A Clinical and Economic Comparison of Rasburicase and Allopurinol in the Treatment of Patients With Clinical or Laboratory Tumor Lysis Syndrome

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Abstract

Management of tumor lysis syndrome (TLS), a potentially fatal oncologic complication after initiation of chemotherapy or other cytotoxic treatment or occurring spontaneously before treatment, has a significant economic effect. In this retrospective study of hospital administrative data from pediatric and adult patients with laboratory or clinical TLS we found that patients treated with rasburicase, compared with those who received allopurinol, had significantly greater mean reduction in uric acid levels, significantly shorter intensive care unit and overall hospital lengths of stay, and lower total hospitalization costs.

Background: The aim of the study was to compare reductions in uric acid (UA), length of stay (LOS), and hospitalization costs in patients with tumor lysis syndrome (TLS) treated with rasburicase or allopurinol. **Patients and Methods:** This retrospective study of administrative data included hospitalized pediatric and adult patients who had clinical or laboratory TLS and received rasburicase or allopurinol. Each rasburicase-treated patient was propensity score-matched with 4 allopurinol-treated patients. Mean changes in UA within $\leq$ 2 days of treatment initiation were determined. Economic outcomes included mean number of days in the intensive care unit (ICU), total LOS, costs/hospitalization, and costs/percentage change in UA. **Results:** Twenty-six rasburicase-treated patients were matched with 104 allopurinol-treated patients. Reduction in plasma UA was 5.3 mg/dL greater for patients treated with rasburicase than for patients treated with allopurinol ($P < .0001$). Length of ICU stay was 2.5 days less for patients treated with rasburicase than for patients treated with allopurinol ($P < .0001$), and total LOS was 5 days less for patients treated with rasburicase than for patients treated with allopurinol ($P = .02$). Total costs per patient were $20,038 lower for patients treated with rasburicase than for patients treated with allopurinol ($P < .02$). Cost per percentage UA reduction was also lower for patients treated with rasburicase versus patients treated with allopurinol ($3899 vs. $16,894; $P < .001$). **Conclusion:** In this analysis of TLS patients who received care in real-world settings, rasburicase versus allopurinol was significantly more effective in treating hyperuricemia and was associated with significantly shorter ICU and overall hospital stays and lower total inpatient costs.

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Introduction

Tumor lysis syndrome (TLS) is a potentially fatal oncologic complication characterized by metabolic disturbances consequent to rapid release of nucleotides, proteins, and other contents of tumor cells that have undergone lysis.[1] Most often, TLS follows initiation of chemotherapy or other cytotoxic treatment, but it can occur spontaneously before treatment.[2] It most commonly occurs in certain hematological cancers, particularly non-Hodgkin

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lymphomas (NHLs) and acute leukemias, but it can also develop in other tumor types, particularly where there is a high proliferative rate, large tumor burden, or high sensitivity to cytotoxic therapy.[3,4]

Tumor lysis syndrome has been defined in terms of laboratory abnormalities and clinical manifestations. Using the definition developed by Cairo and Bishop,[2] a diagnosis of laboratory TLS requires the presence of $\geq$ 2 characteristic laboratory abnormalities—hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalcemia—within 3 days before or 7 days after initiation of chemotherapy. Hyperphosphatemia and hyperkalemia consequent to tumor lysis might be exacerbated by renal insufficiency. A review of published case reports and series found that 42 of 105 patients (40%) have received renal replacement therapy, including hemodialysis and peritoneal dialysis.[5] Even when not life-threatening, TLS might require delay administration of chemotherapy or necessitate dose reductions.[6]

Management of TLS has a considerable economic effect. In the United States, among patients with hematologic cancers, renal dialysis has been associated with a more than doubling of inpatient length of stay (LOS) and a tripling of costs.[7] In a European analysis, costs in patients with TLS were 11 times higher than in patients with hyperuricemia but no TLS, with increased costs attributable mainly to intensive care unit (ICU) stays.[8] Current management of patients at risk for TLS depends on the individual patient's level of risk defined according to type of malignancy, white blood cell counts, and type of therapy.[1,3] Allopurinol and its main metabolite reduce uric acid (UA) formation by inhibiting xanthine oxidase, the enzyme catalyzing oxidation of hypoxanthine to xanthine and xanthine to UA.[3,9] Because allopurinol does not reduce levels of preexisting UA, it might take several days to improve hyperuricemia.[3] Additional limitations of allopurinol include risk of allergic reactions and possible clinically significant interactions with common chemotherapeutic agents. Finally, allopurinol can cause accumulation of xanthine, which can crystallize in the renal tubule, potentially resulting in acute obstructive uropathy.[3]

Rasburicase is a recombinant form of urate oxidase, an enzyme endogenous in many nonhuman mammalian species that catalyzes enzymatic oxidation of UA to allantoin.[2,10] Allantoin is more readily excreted than UA and is 5 to 10 times more soluble.[11,12] The recombinant molecule carries reduced liability for allergic reactions, including anaphylaxis, that have been associated with nonrecombinant urate oxidase.[10] Unlike allopurinol, rasburicase reduces plasma UA concentrations in patients at high risk of TLS within 4 hours of administration.[13,14] Rasburicase has also shown superiority to allopurinol in overall antihyperuricemic efficacy, measured according to change in plasma UA concentrations[14] or plasma UA response rates.[13] Reduced need for dialysis with use of rasburicase has been suggested because of lower rates of dialysis in studies of rasburicase-treated patients than in studies of patients not receiving the agent,[15] although no comparative trials designed to evaluate this outcome have been reported.

The clinical efficacy of rasburicase notwithstanding, estimated drug acquisition costs (in children, approximately $1575 per day, and in adults, approximately $7690 per day) have led to questions about cost-effectiveness.[16-18] To address the cost-effectiveness of rasburicase in TLS, we conducted a hospital database analysis of pediatric and adult patients treated for documented TLS. We included in our study a comparison of changes in UA levels and comparisons of duration of ICU care, overall hospital LOS, and costs between patients who were treated with allopurinol and those treated with rasburicase.

Patients and Methods

Study Design and Data Source

This was a retrospective cohort study of administrative data. No institutional board approval was required. For the analysis we used the Cerner Health Facts database.[19] This database captures and stores deidentified, longitudinal electronic health record patient data and then aggregates and organizes these data into data sets to facilitate analysis and reporting.[19] Patient data are obtained from more than 400 US hospital facilities. The database is comprised of patient demographic characteristics, encounters, diagnoses, prescriptions, procedures, laboratory tests, locations of services/patients (eg, ICU), and hospital information and billing data. Clinical records are collected with time-stamped and sequenced information on pharmacy, laboratory, admission, and billing data from all patient care locations.

Patient Selection

All patients of any age who were hospitalized and received rasburicase or allopurinol between January 1, 2005 and March 31, 2009 were initially selected. Patients were required to have clinical or laboratory TLS 5 days before or 2 days after the index hospital admission. Allopurinol-treated patients with a diagnosis of gout (274.x) for inpatient encounters on or within 12 months before first use of allopurinol were excluded. To minimize differences in baseline demographic characteristics between the 2 cohorts, propensity score (PS) matching was used. The PS is defined as the probability of receiving rasburicase versus allopurinol and is calculated from a nonparse logistic regression model that is adjusted for age, gender, tumor type, baseline UA concentration, type of hospital admission (ICU vs. other), ICU admission before the index, Charlson comorbidity index, hospital characteristics, payer type, and other risk factors. Each rasburicase patient was PS-matched with 4 allopurinol patients via a 5:1 digit greedy algorithm.[20]

Outcomes

The effectiveness of rasburicase and allopurinol in treating hyperuricemia was evaluated by determining changes in UA concentrations within 2 days of treatment initiation (ie, the difference between the UA value collected within 1 day before initiating treatment and the last UA value within 2 days after start of treatment). Changes in serum creatinine, potassium, and phosphorous were also evaluated using the same method.

Economic outcomes included mean hospital LOS, mean number of days in the ICU, and total health care costs per hospitalization. Costs per mg/dL change in plasma UA concentration were calculated and compared at the cohort level. Hospital charges were converted to hospital costs by applying a 0.6 cost to charge multiplier, obtained from a Hospital Cost to Charge report from the US Department of Health and Human Services.

Statistical Analysis

Analyses of demographic variables were done using t test for continuous variables and χ^2 for categorical variables. Generalized linear models were used to evaluate differences in all outcomes.