RESEARCH ARTICLE

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Fixed-Dose Recombinant Urate Oxidase in the Treatment of Paediatric Tumour Lysis Syndrome: A Regional Cancer Centre Experience

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Abstract

Background: Tumor lysis syndrome (TLS) is an oncologic emergency commonly seen in children with hemato-lymphoid malignancies. Recombinant urate oxidase (RUO) is used in both the prophylaxis and treatment of TLS. However, in resource-constrained countries, its role is mostly limited to the treatment of established TLS and data regarding the use of RUO and its outcome is sparse. **Objective:** To describe the outcome of Pediatric TLS following the use of a fixed – dose of RUO. **Methods:** A retrospective chart review of all children <15 years of age admitted in the Department of Paediatric Oncology, Kidwai Cancer Institute from April 2017 to July 2018 with TLS and treated with a single, fixed – dose (1.5 mg) RUO was undertaken. **Results:** During the study period, 255 children with hemato-lymphoid malignancies were diagnosed to be at risk of developing TLS. Of these, only 22 (8.6%) children developed TLS and received RUO. Among those with TLS, 15 (68.2%) had Acute Lymphoblastic Leukemia (ALL) while 7 (31.8%) had Non - Hodgkin lymphoma (NHL). 91% (20/22) children had spontaneous TLS and the remainder developed therapy-related TLS. Median age at presentation was 8 years (IQR 5.25,1.75) with 4.5:1 male: female ratio. The mean urate level at admission was 19.12 mg/dl (+/- 8mg/dl) (Range: 10.7–34.5). 91% (20/22) children received RUO at less than 0.15 mg/kg and the median dose of RUO was 0.05 mg/kg (IQR 0.038-0.08). Of the 22 children with TLS, 2 children failed to achieve normal serum urate levels at 24 hours in response to a single fixed-dose of RUO and hence received an extra dose of RUO. Serum urate levels remarkably declined following RUO administration from 19.12 mg/dl (+/-8) to 8.2 mg/dl (+/-3.9), 3.99 mg/dl (+/-1.6) and 2.84 mg/dl (+/-1.3) at 12h, 24h and 48h respectively. AKI was present in 15 (68.2%) children. The median eGFR of the group at diagnosis was 49 ml/min/1.73m^2 (IQR 26.3, 70). None of the children required hemodialysis. No significant adverse events occurred. **Conclusion:** Fixed-dose RUO can achieve rapid, adequate and sustained drop in serum urate levels in Paediatric TLS. It is a useful strategy for managing TLS in resource-constrained settings.

Keywords: Rasburicase- tumour lysis syndrome- hyperuricemia- haematological malignancies- renal failure

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Introduction

Tumor lysis syndrome (TLS) is a metabolic oncologic emergency characterised by the triad of hyperuricemia, hyperphosphatemia and hyperkalemia arising due to the abrupt and massive release of intracellular components into systemic circulation following lysis of malignant tumour cells (Coiffier et al., 2008). Rasburicase, a recombinant urate oxidase (RUO) was approved by FDA for use in Paediatric TLS in the year 2002 at a dose of 0.15-0.2mg/kg as a single daily dose for 5 days (Kennedy et al., 2011). However, the high cost associated with administering the drug at the recommended dose and schedule has discouraged its routine use in managing children with TLS in low-middle income countries like India where treatment abandonment due to financial constraints is common (Smita et al., 2018). Hence, over the last few years, an attempt was made in the department of Paediatric Oncology, Kidwai Cancer Institute to treat TLS with a fixed-dose of RUO, based on literature from adult studies, as very few studies in children address this issue (Trifilio et al., 2011; Vadhan Raj et al., 2012). The present study aims to describe the utility of fixed-dose RUO in the management of Paediatric TLS in resource-constrained settings.

Materials and Methods

A retrospective chart review of all children <15 years of age admitted in the Department of Paediatric Oncology,

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Kidwai Cancer Institute from April 2017 to July 2018 with TLS and treated with a single, fixed – dose (1.5 mg) of RUO was undertaken. TLS was defined as presence of either laboratory or clinical TLS. Laboratory TLS and clinical TLS were defined based on criteria published by Cairo and Bishop (Table 1) (Coiffier et al., 2008). Those children with isolated hyperuricemia without evidence of laboratory/clinical TLS did not receive RUO (i.e., RUO prophylaxis was not practised) and were excluded from the study. Data on patient history, clinical findings, anthropometry, laboratory investigations and follow up were obtained from case records.

Baseline laboratory investigations included complete haemogram, renal function tests, lactate dehydrogenase, uric acid and electrolytes (potassium, sodium, calcium, phosphorus). Appropriate supportive therapy was provided to all children with TLS and this included hydration, diuretics and allopurinol as per unit protocol. RUO at a single, fixed-dose of 1.5 mg (single vial) was administered as an intravenous infusion in normal saline over 30 minutes to all children diagnosed with TLS irrespective of body weight. This strategy was employed to minimise treatment cost and drug wastage in our resource limited setting. Biochemistry investigations were repeated at 12, 24, 48, 72, 96 and 120 hours from the time of RUO administration. Urine output and glomerular filtration rate as estimated using the Schwartz formula was monitored and documented. Also, children were monitored for adverse events attributable to RUO. Blood samples for serum uric acid levels following RUO administration were transported in ice packs and processed within 4 hours of sample collection, in accordance with recommendations specified by the manufacturer, to avoid spuriously low values that may be obtained due to ex-vivo enzymatic urate degradation. Those children with persistent elevation of uric acid levels above 8 mg/dl at 24 hours after the initial RUO administration received a second dose. Hemodialysis was contemplated if oliguric renal failure and dyselectrolytemia did not respond to hydration and RUO. The data so collected was analyzed using Statistical Package for Social Sciences (SPSS) version 15. Univariate analysis including measures of central tendency, frequency distribution and dispersion was employed to interpret data.

Results

During the study period, nearly 790 registrations were made in the Department of Pediatric Oncology, Kidwai Cancer Institute. Of these, 255 children were diagnosed with hematolymphoid malignancies at risk of developing TLS which included ALL (79.2%), AML (9%) and NHL (11.8%). Based on the risk stratification proposed by Coifferet al1, 50 (20%) and 52 (20%) children belonged to high risk and intermediate risk category respectively while 153 (60%) belonged to low risk category. Among the 255 children at risk, only 22 (8.6%) developed TLS. Clinical characteristics of the study group are described in Table 2. Median age at presentation was 8 years (IQR 5.25, 1.75) with 4.5:1 Male: Female ratio. Median duration of symptoms prior to presentation was 9 days (IQR: 7, 14). Among children with leukemia, hyperleucocytosis (i.e., >1lakh/µL total count) was present in 12/16 (75%) children. Median WBC count was 1,45,000/µL (Range: 13,300/µL – 4,78,0000/µL). Four fold elevation in LDH was seen in 20/22 patients with a median value of 1,508 IU/L (Range: 733 – 5,166 IU/L). The mean uric acid level at admission was 19.12 +/- 8 mg/dl (Range: 10.7 – 34.5). All children received RUO at a single, fixed-dose of 1.5 mg except two children (both with baseline uric acid levels > 30mg/dl) who failed to achieve normal serum urate levels at 24 hours following RUO and hence received an extra dose. 91% (20/22) children received RUO at less than 0.15 mg/kg and the median dose of RUO was 0.05 mg/kg (IQR 0.038-0.08).

Serum uric acid levels remarkably declined following a single dose of RUO from 19.12 +/- 8 mg/dl at presentation

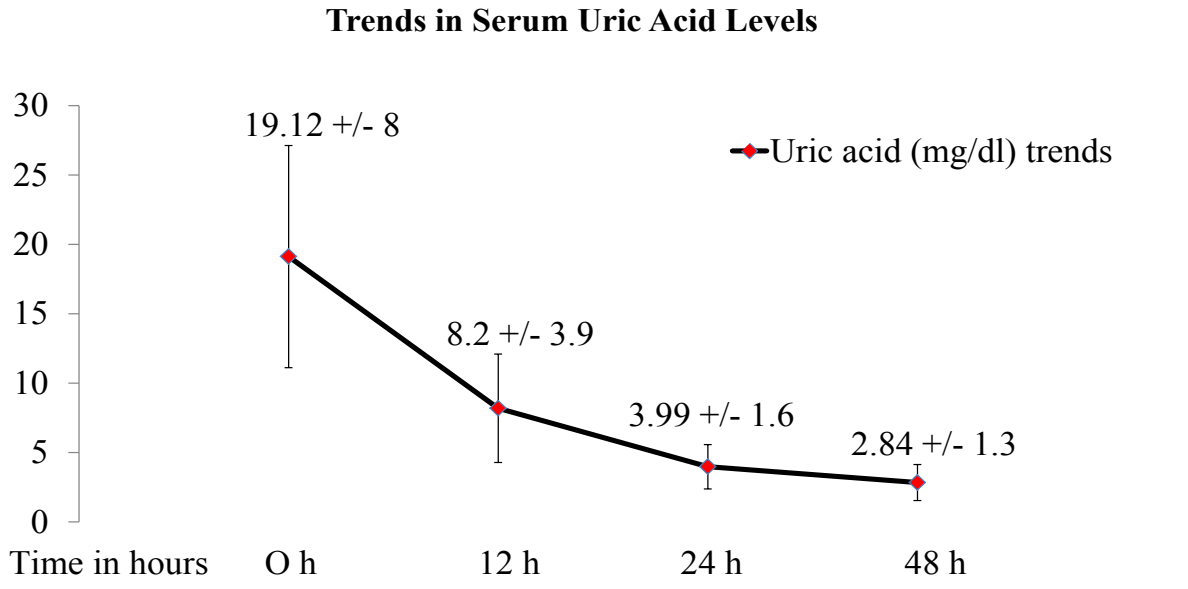

Figure 1. Trends In Serum Uric Acid Levels

Table 1. Bishop and Cairo Criteria for TLS

Clinical TLS	Laboratory TLS
2 or more of the following criteria within 3 days prior to or 7 days after initiation of chemotherapy: • Uric acid : ≥ 8 mg/dl or 25% increase from baseline • Potassium: ≥6 mEq/l or 25% increase • Phosphorus: ≥4.5 mg/dl or 25% increase from baseline • Calcium: ≤7 mg/dl or 25% decrease from baseline	Laboratory tumor lysis plus 1 or more of the following: • Seizure • Cardiac dysthymias or sudden death • Creatinine >1.5 times of age adjusted reference range

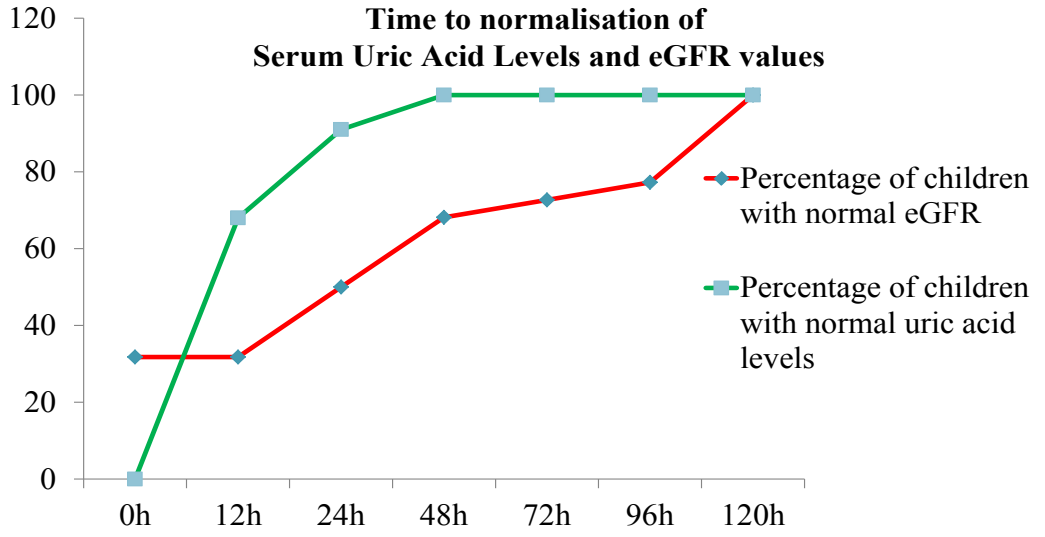

Figure 2. Time to Normalisation of Serum Uric Acid Levels and eGFR Values

to 8.2 +/- 3.9 mg/dl, 3.99 +/- 1.6 mg/dl and 2.84 +/- 1.3 mg/dl at 12h, 24h and 48h respectively as shown in Fig 1. The corresponding percentage drop in mean serum uric acid levels after RUO administration was 57%, 80% and 85% at 12h, 24h and 48h respectively. Time taken for normalisation of serum urate levels is represented in Figure 2. AKI was present in 15 (68.2%) children. The median eGFR of the group at diagnosis was 49 ml/min/1.73m2 (IQR 26.3, 70). eGFR improved steadily after RUO administration with median values at 12h, 24h and 48 h being 57.44 (IQR 29.48, 76.5), 73.22 (IQR 37.7, 83.63) and 98.1 (IQR 50.54, 123.33) respectively (Fig 3). Correspondingly, a marked percentage improvement in eGFR at 12hrs, 24hrs and 48 hrs was noted to be 17.39%, 49.4% and 100% respectively. Time taken to normalisation of eGFR was found to lag behind the time for serum uric acid levels to normalise as depicted in Figure 2. None of the children required hemodialysis. No significant adverse

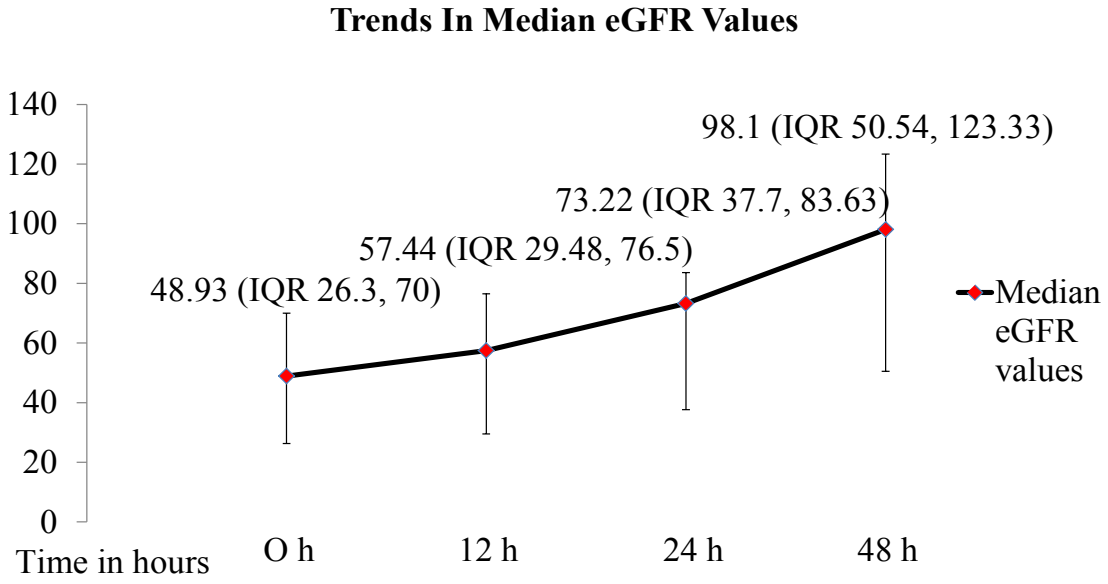

Figure 3. Trends In Median eGFR Values

Table 2. Clinical Characteristics of the Study Group (n = 22)

Parameter	Number (n)	Percentage (%)
Age (Years)		
≤5	6	27.2
6-10	8	36.4
>11	8	36.4
Sex		
Male	18	81.8
Female	4	18.2
Symptomatology at presentation		
Fever	8	36.4
Generalised Lymphadenopathy	15	68.2
Dyspnoea due to mediastinal mass	9	41
Bony pains	7	31.8
Pallor	18	81.8
Bleeding	11	50
Hepatosplenomegaly	17	77.3
Diagnosis		
Pre-T ALL	10	45.5
Pre-B ALL	5	22.7
Burkitt Lymphoma/Leukemia	4	18.2
T-Lymphoblastic lymphoma	3	13.6
Risk stratification		
High	16	72.7
Intermediate	5	22.7
Low	1	4.6
TLS category		
Laboratory TLS	22	100
Clinical TLS	6	27.3
TLS Onset		
Spontaneous	20	90.9
Therapy induced	2	9.1
Acute Kidney Injury at presentation		
No AKI	7	31.8
Risk	4	18.2
Injury	6	27.3
Failure	5	22.7

events occurred in the study group. Of the 22 children who received RUO for TLS, 10(45.5%) are in remission and the remainder died subsequently due to sepsis during induction (n=4), failure to achieve remission following induction chemotherapy (n=5) and very early leukemic relapse (n=3).

Discussion

Tumour lysis syndrome can present with diverse clinical features ranging from asymptomatic dyselectrolytemia to life-threatening cardiac arrhythmias, renal failure and seizures (Coiffier et al., 2008). Allopurinol, a xanthine oxidase inhibitor and Rasburicase, a recombinant urate oxidase have been commonly used as hyperuricemic agents in this regard. Currently, it is recommended that the risk of development of TLS be assessed based on tumour type, tumour burden and cytoreductive intensity followed by risk stratification into low, intermediate and high risk groups (Coiffier et al., 2008). While allopurinol with hydration is required for all risk groups, Rasburicase is indicated as prophylaxis in the high risk group and as therapy for frank TLS (Coiffier et al., 2008). In resource-limited settings, its use is mainly limited to the treatment of established TLS and not as prophylaxis (Gopakumar et al., 2017; Kukkar et al., 2016; Latha et al., 2015). Also, the dosage and schedule used is not in accordance with international guidelines and is often administered as a single, fixed-dose (Gopakumar et al., 2017; Kukkar et al., 2016; Latha et al., 2015). A single vial of 1.5mg of RUO (Generic drug) in India costs around 8000 INR (123 U.S. dollar). Restricting its use to a single dose is aimed at reducing cost by 80%. While data from studies in adult patients supports such a practice, its role in the paediatric age group is poorly defined (Trifilio et al., 2011; Vadhan Raj et al., 2012).

In our experience, a single, fixed-dose of RUO was adequate in achieving target urate levels in most cases. Dose repetition was required in two out of three children with baseline urate levels greater than 30mg/dl. While Gopakumar et al., (2017) administered repeat doses of RUO in 33% children, other studies (Kukkar et al., 2016; Latha et al., 2015) did not repeat doses in their cohorts. A retrospective study in adults by Trifilio et al (2011) demonstrated that the baseline serum urate level is the best predictor of treatment success with single-dose RUO. Also, Vadhan Raj et al., (2012) stated that a subset of high risk patients may require repeat dosing. Based on these findings, we recommend repeat dosing of RUO in children with baseline urate levels >30mg/dl.

While allopurinol alone can achieve a drop of 12% in mean uric acid levels at 4 hours following its administration, RUO at 0.15 mg/kg is expected to achieve about 85-90% drop in mean uric acid levels at 4 hours following its administration (Goldman et al., 2001). In our study, with RUO given at a median dose of 0.05 mg/kg, the percentage decrease in uric acid was 57% at 12 hours and 80% at 24hours, comparable with other studies that have used fixed-dose of RUO (Gopakumar et al., 2017; Latha et al., 2015). Although the percentage drop in mean urate levels using fixed-dose RUO is lower than the drop achieved by a single full dose of RUO, it has been shown to be adequate in successfully reversing hyperuricemia and urate nephropathy (Gopakumar et al., 2017; Latha et al., 2015).

Time taken for normalisation of uric acid levels in the study population was 48 hours while that for normalisation of eGFR was 120 hours. Recovery of renal function was found to lag behind urate level normalisation in our study by 96 hours. In comparison, while Latha et al (2015) reported normalisation of urate levels and renal parameters at 48 and 72 hours respectively, Kukkar et al (2016) revealed normalisation of UA and creatinine

levels at 24 hours and 48 hours in all their patients. The renal parameters assessed in these studies mainly include creatinine which usually is a less sensitive indicator of renal function than eGFR as derangement of creatinine values occur only at a significant loss of nephron function. This probably explains the difference in delay of renal recovery between these studies.

The use of RUO has brought down significantly, the need for dialysis in TLS. About 1.5% pediatric patients were found to require dialysis despite the use of full dose RUO in a multicentre trial by Jeha et al., (2005). Gopakumar et al., (2017) reported dialysis requirement in 11% children with the use of fixed-dose RUO. However, in most other studies, single/fixed-dose RUO was sufficient to normalise renal parameters in all patients without the need for dialysis (Kukkar et al., 2016; Latha et al., 2015). RUO is known to be associated with adverse reactions such as fever, allergy and transaminitis. Hemolysis and methemoglobinemia can occur in G6PD deficient individuals. No significant adverse events were reported by any of the studies using single/fixed-dose RUO including our study (Gopakumar et al., 2017; Kukkar et al., 2016; Latha et al., 2015).

Ours is one of the few studies from LMIC describing the utility of fixed-dose RUO in paediatric TLS. The small sample size in this study is due to limiting the use of RUO to established TLS and not extending it for the prophylaxis of TLS as in other adult studies. Also, owing to the small sample size, identification of factors associated with therapeutic failure, need for repeat dosing and dialysis was not possible. Large, multicentric studies are required to determine the same.

In conclusion, our study demonstrates the role of a single, fixed-dose of RUO in achieving rapid, adequate and sustained drop in serum urate levels as well as in improving renal function in paediatric TLS. The clinical utility, low cost, ease of administration and fewer adverse effects make this a promising strategy for managing TLS in resource-constrained settings.

Author Contribution Statement

AL: conceived and designed the study. JM, PGC: conducted the study, analyzed the data and drafted the paper; PM helped in data collection, analysis and in revising the manuscript. NK and AL: revised the manuscript for important intellectual content. The final manuscript was approved by all authors.

Acknowledgements

Ethical considerations

The study was approved by the Institution's Scientific Research Board and ethical approval was obtained from the Institution's Ethics Committee.

Availability of data

Study data is available with the corresponding author and may be provided upon request.

Conflict of Interest

The authors declare that they have no competing interests.

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