Review

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Posted Date: 22 April 2025

doi: 10.20944/preprints202504.1815.v1

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 doi:10.20944/preprints202504.1815.v1

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The Use of Single-Dose Rasburicase for the Prevention and Treatment Tumor Lysis Syndrome in Pediatric Patients: A Narrative Review

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Abstract: Rasburicase is licensed for the management of tumor lysis syndrome (TLS) at a daily dose of 0.2 mg/kg for five days. The use of a single-dose treatment is popular in adult oncology but information in pediatric use is limited. From a literature search, all case reports and series, comparative studies, and reviews in which pediatric oncology patients received single-dose rasburicase were selected for further analysis. Treatment success was determined by normalization of serum uric acid in the absence of serious complications. Thirteen articles with a total of 348 children were included. A fixed-dose regimen was used in 195, while 153 received weight-based dosing. With fixed dosing, successful treatment was seen in 91.8% and 89.2% at rasburicase doses ≥ 3mg and 1.5mg, respectively (P=0.23). However, there were four mortalities in the lower-dose group. For weight-based dosing, success was observed in 89.2% and 66.7% at doses ≥ 0.15 mg/kg and < 0.15mg/kg, respectively (P=0.0029). One child required dialysis in the lower-dose group. Single-dose rasburicase for the prevention and treatment of TLS in pediatric oncology is a pharmacoeconomically appealing approach. A fixed dose of at least 3mg or 0.15mg/kg by body weight is recommended.

Keywords: acute lymphoblastic leukemia; burkitt lymphoma; hyperuricemia; rasburicase; tumor lysis syndrome; urate oxidase

Introduction

Tumor lysis syndrome (TLS) is a severe metabolic event that complicates rapidly growing and bulky cancers that are often chemosensitive in both adults and children [1,2]. TLS is more commonly seen in hemic malignancies, but is occasionally encountered in patients with solid tumors [3,4]. The rapid cellular turnover and tumor breakdown results in a burst of intracellular electrolytes into the circulation and accelerated purine catabolism. This leads to increases in serum potassium, phosphate, xanthine, and uric acid, and decrease in serum calcium. TLS may occur spontaneously, but more often after the initiation of chemotherapy. Occasionally, a single dose of corticosteroid given as a premedication for treatment or prophylaxis of hypersensitivity reaction prior to blood product transfusion can unexpectedly trigger a full-blown TLS in patients with lymphoid malignancies [5,6]. Acute kidney injury with obstructive uropathy secondary to nephrolithiasis associated with xanthine, urate, or phosphate stones may result in renal shutdown and hypertension. Hyperkalemia may lead to cardiac arrhythmias. Hypocalcemia may result in tetany and seizures. Renal replacement therapy may be indicated for treatment of azotemia, fluid overload, hyperkalemia, hyperphosphatemia, and metabolic acidosis. Mortality may occur as a direct consequence from TLS or indirectly from infectious or hemorrhagic complications associated with simultaneous pancytopenia after chemotherapy [2].

Hande and Garrow were the first to propose diagnostic criteria for TLS and differentiate the milder, laboratory TLS from the more serious clinical category in 1993 [7]. Patients with laboratory

 doi:10.20944/preprints202504.1815.v1

TLS did not generally require additional treatment, whereas those who developed clinical TLS may deteriorate and require dialysis. With these parameters, they were able to show that clinical TLS was uncommon when lymphoma patients were treated with allopurinol. Pre-treatment renal insufficiency and elevated serum lactate dehydrogenase were predictive of the occurrence of clinical TLS. With the availability of new treatments in the new millennium, Cairo and Bishop built on the Hande-Garrow criteria and defined TLS with more relevant parameters [8]. In essence, abnormal biochemistries at baseline, in addition to significant changes from baseline, qualified for the diagnosis of TLS. Also, the time of occurrence spanned for a 10-day period and included spontaneous onset of TLS (Table 1). In the absence of TLS, Cairo and Bishop categorized patients into low-risk and high-risk groups with respect to their propensity to develop TLS according to their underlying malignancy, tumor burden, chemosensitivity, prevailing leukocyte counts, and serum lactate dehydrogenase measurement. Howard et al. further modified the criteria and eliminated the inclusion of fluctuations in biochemistry in the diagnosis. Moreover, at least two biochemical derangements had to be present simultaneously to qualify for the diagnosis of TLS. They also added symptomatic hypocalcemia as a parameter for the diagnosis of clinical TLS [9].

Table 1. Proposed diagnostic criteria for tumor lysis syndrome.

	Hande-Garrow (1993) [7]	Cairo-Bishop (2004) [8]	Howard-Pui (2011) [9]
Laboratory TLS	Two of the following within 4 days of treatment: Phosphate > 25% increase Potassium > 25% increase Uric acid > 25% increase Urea > 25% increase Calcium > 25% decline	Two of the following, 3 days before to 7 days after treatment commencement: Phosphate ≥ 2.1 mmol/L, or > 25% increase Potassium ≥ 6 mmol/L, or > 25% increase Uric acid ≥ 476 μmol/L (8 mg/dL), or > 25% increase Calcium ≤ 1.75 mmol/L, or > 25% decline	Two of the following at the same time, 3 days before to 7 days after treatment commencement: Phosphate ≥ 2.1 mmol/L or ULN Potassium ≥ 6 mmol/L or ULN Uric acid ≥ 476 μmol/L (8 mg/dL), or ULN Calcium ≤ 1.75 mmol/L, or LLN
Clinical TLS	Laboratory TLS + one of the following: Potassium > 6 mmol/L Creatinine > 221 μmol/L (2.5 mg/dL) Calcium < 1.5 mmol/L Severe cardiac arrhythmia Sudden death	Laboratory TLS + one of the following: Creatinine ≥ 1.5 ULN Cardiac arrhythmia Sudden death Seizure	Laboratory TLS + one of the following: Creatinine ≥ 1.5 ULN Cardiac arrhythmia Sudden death Seizure Symptomatic hypocalcemia
Remarks	Spontaneous TLS not included	Spontaneous TLS included	Spontaneous TLS included Abnormalities should not be attributable from other causes

Abbreviations: TLS, tumor lysis syndrome; ULN, upper limit of normal

Patients who are at risk for TLS are managed with vigorous intravenous hydration therapy and close monitoring of fluid balance and serum electrolyte changes [2,10]. Allopurinol, a xanthine oxidase inhibitor, is recommended to block the production of uric acid. Although uric acid is more soluble at higher urine pH and thus may benefit from alkalinization of urine, the increased risk of precipitation with phosphate stones may offset the potential benefits of adding sodium bicarbonate

 doi:10.20944/preprints202504.1815.v1

into the intravenous fluids [2,8]. Despite these measures, severe TLS that necessitates the use of rescue renal replacement therapy still occurs in more than 30% of high-risk non-Hodgkin lymphoma and acute leukemia cases [11]. The introduction of non-recombinant urate oxidase as an extract from Aspergillus flavus started a new chapter of a highly effective treatment for hyperuricemia associated with TLS [12]. By breaking down uric acid into the highly soluble allantoin, urate oxidase was found to be a game-changing compound in pediatric oncology. The non-recombinant product, however, was limited by its supply and potential toxicities related to hypersensitivity [12,13]. In 2002, the recombinant form of urate oxidase or rasburicase was approved by the Food and Drug Administration [13,14] following the successful results published by Goldman et al. [15] and Pui et al. [16] Based on the highly successful results on the management of hyperuricemia, intravenous rasburicase was licenced at a dose of 0.2 mg/kg/day for consecutively five days with the first dose given prior to the commencement of chemotherapy.

The author was the first to report on the use of rasburicase as a single-dose regimen in children at high risk for TLS [17]. In 2002, the year when rasburicase was commercially available, a 5-year-old male was admitted to the hospital with advanced stage Burkitt lymphoma with acute kidney injury. That time, rasburicase was not listed in the hospital formulary. To avoid the use of dialysis, the hospital administration gave permission to purchase a single dose of the urate oxidase, balancing the patient's need and the financial constraints. As rasburicase was supplied in a single box containing three 1.5mg doses, it was decided to use the 4.5mg (about 0.2mg/kg) as a single intravenous infusion. The child managed to go through the first five days of treatment with prednisolone, vincristine, and cyclophosphamide uneventfully, with normalization of serum uric acid and creatinine levels (unpublished observation).

Because of the successful experience, the hospital granted the permission of using rasburicase for the next three cases of lymphoid malignancies at risk for overt TLS. The results were published in 2003 [17]. The cases included two children (aged 11 and 13 years) with acute lymphoblastic leukemia and presenting leukocyte counts > 100 × 10[9]/L, and a 4-year-old child with Burkitt leukemia with laboratory TLS. All were treated with a fixed dose of rasburicase 4.5mg intravenously. The plan was to add on a second dose of rasburicase if the serum uric acid bounced back to normal ranges. However, all of them had rapid clearance of uric acid from the blood and the serum levels remained below the lower limit of normal throughout the first week, and hence only a single dose of rasburicase was used in each of them.

In the last two decades, our experience was successfully duplicated in various countries in both adult and pediatric patients with some modifications. In some centers, a fixed single dose was used with doses ranged from 1.5 mg to 7.5 mg [18–20]. Others employed a single dose calculated according to the body weight of the recipient [21–23]. There was a variation in the dosage that ranged from 0.05 mg/kg to 0.2 mg/kg of body weight. A recent systematic review and meta-analysis found 19 studies on the use of single-dose rasburicase for the management of TLS [24]. The majority of the studies were on adults and only four were conducted on pediatric patients. Because of the limited number of patients and inaccuracies inherent in the study, no meaningful conclusions could be made for the use of rasburicase as a single dose in children.

Thus, the current review was carried out to examine and summarize the experience of the use of single-dose rasburicase in pediatric hematology and oncology from the published literature.

Methods

A literature review was conducted across the databases of MEDLINE, EMBASE, and PUBMED using keyword search with the terms "rasburicase" AND ("single dose" OR "fixed dose") AND ("child" OR "pediatric"). Additional searches were made by going through the citations from the selected publications. Articles that described or studied the use of single-dose rasburicase for the prevention and treatment of TLS in pediatric oncology patients, 18 years old or less, were included. For studies that included both adult and pediatric patients, only the pediatric data were extracted for the purposes of this study. Conference abstracts were excluded.

 doi:10.20944/preprints202504.1815.v1

TLS was classified into laboratory and clinical forms according to clinical and laboratory data as described by the Cairo-Bishop criteria, that occurs three days before or seven days after the commencement of anti-cancer therapy [8]. Fixed dosing was defined as the use of the same dose of rasburicase for all patients in the same study irrespective of age or body weight, or at most a 2-tier system in which two different doses of the drug were used according to a pre-defined age or weight. Weight-based dosing was defined as a calculated dose of rasburicase according to body weight, or a more than 2-tier system in which progressively higher doses of rasburicase was prescribed in accordance with increasing body weight or age.

Treatment success referred to the normalization of serum uric acid after 24 or 48 hours of treatment if the patient was hyperuricemic at the beginning, or maintenance of normal serum levels if the initial uric acid measurement was not elevated, without the use of renal replacement therapy, serious cardiac arrhythmias, or death during induction treatment from any cause.

The patients' age, sex, primary diagnosis, occurrence of laboratory or clinical TLS, how the rasburicase was dosed, and treatment outcome were described as far as the data could be extracted from each publication. They were categorized into two groups according to the way rasburicase was dosed, namely, fixed dosing and weight-based dosing. Within each group, patients were further divided into a higher-dose and a lower-dose group. With fixed dosing, the higher-dose group referred to a rasburicase dose of 3mg or more, while the lower-dose referred to a dose of 1.5mg or less. For patients treated on weight-based dosing, the higher-dose group corresponded to a dose of 0.15mg/kg or more, while the lower-dose group corresponded to dose ranges of 0.1-0.15mg/kg, 0.1mg/kg or less.

Categoric data were compared using Fisher exact test, 2-tailed, with the GraphPad online calculator (https://www.graphpad.com/quickcalcs/contingency1/). A P value of < 0.05 was considered significant.

Results

After deduplication, the literature search yielded 61 publications. Twenty-seven publications were excluded as they did not meet the inclusion criteria. Twenty meeting abstracts were also excluded. Of note, 10 of the abstracts were followed by full papers that were included in the later analysis. One systematic review and meta-analysis that included both adult and pediatric patients was identified [24]. The other 13 articles that included a total of 348 pediatric patients treated with single-dose rasburicase for prevention and treatment of TLS were included for analysis.

Among the 13 publications, there were four case reports that detailed the treatment of 13 children [17,21,25,26], five case series containing 148 children [27–31], three case series with patients of all ages of which 139 were pediatric patients [32–34], and a comparative study in which 48 children were randomized to receive different doses of rasburicase [35]. The findings were summarized in Table 2.

Table 2. Summary of the 13 case reports and series of pediatric oncology patients treated with single-dose rasburicase.

References	Sex/Age	Diagnosis	TLS	WBC ($\times 10^9$/L)	Urate (mg/dL)	Creatinine (mg/dL)	Rasburicase dose	Remarks
Case Reports								
Lee	M/11	ALL	Lab	173	13.8	1.3	4.5 mg	Resolved
	M/4	BL	Lab	NA	11.9	0.5	4.5 mg	Resolved
	M/13	ALL	Lab	198	11.4	?	4.5 mg	Resolved
Latha	M/8	ALL	Clinical	5.41	18.4	3	0.15 mg/kg	Resolved

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	F/7	ALL	Clinical	24.7	30	2.9	0.15 mg/kg	Resolved
	M/13	ALL	Clinical	4.67	32.2	2.1	0.15 mg/kg	Resolved
	M/13	ALL	Clinical	1.10	23.6	2.6	0.15 mg/kg	Resolved
	F/12	ALL	Clinical	0.68	9.7	1.7	0.15 mg/kg	Resolved
	M/6	ALL	Clinical	522	31.2	1.8	0.15 mg/kg	Resolved
	M/13	ALL	Lab	34.8	10.3	1.4	0.15 mg/kg	Resolved
Hooman	M/5	ALL	Clinical	38.7	44	2.8	0.1 mg/kg	Resolved
Liu	?/8	ALL	Lab	>400	13.2	0.8	6 mg	Hyperurice mia resolved
	?/1.5	ALL	Lab	120	8.5	0.5	2.5 mg	Well
Case series (pediatrics)								
Syrimi	19 cases	ALL/WBC>100 NHL III/IV NBL HB	Lab 5 HR 14	?	?	?	0.2 mg/kg	Successful prophylaxis after single dose in 15 and > 1 doses in 4 when urate rebound > 400µmol/L
Jayabose	41 cases	ALL 36 NHL 4 AML 1	Lab 36 HR 5	?	>7 in 36	≥1.3 in 9	0.1-0.15 mg/kg	Successful prophylaxis after single dose in 27 and > 1 doses in 13 1 needed dialysis
Alavi	48 cases	ALL 22 AML 4 NHL 5 WT 5 Others 12	Lab 45 Clinical 3	?	Elevated in all	Elevated in 3	0.2 mg/kg	Successful after single dose in 44 and > 1 doses in 4
Appaji	22 cases	ALL 15 NHL 7	Lab 16 Clinical 6	?	10.7-34.5	Elevated in 15	1.5 mg	Successful after single dose in 20 and > 1 doses in 2

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Gopakumar	18	ALL 12 NHL 6	All had Clinical/Lab TLS	?	?	?	1.5 mg	6 needed > 1 doses; 2 needed dialysis; 2 died from TLS; 1 died from bleeding; 1 died from infection
Case series (pediatric cases extracted from the whole series)								
Gupta	24 (< 18yo) cases (out of 55)	?	? (21.8% of 55 had TLS)	?	?	?	1.5 mg (<30 kg) in 6; 3 mg (>30 kg) in 18	Successful after single dose in all
Philips	105 (< 18yo) cases (out of 186)	?	? (68.2% of 186 had TLS)	?	?	?	1.5 mg	Pediatric outcome not mentioned; 2 needed dialysis and 6 deaths in the whole group
Kukkar	10 pediatric cases (out of 15)	?	Not classified	?	?	?	0.15 mg/kg	Successful after single dose in all (urate < 7.5)
Comparative study								
Savva	48 cases	Leukemia 34 Lymphoma 10 RMS 4	Lab 33 HR 15	?	?	?	WBD: 0.15-0.2 mg/kg vs FD 6 mg flat	Normalization of urate (< 5 mg/dL) at 24hr: WBD, 23/27 FD, 17/21 (P=0.715)

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BL, Burkitt lymphoma; FD, fixed dosing; HB, hepatoblastoma; HR, high-risk; Lab, laboratory; NA, not available; NBL, neuroblastoma; NHL, non-Hodgkin lymphoma; RMS, rhabdomyosarcoma; TLS, tumor lysis syndrome; WBC, white blood cell count; WBD, weight-based dosing; WT, Wilms tumor; yo, years old; ?, not specified.

The exact underlying malignancies were specified in 200 children. They included acute lymphoblastic leukemia (97, 48.5%), acute myeloid leukemia (5, 2.5%), unspecified leukemia (34, 17.0%), non-Hodgkin lymphoma (43, 21.5%), and solid tumors (21, 10.5%).

The indications for the use of rasburicase were specified in 209 cases. Treatment for TLS was the indication in 175 (83.7%). Among them, the TLS was classified as laboratory (141, 67.5%), clinical (16, 7.6%), or unspecified (18, 8.6%). Thirty-four (16.3%) were treated with rasburicase when they were considered high risk for TLS.

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A fixed dose of rasburicase, ranging from 1.5 mg to 6 mg, was used in 195 cases. At a single dose of 3 mg, 4.5 mg, or 6 mg, successful treatment was seen in 45 (91.8%) of 49 cases. Hyperuricemia resolved or was prevented in the other four patients with additional doses of rasburicase. A dose of rasburicase at < 3 mg was used in 146 children, but the response to treatment was only available in 47. Thirty-nine (84.8%) responded successfully to a single dose of rasburicase. The difference was not statistically significant (P=0.23). However, among the 18 children with TLS who received a dose of rasburicase 1.5 mg as reported by Gopakumar et al., two of them required dialysis and succumbed to the complications of TLS [29]. Another two children died from bleeding and infection, respectively. Philips et al. reported 186 adults and children of which 105 patients were under 18 years of age. All of them received a single dose of rasburicase 1.5 mg. Two patients needed dialysis and there were six mortalities [32]. However, it was not mentioned if any of the pediatric patients were affected by these adverse events.

In 153 children, the dose of rasburicase administered was based on the child's body weight. The doses or dose ranges included 0.1 mg/kg in 1 (0.7%), 0.1-0.15 mg/kg in 41 (26.8%), 0.15 mg/kg in 17 (11.1%), 0.15-2.0 mg/kg in 27 (17.6%), and 0.2 mg/kg in 67 (43.8%), respectively. Successful treatment was reported in 89.2% (99/111) of the higher dose group who received ≥ 0.15 mg/kg of rasburicase, whereas 66.7% (28/42) succeeded in the lower dose group (P=0.0029). No serious complications were observed in the higher dose group, but one child who received <0.15 mg/kg of rasburicase needed dialysis [31]. No mortality was reported, however.

Yu et al. performed a systematic review and meta-analysis from 19 clinical studies on the use of single-dose rasburicase in adult and pediatric patients published before July 2016 [24]. They included 15 adult studies with 906 subjects. Their analysis concluded that a single dose of rasburicase at 6 mg, 7.5 mg, or 0.15 mg/kg consistently and significantly lowered serum uric acid compared with single doses of 4.5 mg or less. For pediatric patients, only two studies published in full paper containing 26 children were included. Thus, no specific conclusion could be reached.

Discussion

Tumor lysis syndrome is a unique combination of metabolic derangements that complicates advanced, rapidly proliferating, and often chemo-sensitive malignancies. The hallmarks of the accelerated cellular breakdown comprise hyperkalemia, hyperphosphatemia, hypocalcemia, and hyperuricemia. Each of these biochemical abnormalities carries its own specific toxicities and together they may jeopardize the cardiovascular system, central and peripheral nervous system, and may cause acute kidney injury. In particular, the precipitation of uric acid crystals and/or calcium phosphate in the renal tubules may lead to acute renal failure and the need for dialysis treatment [1,2,8].

The prevention and control of elevated serum uric acid levels and its crystallization in the renal tubules is the mainstay treatment in TLS in both adult and pediatric patients. The management starts with recognizing TLS as an inherent risk at the time of diagnosis and prior to anti-cancer therapy in most extra-cranial malignancies [2]. The propensity of any patient to develop TLS depends on the underlying oncologic diagnosis and disease burden, the patient's health status such as age and pre-existing renal disorders, and the planned treatment and its likelihood for rapid response [36]. Hyperhydration (with isotonic fluids > 3 L/m[2]/24 hours) with forced diuresis to avoid excessive fluid retention and close monitoring and fluid and electrolytes balance is a universally adopted treatment before and during the induction treatment for cancer or leukemia. For patients at low-risk (< 1%) for TLS, additional pharmacologic treatment may not be necessary [9,36].

For patients at intermediate- or high-risk (1-5% or > 5%, respectively) for TLS, the use of allopurinol, a xanthine oxidase inhibitor that stops the breakdown of hypoxanthine and xanthine into uric acid, is commonly used [36]. Compared with febuxostat, another xanthine oxidase inhibitor, allopurinol is still the preferred treatment because of its lower cost, faster onset of action, and lack of cardiovascular toxicities [2]. Treatment with febuxostat is indicated when the patient is allergic or

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intolerant to allopurinol, or when the patient is tested positive for HLA-B58:01 that predicts allopurinol hypersensitivity reactions [37]. However, the efficacy of allopurinol in patients at high-risk for TLS is controversial as xanthine is less soluble than allopurinol and hence patients are still at risk for acute kidney injury with xanthine stones [38,39].

The availability of intravenous rasburicase, a recombinant urate oxidase, provides an effective way to treat TLS and to prevent its occurrence in at risk patients. Two landmark studies were published in 2001 that led to its approval by the Food and Drug Administration. Pui et al. [16] treated 131 children and young adults aged 20 years or less with leukemia or lymphoma prospectively. They were given rasuburicase 0.15 mg/kg or 0.2 mg/kg for five to seven consecutive days because of high disease burden or hyperuricemia. A rapid fall in serum uric acid was seen at four hours after treatment and none required dialysis. Goldman et al. [15] randomized 52 children with leukemia or lymphoma, with either large disease burden or hyperuricemia, to treatment with allopurinol or rasburicase. Allopurinol was dosed at 300 mg/m2 divided in three daily doses in 25 children and rasburicase was given at 0.2 mg/kg daily for five to seven days in 27 cases. Patients who received rasburicase had significantly lower serum uric acid levels starting from 4 hours to 96 hours after first dose. Among those with hyperuricemia, the baseline creatinine at 144% of age/sex-defined mean dropped to 102% after 4 days in the rasburicase group. The corresponding measurements were 132% and 147% in the allopurinol. One patient who received allopurinol treatment required dialysis. As a result, rasburicase treatment was recommended at a dose of 0.2 mg/kg daily for five days for the treatment and prevention of tumor lysis syndrome [13].

The initial success of the first patient we treated with rasburicase in which 20% of the recommended dose aborted a seemingly doomed complication was encouraging. A retrospective study reporting on the compassionate use of rasburicase published in 2001 in which 173 pediatric and 72 adult oncology patients were treated with rasburicase 0.2 mg/kg daily for one to seven days suggested that the treatment might be effective when used less than the recommended duration of treatment [40]. And our next three cases were therefore treated in the same manner with a single, fixed dose of 4.5 mg intravenously four hours prior to the commencement of chemotherapy [17]. In the following years, as mentioned in previous sections, alternative regimens using single fixed doses that were different from ours, or single, weight-based dosing were reported. In 2010, Giraldez and Puto mentioned that most US centers had a protocol of a single, flat dose ranging from 3 mg to 9 mg for the treatment and prevention of TLS [41].

In 2016, Yu et al. [24] published a systematic review and meta-analysis on prospective or retrospective studies and randomized clinical trials of the use of single-dose rasburicase for the management of TLS in either adult or pediatric patients. They identified 15 studies in adult patients. Pooling the data together, their analysis found that, when a single fixed dose of rasburicase was used, the response rates were superior with 6 mg (0.90; 95% confidence interval 0.83 – 0.97) and 7.5mg (0.99; 95% confidence interval 0.96 – 1.00) than lower doses. With weight-based dosing, the response rate from a dose of 0.15 mg/kg (0.94; confidence interval 0.86 – 1.00) was better than lower-dose regimens.

With respect to pediatric data, Yu et al. [24] drew reference to four publications with a total of 92 children. However, two of the reports were conference abstracts from India in 2013 that were not followed by any full publication [42,43]. Of the remaining two studies, Yu et al. collected 53 cases published by Syrimi et al. [28] However, a closer look at the publication found that only 19 of them received a single dose of rasburicase. Thus, the analysis concerning pediatric data was inaccurate. Added to the seven cases reported by Latha et al. [26], the systematic review only recovered 26 children managed with a single-dose rasburicase and hence no meaningful recommendations could be made.

Nevertheless, with the consistent effectiveness of single-dose rasburicase used at adequate dosages, the regimen is now popular. Compared with the standard dosing, the use of single-dose rasburicase comes with a significant financial advantage. Among adult patients, the adoption of single-dose regimens results in a 90% cost saving or about USD20,000 per patient prior to the year

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2010 [18,22]. Although the absolute saving among pediatric patients is less compared with adults, the percentage and actual cost reduction is still substantial [17,21].

It should be noted that single-dose rasburicase treatment is not associated with less side effects compared with the standard dosing. In particular, acute hemolysis in subjects with glucose-6-phosphate dehydrogenase (G6PD) deficiency often occurs after the first dose [44,45]. Therefore, the precaution of excluding patients with G6PD deficiency prior to the commencement of rasburicase cannot be over-emphasized [46].

Although the current review is able to gather a total of 348 children treated with a single dose of rasburicase from the medical literature, it is limited by the quality of data due to the heterogeneity of the design, the non-randomized and retrospective observational nature of the studies. Nevertheless, a minimal flat dose of 3 mg or a calculated dose of 0.15 mg/kg as a single dose appears to be safe and cost-effective in the prevention or treatment of TLS in pediatric hematology and oncology patients.

Disclosure: The author declares no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The author had full access to all the data in the review and takes responsibility for the integrity of the data and the accuracy of the data analysis. The author attests to meeting the four criteria recommended by the ICMJE for authorship of this manuscript.

Abbreviations: G6PD, glucose-6-phosphate dehydrogenase; TLS, tumor lysis syndrome.

Ethical Approval and Informed Consent: Not applicable.

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