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RESEARCH ARTICLE

Effect of Allopurinol administration on the uric acid level and kidney function in paediatrics with tumour lysis syndrome (TLS) and high-risk TLS

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Keywords
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Abstract

Background: Tumor lysis syndrome (TLS) is a life-threatening oncologic emergency because of the release of tumour cell components such as uric acid, which can lead to hyperuricemia and acute kidney injury (AKI). **Objective:** To analyse serum uric acid, creatinine, and BUN levels pre- and post-allopurinol administration. **Method**: This study was a prospective observational study conducted from March to July 2020. Inclusion criteria were haematological malignancies in paediatric patients with TLS and high-risk TLS who received allopurinol 10 mg/kg/day in 2-3 divided doses. Collected data were the serum uric acid, creatinine, and BUN levels pre-and post-allopurinol administration. **Result:** There were 14 sample in total during the study. There was a significant difference in uric acid level on day six after allopurinol administration compared to baseline in patients with high-risk TLS ($p < 0.05$). **Conclusion:** Allopurinol was inadequate in reducing uric acid levels in TLS patients but adequate in reducing uric acid levels in patients with high-risk TLS.

Introduction

Tumour lysis syndrome (TLS) is a critical oncological emergency (Li *et al*., 2015). It is found in children with 25% leukaemia and 23% lymphoma tumours of the central nervous system by 16.6% and 8–10% of neuroblastoma (Tazi *et al*., 2011). This complication can manifest before, during, and after chemotherapy (Villas, 2019). Tumour cells lyse and release several intracellular components, such as nucleic acid metabolised into uric acid. Excessive uric acid release can lead to hyperuricemia and acute kidney injury (AKI) risk (Edeani & Shirali, 2011).

Patients with high-risk TLS or those who have experienced TLS need immediate management to prevent further complications. One of the treatments is allopurinol administration to reduce and prevent the formation of uric acid. Therefore, it can prevent acute kidney injury from precipitation from uric acid crystals (Williams & Killeen, 2019). This study analysed serum uric acid, creatinine, and blood urea nitrogen (BUN) levels pre-and post-allopurinol administration in paediatric patients with TLS and high-risk TLS associated with hematologic malignancies.

Methods

This study was a prospective observational study conducted from March to July 2020. The inclusion criteria were male or female paediatric patients with hematologic malignancies Acute Lymphoblastic Leukaemia (ALL), Acute Myeloid Lymphoblastic (AML), Chronic Myeloid Leukaemia (CML), Hodgkin's lymphoma, or Non-Hodgkin's Lymphoma (NHL) who experienced TLS or high-risk TLS. The patients received allopurinol 10 mg/kg/day divided into 2–3 doses and were ≤16 years old. The study was carried out at the

Paediatric Ward Dr. Soetomo Teaching Hospital. The exclusion criteria were paediatric patients with hyperuricemia not caused by hematologic malignancies (gout, tofus) and paediatric patients with acute and chronic renal impairment (non-TLS). The criteria for dropout were paediatric patients who passed away, families who withdrew from the study, patients allergic to allopurinol, or paediatric patients who were forced home.

After allopurinol administration, the blood samples were taken and analysed at baseline (day zero), day three, and day six. The Paired *t*-test was used to analyse each variable between the group on days three and six, with a significance level of 5%. The Ethical Committee, Dr. Soetomo Teaching Hospital approved this study protocol.

Results

The total sample obtained from March to July 2020 was 14 patients. The baseline characteristics of the patients admitted to the hospital are shown in Table I. The baseline characteristic of patients with hematologic malignancy with TLS showed abnormalities in uric acid levels, creatinine serum, and BUN due to a large number of tumour cell lysis results in decreased kidney function. The patients with high-risk TLS showed similar abnormalities, but their kidney function was still good.

Table I: Patient characteristics of haematological malignancy with TLS and high-risk TLS

Patient characteristics	Total patients (N) and percentage of patients (%)		Mean ± SD	
	High-risk TLS	TLS	High-risk TLS	TLS
Gender				
Female	1 (17)	4 (50)		
Male	5 (83)	4 (50)		
Age (year)				
Toddler	3 (50)	0 (0)		
Child	2 (33)	4 (50)		
Adolescent	1 (17)	4 (50)		
Diagnosis				
ALL†	4 (66)	6 (75)		
AML†	2 (34)	0 (0)		
CML†	0 (0)	1 (12.5)		
NHL†	0 (0)	1 (12.5)		
Weight (kg)			21.5±19.5	38.1±8.1
Height (m)			1.1±0.3	1.4±0.1
BSA (/m^2) †			0.8±0.4	1.2±0.2
WBC (/mm^3) †			347055±350365	54109±51745
Patients never had chemotherapy	4 (67)	4 (50)		
Patients with a history of chemotherapy	2 (33)	4 (50)		
Uric acid (mg/dL)			7.6±0.3	11.7±0.3
Creatinine serum (mg/dL)			0.44±0.18	1.10±0.56
BUN (mg/dL)			12.7±7	24±21
eGFR (ml/minutes/1.73m^2) †			142.00±13.00	79.82±44.38

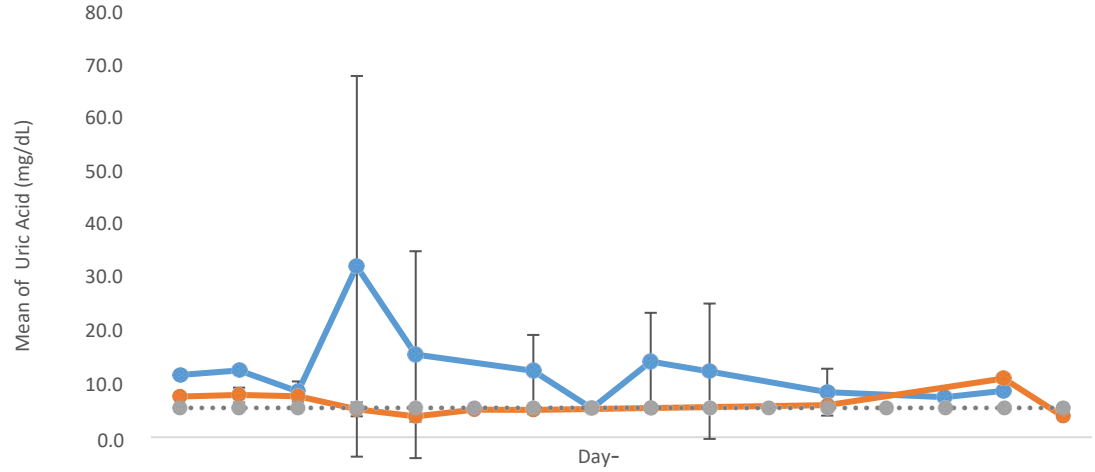
†ALL (Acute Lymphoblastic Leukaemia); AML (Acute Myeloid Lymphoblastic); CML (Chronic Myeloid Leukaemia); NHL (Non-Hodgkin Lymphoma); BSA (Body Surface Area); WBC (White Blood Cell); and eGFR (estimated Glomerular Filtration Rate)

The profile of uric acid levels in patients with hematologic malignancies with TLS showed fluctuating values exceeding the normal limits (>5.5 mg/dL) compared to those with high-risk TLS, as shown in Figure 1. Many tumour cells cause this lyse due to the progress of the patient's disease or still undergoing chemotherapy.

Creatinine serum is the main parameter to determine renal function. The mean profile of creatinine serum fluctuated, exceeding the standard limit in patients with TLS compared to those with high-risk TLS and BUN showed a similar result (Figure 2). There was a significant difference in uric acid level on day six compared to baseline in patients with high-risk TLS ($p <$

0.05). Allopurinol can reduce uric acid levels in patients (Table II).

The renal function of patients with high-risk TLS did not show a significant difference compared to baseline (p > 0.05) because they were still in the normal range. In patients with hematologic malignancy with TLS, there was no significant difference in uric acid parameters or renal function on days three and six compared to baseline (p > 0.05). This shows that allopurinol cannot reduce uric acid levels, which are still high in patients with TLS.



	D0	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15
TLS (n=8)	11.7	12.5	8.6	32.1	15.5		12.5	5.4	14.2	12.4		8.4		7.5	8.7	
High Risk TLS (n=6)	7.6	7.9	7.7	5.2	3.9	5.2	5.1		5.5			6.0			11.0	4.0
Normal	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5

Figure 1: Mean uric acid level profile of patients with haematological malignancy with TLS and high-risk TLS

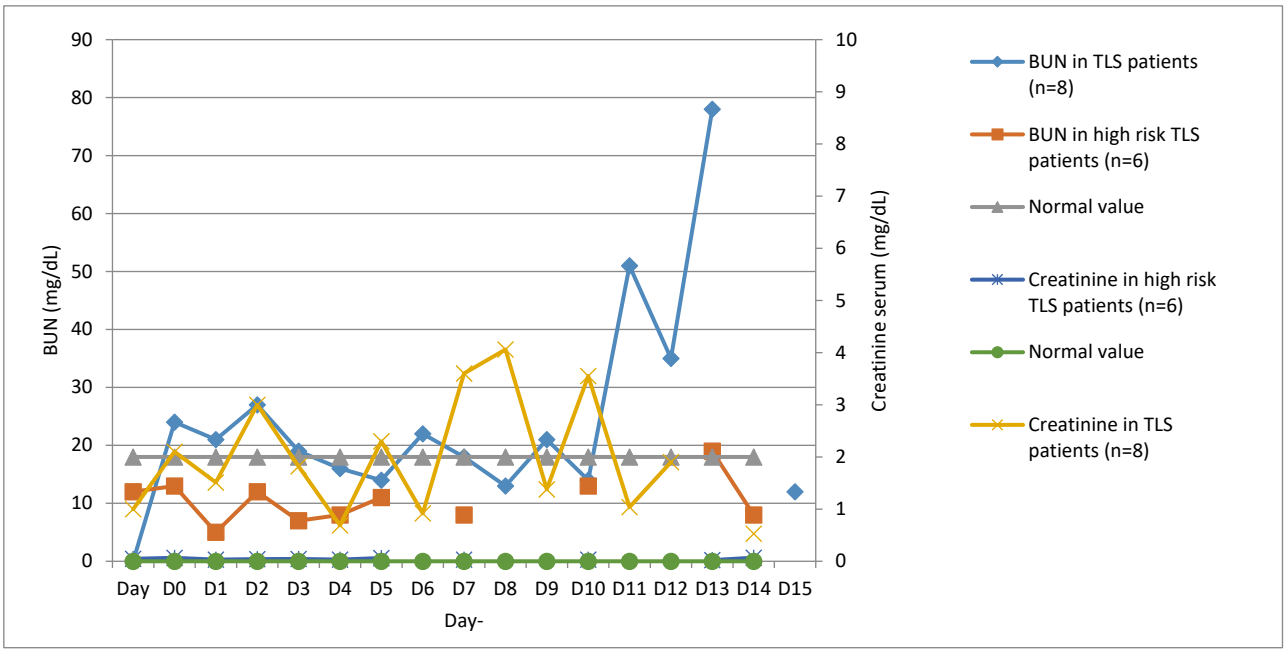


Figure 2: Mean creatinine serum and BUN levels profile of patients with haematological malignancy with TLS and high-risk TLS

Table II: Differences in the significance value of each parameter in haematological malignancy patients

Parameters	TLS					High-risk TLS				
	D0	D3	*p*	D6	*p*	D0	D3	*p*	D6	*p*
Uric acid	11.70	32.10	0.142	12.50	0.850	7.60	5.20	0.117	5.10	0.016†
Creatinine	1.10	3.00	0.184	2.30	0.286	0.44	0.37	0.773	0.57	0.408
BUN	24	19	0.729	22	0.764	12	12	0.845	11	0.553

†$p < 0.05$

Discussion

TLS occurs when tumour cells are destroyed and lysed due to chemotherapy or rapid, aggressive, and spontaneous lysis of proliferating tumour cells (Li *et al*., 2015). Tumour cells lyse and release various intracellular components, such as nucleic acids, which can develop into hyperuricemia and AKI (Edeani & Shirali, 2016; Aslan *et al*., 2019). Baseline patients with TLS showed abnormalities in uric acid levels and kidney functions due to the accumulation of uric acid in the bloodstream (Table I) (Den Bakker *et al*., 2018). Baseline patients with high-risk TLS showed abnormal uric acid levels, but the excretory function was still good.

Paediatric patients have the highest percentage of TLS because they have an increased sensitivity to chemotherapy (Li *et al*., 2015). Cytotoxic-nephrotoxic chemotherapy can trigger tumour cell lysis such as methotrexate, vincristine, cytarabine, and daunorubicin (Arozal *et al*., 2010; Lameire, 2014; Sury, 2019; Bewersdorf & Zeiden, 2020). In addition, imatinib (tyrosine kinase inhibitor) in patients with CML through target cell therapy can also induce TLS (Lameire, 2014; Williams & Killeen, 2019;).

Patients with ALL are one of the haematological malignancies that cause a high incidence of TLS due to the administration of aggressive chemotherapy. In patients with Non-Hodgkin lymphoma (NHL), it is caused by a high tumour burden leading to rapid, aggressive, and spontaneous tumour proliferation (Sevinier *et al*., 2011). Chronic Myelogenous Leukemia (CML) is a hematologic malignancy with low-risk factors, but the administration of imatinib will change the level to moderate risk of TLS (Edeani & Shirali, 2016; Sury, 2019; Williams & Killeen, 2019). In this study, patients with Chronic Myelogenous Leukemia (CML) had experienced TLS.

Allopurinol has a vital role in preventing the formation of uric acid. All patients with haematological malignancy and high-risk TLS received allopurinol at 10 mg/kg/day divided into 2-3 doses. The recommended dosage in children is 10 mg/kg/day divided into 2-3 doses (Tazi *et al*., 2011). The recommendation with a GFR of 10-50 ml/minute is 50% of the usual dose, while in children with glomerular filtration rate (GFR) of <10 ml/minute is 30% (Jones *et al*., 2015). Allopurinol has a half-life of 12-24 hours (Sury, 2019).

In this study, the mean uric acid levels exceeded normal in patients with TLS, and there was no significant decrease on days 3 and 6 compared to baseline. This is due to many tumour cell lysis and overproduction of nucleic acids, which are metabolised into hypoxanthine and converted into uric acid by xanthine oxidase (Benn *et al*., 2018; Villas, 2019). This shows that allopurinol alone cannot reduce uric acid levels in patients with TLS.

On the other hand, those with high-risk TLS showed a decrease in uric acid levels on day three (Figure 1) and day six with $p = 0.016$ (Table II). The selection of day three is based on previous studies that show a decrease in uric acid levels at 61 hours compared to 24 hours (Renyi *et al*., 2007). Another study reveals that uric acid levels can be reduced with allopurinol on day six (Wilson & Berns, 2012).

Patients who have experienced TLS should change allopurinol to rasburicase (recombinant form urate oxidase enzyme) which catalyses uric acid to allantoin (Tazi *et al*., 2011; Villas, 2019). The mechanism is through two genes that code for proteins to catalyse urate oxidase into 5-hydroxyurea (HIU). Hydrolysis of 5-HIU results in 2-oxo-4-hydroxy-4-carboxy-5-ureidoimidazoline (OHCU), while decarboxylation of OHCU forms S-(+)-alantoin (McDonagh *et al*., 2014). Allantoin is a metabolite with a solubility ten times higher than uric acid and will be easier to excrete through the kidneys (Tazi *et al*., 2011). Rasburicase can reduce uric acid levels after four hours, and the recommended dose is 0.20 mg/kg via infusion for 30 minutes for five days (Tazi *et al*., 2011).

The renal function of patients, including creatinine and BUN Levels, was monitored regularly. The mean creatinine serum and BUN levels fluctuated, exceeding the normal limits in patients with TLS, as shown in Figure 2. Moreover, no significant decrease was observed on days three or six, and in the acidic pH conditions, uric acid is difficult to dissolve, causes urate precipitation, and obstructs the renal tubules (Aslan *et al*., 2019). A uric acid level of ≥10 mg/dL is at risk of developing nephrolithiasis (Hoff *et al*., 2020). Patients with a high risk of TLS have a renal function within normal limits, which shows that the

excretory function of the patient can be optimal, as proven by no significant difference in the renal function.

This study did not compare allopurinol and other drugs that can reduce uric acid levels and prevent acute kidney injury (AKI) in TLS patients. Therefore, studies are needed to compare allopurinol and rasburicase in TLS patients.

Conclusion

The administration of allopurinol can reduce uric acid levels and renal function. Allopurinol 10 mg/kg/day was inadequate in lowering the uric acid level in TLS patients. Meanwhile, the high risk of this complication can prevent uric acid levels and maintain renal function. The standard uric acid, serum creatinine, and BUN levels on day six for patients were 25%, 0%, and 50%, respectively. In contrast, those with a high risk of TLS were 67%, 100%, and 67%, respectively.

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