

Avoiding Dialysis in Tumour Lysis Syndrome: Is Urate Oxidase Effective? – A Case Report and Review of Literature

Wan-Yee Teo,¹*MBBS, MRCPCH (Lond)*, Tsee-Foong Loh,²*MBBS, MMed (Paeds), FRCP*, Ah-Moy Tan,³*MMed (Paeds), FRCP (Edin), FAMS*

Abstract

Introduction: Hyperuricaemia in tumour lysis syndrome (TLS) can cause acute renal failure (ARF), necessitating dialysis. Recombinant urate oxidase (rasburicase) converts uric acid to soluble allantoin, which is excreted easily. **Case Report:** An 8-year-old boy with stage 3 Burkitt's lymphoma, TLS was successfully treated with hyper-hydration, diuretics and rasburicase, without dialysis. This is the first paediatric case in Kandang Kerbau Women's & Children's Hospital (KKH) in which rasburicase was used. We review the literature on the effectiveness of urate oxidase in avoiding dialysis in TLS. **Treatment and Outcome:** Our patient developed rapidly rising serum uric acid (SUA) and progressive renal impairment. Hyper-hydration and rasburicase (0.2mg/kg) were administered. SUA rapidly decreased from 1308 to 437 mmol/L within 12 hours. Urate oxidase has shown better results than allopurinol. There was a need for dialysis in 0.4% to 1.7% of patients with haematological malignancies given rasburicase, compared to 20% in patients given allopurinol. **Conclusions:** Rasburicase can reverse renal insufficiency. Though expensive, it may be cost-effective by lowering incidence of dialysis, shortening the duration of intensive care and hospitalisation, allowing early chemotherapy.

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Key words: Acute renal failure, Hyperuricemia, Recombinant urate oxidase, Renal insufficiency

Introduction

Tumour lysis syndrome (TLS) is frequently associated with lymphoproliferative malignancies. It is the result of massive spontaneous or chemotherapy-induced cytotoxicity, leading to the release of intracellular metabolites. Hyperuricaemia from breakdown of large amount of nucleic acids in lysed tumour cells causes renal dysfunction from precipitation of uric acid leading to intraluminal tubular obstruction. This results in acute renal failure (ARF), necessitating dialysis. Standard treatment of TLS aims to clear high plasma levels of potassium, uric acid, phosphorus; correct acidosis; prevent ARF by hyper-hydration, and dialysis in ARF. The management of hyperuricaemia traditionally involves the use of allopurinol, hyper-hydration and urine alkalinisation.¹ Allopurinol blocks the metabolic conversion of hypoxanthine and xanthine to uric acid, preventing the rise of uric acid, but does not degrade uric acid already present. It has to be given with alkaline hyperdiuresis to clear renal uric acid crystals, a process that

takes about 10 days. A new modality is recombinant urate oxidase (rasburicase), which catalyses conversion of uric acid to more soluble allantoin (5 to 10 times more soluble than uric acid; excreted more easily); it acts at the end of the purine pathway and does not lead to the accumulation of intermediary metabolites (xanthine), hence limiting the risk of renal damage. It has a rapid onset of action of 4 hours, hence a potential role in reversing renal insufficiency which may avoid the need for dialysis² (Fig. 1).

Case Report

We present a case of an 8-year-old boy diagnosed with stage 3 Burkitt's lymphoma who presented with ileocolic intussusception and had to undergo emergency laparotomy and right hemicolectomy. Postoperatively, he developed TLS with hyperuricaemia, hyperkalaemia and renal impairment that was rapidly and successfully managed with hyper-hydration, diuretics and rasburicase, without requiring dialysis. This is the first paediatric case in Kandang Kerbau Hospital (KKH) in which rasburicase was used. We

¹ Department of Paediatric Medicine, KK Women's & Children's Hospital, Singapore

² Division of Children's Intensive Care Unit, Department of Paediatric Subspecialties, KK Women's & Children's Hospital, Singapore

³ Division of Paediatric Haemato-oncology, Department of Paediatric Subspecialties, KK Women's & Children's Hospital, Singapore

Address for Correspondence: Dr Teo Wan Yee, Department of Paediatric Medicine, KK Women's & Children's Hospital, 100 Bukit Timah Road, Singapore 229899.

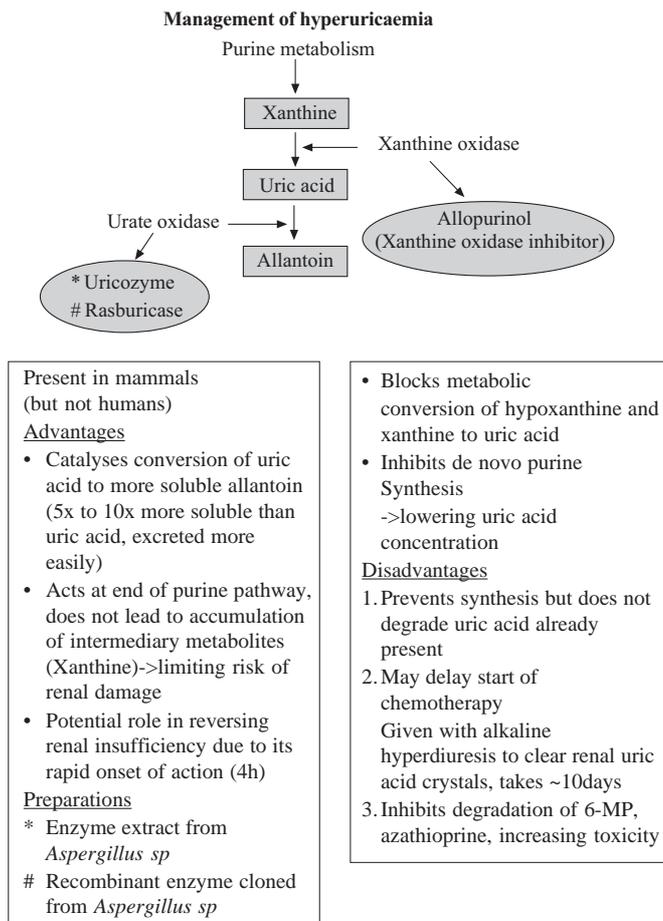


Fig. 1. Comparing mechanisms of action of rasburicase versus allopurinol.

reviewed the available literature on the effectiveness of urate oxidase in avoiding dialysis in TLS.

Treatment and Outcome

Our patient was an 8-year-old Indian boy with a history of autism who presented with acute abdominal pain. Clinical findings were that of an abdominal mass. Computed tomography (CT) and ultrasound findings were consistent with intussusception with a mass, suggestive of lymphoma. He underwent emergency laparotomy and right hemicolectomy. Postoperatively, he developed TLS with a rapidly rising serum uric acid (SUA) from 1040 to 1308 mmol/L within 11 hours on the day of surgery, with concurrent hyperkalaemia, hyperphosphataemia, hypocalcaemia and progressive renal impairment (rising serum creatinine and oliguria) (Table 1). Correction of serum potassium with per rectal resonium, diuretics (frusemide) and correction of acidosis with sodium bicarbonate were initiated. Therapy including hyperhydration, diuretics and alkalisation did not lower SUA levels. His clinical condition deteriorated (i.e., oliguria and evidence of TLS) despite continuation of above measures.

A dose of rasburicase (0.2 mg/kg) was obtained and instituted within 18 hours from the time SUA was raised at 1040 mmol/L. After rasburicase was started, his clinical and biochemical status improved without any change to previous ongoing therapy. There was good and rapid response with lowering of SUA to 1075 mmol/L within 2 hours of administration of rasburicase and 9 hours after hyper-hydration was instituted. SUA decreased to 437 mmol/L within 12 hours of the administration of the first dose of rasburicase (29 hours after initial uric acid of 1040 mmol/L). A second dose of rasburicase (0.2 mg/kg) 12 hours from the first with subsequent lowering of SUA to <30 mmol/L for a few days. Chemotherapy was instituted on postoperative day 4 (POD 4). On POD 5, SUA rose to 308 mmol/L for which a third dose of rasburicase (0.1 mg/kg) was given within 5 hours. On POD 6, SUA rose to 371 mmol/L and a fourth dose of rasburicase (0.1 mg/kg) was given 12 hours after the third dose and SUA decreased to 61 mmol/L within 8 hours of the fourth dose. Renal impairment resolved with gradual lowering of serum creatinine and improvement of urine output after the first dose of rasburicase was given, together with diuretics and hyper-hydration. Hyperkalaemia did not recur after the first episode. The patient did not have evidence of methaemoglobinaemia.

Discussion

Effectiveness of Rasburicase in Lowering SUA

Previous literature has shown recombinant urate oxidase (rasburicase) to be effective in the treatment of hyperuricaemia. Studies comparing recombinant urate oxidase with xanthine oxidase inhibitor (allopurinol) in the treatment of hyperuricaemia in TLS have shown better results with urate oxidase. Rasburicase was initially studied in paediatric patients with acute lymphoblastic leukaemia and aggressive non-Hodgkin's lymphoma.³ In a phase I/II study, all 131 patients with newly diagnosed acute lymphoblastic leukaemia (ALL) or stage III/IV non-Hodgkin's lymphoma (NHL) experienced rapidly decreased SUA after receiving recombinant urate oxidase. In a phase III trial, children with newly diagnosed ALL or stage III/IV NHL were stratified and randomised to receive recombinant urate oxidase or allopurinol. Results showed that the 27 patients who received recombinant urate oxidase had a significantly lower SUA.⁴

In a study by Bosly et al,⁵ in 166 pediatric patients who had leukaemia (74%), lymphoma (24%), or solid tumours (3%) who were treated with rasburicase, mean SUA level in 29 hyperuricaemic children decreased from 15.1 to 0.4 mg/dL. Prophylactic administration of rasburicase to prevent TLS during chemotherapy-reduced SUA levels from a mean of 4.4 to 0.8 mg/dL in 93 non-hyperuricaemic children ($P < 0.001$). The response rate was 100%.

Table 1. Tumour Lysis Syndrome in our Patient

Date/Time	Op day		POD1			POD2	POD3	POD4	POD5	POD6	POD7
	1040h	2125h	0023h	0544h	1537h	0413h	0527h	0653h	0528h	0505h	1529h
Rasburicase administered			6 mg↓		6 mg↓				3 mg↓	3 mg↓	
Serum uric acid	1040	1308		1075	437	<30	<30	36	308	371	<30
Serum calcium	2.39	2.13	1.68	1.46		1.66	2.23	2.43	1.93	2.46	3.2
Serum phosphate	0.5	1.08	2.81	2.95		2.47	0.87	1.0	1.91	1.48	0.77
Serum potassium	7.4	7.0	5.9	5.7		3.2	3.4	3.0		4.3	3.2
Serum urea	1.0	2.8		7.1		10.7	6.4	4.1		9.2	11.4
Serum creatinine	74	127		153		118	67	69		28	37
Urine output (mL/kg/h)	0.6		5.2			5.8	4.9	3.0	5.6	7.4	2.8
Diuretics administered	60 mg↑			60 mg↑		(30 mg/dose)↑↑↑↑↑					

Op day: operative day; POD: postoperative day

In another study by Pession and Barbieri,⁶ 26 children with malignancy at risk for TLS, submitted to treatment (group 1) or prophylaxis (group 2) of acute hyperuricaemia with rasburicase which significantly decreased SUA in all patients. Control of SUA was obtained in both groups within 24 h of the first dose with a response rate of 100% (group 1) and 93% (group 2). In a study by Shin et al,⁷ SUA endpoint (≤ 7.0 mg/dL) was reached in 97.3% of the patients and SUA levels were significantly reduced in all patients ($P < 0.001$). In a randomised prospective trial comparing rasburicase versus allopurinol in children with haematological malignancies at high risk of TLS, rasburicase significantly lowered the mean uric acid area under the curve 0 to 96 hours (128 ± 70 mg/dL/hour versus 329 ± 129 mg/dL/hour; $P < 0.001$) and 4 hours post-uric acid by 86% versus 12% ($P < 0.001$).⁸

Effectiveness of Rasburicase in Preventing Dialysis

Although rasburicase has been proven to be an effective treatment for hyperuricaemia, there is limited data on the effectiveness of urate oxidase in lowering serum creatinine and its role in avoiding dialysis in TLS has yet to be ascertained.

Conventional management of hyperuricaemia involved the use of aggressive hydration, urinary alkalinisation and allopurinol. Despite these measures, as many as 14.1% to 25% of high-risk patients may still develop renal failure,^{9,10} and many cannot receive chemotherapy as planned.¹¹

In several studies in which paediatric patients in TLS were treated with rasburicase, serum creatinine levels decreased significantly^{4,6,12,13} and none of the patients required dialysis.^{4,12,13} In a study by Pui,⁴ 27 patients who received recombinant urate oxidase had a significantly more rapid decline in serum creatinine level than did the 25

who took allopurinol. In the study by Cairo,⁸ in the hyperuricaemic group, baseline creatinine level decreased from 144% to 102% by 96 hours following rasburicase compared to an increase from 132% to 147% following allopurinol.

The need for dialysis was 0.4%⁸ to 1.7%¹⁴ in patients with haematological malignancies at risk for TLS who received rasburicase, compared to 20% in patients who had received allopurinol.¹¹

Rasburicase is considerably more expensive than standard management strategies and should be reserved for patients with either renal dysfunction, significant elevations in SUA values, or large tumour burdens.¹⁵

One study¹⁶ showed a single urate oxidase infusion readily reduced serum uric acid levels in all 4 patients. Furthermore, renal insufficiency, determined by serum creatinine concentrations, improved in 3 of the 4 patients. The possibility of using a single-dose regimen of rasburicase compared to the conventional 5-day regimen remains to be explored. Another study reported episodes of TLS successfully treated with rasburicase in a lower dose than recommended.¹⁷

High-risk Factors Predisposing to TLS

Both host-related and tumour-related factors predispose cancer patients to hyperuricaemic syndromes.¹⁸ Host-related factors include low urinary flow, pre-existing hyperuricaemia, renal failure, dehydration, acidic urine, and suppressed renal uric acid excretion. Tumour-related risk factors include a high tumour cell proliferation rate, large tumour burden, and tumour chemosensitivity. Acute renal failure may occur after cytoreductive chemotherapy in patients with active disease and a high tumour burden. Patients with advanced Burkitt's leukaemia/lymphoma,

high-grade lymphoma, or acute leukaemia with elevated leukocyte counts are at high risk for complications of hyperuricaemia.

Hyperleukocytosis occurs in 5% to 22% of paediatric patients with acute leukaemia. Efficacy of rasburicase in marked hyperleukocytosis is not well known.¹⁹ In all 3 patients who received rasburicase, minimal metabolic disturbance occurred. White blood count (WBC) reduction strategies may not be required solely for the risk of tumour lysis syndrome in patients with very high WBC ($>200 \times 10^9/L$) who are treated with rasburicase.

Patients with the highest risk of developing a TLS may benefit from the prophylactic use of urate oxidase.²⁰

Early recognition of metabolic abnormalities in cancer patients at risk for hyperuricaemia is essential for proper therapy. Prospective studies to assess the incidence of and risk factors for hyperuricaemic syndromes in patients treated with uricolytic agents are needed.¹⁸

Side Effects

Recognised side effects of rasburicase include anaphylaxis, haemolysis in glucose-6-phosphate dehydrogenase deficiency, methemoglobinaemia and production of antibodies.

Future of Urate Oxidase

Rasburicase is considerably more expensive compared to allopurinol. Current and future trials will evaluate alternate doses and schedules of rasburicase to maintain its efficacy while reducing its cost. Studies suggest that hyperuricaemia in children at risk for tumour lysis can be managed with a briefer regimen of rasburicase than the recommended 5- to 7-day course. It may be more cost-effective to identify high-risk group for hyperuricaemia to give rasburicase for treatment/prophylaxis. These risk factors include low urinary flow, pre-existing hyperuricaemia, renal failure, dehydration, acidic urine, suppressed renal uric acid excretion, high tumour cell proliferation rate, large tumour burden, tumour chemosensitivity (advanced Burkitt's leukaemia/lymphoma, high-grade lymphoma, or acute leukaemia with elevated leukocyte counts are at high risk for complications of hyperuricaemia).¹⁸ Prospective studies to assess incidence of and factors for hyperuricaemic syndromes in patients treated with uricolytic agents are needed. These will increase the cost-effectiveness of the use of rasburicase in TLS.

There is a need for prospective studies for the use of rasburicase in TLS to avoid ARF and the need for dialysis, as there is limited literature on the effectiveness of urate oxidase in lowering serum creatinine and its role in avoiding dialysis in TLS has yet to be ascertained.

Conclusion

Metabolic problems in TLS can have major deleterious impact on morbidity and mortality of lymphoproliferative malignancies. Rasburicase is an efficacious and safe drug that decreases serum uric acid. It has a rapid onset of action of 4 hours; it has a potential role in reversing renal insufficiency. It is expensive but may be cost-effective by lowering incidence of dialysis, allowing a shorter duration of intensive care and hospitalisation. By treating urate nephropathy and allowing chemotherapy to be started early, it may improve the outcome of patients. The possibility of using single-dose rasburicase (treatment/ prophylaxis) and a shorter course in the treatment of hyperuricaemia needs to be explored. These will increase the cost-effectiveness of rasburicase. There is a need for a protocol and prospective study for the use of rasburicase in TLS to avoid ARF and the need for dialysis and while maximising its cost-effectiveness.

Conflicting Interests

The use of this drug did not require sanction, as it is a Singapore registered drug. The doctors have no conflict of interests or commercial pressures to use the drug. The patient bore the full cost of the drug and its use was without prejudice.

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