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Original Article

Efficacy of a Reduced-dose Rasburicase: Single-institution Experience in India

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Abstract

Background: Tumor lysis syndrome (TLS) is an oncological emergency associated with life-threatening metabolic abnormalities. Hyperuricemia is a feature of TLS and is treated with hydration, urine alkalinization, and allopurinol. Rasburicase lowers uric acid (UA) rapidly at the labeled dose of 0.15–0.2 mg/kg/day for 5 days. In a developing country like India where affordability is one major limitation to medical care, the use of rasburicase at the dose recommended by the US Food and Drug Administration (FDA) is not always possible. There is no convincing data suggesting the efficacy of a lower dose of rasburicase (1.5 mg or 3 mg) in the treatment of TLS. We conducted a retrospective study from January 2015 to June 2016 to assess the efficacy of a reduced-dose rasburicase in patients with TLS. **Materials and Methods:** All the patients with TLS were given rasburicase (single dose of 1.5 mg) on day 1 of chemotherapy. Serum UA, potassium, creatinine, and calcium levels were monitored every 24 h. All the patients who did not achieve normalization of UA with one dose of rasburicase were given another 1.5 mg of rasburicase. **Results:** Out of 90 patients, 54 patients (60%) had normalization of UA levels after 1.5 mg of rasburicase and 16 (18%) patients required 3 mg of rasburicase for bringing down the UA level to normal. The low serum UA levels were maintained even on the 3rd day of rasburicase. Rasburicase was well tolerated, and there was no death due to TLS. Thirty-one patients (64%) had normalization in the serum creatinine levels after rasburicase. **Conclusion:** We conclude that a low dose of rasburicase (1.5 mg or 3 mg) is cost effective in reducing serum UA (especially for low-risk and intermediate-risk TLS) and the higher dose as recommended by the US FDA is required only for patients with high-risk TLS.

Keywords: *Low dose, rasburicase, tumor lysis syndrome*

Introduction

Tumor lysis syndrome (TLS) is an oncological emergency associated with potentially life-threatening metabolic abnormalities.[1] Hyperuricemia is a feature of TLS and is treated with hydration, urine alkalinization, and allopurinol. Allopurinol inhibits the conversion of hypoxanthine to xanthine and xanthine to uric acid (UA) by inhibiting xanthine oxidase. It has no direct effect on existing UA. Rasburicase being a recombinant urate oxidase is highly efficacious in TLS. Rasburicase lowers UA rapidly to very low levels at the labeled dose of 0.15–0.2 mg/kg daily for 5 days by converting UA to allantoin which is rapidly excreted. Despite this dramatic effect on UA, rasburicase has not been shown to have any beneficial impact on survival. There are various studies suggesting the effectiveness of a reduced dose of rasburicase (3 mg to 6 mg single dose). In a developing country like India where affordability is one of the major limitations to medical care, the use of rasburicase at the dose recommended by the US Food and Drug Administration (FDA) is not always possible. There is no convincing data from India suggesting the efficacy of a lower dose of rasburicase (1.5 mg or 3 mg) in the treatment of TLS.

Objectives

The objective is to study the efficacy of a reduced dose of rasburicase (1.5 mg or 3 mg) in adult patients with TLS.

Materials and Methods

A retrospective review from January 2015 to June 2016 was conducted in adult oncology patients who received rasburicase. We evaluated the efficacy of a reduced dose of rasburicase (1.5 mg or 3 mg) in patients aged 18–72 years presenting with clinical or laboratory TLS[1] [Table 1] to our institution. These patients were

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administered rasburicase, hydration (3 L/m^2/day), and chemotherapy on day 1. Patient's biochemistry parameters such as serum UA, serum potassium, serum creatinine, and serum calcium were studied before and after giving rasburicase. All the patients with TLS [Bishop and Cairo definition of clinical and/or laboratory TLS is shown in Table 1] received 1.5 mg of rasburicase on the 1st day, and the response was studied in terms of decrease in UA levels or decrease in serum creatinine levels. Those patients who did not achieve normal UA level within 24 h of 1.5 mg of rasburicase were given one more dose of rasburicase (1.5 mg). All patients were also evaluated for the change in serum creatinine, serum calcium, and serum potassium levels, postrasburicase administration.

Results

The median UA level was 9.9 mg/dl (8.2–13.4 mg/dl). A total of 90 patients received low-dose rasburicase. Out of 90 patients, 54 patients (60%) had normalization of UA levels after 1.5 mg of rasburicase and 16 (18%) patients required 3 mg of rasburicase for bringing down the UA level to normal. The low serum UA levels were maintained even on the 3rd day of rasburicase. Twenty patients (22%) did not achieve normal UA levels even with 3 mg of rasburicase although they had more than 50% reduction in UA levels. All the patients who did not acheive normal UA levels after 3 mg rasburicase had high risk[2] [Table 2] of TLS. Rasburicase was well tolerated, and there was no death due to TLS among the patients studied. Out of 90 patients, 48 patients (53%) had elevated creatinine due to TLS. The median serum creatinine level was 3.8 mg/dl (1.9–5.4 mg/dl). Thirty-one patients (64%) had normalization in the serum creatinine levels after rasburicase. Two patients of Burkitt's lymphoma required hemodialysis due to acute renal failure. The cost of one dose (1.5 mg) of rasburicase was Rs. 6000 as compared to the usual FDA recommended dose (0.15 mg/kg/day) which comes out to be Rs. 36,000 per day.

Table 1: Bishop and Cairo criteria for TLS

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

Discussion

TLS and hyperuricemia are serious complications with significant morbidity and potential mortality in patients with hematologic malignancies undergoing anticancer therapy. Allopurinol has been used for many years in the prevention and management of TLS-related hyperuricemia. However, allopurinol should be administered for ≥3 days for the achievement of significant reduction in UA levels. Rasburicase offers a potential advantage over allopurinol by its rapid onset of action, reducing preexisting pool of UA within few hours.[3] The results of our study demonstrate that a fixed low-dose rasburicase is a highly effective agent for the management of hyperuricemia associated with TLS. We also find that the cost of rasburicase reduces by one-sixth when using a fixed low dose for TLS. All patients at potential risk and majority of high-risk patients responded to a reduced dose, indicating that in appropriately monitored patients, single dose followed by dosing as needed can be cost saving. Our results are similar to the results of Hummel *et al*.[4] wherein fifty patients were studied to evaluate the efficacy of low-dose rasburicase in TLS [Table 3].[4-11]

Conclusion

As per our knowledge, this is the largest study conducted for evaluating the efficacy of low-dose rasburicase. A reduced dose of rasburicase at 1.5 mg single dose (repeated only

Table 2: Risk stratification of TLS patients

Low risk	Intermediate risk	High risk
Multiple myeloma	Neuroblastoma, GCT, SCLC	AML with TLC >100,000/mm^3
CML	CLL with TLC >50,000/mm^3	ALL with TLC >100,000/mm^3 or LDH >2 × ULN
CLL with TLC <50,000/mm^3	AML with either TLC >25,000-1,00,000/mm3 or with LDH >2 × ULN	Stage III/IV Burkitt's lymphoma, any stage Burkitt's lymphoma with LDH >2 × ULN
Hodgkin's lymphoma	Intermediate-grade NHL with LDH >2 × ULN	Stage III/IV lymphoblastic lymphoma or any stage lymphoblastic lymphoma with LDH >2 × ULN
AML with TLC <25,000/mm^3 and LDH <2*ULN	ALL with TLC <100,000/mm^3 and LDH <2 × ULN	Intermediate-risk disease with renal dysfunction
Adult ALCL	Burkitt's lymphoma with LDH <2 × ULN	Intermediate-risk disease with elevated serum uric acid or potassium levels

LDH – Lactate dehydrogenase; ULN – Upper limit of normal; NHL – Non-Hodgkin's lymphoma; CML – Chronic myeloid leukemia; CLL – Chronic lymphocytic leukemia; AML – Acute myeloid leukemia; ALCL – Anaplastic large cell lymphoma; GCT – Germ cell tumor; SCLC – Small cell lung cancer; TLC – Total leukocyte count, ALL – Acute lymphoblastic leukemia

Table 3: Other studies on efficacy of low dose rasburicase

Study	*n*	Malignancy	Dose of rasburicase	Number of doses
Lee *et al*.[5]	3	ALL	0.08-0.26 mg/kg	1
McDonnell *et al*.[6]	11	3 NHL B-cell, 1 Burkitt's lymphoma, 3 AML, 1 CMML, 1 MDS	0.0232-0.1361 mg/kg	1
Liu *et al*.[7]	8	3 AML, 2 ALL, 2 NHL, 1 CML	0.141-0.178 mg/kg	1
Trifilio *et al*.[8]	43	20 plasma cell dyscrasias, 10 NHL, 7 AML, 3 CLL, 1 MDS	3 mg	1, except for 6 additional doses (2 doses, 1.5 mg; 4 doses, 3 mg)
Hutcherson *et al*.[9]	11		0.045-0.1 mg/kg	1, except for 1 additional dose (0.1 mg/kg)
Hummel *et al*.[4]	50	14 NHL, 9 AML, 7 CLL, 6 CMP/MDS 5 ALL, 5 multiple, 4 solid tumor	0.031-0.11 mg/kg	Given as 1 (25 of 50 patients) to 3 doses
Reeves and Bestul.[10]	17	14 NHL, 3 AML	7.5 mg	1
Campara *et al*.[11]	21	9 AML, 3 NHL, 3 multiple myeloma, 3 myelofibrosis, 2 chronic leukemia, 1 plasma cell leukemia	0.11-0.24 mg/kg	1
Our study	90	7 multiple myeloma, 10 CLL, 6 CML, 22 ALL, 17 GCT, 09 Burkitt's lymphoma, 08 AML, 11 DLBCL	1.5 mg	1 or 2 doses depending on the response to single dose

NHL – Non-Hodgkin's lymphoma; AML – Acute myeloid leukemia; CML – Chronic myeloid leukemia; CLL – Chronic lymphocytic leukemia; GCT – Germ cell tumor; ALL – Acute lymphocytic leukemia; CMML – Chronic myelomonocytic leukemia; MDS – Myelodysplastic syndrome; CMP – Common myeloid progenitors; DLBCL – Diffuse large B-cell lymphoma; ALL – Acute lymphoblastic leukemia

if necessary clinically) is very efficacious in TLS. We conclude that a low dose of rasburicase (1.5 mg or 3 mg) is cost saving and effective in reducing serum UA (especially for low-risk and intermediate-risk TLS) and the higher dose as recommended by the US FDA probably is required only for patients with high risk of TLS.

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Conflicts of interest

There are no conflicts of interest.

References

1. Howard SC, Jones DP, Pui CH. N Engl J Med 2011;364:1844-54.
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;149:578-86.
3. Hande KR, Garrow GC. Acute tumor lysis syndrome in patients with high-grade non-Hodgkin's lymphoma. Am J Med 1993;94:133-9.
4. Hummel M, Reiter S, Adam K, Hehlmann R, Buchheidt D. Effective treatment and prophylaxis of hyperuricemia and impaired renal function in tumor lysis syndrome with low doses of rasburicase. Eur J Haematol 2008;80:331-6.
5. Lee AC, Li CH, So KT, Chan R. Treatment of impending tumor lysis with single-dose rasburicase. Ann Pharmacother 2003;37:1614-7.
6. McDonnell AM, Lenz KL, Frei-Lahr DA, Hayslip J, Hall PD. Single-dose rasburicase 6 mg in the management of tumor lysis syndrome in adults. Pharmacotherapy 2006;26:806-12.
7. Liu CY, Sims-McCallum RP, Schiffer CA: A single dose of rasburicase is sufficient for the treatment of hyperuricemia in patients receiving chemotherapy. Leuk Res 2005;29:463-5.
8. Trifilio S, Gordon L, Singhal S, Tallman M, Evens A, Rashid K, *et al*. Reduced-dose rasburicase (recombinant xanthine oxidase) in adult cancer patients with hyperuricemia. Bone Marrow Transplant 2006;37:997-1001.
9. Hutcherson DA, Gammon DC, Bhatt MS, Faneuf M. Reduced-dose rasburicase in the treatment of adults with hyperuricemia associated with malignancy. Pharmacotherapy 2006;26:242-7.
10. Reeves DJ, Bestul DJ. Evaluation of a single fixed dose of rasburicase 7.5 mg for the treatment of hyperuricemia in adults with cancer. Pharmacotherapy 2008;28:685-90.
11. Campara M, Shord SS, Haaf CM. Single-dose rasburicase for tumour lysis syndrome in adults: Weight-based approach. J Clin Pharm Ther 2009;34:207-13.