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ORIGINAL ARTICLE

Efficacy of Single Dose Rasburicase (1.5 mg) for Prophylaxis and Management of Laboratory Tumor Lysis Syndrome

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Abstract Rasburicase is a recombinant urate oxidase enzyme approved for use in tumor lysis syndrome (TLS) and it acts by reducing serum uric acid levels. Using rasburicase at the recommended dose of 0.2 mg/kg/day for 5 days is expensive and it is not known whether this extended schedule is clinically beneficial compared to a single fixed dose of 1.5 mg. The aim of the present study was to evaluate the efficacy of single dose rasburicase 1.5 mg in prevention and management of TLS. Rasburicase is available as single use 1.5 mg vial. At our institution a single dose of rasburicase 1.5 mg irrespective of bodyweight has been used in adults and in children a dose of 0.15 mg/kg (maximum 1.5 mg) has been used since 2012 for prevention and management of TLS and subsequent doses are given based on biochemical response and clinical condition. We retrospectively analysed the case records of patients who had received rasburicase from January 2012 to January 2017. The study included 186 patients with hematological malignancies who received rasburicase. Children accounted for 56.4% (n = 105) patients and males comprised 73% (n = 135). Rasburicase was used prophylactically in 59 (31.7%) patients, for laboratory TLS in 76 patients (40.8%) and for clinical TLS in 51 (27.4%) patients. Single fixed dose rasburicase prevented laboratory/clinical TLS in 87% of the prophylactic group and prevented clinical TLS in 72% of the laboratory TLS group. None of the patients in prophylactic and laboratory TLS group developed clinical TLS. However, majority of the patients with clinical TLS required more than one dose rasburicase. Single dose of 1.5 mg (1 vial) rasburicase is efficient in preventing and managing laboratory TLS and is economically viable in resource constrained settings.

Keywords Tumor lysis syndrome · Rasburicase · Renal failure

Introduction

Tumor lysis syndrome (TLS) is an oncological emergency which is observed in some malignancies before and after cytotoxic treatment and results in the release of potassium, phosphate, and nucleic acids into the systemic circulation. Catabolism of the nucleic acids to uric acid leads to hyperuricemia; the marked increase in uric acid excretion can result in the precipitation of uric acid in the renal tubules and renal vasoconstriction, impaired autoregulation, decreased renal flow, oxidation, and inflammation ultimately resulting in acute kidney injury. Hyperphosphatemia with calcium phosphate deposition in the renal tubules can also cause acute kidney injury. [1]. Laboratory TLS is defined by the simultaneous occurrence (within the same 24-h period) of two or more of four classic metabolic derangements (hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia), either 3 days before or 7 days after initiation of cytotoxic chemotherapy [2]. Clinical TLS is defined as laboratory TLS plus one or more of the following: increased serum creatinine level (1.5 times upper limit of normal), cardiac arrhythmias, seizures, or death [2]. Rasburicase is a recombinant urate oxidase approved for the management of hyperuricemia in TLS [3, 4]. The recommended dose of rasburicase is 0.15–0.2 mg/kg per day for 5 days for TLS management. Studies have shown much lesser doses to be effective in preventing TLS [5–13].

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Evidence indicates a single 3-mg dose is effective in the prophylaxis and treatment of hyperuricemia in adults with uric acid levels up to 12 mg/dl, and uric acid levels continuing to decline beyond 24 h in most patients without additional treatment [5]. However, the optimal dose and duration of rasburicase is controversial. The schedule of rasburicase can impact the overall cost of treatment especially in a resource challenged setting. In our hospital, single vial of rasburicase (1.5 mg) irrespective of bodyweight has been used in adults and in children a dose of 0.15 mg/kg (maximum 1.5 mg) has been used since 2012 for prevention and management of TLS and subsequent doses of 1.5 mg have been given based on biochemical response and clinical condition. The aim of the present study was to evaluate the efficacy of single dose rasburicase 1.5 mg in prevention and management of TLS.

Patients and Methods

Data of all patients who received rasburicase between January 2012 and January 2017 was collected from the case records. Patients records where analysed to check the baseline parameters of tumor lysis syndrome (renal function test, calcium, uric acid, phosphorus, potassium). Based on these parameters and the clinical condition, patients were grouped into three groups for their indication for using rasburicase. Group 1 consisted of patients who were given rasburicase prophylactically due to high white blood cell (WBC) counts or only elevated uric acid levels for prevention of TLS. Group 2 consisted of patients who received rasburicase for laboratory TLS and group 3 patients received rasburicase for clinical TLS.

Rasburicase was administered immediately after the availability of patients biochemical and hematological reports, this was usually between 2 and 6 h after admission. Biochemical parameters were monitored at least twice a day for patients at risk of TLS (prophylactic group) and in patients with established TLS (laboratory and clinical TLS group) they were monitored every 6 h till the resolution of TLS. Majority of the patients received generic rasburicase (NATCO pharma, India), few patients received the innovator rasburicase (Astra Zeneca, India). The choice of brand of rasburicase was dependent on the availability in the hospital pharmacy at the time of administration. The 24-h iced uric acid levels after the last dose of rasburicase was collected and analysed to see the response to rasburicase. The number of doses of rasburicase required to bring the uric acid levels < 7 mg/dl was analysed. The 24-h parameters of renal function test, calcium, phosphorus, potassium after the last dose of rasburicase was also collected to check the effect of rasburicase. All patients in addition to rasburicase received standard of care hydration 3 L/m^2 and allopurinol 10 mg/kg in three divided doses as per renal function test.

Results

The study included 186 patients who received rasburicase from January 2012 to January 2017. Pediatric cases (age < 18 years) accounted for 56.4% of patients (n = 105) and males comprised of majority of the cases 73% (n = 135). The common indication for the use of rasburicase included acute lymphoblastic leukaemia (ALL) in 67.7% (n = 126) patients, AML in 10.2% (n = 9) and aggressive lymphomas in 15% (n = 28). Rasburicase was used prophylactically in 59 (31.7%), for treating laboratory TLS in 76 (40.8%) and for treating clinical TLS in 51 (27.4%) patients. Table 1 provides the baseline characteristics of the study patients.

In the prophylactic group (n = 59), the mean uric acid level was 5.6 mg/dl (range from 1.2 to 20 mg/dl). Uric acid < 8 mg/dl was seen in 93% and 1.5 mg rasburicase was delivered 67 times. Hyperleucocytosis was the most common indication for using rasburicase with the mean WBC count of 11,4792 (range 1500–500,000/cumm). Single dose of 1.5 mg (median dose = 1) was effective in preventing TLS in 87% and reduced the uric acid levels by 58.6% per dose.

In the group with laboratory TLS (n = 76), uric acid levels > 8 mg/dl was seen in 78% and single dose (median dose = 1) was effective in preventing clinical TLS in 72%. The mean uric acid level was 10.6 mg/dl (range 3.4–30 mg/dl). Rasburicase was administered 105 times in

Table 1 Baseline characteristics

Age	
< 18 years	105 (56.4%)
> 18 years	81 (43.6%)
Gender	
Male	135 (73%)
Female	51 (27%)
Diagnosis	
Acute lymphoblastic leukemia	126 (67.7%)
Acute myeloid leukemia	19 (10.2%)
Lymphoma	37 (19.8%)
Leukaemia undiagnosed	4 (2.3%)
Groups	
Prophylactic	59 (31.7%)
Laboratory TLS	76 (40.8%)
Clinical TLS	51 (27.4%)

TLS Tumor Lysis Syndrome

Table 2 Results of studies of low dose rasburicase

Study (design)	No. of patients	Malignancy	Rasburicase regimen	Results
J Coutsouvelis[8] (Prospective study-2013)	41 (adults)	Aggressive Lymphomas, AML, ALL	3 mg/day	20 pts with normal uric acid levels required only single dose to prevent TLS, out of 19 pts with elevated uric acid, single dose was effective in 14 cases
Trifilio[5] (Retrospective chart review 2010)	247 (adults)	Plasma cell neoplasm, NHL, AML, CLL, MDS	3 mg × 1	a single 3-mg dose of rasburicase, used with close monitoring, is sufficient to treat most adults with uric acid levels up to 12 mg/dl
Vines[15] (Retrospective chart review 2010)	34 (adults)	AML, ALL, NHL, MM, HD, solid tumor	6 mg × 1	UA normalized to less than 4 mg/dL by day 3, 2 pts required repeat dose
McBride[13] (Retrospective chart review 2013)	373 (adults)	Hematologic (AML, lymphoma, MM) or solid tumor	3 mg × 1 (n = 38) 6 mg × 1 (n = 99) 7.5 mg × 1 (n = 43) Wt-based (median 0.16 mg/kg) × 1 (n = 193)	UA reported on 319 patients—UA normalized in 313 patients within 24 h. No statistical significant difference across doses. Study concluded that 6 mg may be most appropriate single dose
Herrington[7] (Retrospective chart review 2015)	45 patients (adult)	Acute and chronic leukemia, NHL, HD, MM, other	1.5 mg (n = 6) 3 mg (n = 26) 4.5 mg (n = 1) 6 mg (n = 12)	UA normalized to less than 8 mg/dL in 80% of patients. Five patients required repeat dose. Greater reduction in UA seen with higher doses of rasburicase
Vadhan-Raj[14] (Prospective study-RCT 2012)	82 (adults)	Acute leukemia, aggressive lymphomas	0.15 mg/kg single dose versus 5 daily dose	Seventy-nine patients (99%) experienced normalization in their UA within 4 h after the first dose; 84% to an undetectable level (< 0.7 mg/dl)
Latha[10] (Retrospective chart review 2015)	7 (pediatric)	Acute lymphoblastic leukemia	Single dose 0.15 mg/kg	All patients responded to a single dose
Jayabose[16] (Retrospective chart review 2015)	41 pediatric	Acute leukemia, NHL	Single dose 0.15 mg/kg	Twenty-seven needed only one dose; 12 needed 2 or 3 doses; and two needed 5 doses each. One child required dialysis
Kukkar[17] (Retrospective chart review 2016)	15 (10 pediatrics and 5 adults)	hematologic malignancies at risk for TLS	Single dose 0.15 mg/kg	single dose of rasburicase produced a rapid and sustained therapeutic effect of lowering the plasma UA levels in all the 15 patients
Antony R[11] (Retrospective chart review 2015)	55 patients (adult)	High risk haematological and solid tumors	Single 1.5 mg dose	52 patients UA levels reduced with 24 h, by day 3 all patients UA levels reduced

Pts patients, *NHL* Non hodgkins lymphoma, *AML* acute myeloid leukemia, *ALL* acute lymphoblastic leukemia, *CLL* chronic lymphoblastic leukemia, *TLS* tumor lysis syndrome, *MM* multiple myeloma, *UA* Uric Acid

this group with reduction of uric acid per dose by 64%. The mean WBC counts in this group was 92,686/cumm (range 1200–380,000/cumm). No patient in the prophylactic or laboratory TLS group developed clinical TLS.

In the high-risk group of clinical TLS (n = 51), the mean uric acid level was 12.8 mg/dl (range 3.7–31 mg/dl). In this group, 21/51 patients (41%) got 1 dose (1.5 mg) of rasburicase, 16/51 (31%) got 2 doses, 11/51 (22%) got 3 doses, 2/51 (4%) got 4 doses and 1/51 (2%) got 5 doses. The mean uric acid level after the use of rasburicase was 4.7 mg/dl and single dose of rasburicase reduced uric acid levels by 61.4%. Two patients required hemodialysis and there were 6 deaths (11.3%) most likely due to clinical TLS. 47 (92.2%) of these cases presented with spontaneous

TLS and only 4 (7.3%) patients developed TLS after initiation of chemotherapy.

High counts > 50,000/cumm, along with elevated uric acid > 8 mg/dl was seen in 44/186 (24%) patients. Out of which 2 patients belonged to the prophylactic group, 24 belonged to the biochemical TLS group, and 18 to the clinical TLS group.

Discussion

TLS needs early and effective management. Aggressive hydration and anti-hyperuricemic drugs are the cornerstone in management of TLS. Hyperuricemia is one of the components of TLS and studies have shown rasburicase to be very effective in rapidly reducing the uric acid levels as compared to using allopurinol alone [4]. Delay in managing laboratory TLS may lead to clinical TLS and thus delay definitive treatment and this in turn may lead to poor outcomes. The cost of 1.5 mg vial of generic rasburicase is about Rs 8000, if we follow the manufacturer recommended schedule of 0.2 mg/kg/day for 5 days, then the total dose for a 60 kg adult would be 12 mg/day and the cost of treatment for 5 days will be Rs 320,000, which is beyond the reach of majority of patients in resource constrained settings. Studies have shown that single dose of rasburicase starts reducing uric acid levels within 4 h and complete normalization occurs within 24 h [14]. Rasburicase has a half-life of 16–23 h, a single dose of 1.5 mg can rapidly bring down the uric acid and further control of TLS can be achieved with hydration and allopurinol in majority of the cases. Our study shows in the prophylactic and in the laboratory TLS group a single dose of rasburicase was sufficient and prevents progression to clinical TLS and was efficient in reducing 24-h uric acid levels by 55–60%. No patient in both the groups went on to develop clinical TLS. Most patients had sustained reduction in uric acid levels, and further doses of rasburicase were only used in very few patients to bring the uric acid below 7 mg/dl. Fixed dose studies have been done with 3, 4.5 and 6 mg [8, 9, 15] (Table 2). Studies from India have used single dose based on body weight and with small sample size in the pediatric age group [10, 16, 17]. Our study shows similar results to another study from India using single 1.5 mg fixed dose of rasburicase [11]. In the group with clinical TLS the median dose of rasburicase delivered per case was 2. However, even in this group a single dose of rasburicase reduced uric acid levels by 60%, and 24-h mean creatine levels came down to 1.8 mg/dl. There was no incidence of documented hypersensitivity reactions or hemolysis in any of the cases studied. G6PD testing was not done as in majority of the patients as rasburicase was given in emergency and G6PD deficiency is uncommon in our patient population.

Conclusion

Single dose of 1.5 mg rasburicase is efficient in preventing and managing laboratory TLS in majority of the patients and in patients with clinical TLS more doses are required. The optimal dosing of rasburicase needs to analysed in well planned prospective studies.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in the study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants prior to starting the treatment.

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