IJBC 2016; 8(2): 33-37

Iranian Journal of Blood & Cancer

Journal Home Page: www.ijbc.ir

ORIGINAL ARTICLE

The Efficacy of Single Dose Rasburicase in Prevention or Treatment of Tumor Lysis Syndrome in Children

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ARTICLE INFO

Article History:
Received: 01.02.2016
Accepted: 26.04.2016

Keywords:
Malignancy
Rasburicase
Hyperurecemia
Tumor lysis syndrome

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ABSTRACT

Background: Tumor lysis syndrome (TLS) is a major metabolic complication in patients with malignancy after initiation of chemotherapy or spontaneously without treatment. The role of Rasburicase (a recombinant urate-oxidase enzyme) in prevention and treatment of TLS has been demonstrated in recent years. We aimed to investigate the efficacy of a single dose of rasburicase in reducing the risk of TLS in children at high risk.

Methods: we conducted a retrospective analysis of 560 children with various malignancies in a single referral center. On the basis of the reference values previously established in our center hyperuricemia and TLS were defined. Tumor lysis syndrome development was the primary outcome. 48 children with a mean age of 7.1 years (range: 3 months to 15.8 years) developed tumor lysis syndrome. The most common malignancies were B-precursor acute lymphoblastic leukemia (ALL) (45%) followed by non-Hodgkin lymphoma (NHL) and Wilms' tumor (each 10.4%), respectively. They received normal saline intravenously at a rate of 4-5 L/m^2/day in 24-48 hours prior to initiating chemotherapy. Plasma samples were drawn to detect uric acid, calcium, phosphate, potassium, creatinine and blood urea nitrogen (BUN) 4 hours before administering a single dose of IV rasburicase (0.2 mg/kg over 30 minute). Laboratory markers were evaluated again 4 and 24 hours after administering rasburicase.

Results: All patients with diagnosis of TLS had significantly decreased uric acid levels following single dose of rasburicase except 1 patient (2.1%) (P<0.001). Mean plasma uric acid concentration before treatment was 10.0±4.2 mg/dL and 4 hours after treatment declined to 2.2±5.5 (P<0.001). Hyperphosphatemia was also detected in 43.7% of these 48 cases which significantly decreased to 16.7% (P=0.012). Plasma uric acid levels remained low one day after treatment. No side effects were detected.

Conclusion: Rasburicase is a safe and highly effective drug in children with hyperuricemia in the setting of malignancy at risk of developing TLS.

Please cite this article as: Alavi S, Ebadi M, Esteghamati S, Kaji Yazdi M. The Efficacy of Single Dose Rasburicase in Prevention or Treatment of Tumor Lysis Syndrome in Children. IJBC 2016; 8(2): 33-37.

Introduction

In the presence of myeloproliferative disorders and hematologic malignancies, nucleic acids, resulting from increase in tumoral cell mass are catabolized. Increase in purine metabolism results in hyperuricemia and tumor lysis syndrome (TLS).[1] Tumor lysis syndrome occurs due to the release of tumor cell contents leading to electrolyte abnormalities including hyperkalemia, hyperphosphatemia, hyperuricemia, and metabolic acidosis.[2] It may result in acute renal failure (ARF) due to the deposit of excessive amounts of uric acid crystals in renal tubules and cause renal failure with consequent negative influence on the disease prognosis.[3] Despite careful management of metabolic disturbances in order

to decrease the likelihood of developing ARF, it is still observed in 25% of pediatric patients with advanced Burkitt lymphoma and type B ALL.[4,5]

Rasburicase (Elitek®) is a recombinant urate-oxidase enzyme produced by a genetically modified Saccharomyces cerevisiae strain[6] which can be used in both prevention and rapid management of hyperuricemia. The superiority of Rasburicase to other medications including allopurinol in both prophylaxis and treatment of TLS has been reported in several studies.[1,7,8] An advantage of rasburicase over allopurinol is that by inhibiting urate-oxidase, rather than xanthine oxidase, xanthine will not accumulate, hence preventing xanthine nephropathy.[8] By comparing two groups of pediatric patients who received comparable chemotherapy regimens, 2.6% of patients in rasburicase group required dialysis vs. 16% in the allopurinol group.[9] Rasburicase has been the focus of attention especially for pediatric oncologists as an effective factor in the prevention of TLS, nonetheless no study has evaluated its efficacy in our country.

Herein, the authors aimed to study the effects of single dose rasburicase on pediatric patients with malignancies who developped TLS in a referral pediatric center from Iran.

Patients and Methods

In this cross-sectional study, all children (<18 years old) with malignancy in a period of 10 years, presenting to our center were analyzed for the development of TLS. TLS was defined as serum uric acid level higher than 7.5 mg/dL or serum creatinine or lactate dehydrogenase (LDH) level two-folds higher than the upper limit of normal range. Rasburicase was prescribed for patients with evidence of TLS without any history of atopia, asthma or glucose 6-phosphate dehydrogenase (G6PD) deficiency , since rasburicase is contraindicated in these patients.[2] In addition, patients who were previously treated with rasburicase, Uricozyme or allopurinol within the previous 7 days were not included.

48 out of 560 patients had developed TLS. Intravenous normal saline (4-5 liters/m^2/day) was initiated 24-48 hours before starting chemotherapy. Four hours before administering rasburicase, blood samples were drawn and serum levels of uric acid, LDH, calcium, phosphorus, potassium, creatinine as well as leukocyte count were measured. chemotherapy was initiated 4-24 hours after the first dose of rasburicase (i.e., all patients received rasburicase before or during the first cycle of chemotherapy). A single dose rasburicase was administered intravenously (0.2 mg/kg in 30 minutes). Serum uric acid levels were measured 4 and 24 hours after using rasburicase.[4] Also, calcium, phosphorus, potassium, creatinine and BUN serum levels were measured once more after rasburicase administration. A checklist was designed which included various items including age, sex, initial diagnosis, laboratory assays, and any side effects attributed to rasburicase. Mean and standard deviation (±SD) were used to express continuous data and frequency (percentage) for categorical data. The efficacy of rasburicase in decreasing serum levels of assayed markers was tested by repeated measure analysis with a confidence level of 95%. A P value of 0.05 was considered statistically significant.

Primary endpoint was regarded as the development of TLS, either laboratory or clinical TLS, as defined by Cairo and Bishop[10]; briefly, the diagnosis of laboratory TLS was made when 2 or more abnormal laboratory test results were detected 3 days prior to or 7 days after starting chemotherapy including:

uric acid >7.5 mg/dL or 25% increase from baseline; Potassium >6 mmol/L or 25% increase from baseline; Phosphorous >4.5 mg/dL or 25% increase from baseline; Calcium >7 mg/dL or 25% decrease from baseline.

Clinical TLS was described as the presence of laboratory TLS combined with one clinical sign including creatinine> 1.5 times upper normal limit; cardiac arrhythmia; sudden death and seizure.[2] Secondary outcome was described as adverse events especially acute kidney injury Significant reduction in serum uric acid (<6.5 mg/dl) and creatinine was also evaluated as the secondary outcome. Complete physical examination and toxicity assessment were performed at 4 and 24 h after receiving rasburicase.

Parents were informed about the study protocol and written informed consent was obtained. The study protocol was approved by the ethics committee of Shaheed Beheshti university of medical sciences and was in accordance with the ethical guidelines of the 1975 Declaration of Helsinki.[11]

Results

Twenty eight (58.3%) girls and 20 (41.7%) boys with a mean age of 7.1 (±4.5) years (range: 3 months-15.8 years) with various malignancies developed TLS (table 1). 3

Table 1: Frequency distribution of malignancies diagnosed in 48 pediatric patients treated by rasburicase

	Frequency	Percentage
B-precursor ALL (acute lymphoblastic leukemia)	22	45.8%
Non-Hodgkin lymphoma	5	10.4%
Wilms' tumor	5	10.4%
Acute myeloblastic leukemia	4	8.3%
Neuroblastoma	3	6.3%
Juvenile myelomonocytic leukemia	3	6.3%
Mature B-cell ALL	2	4.2%
T-cell ALL	1	2.1%
Germ cell tumor	1	2.1%
rhabdomyosarcoma	1	2.1%
Adrenal carcinoma	1	2.1%

(6.25%) children had renal failure at baseline. Table 2 shows the baseline characteristics of the patients before administering rasburicase.

Secondary Outcome

A total of 97.91% of patients with TLS responded to treatment with rasburicase (normalization of uric acid levels). All laboratory markers improved both 4 h and 24 h after rasburicase therapy; changes in uric acid, BUN, Phosphorus and calcium were significant, whereas creatinine and potassium improved only slightly without a statistically significant difference (table 3). However, the number of patients with significant improvement in laboratory markers was only significant in terms of hyperurecemia which decreased from 48 patients to 1 patient. Mean±SD uric acid level was initially 10±4.2 mg/dL which significantly decreased to 2.2±5.5 after 4 hours (P<0.001). Serum uric acid level remained low after 24 hours and its maximum level was 21 mg/dL; nonetheless, hyperuricemia recurred in 4 children including a 7-year-old female with B-precursor ALL and a 2-year-old girl with acute myelogenous leukemia (AML). These patients received a second injection of rasburicase, leading to correction of hyperuricemia. The other patient who suffered hyperuricemia after 24 hours included a 12-year-old boy with mature B-cell ALL, requiring a second administration of rasburicase. The fourth patient was a 3-month-old girl with B-precursor ALL who required rasburicase for 4 times to reach a normal uric acid level.

The number of patients with other abnormal laboratory markers also decreased, yet the difference was not significant (table 4). As shown in tables 3 and 4, all patients had hyperuricemia and 3 (6.25%) had renal failure at baseline which decreased to 2 patients after rasburicase therapy. No side effect including nausea, vomiting, fever, headache, abdominal pain, constipation, diarrhea, mucositis or rash was reported in the patients.

Discussion

Herein, the efficacy and safety of rasburicase in children

Table 2: Baseline characteristics of 48 pediatric patients with malignancies before administering rasburicase are depicted

	B-precursor ALL (N=22)	NHL (N=5)	Wilms' tumor (N=5)	AML (N=4)	Others (N=12)	Total (N=48)
Age, year	7.7 (±5)	11.2 (±2.6)	5.4 (±0.8)	4.1 (±3.5)	6.1 (±4.1)	7.1 (±4.5)
Gender, male	8	2	3	1	6	20
Leukocyte count, $\times 10^9$	54.7 (±66.7)	8.7 (±3.8)	11.1 (±2.9)	34.2 (±20.3)	48.1 (±56.3)	42.7 (±56.1)
Hemoglobin, gr/dL	9.5 (±2.8)	9.7 (±2.2)	10.3 (±2.0)	8.8 (±1.3)	8.7 (±1.8)	9.3 (±2.3)
Platelet count, $\times 10^9$	86.0 (±63.5)	348.6 (±249.6)	363.3 (±4.1)	139 (±15.7)	171.9 (±204)	164 (±170.5)
Uric acid, mg/dL/N*	9.5 (±3.0)/22	10.9 (±2.7)/5	10.4 (±1.2)/5	8.8 (±1.3)/4	10.9 (±7.1)/12	10 (±4.2)/48
BUN, mg/dL/N*	18.8 (±11.7)/5	13.4 (±2.2)/0	10.6 (±5.8)/0	11.0 (±5.5)/0	24.4 (±28.3)/3	18.0 (±16.4)/8
Cretinine, mg/dL/N*	0.7 (±0.4)/1	0.7 (±0.2)/0	0.6 (±0.4)/0	0.5 (±0.1)/0	1.1 (±1.4)/2	0.8 (±0.8)/3
Calcium, mg/dL /N*	9.0 (±1.4)/21	9.6 (±1.0)/5	8.8 (±0.7)/5	9.5 (±0.8)/4	8.6 (±1.3)/11	9.0 (±1.2)/46
Phosphorus, mg/dL/N*	4.6 (±1.9)/10	4.2 (±0.6)/1	3.8 (±0.8)/1	4.8 (±2.0)/3	4.7 (±2.0)/6	4.5 (±1.7)/21
Potassium, mg/dL/N*	4.1 (±0.7)/0	4.0 (±0.4)/0	5.0 (±1.5)/1	4.6 (±0.6)/0	4.2 (±0.8)/0	4.2 (±0.8)/1

N* presents number of patients with abnormal level in each malignancy category
All data are presented as mean (±standard deviation) except for gender which is frequency.

Table 3: Comparison of uric acid, creatinine, BUN, calcium, phosphorus, and potassium serum values at baseline, 4 hours and 24 hours after using rasburicase in 48 pediatric patients with malignancies

	Baseline	4 hours	24 hours	P value
Uric acid, mg/dL	10 (±4.2)	2.2 (±2.5)	2.1 (±3.2)	<0.001
BUN, mg/dL	18 (±16.4)	15.1 (±16)	14.7 (±15.9)	0.043
Creatinine, mg/dL	0.8 ±(±0.8)	0.7 (±0.5)	0.7 (±0.8)	0.221
Calcium, mg/dL	9 (±1.2)	8.8 (±9.4)	8.5 (±0.85)	0.079
Phosphorus, mg/dL	4.5 (±1.7)	4.2 (±1.3)	3.8 (±0.9)	0.007
Potassium, mg/dL	4.2 (±0.8)	4.1 (±0.9)	4 (±0.8)	0.486

P values were obtained applying Friedman test and repeated measure analysis

Table 4: Comparison of the frequency of patients with abnormal laboratory values at baseline, 4 hours and 24 hours after administration of rasburicase

	Baseline	4 hours	24 hours	P value
Hyperuricemia	48 (100%)	1 (2.1%)	1 (2.1%)	<0.001
Elevated BUN	8 (16.7%)	5 (10.4%)	7 (14.6%)	0.861
Elevated creatinine	3 (6.25%)	2 (4.2%)	2 (4.2%)	0.861
Hypercalcemia	46 (95.8%)	48 (100%)	43 (89.6%)	0.058
Hyperphosphatemia	21 (43.75%)	18 (37.5%)	8 (16.7%)	0.012
Hyperkalemia	1 (1.2%)	1 (1.2%)	1 (1.2%)	1

P values were calculated by Pearson chi-squared test

with tumor lysis syndrome was investigated in a single pediatric oncology center in Tehran, Iran. Rasburiucase was found to effectively decrease hyperuricemia, and hyperphosphatemia, but not other electrolyte abnormalities. In addition, it significantly decreased the number of patients with hyperphosphatemia after 24 hours ($P<0.05$), but not other abnormalities. Response rate was 97.91% (47/48) in this study which is in the same line with the 93% response rate observed in a meta analysis on prospective observational studies.[12] However, the number of patients with significant improvement in laboratory markers was only significant in terms of hyperurecemia which decreased from 48 patients to 1 patient. Previously some studies have pointed to high baseline uric acid levels and white blood cell counts as determinants of poor response rate.

TLS mostly develops in patients with NHL, ALL and AML,[13] accordingly most patients in this study had ALL and NHL. It is well described in the literature that hyperurecemia is the most important factor in the development of TLS, therefore, the cardinal purpose of applying rasburicase is to decrease uric acid levels followed by TLS prevention.

Rasburicase is known as a safe and effective urolytic agent for the management of malignancy-associated hyperuricemia in patients suffering from leukemia or lymphoma including those with hyperleukocytosis.[14-16] Introduction of rasburicase as an effective medication in preventing chemotherapy-associated hyperuricemia and TLS has led to studying this agent in different patient populations. Most studies on pediatric patients have demonstrated promising results.[16] Moreover, its superiority over other agents has been described. Goldman et al.[1] compared allopurinol with rasburicase (0.2 mg/kg) in 52 children with leukemia or lymphoma at high risk for TLS. At the end of the trial, mean serum uric acid level was lower in the rasburicase group (7.1 mg/dL) vs. allopurinol group (7.8 mg/dl), indicating the greater efficacy of rasburicase. In addition, uric acid decline was found to be more rapid in the rasburicase group; it declined significantly in 86% of patients after 4h of administration. They concluded that rasburicase is an effective alternative to allopurinol in patients with leukemia or lymphoma undergoing chemotherapy. In another study[15] the usefulness of rasburicase (0.15 or 0.2 mg/kg) in 131 children or adolescents with recently diagnosed leukemia or lymphoma was assessed for 5-7 days. Similar to our findings, a rapid decline in uric acid level was observed in all patients. The authors increased the dose to 0.2 mg/kg, since hyperuricemia was not corrected in some patients and therefore an additional 0.2 mg/kg dose of rasburicase was administered in these patients. In addition, uric acid can increase after the first 24-hour of starting chemotherapy, hence close monitoring of serum uric acid level seems crucial. Likewise in the present study, hyperuricemia recurred in 8.33% (4/48) of patients after the first dose. Three of these patients, a 7-year-old female with B-precursor ALL and a 2-year-old girl with acute myelogenous leukemia (AML) and a 12-year-old male with B-cell ALL, accomplished normal serum uric acid levels after the second injection after 24 h. Nonetheless, the fourth patient, 3-month-old girl with B-precursor ALL, underwent 4 consequent injections to reach a normal uric acid level.

Since TLS is observed 6-72 h after initiation of therapy, 2 sets of evaluation was performed 4-24 h after initiation of rasburicase in this study in accordance with the FDA guidelines.[17] Also, the dosage which has been recommended by the FDA for children is 0.15 - 0.2 mg/kg once daily for maximum period of 5 days.[17] Therefore, a single dose of 0.2 mg/kg was used in this study.

Rasburicase is usually well tolerated; however, serious side effects may occur such as anaphylaxis, rash, hemolysis, and mehemoglobinemia. Fortunately these serious adverse events are rare and only occur in less than 1% of patients.[17] In the current study, no major or minor side effect was observed. In addition to significant decrease in uric acid level, serum phosphorus as well as BUN level decreased significantly. Shin et al.[18] also reported similar findings regarding significant decrease in phosphorus level after administering rasburicase in pediatric patients. Hyperphosphatemia is frequently observed after chemotherapy due to release from malignant cells. Released phosphate forms a complex with calcium, followed by deposition in kidney tubules with consequent development of kidney injury. In addition to malignant tumoral mass, chemotherapy per se can result in hyperphosphatemia.[19] Before starting rasburicase in this study, almost half of the patients (43.5%) had hyperphosphatemia which significantly decreased to about 17% after 24 hours. Although mean values for BUN decreased significantly after 24 hours, the number of patients with abnormal BUN at baseline (8 cases) did not significantly decrease after 24 hours (7 cases). About hyperkalemia, we could not conclude a significant finding as there was only one patient with hyperkalemia and after 24 hours there was still one patient with hyperkalemia. The same applied to serum creatinine level as there were 3 patients with abnormally elevated levels of creatinine which decreased to 2 patients after 24 hours.

Conclusion

Although rasburicase is widely used in developed countries for prophylaxis against chemotherapy-associated hyperuricemia, the experience with this medication in our country is limited. Rasburicase was found to be an effective and safe medication in the management of hyperuricemia, hence the authors recommend its usage in pediatric patients with malignancies at risk for TLS and hyperuricemia.

Conflict of Interest: None declared.

References

1. Goldman SC, Holcenberg JS, Finklestein JZ, Hutchinson R, Kreissman S, Johnson FL, et al. A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis. Blood. 2001; 97(10):2998-3003. doi: http://dx.doi.org/10.1182/blood.

V97.10.2998.
2. Cairo MS, Coiffier B, Reiter A, Younes A, TLS Expert Panel. Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: an expert TLS panel consensus. Br J Haematol. 2010; 149(4):578-86. doi: 10.1111/j.1365-2141.2010.08143.x. PubMed PMID: 20331465.
3. Bosly A, Sonet A, Pinkerton CR, McCowage G, Bron D, Sanz MA, et al. Rasburicase (recombinant urate oxidase) for the management of hyperuricemia in patients with cancer: report of an international compassionate use study. Cancer. 2003;98(5):1048-54. PubMed PMID: 12942574.
4. Coiffier B, Altman A, Pui CH, Younes A, Cairo MS. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol. 2008;26(16):2767-78. doi: 10.1200/JCO.2007.15.0177. PubMed PMID: 18509186.
5. Oda M, Satta Y, Takenaka O, Takahata N. Loss of urate oxidase activity in hominoids and its evolutionary implications. Mol Biol Evol. 2002;19(5):640-53. PubMed PMID: 11961098.
6. Stokes DN. The tumour lysis syndrome. Intensive care aspects of paediatric oncology. Anaesthesia. 1989;44(2):133-6. doi: 10.1111/j.1365-2044.1989.tb11163.x. PubMed PMID: 2929936.
7. Cairo MS. Prevention and treatment of hyperuricemia in hematological malignancies. Clin Lymphoma. 2002;3:S26-S31. doi: 10.3816/CLM.2002.s.012. PubMed PMID: 12521386
8. Rényi I, Bárdi E, Udvardi E, Kovács G, Bartyik K, Kajtár P, et al. Prevention and treatment of hyperuricemia with rasburicase in children with leukemia and non-Hodgkin's lymphoma. Pathol Oncol Res. 2007;13(1):57-62. PubMed PMID:17387390.
9. Patte C, Sakiroglu C, Ansoborlo S, Baruchel A, Plouvier E, Pacquement H, et al. Urate-oxidase in the prevention and treatment of metabolic complications in patients with B-cell lymphoma and leukemia, treated in the Societe Francaise d'Oncologie Pediatrique LMB89 protocol. Ann Oncol. 2002;13(5):789-95. doi: 10.1093/annonc/mdf134.
10. Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol. 2004;127(1):3-11. doi: 10.1111/j.1365-2141.2004.05094.x . PubMed PMID: 15384972.
11. Smith T. Ethics in medical research: a handbook of good practice. New York: Cambridge University Press; 1999.
12. Lopez-Olivo MA, Pratt G, Palla SL, Salahudeen A. Rasburicase in tumor lysis syndrome of the adult: a systematic review and meta-analysis. Am J Kidney Dis. 2013;62(3):481-92. doi: 10.1053/j.ajkd.2013.02.378. PubMed PMID: 23684124.
13. Annemans L, Moeremans K, Lamotte M, Garcia Conde J, van den Berg H, Myint H, et al. Incidence, medical resource utilisation and costs of hyperuricemia and tumour lysis syndrome in patients with acute leukaemia and non-Hodgkin's lymphoma in four European countries. Leuk Lymphoma. 2003;44(1):77-83. doi: 10.1080/1042819021000054661. PubMed PMID: 12691145.
14. Pession A, Barbieri E, Santoro N, Paolucci P, Porta F, Locatelli F. Efficacy and safety of recombinant urate oxidase (rasburicase) for treatment and prophylaxis of hyperuricemia in children undergoing chemotherapy. Haematologica. 2005;90(1):141-2. PubMed PMID: 15642687.
15. Pui CH, Mahmoud HH, Wiley JM, Woods GM, Leverger G, Camitta B, et al. Recombinant urate oxidase for the prophylaxis or treatment of hyperuricemia in patients with leukemia or lymphoma. J Clin Oncol. 2001;19(3):697-704. PubMed PMID: 11157020.
16. Macfarlane RJ, McCully BJ, Fernandez CV. Rasburicase prevents tumor lysis syndrome despite extreme hyperleukocytosis. Pediatr Nephrol. 2004;19(8):924-7. doi:10.1007/s00467-004-1524-y. PubMed PMID: 15179573.
17. Ueng S. Rasburicase (Elitek): a novel agent for tumor lysis syndrome. Proc (Bayl Univ Med Cent). 2005;18(3):275. PubMed Central PMCID: PMC1200736.
18. Shin HY, Kang HJ, Park ES, Choi HS, Ahn HS, Kim SY, et al. Recombinant urate oxidase (Rasburicase) for the treatment of hyperuricemia in pediatric patients with hematologic malignancies: results of a compassionate prospective multicenter study in Korea. Pediatr Blood Cancer. 2006;46(4):439-45. doi: 10.1002/pbc.20555. PubMed PMID: 16123985.
19. Flombaum CD, editor. Metabolic emergencies in the cancer patient. Semin Oncol. 2000;27(3):332-34. PubMed PMID: 10864220.