Efficacy of lower-dose rasburicase in the prevention of hyperuricemia in patients at risk of tumor lysis syndrome

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Introduction & Purpose

Tumor lysis syndrome (TLS) is a potentially life-threatening, therapy-related complication associated with the treatment of certain hematological cancers or solid cancers with significant tumor burden.

Characterized by hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia, these disturbances can lead to severe renal impairment, cardiac arrhythmia, seizure, or even death.

Rasburicase, a recombinant urate oxidase enzyme, is FDA approved to lower uric acid levels in patients at risk of TLS to prevent the metabolic complications which cause these problems.

Mercy Health System's current rasburicase dosing protocol recommends patients at risk of TLS receive a one-time prophylactic dose of 3, 6, or 7.5 mg based on weight. Recent studies have shown rasburicase's efficacy in preventing hyperuricemia at doses at low at 1.5 mg, regardless of weight.

This study seeks to evaluate the optimal dosing schedule for rasburicase in TLS prevention based on a medical record review of Mercy Health System patients who received rasburicase.

Objectives

Primary Objective:

- To determine the non-inferiority of 3 mg and 6 mg doses of rasburicase versus doses of 7.5 mg or more in the prevention of hyperuricemia in high- and intermediate-risk patients receiving rasburicase prior to chemotherapy.

Secondary Objectives:

- To determine the incidence of repeated rasburicase administration in TLS prevention
- To determine the incidence of rasburicase use in non-oncology patients

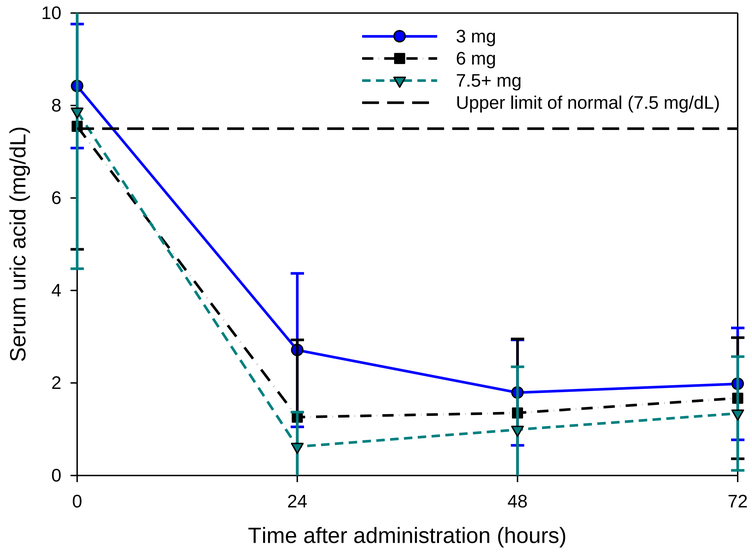
Study Population

	3 mg (N=17)	6 mg (N=93)	7.5+ mg (N=23)
Age - yr ± SD	71.5±17.8	64.9±13.3	69.9±16.3
Weight - lbs. ± SD	84.8±15	86±18.9	93.2±21.4
Female sex - no. (%)	10 (58.8)	38 (40.9)	9 (39.1)
Baseline serum uric acid - mg/dL ± SD	8.42 (1.34)	7.55 (2.66)	7.87 (3.4)
High TLS risk - no (%)	3 (17.6)	29 (31.2)	5 (21.7)
NHL - no. (%)	2 (11.8)	37 (39.8)	5 (21.7)
ALL - no. (%)	2 (11.8)	3 (3.2)	0 (0)
AML - no. (%)	1 (5.9)	15 (16.1)	2 (8.7)
CLL - no. (%)	3 (17.6)	9 (9.7)	5 (21.7)
Other blood cancers - no. (%)	4 (23.5)	15 (16.1)	7 (30.4)
Solid tumors - no. (%)	5 (29.4)	14 (15.1)	4 (17.4)

Methods and Materials

- A 24-month report of rasburicase use in across Mercy Health System was reviewed from January 1, 2018 to January 1, 2020.
- Patients that received rasburicase for TLS prevention were included. Patients were excluded if they had laboratory or clinical TLS or did not have laboratory values required to evaluate the efficacy of rasburicase.
- The primary endpoint was whether serum uric acid was within normal limits (<7 mg/dL) 24, 48, and 72 hours after administration.
- Statistical analysis was performed using Pearson's chi-square test and Student's t tests to determine statistical significance of results.
- Power was set at 90%, alpha at 0.05, and non-inferiority margin at 1.2

Change in serum uric acid over time after rasburicase administation



Successful hyperuricemia prevention

Rasburicase dose	24 hrs	48 hrs	72 hrs
3 mg - no. (%)	17 (100)	17 (100)	17 (100)
6 mg - no. (%)	93 (100)	93 (100)	93 (100)
7.5+ mg - no. (%)	23 (100)	23 (100)	23 (100)

Results

- The report yielded 322 administrations, of which 133 met study criteria to be used.
- Reasons for disqualification included diagnosis of TLS (60), no values recorded (60), death of patient before values could be recorded (13), and age less than 18 years (4).
- In all cases of rasburicase administration for the prevention of TLS, serum uric acid levels remained within normal limits at 24, 48, and 72 hours after administration, regardless of dose.
- No statistical significance was seen in prevention success in 3 mg (100%), 6 mg (100%), and 7.5+ mg (100%) doses (p<0.001).
- No statistically significant difference in weight was found between groups (3 vs 6 p=0.773; 6 vs 9 p=0.15; 3 vs 9 p=0.153).
- No statistically significant difference in baseline serum uric acid was found between groups (3 vs 6 p=0.191; 6 vs 9 p=0.627; 3 vs 9 p=0.534).
- All administrations for TLS prevention were one-time doses. No instances of repeat dosing were reported.
- Of the 322 administrations reported, 3 (0.9%) were used to treat hyperuricemia not associated with malignancy.

Discussion

- Given that power was not met, and a statistical significance was not shown between groups, data cannot confirm differential effects of these doses on hyperuricemia prevention without potentially committing a type II error. However, had *a priori* power been set anticipating zero difference in outcomes, power would have been met.
- Due to 100% of patients in all groups achieving hyperuricemia prevention, Pearson's chi-square test was unable to be performed. Significance between groups was determined by Student's t test.
- A significant reason for small sample size was the lack of serum uric acid levels reported in days following rasburicase administration. This represents an opportunity within the ministry to improve patient care and quality of future rasburicase research.
- The results of this study support previous studies with regards to the non-inferiority of low-dose rasburicase in TLS prevention.
- Had all patients in this study received a 3 mg dose, rasburicase use would have been decreased by 53%, reducing costs to provider and patient and minimizing adverse reactions.
- Given that 100% of all doses prevented hyperuricemia, consideration should be given to adopting the use of doses lower than 3 mg.
- Study limitations include:
  - Small sample size
  - Single institution study

Conclusions

- This study demonstrated the non-inferiority of 3 mg and 6 mg versus 7.5+ mg rasburicase doses in preventing hyperuricemia.

Disclosure Statement

None of the authors have any financial or professional conflicts to disclose.

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