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

Background: 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. It is characterized by hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia following rapid tumor cell lysis. These metabolic 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 plasma levels in patients with or at risk of TLS to prevent the metabolic complications which cause these problems. According to manufacturer's recommendation, rasburicase is dosed based on weight (0.2 mg/kg) and administered via IV daily for 5 days. Many studies have evaluated the efficacy of lower doses and less administrations of rasburicase with positive results, and some doctors within Mercy Health System have adopted these dosing schedules. The primary objective of this study is 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 tumor lysis syndrome (TLS) in high- and intermediate-risk patients receiving rasburicase prior to chemotherapy administration. Secondary objectives include determining the incidence of repeat rasburicase administration necessary in all dosing schedules of rasburicase in patients of all risk levels and determining the incidence of inappropriate use of rasburicase, i.e. administration for disease states other than TLS or TLS prevention.

Methods: Retrospective chart review will be utilized to evaluate treatment success, defined as maintenance of plasma uric acid levels within normal limits 24, 48, and 72 hours after administration, in cancer patients receiving rasburicase in patients who received rasburicase for TLS prevention from January 1, 2018 to January 1, 2020. This project is currently under Mercy Health System IRB review. Collected data will include patient age, sex, weight, diagnosis, TLS risk level, rasburicase dose, and serum uric acid levels at 0, 24, 48, and 72 hours. All data will be de-identified. Power will be set at 90%, alpha at 0.05, and non-inferiority margin at 1.2. 33 subjects are required in each group (99 total) to meet power. Data will be used to evaluate non-inferiority of lower doses of rasburicase as compared to higher doses.

Results and Conclusion: 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.

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