levels in RBCs were extremely low in this patient. Allopurinol was undetectable and oxypurinol was in the same range in plasma of all patients. (Hypo)xanthine levels were much higher in the patient with TLS.

There are several explanations for these findings. A

Table 1.

	Four patients mean ± S.D.	Patient with TLS
6MP and its metabolites in plasma (μ*M*)		
6MP (mean 0–24 h)	25.0 ± 17.8	57
A.U.C.* (μM . h)	637 ± 226	2444
Thioxanthine (24 h)	1.8 ± 2.1	47
Thiouric acid (24 h)	0.5 ± 1.0	20
Methyl-6MP (mean 0–24 h)	0.9 ± 0.4	2
Methyl-6MP-riboside (48 h)	0.1 ± 0.1	0
MetIMP in RBCs (pmol/8.10^8 RBC)		
24 h	1248 ± 1160†	64
48 h	832 ± 752†	72
Oxypurinol in plasma (μ*M*)		
Mean 0–48 h	53.4 ± 30.4	47
Purine bases in plasma (μ*M*)		
Hypoxanthine (0 h) (normal < 4 μM)‡	6.7 ± 5.1	84
Xanthine (0 h) (normal < 2 μM)‡	17.0 ± 8.1	334

* A.U.C.= area under the concentration time curve. † MetIMP levels were in the range 400–2912 pmol/8.10^8 RBC at 24 h and of 200–1896 pmol/8.10^8 RBCs at 48h after start of the infusion ‡ Normal ranges of hypoxanthine and xanthine from healthy children.

HGPRT deficiency in the patient with TLS was excluded. A thiopurine methyltransferase deficiency was unlikely because MetIMP and methyl-6MP are both produced by this enzyme and methyl-6MP levels were highest in the patient with TLS. Allopurinol overtreatment was excluded by the levels of oxypurinol. The WHO grade 1 renal toxicity in the patient with TLS might have contributed to the high plasma levels of 6MP, its catabolites and (hypo)xanthine, but cannot explain the low MetIMP levels.

The low MetIMP levels suggest that the anabolic pathway of 6MP was only minimally active in the patient with TLS, despite high 6MP levels. Although RBCs are not the target cells for 6MP cytotoxicity they are a model for the study of the anabolic pathway of 6MP because they can convert 6MP via HGPRT into MetIMP and thioguanine nucleotides. Tumor lysis, with increased breakdown of nucleotides, RNA and DNA, causes high levels of endogenous purine bases, as reflected by the high concentrations of (hypo)xanthine. The relative inactivity of the anabolic pathway of 6MP in the patient with TLS is probably caused by competition for HGPRT between 6MP and hypoxanthine

Our data show evidence for a decreased anabolism and thus a decreased efficacy of HD-6MP in a patient with TLS. This seems to be based on competition between 6MP and hypoxanthine, which is available in excess during tumor lysis. The high levels of 6MP and its catabolites may result in hematuria and crystalluria [4] and may cause further renal failure.

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