

Effects of Recombinant Urate Oxidase (Rasburicase) and Allopurinol for Prophylaxis and Treatment of Hyperuricemia in Patients with Leukemia and Lymphoma

Khadijeh Arjmandi,¹ Reza Taghipor,¹ Maryam Tashvighi,² Danial Jafari,¹

1. Hematology Oncology Center, Aliasghar Children Hospital, Tehran University of Medical Sciences. Tehran, Iran.

2. Azad Islamic University, Ghom, Iran.

Corresponding author: Khadijeh Arjmandi, Hematology Oncology Center, Aliasghar Children Hospital, Tehran University of Medical Sciences. Tehran, Iran. (Phone: +98 21 22 09 15 18, Fax: +98 21 22 09 63 66)

Abstract

Background: Efficacy of rasburicase in pediatric patients with leukemia and lymphoma is proved. This study aims to weigh efficacy and safety of rasburicase versus more conventional therapy, allopurinol, and to compare their safety and properties in tumor lysis syndrome (TLS) of leukemia and lymphoma patients.

Materials and Methods: The study was done with a retrospective cohort design. Patients were selected from our hematology ward admitted from 2005 through 2008. Patients were put into two groups based on their blood levels of uric acid, before initiation of chemotherapy; treatment group (the Uric Acid level of 6.5 mg/dl or more) and the prophylaxis group (the uric acid level below 6.5 mg/dl). Evaluation of effectiveness of therapy was performed after 24, 48, 72-hour, and longer periods.

Results: Of 184 patients; 69% had leukemia, and 31% lymphoma. Twenty patients were treated with rasburicase and 164 with allopurinol. Mean age of patients was 7.93 ± 4.247 years old. 60.8% were male and 39.2% were female. According to Chi-square test results, there was no significant difference between two agents regarding prophylaxis (chi-square = 4.247, p-value = 0.193) and treatment (chi-square = 0.780, p-value = 0.677). Most of the response to each agent was seen in the first 24 hours after drug administration. Mean level of uric acid reduced from 7.4 to 3.4 mg/dl in rasburicase, and from 5.4 to 3.9 mg/dl in allopurinol group. Mean duration of treatment for rasburicase was 2 days, and for allopurinol 6 days. Adverse effects were minimal in both groups (in rasburicase 1.6% and in allopurinol 5.4%).

Conclusion: Rasburicase seems to be highly efficient in both prophylaxis and treatment of Hyperuricemia. Due to high costs in our practice, it was only administered to 20 patients with high levels of blood uric acid or leukocytosis. It prepares patients for chemotherapy faster and decreases cost of hospital stay indirectly by lowering cost of treatment. Allopurinol, alternatively showed equal efficiency and comparable results. Thus, it can be used safely and effectively until rasburicase becomes more widely available and more cost-effective.

Keywords: Hyperuricemia, Rasburicase, Allopurinol, Leukemia, Lymphoma.

Introduction

Tumor lysis syndrome (TLS) is caused spontaneously or secondary to anticancer therapy in patients with hematologic malignancies. It is manifested by hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcaemia. Hyperuricemia is defined as serum plasma levels of 7 to 8 mg/dl of

uric acid. Hyperuricemia is the most common metabolic abnormality of TLS complicated by acute renal failure. Uric acid is the end product of purine catabolism and its blood levels are increased secondary to release of purines through cytolysis caused by anticancer chemotherapy.¹⁻⁵

Uric acid is not entirely soluble in urine. Acidic pH levels of urine causes uric acid to crystallize in renal tubules and collecting ducts, resulting in obstruction of urinary flow and uric acid nephropathy and acute renal failure.^{4,6} Hyperuricemia can exist before initiation of chemotherapy, and this increases the likelihood of clinical TLS.^{2,7} But more typically it occurs 12 to 72 hours after initiation of chemotherapy and kidneys play a central role in clearing these agents from bloodstream.⁸

TLS occurs in tumors with high growth rates developing significant masses, tumors with diffuse organ involvement, and tumors with high sensitivity to anticancer agents. It occurs most commonly in Burkitt's lymphoma, lymphoblastic lymphoma, and acute lymphoblastic leukemia particularly T cell with leukocytosis. Prompt treatment effectively decreases morbidity of TLS. Patients with recent diagnosis of leukemia or non-Hodgkin's lymphoma should be adequately hydrated, receive sodium bicarbonate for urine alkalinisation, and most importantly antiuricemic agents (e.g. allopurinol) to prevent TLS. These measures are effective in the majority of patients to prevent TLS and acute renal failure. After these acute metabolic derangements are addressed, induction of chemotherapy may be initiated. Among these measures, overhydration is the single most important. Patients should receive two to four times maintenance fluid volume daily. Hydration causes increased urine output and improves glomerular filtration rate.

Allopurinol decreases uric acid levels by inhibition of xanthine oxidase activity. Xanthine oxidase converts hypoxanthine to xanthine. Urine alkalization helps solubility of uric acid but urine pH should not exceed 7.5. Higher pH could result in formation of xanthine and hypoxanthine stones.

Rasburicase is an analogue of urate oxidase which converts uric acid to allantoin. It is five to ten times more soluble than uric acid and facilitates excretion of uric acid through urine. Possible side effects including allergic reactions are not common. Several studies proved its efficacy and safety in humans. Urate oxidase is administered via intravenous route, in doses of 0.1 to 0.2 mg per kilogram of body weight over a period of 30 minutes for five days.

Efficacy of rasburicase in pediatric patients with leukemia and lymphoma has been proved, and

statistically it has superior effect on rapid control of uric acid levels during chemotherapy. Preliminary results indicate cost-effectiveness of rasburicase in TLS treatment and suggested it as a cost-effective method of prophylaxis against TLS too.⁹⁻¹² Our goal was to evaluate rasburicase and allopurinol in terms of efficacy and safety and rate of uric acid lowering in treatment and prophylaxis groups.

Materials and Methods

This study was carried out in a retrospective Cohort fashion. All patients with leukemia or lymphoma admitted to our hematology ward through 2005 to 2008 were included in the study. They have been treated with either rasburicase or allopurinol, and were put into two groups according to their initial blood uric acid levels. The treatment and prophylaxis group had uric acid levels of 6.5 mg/dl or higher and lower than 6.5 mg/dl, respectively. Rasburicase was administered at doses of 0.15 to 0.20 mg/kg in 50 cc normal saline solution over a period of 30 minutes through intravenous infusion. Allopurinol was administered orally at a dose of 10 mg/kg daily. The exclusion criteria for patients receiving rasburicase were history of allergy or hypersensitivity, G6PD deficiency, and methemoglobinemia.

Response to therapy was determined as lowering blood levels of uric acid to less than 6.5 mg/dl in treatment group, and maintaining levels of uric acid below 6.5 mg/dl in prophylaxis group. Blood uric acid levels were measured at 24, 48, 72-hour, and longer intervals in cases of inadequate response to therapy.

Data was analyzed using computer software evaluating Chi-square and T-test. P-value less than 0.05 was considered statistically significant. Ethical matters were addressed according to Helsinki treaty. The most fundamental issue facing our study was limited number of patients in rasburicase group. Costs and availability of rasburicase in our practice was another obstacle in this study. We must mention that we used rasburicase in patients with hyperuricemia or leukocytosis who were prone to TLS.

Results

Of 184 patients, 127 had leukemia and 57 had lymphoma. Twenty patients were treated with rasburicase, and 164 with allopurinol. Mean age of patients was 7.93 years; 6.95 ± 5.11 years in rasburicase group and 8.05 ± 4.13 years in allopurinol group, with no significant statistical difference between two groups ($T = -1.099$; $p\text{-value} = 0.27$). Of 184 patients, 112 (60.8%) were male and 72 (39.2%) were female. Twelve (60%) male and 8 (40%) female patients in rasburicase group, and 100 (61%) male and 64 (39%) female patients in allopurinol group were included. This shows no statistical difference between two groups in terms of gender. In rasburicase group, 12 patients (60%) had leukemia and 8 patients (40%) had lymphoma. In allopurinol group, 115 patients (70.12%) had leukemia and 49 patients (29.88%) had lymphoma, indicating no significant statistical difference between two groups. Rasburicase group had 9 patients (45%) in treatment group and 11 patients (55%) in prophylaxis group. Allopurinol group had 116 patients (70.7%) in prophylaxis and 48 patients (29.3%) in treatment group. There was no significant statistical difference between patients receiving either regimen.

Of 20 patients under treatment with rasburicase, 16 patients (80%) received 0.15 mg/kg dose and 4 patients (20%) were treated with 0.20 mg/kg dose. All patients in allopurinol group received a 10 mg/kg dosage. Rasburicase was administered for a mean duration of 2 days, and allopurinol for 6 days. All patients (100%) responded to treatment in treatment group. In rasburicase group, 77.7% of patients responded in 24 hours and 22.3% in 48 hours. In allopurinol group, 64.5% of patients in 24 hours, 31.2% in 48 hours, and 4.3% in 72 hours or more responded to treatment.

All patients (100%) in prophylaxis group had response to therapy; 90.9% of rasburicase group in 24 hours, and 9.1% in 72 hours. In allopurinol group, 95.6% had response to treatment in 24 hours, 0.8% in 48 hours, and 3.6% had response to treatment in 72 hours or more. Duration of treatment was significantly different between two groups (table 1). There was no statistical difference in duration of drug administration between patients who received either rasburicase or allopurinol for treatment and for prophylaxis. Main response was achieved at 24 hours in both groups. Mean uric acid levels in both groups of rasburicase and allopurinol before and after drug administration are demonstrated in table 2.

Table 1.

	Mean duration (days)	No. of patients	Minimum	Maximum	Standard deviation
Rasburicase	2	20	1	5	0.918
Allopurinol	5.87	164	1	13	2.783

Table 1. Mean duration of drug administration in rasburicase and allopurinol groups.

Table 2.

	No. of patients	Mean of uric acid before treatment	Standard deviation	Mean of uric acid after treatment	Standard deviation	Reduction percent
Rasburicase	20	7.4300	6.63643	3.4402	2.11611	54.05
Allopurinol	164	5.4732	2.51301	3.9791	1.46943	27.77
Total	184	5.6859	3.25127	3.9205	1.55450	30.35

Table 2. Mean of uric acid before and after treatment, and reduction percent in rasburicase and allopurinol groups.

Discussion

This study showed efficacy of rasburicase in controlling hyperuricemia in patients with leukemia and lymphoma. This study also compared its efficacy with more common therapy, allopurinol, and showed both to be effective in treatment of hyperuricemia. Side effects and adverse reactions in both agents were minimal. Patients studied had high blood uric acid levels (31% of patients) or were at risk for TLS (prophylaxis group, 69% of patients).

Mean uric acid levels were decreased with administration of either rasburicase or allopurinol. Bosly et al reported that prophylactic use of rasburicase decreased uric acid levels from 4.4 mg/dl to 0.8 mg/dl which is in accordance to our findings.¹³ In rasburicase group, uric acid level decreased from 13.2 to 4.7 mg/dl in treatment group and 2.7 to 2.3 mg/dl in prophylaxis group. Pui et al reported a decrease of uric acid with rasburicase from 9.7 to 1 mg/dl in treatment group and 3.4 to 0.5 mg/dl in prophylaxis group.¹⁴ Goldman reported a 86% decrease of uric acid in patients under treatment with rasburicase and 12% in allopurinol group, favoring rasburicase in respect to its ability to decrease blood uric acid level.¹⁵ We had similar findings; a 54% decrease of uric acid with rasburicase and 27% with allopurinol, again emphasizing rasburicase superiority to allopurinol. This advantage has been maintained in treatment group (64% with rasburicase versus 38% with allopurinol).

Rasburicase is well tolerated in terms of its adverse effects. We encountered only 3 cases with adverse reactions (1.6% of patients); rash in 2 patients (1%) and fever in 1 (0.5%) which did not result in discontinuation of therapy. Bosly et al reported a 1% rate of adverse effects. In patients treated with allopurinol, 5.4% of patients experienced adverse effects; 5 (2.7%) had rash, 5 (2.7%) had vomiting.¹³

Renal function was assessed using serum creatinine level during treatment. Elevated levels of serum creatinine were seen in 3.8% of patients on rasburicase and 16.3% of patients on allopurinol. If serum creatinine level at the initiation of therapy is considered, high levels were noted in 3.3% of patients in rasburicase group and 3.8% of allopurinol group. These figures are statistically different, which can be explained by higher probability of selecting patients at high risk for treatment of

rasburicase. Overall none of the patients needed hemodialysis. In another study, patients receiving rasburicase had 4 days of elevated serum creatinine, which was in accordance with our findings.¹⁶

Annemonn's study showed the cost-effectiveness of rasburicase.¹⁷ Although we did not focus on the economic aspect of therapy, mean days of drug administration was significantly different between two drugs. Rasburicase was given for a mean of 2 days, while allopurinol was administered for a mean of 5.9 days. Rasburicase thus prepares patients for chemotherapy faster and decreases costs of hospital stay, indirectly lowering costs of treatment.

Hyperleukocytosis was noted in 60% of patients in rasburicase group and 21.9% in allopurinol group. Blood leukocyte count was significantly different between rasburicase and allopurinol group. While rasburicase was administered in patients with higher initial blood leukocyte counts, patients in both groups had similar outcome emphasizing the effectiveness of therapy with rasburicase.

Conclusion

Rasburicase is a highly efficient drug in treatment of and prophylaxis for hyperuricemia in patients with leukemia and lymphoma. Thus, it prepares patients for chemotherapy faster and decreases cost of hospital stay indirectly lowering cost of treatment. Also, allopurinol had similar effects and until wider availability of rasburicase, it can safely be used to treat hyperuricemia of malignancies. We suggest using it with hyperhydration and sodium bicarbonate in patients with low risk for TLS.

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