Effectiveness and Safety of Allopurinol, Febuxostat, and Rasburicase in the Prevention of Tumor Lysis Syndrome: A Systematic Review and Network Meta-analysis

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Although prevention is vital in managing tumor lysis syndrome (TLS), no study directly compares various regimens. This study compared the effectiveness and safety of urate-lowering agents in preventing TLS. Databases were searched for randomized controlled trials involving adults with hematologic or solid malignancies on chemotherapy or cytoreductive agents given allopurinol, febuxostat, or rasburicase alone or in combination at any dose, form, or frequency published in English by December 2021. Outcomes included laboratory and clinical TLS expressed as relative risks, adverse events as described by authors, and mean serum uric acid (sUA) as mean differences of area under the curve. A network of meta-analysis and post-hoc meta-analysis based on TLS risk using a random-effects model was done using Stata 14.0 and Review Manager 5.3, respectively. Certainty of evidence was assessed using the GRADE approach. Three studies with a total of 633 participants given allopurinol, febuxostat, rasburicase, or rasburicase combined with allopurinol were included. Rasburicase is more effective than allopurinol in preventing laboratory TLS (relative risk: 0.51; 95% confidence interval [CI]: 0.32–0.81) based on moderate quality evidence. No significant differences were observed in clinical TLS. Adverse events were attributable to toxicities of chemotherapy. Rasburicase alone or in combination with allopurinol was better than allopurinol or febuxostat alone in reducing sUA level. Febuxostat is more effective than allopurinol in lowering sUA levels among patients at high-risk of TLS (mean difference – 125.75; 95% CI: 223.47 to – 28.02). Rasburicase may be the most effective agent in preventing laboratory TLS and maintaining low sUA levels.
Introduction

Tumor lysis syndrome (TLS) is an oncologic emergency among patients receiving chemotherapy for highly proliferative malignancies. It is caused by the abrupt and massive release of intracellular electrolytes from malignant cells lysed by cancer treatment. Laboratory TLS is defined as two or more metabolic abnormalities (hyperuricemia, hyperphosphatemia, hyperkalemia, or hypocalcemia) present in the same 24-hour period within 3 days before the start of therapy or up to 7 days afterward. Clinical TLS, on the other hand, is the presence of laboratory TLS plus an increased creatinine level, seizures, cardiac dysrhythmia, or death. The incidence of TLS ranges from 4% to 42% and usually occurs early in the administration of chemotherapy or radiotherapy. The mortality rate of TLS can be as high as 15% among confirmed cases, and thus requires a high index of suspicion for diagnosis. Close monitoring of electrolytes (at least every 6 hours) and volume status is warranted for all patients at risk of TLS. More importantly, prevention is vital especially in patients at high risk, and includes intravenous hydration and urate-lowering agents such as allopurinol, febuxostat, and rasburicase.

Allopurinol is the most widely known urate-lowering therapy for TLS. Though effective, it cannot decrease preexisting uric acid levels; it can also increase xanthine and hypoxanthine that can cause xanthine nephropathy. Other issues precluding its use include the need for renal adjustment, drug-drug interactions such as with thiazide diuretics and amoxicillin, and drug reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis. On the other hand, febuxostat has been shown to be a viable alternative option to allopurinol; it exhibits a similar mechanism of action but without the need for dose adjustment in renally impaired patients. Finally, rasburicase, a recombinant urate oxidase, has been proven to be highly effective in treating hyperuricemia; it can reduce already elevated levels of uric acid, and it does not cause xanthine accumulation. Adverse events related to rasburicase, though reported to be less than 1%, include hemolytic anemia, methemoglobinemia, and anaphylaxis. Most randomized controlled trials (RCTs) on rasburicase involve only children, while the most recent meta-analysis on adults include mostly retrospective studies, RCTs comparing various doses of rasburicase, and a lone trial comparing allopurinol and rasburicase. While various pharmacologic therapies are available to prevent hyperuricemia, no study compares that regimen is the most effective and safe in the prevention of TLS.

This study aimed to compare the effectiveness and safety of allopurinol, febuxostat, and rasburicase as monotherapy or combination therapies in the prevention of TLS among adults in terms of laboratory TLS and clinical TLS, reduction in serum uric acid (sUA) levels, and adverse events.

Methods

The reporting of this systematic review and network meta-analysis is in line with the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) Extension Statement. Ethics review board approval was waived since this was not an individual patient-level meta-analysis.

Eligibility Criteria

Randomized controlled trials involving adult patients with hematologic malignancies or solid tumors who were about to receive or receiving chemotherapy and cytoreductive agents and published in English from database inception up to December 2021 were selected. Only studies that assessed the effectiveness and safety of allopurinol, febuxostat, or rasburicase in any dose, form, or frequency, alone or in combination, compared with any intervention (including intravenous hydration with crystalloid solutions and sodium bicarbonate) in preventing TLS were included. The primary outcome of interest was the incidence of laboratory and clinical TLS. The secondary outcomes of interest were the types and incidence of adverse drug events, and the area under the curve (AUC) of sUA. Non-RCTs and studies that compared a single type of intervention at varying doses were excluded.

Data Sources, Search Strategies, and Study Selection

Two reviewers (E.M.M. and J.J.B.) independently searched PubMed, the Cochrane Library, and Clinicaltrials.gov using the following search terms: TLS, allopurinol, febuxostat, rasburicase, intravenous hydration, crystalloid solutions, PRsodium bicarbonate. The Cochrane Highly Sensitive Search Strategy was used. The search was limited to two-edge paths, where studies evaluate different interventions of interest but have one common indirect comparator. The reference lists of relevant systematic reviews and meta-analyses were manually searched for additional potentially relevant studies. The same reviewers independently screened the titles and abstracts of the identified articles for relevance based on the inclusion and exclusion criteria. Full texts of potentially relevant articles were retrieved and reviewed for inclusion in the review.

Data Extraction

Two reviewers (E.M.M. and J.J.B.) independently extracted the following data from each included study using the Cochrane data extraction template: study design, baseline characteristics, sample size, interventions used, incidence of laboratory and clinical TLS, the types of adverse drug events, and the AUC of sUA.

Geometry of the Network

Network plots were constructed, with each intervention of interest represented by a node. Head-to-head comparisons between these interventions were shown as a solid line between the nodes, while indirect comparisons were represented by a broken line between nodes. Drugs were not distinguished by dosages, forms, or manufacturers. The size of the nodes is proportional to the number of patients included in the study, and the thickness of the line is proportional to the number of studies that compare the interventions.
Risk of Bias within Studies and Certainty of Evidence
The quality of each study was assessed independently using the Cochrane risk-of-bias tool. Disagreements were resolved by consensus. The overall certainty of evidence for the network meta-analysis was rated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Summary Measures and Data Analysis
Network meta-analysis using a random-effects model was done via Stata 14.0. Risk ratios and mean differences (MD) with 95% confidence intervals (CIs) were estimated for the incidence of clinical and laboratory TLS and AUC of sUA expressed as mg x h/dL, respectively. League tables were generated for each outcome. The Surface Under the Cumulative RAnking curve (SUCRA) was used to determine the relative probability of each intervention to be the best option to prevent TLS. The closer the SUCRA value to 100%, the higher the probability for the intervention to be the most effective. Types of adverse events were described.

Assessment of Inconsistency
Directness, transitivity, coherence, and heterogeneity among the trials were assessed qualitatively by comparing the population, intervention, comparison, and outcome elements of the included studies. Heterogeneity was also quantified using the inconsistency statistic (I²), computed using Review Manager 5.3, with values more than 50% considered as significant heterogeneity. Loop and design consistency were assessed through STATA 14.0.

Risk of Bias across Studies
Due to the limited number of studies, a comparison-adjusted funnel plot to assess for publication bias is not appropriate to be generated for this study.

Additional Analyses
Post-hoc meta-analyses of patients with intermediate and high risk of TLS using the random effects model were also done using Review Manager 5.3.

Results
Study Selection and Study Characteristics
A total of 131 articles were identified from the literature search, of which 128 were excluded because of duplication or eligibility (Fig. 1). Three articles with a total of 633 patients were included. Supplemental Table S1 (available online only) summarizes the characteristics of these studies.

Network Geometry
The largest number of patients was randomized to allopurinol, with a total of 314 patients (Fig. 2). A total of 222 patients were randomized to febuxostat, 94 patients for rasburicase, and 93 patients for rasburicase and allopurinol in combination. Two studies provided evidence for the pairwise combination of febuxostat and allopurinol. The third study was a three-arm trial that compared rasburicase, allopurinol, and the combination of rasburicase and allopurinol.

Risk of Bias within Studies
The studies of Cortes et al and Tamura et al were open label trials, while the studies of Cortes et al and Spina et al did not explicitly mention allocation concealment. The overall risk of bias is low for laboratory TLS, clinical TLS, and AUC of sUA because these parameters are not influenced by blinding, while the overall risk of bias is moderate for adverse events.

Supplemental Fig. S1 (available online only) illustrates the assessment of the risk of bias of the included studies.

Assessment of Network Meta-Analysis Assumptions
Based on qualitative assessment of the included studies, there was no violation of the assumptions of directness and transitivity. For heterogeneity, only the pairwise comparison of febuxostat and allopurinol had more than one study providing evidence. Results were similar across studies for laboratory and clinical TLS, but there was significant heterogeneity for the AUC of sUA (I² = 98%). There was no source of loop and design inconsistency in this study.

Results of Individual Studies
Data for each outcome per intervention group of the individual studies are summarized in Supplemental Table S2 (available online only).

Synthesis of Results
Laboratory Tumor Lysis Syndrome
Pairwise comparisons suggest that rasburicase is more effective than allopurinol (relative risk: 0.52, CI: 0.33–0.82). There were no significant differences found in the rest of the pairwise comparisons (Table 1). Based on the Surface Under the Cumulative RAnking curve (SUCRA) values, rasburicase has the highest probability of being the best intervention, followed by the combination of rasburicase and allopurinol. The third best intervention is febuxostat, while the lowest ranked intervention is allopurinol (Table 1).

Clinical Tumor Lysis Syndrome
No significant differences were found in all the pairwise comparisons (Table 2). The SUCRA values among the four interventions are very close to each other (range: 47.8–59.7%). The rankings are not robust, and other factors need to be considered when choosing one intervention over the other for the prevention of clinical TLS, including their effects on laboratory TLS and sUA levels, as well as adverse effects (Table 2).

Area Under the Curve of Serum Uric Acid
In this context, the lower the MD (mg x h/dL), the lower the AUC. Pairwise comparisons showed that rasburicase is superior to allopurinol (MD: −569.95, 95% CI: −796.38 to −341.62), febuxostat is inferior to rasburicase (MD: 457.07, CI: 180.64–733.52), and rasburicase in combination with allopurinol is superior to febuxostat (MD: −426.08, 95% CI: −702.64 to −149.51) and allopurinol (MD: −538, 95% CI: −765.54 to −311.03).
Table 3). Rasburicase has the highest probability of being the best intervention, followed by rasburicase in combination with allopurinol and febuxostat. The lowest ranked intervention is allopurinol (Table 3).

Adverse Events
The most commonly reported adverse events were related to the blood and lymphatic system, gastrointestinal system, and administration site conditions. The most common serious adverse events were pneumonia, febrile neutropenia, neutropenic sepsis, and neutropenic infection. There were reports of elevated serum transaminase levels that were considered to be related to febuxostat and allopurinol, and potential hypersensitivity reactions to rasburicase or allopurinol. No drug-related life-threatening adverse events or deaths occurred.

Table 1 League table for laboratory TLS with corresponding SUCRA values (%)a

<table>
<thead>
<tr>
<th>Treatment</th>
<th>RR (95% CI)</th>
<th>SUCRA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rasburicase + allopurinol</td>
<td>RR: 0.76 (0.3–1.64)</td>
<td>Febuxostat (33)</td>
</tr>
<tr>
<td>Rasburicase</td>
<td>RR: 1.31 (0.7–2.18)</td>
<td>RR: 1.72 (0.78–3.81) Rasburicase (91.3)</td>
</tr>
<tr>
<td>Rasburicase</td>
<td>RR: 0.68 (0.45–1.02)</td>
<td>RR: 0.9 (0.47–1.71) RR: 0.52 (0.33–0.82) Allopurinol (13.3)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk; SUCRA, Surface Under the Cumulative RAning curve; TLS, tumor lysis syndrome.

aComparisons should be read from left to right. An RR of less than 1 favors column-defining treatment.
Certainty of Evidence
The certainty of evidence assessments for the network meta-analysis estimates is summarized in Supplemental Table S3 (available online only). For the outcomes of laboratory TLS and clinical TLS, most pairwise comparisons had low quality of evidence due to risk of bias and imprecision; only the comparison of allopurinol and rasburicase had moderate quality of evidence due to risk of bias. For the outcome of AUC of sUA, the pairwise comparisons of allopurinol and rasburicase, febuxostat and rasburicase, allopurinol and rasburicase with allopurinol, and febuxostat and rasburicase with allopurinol had moderate quality evidence due to risk of bias.

Results of Additional Analyses
Post-hoc meta-analysis of patients with intermediate risk for TLS did not show a significant difference between febuxostat and allopurinol in terms of the reduction in sUA levels (MD: −97.90, 95% CI: −308.53 to 112.73) as illustrated in Supplemental Fig. S2 (available online only). On the other hand, febuxostat was better than allopurinol in reducing sUA levels (MD: −125.75, 95% CI: −223.47 to −28.02) in patients with high risk of TLS as shown in Supplemental Fig. S3 (available online only).

Discussion
Rasburicase appears to be the most effective urate-lowering agent in preventing laboratory TLS and maintaining low sUA levels. Based on the SUCRA values, rasburicase seems to be superior to rasburicase in combination with allopurinol, febuxostat, or allopurinol alone in terms of incidence of laboratory TLS and MD of AUC of sUA; no conclusion can be made in terms of clinical TLS. Furthermore, no adverse event can be clearly attributed to the treatment groups as they can be likely due to the known toxicities of chemotherapy and underlying malignancy.

Rasburicase is a recombinant urate oxidase enzyme that degrades uric acid into allantoin, a highly soluble product readily excreted in the urine. Compared with febuxostat or allopurinol alone, regimens that have rasburicase had lower incidence of laboratory TLS and MD of AUC of sUA. Similar findings were made in children with lymphoma or leukemia at high risk of TLS. A phase II trial in adults with aggressive non-Hodgkin lymphoma on induction chemotherapy also

Table 2 League table for clinical TLS with corresponding SUCRA values (%)a

<table>
<thead>
<tr>
<th>Treatment</th>
<th>RR: 0.75 (95% CI: 0.09–5.96)</th>
<th>RR: 1.01 (95% CI: 0.21–4.88)</th>
<th>RR: 0.75 (95% CI: 0.17–3.25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raburicase + allopurinol</td>
<td>Febuxostat (59.7)</td>
<td>Rasburicase (50.8)</td>
<td>Rasburicase (50.8)</td>
</tr>
<tr>
<td>Raburicase</td>
<td>Rasburicase (50.8)</td>
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<td>Rasburicase (50.8)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk; SUCRA, Surface Under the Cumulative RAnking curve; TLS, tumor lysis syndrome. Comparisons should be read from left to right. An RR of less than 1 favors column-defining treatment.

Table 3 League table for area under the curve of serum uric acid (mg x h/dL) with corresponding SUCRA values (%)a

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MD: −426.08 (95% CI: −702.64 to −149.51)</th>
<th>MD: 31 (95% CI: −189.34 to 251.34)</th>
<th>MD: −538 (95% CI: −765.54 to −310.46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raburicase + allopurinol</td>
<td>Rasburicase (86.9)</td>
<td>Rasburicase (86.9)</td>
<td>Allospirinol (2.4)</td>
</tr>
<tr>
<td>Raburicase</td>
<td>Rasburicase (86.9)</td>
<td>Rasburicase (86.9)</td>
<td>Allospirinol (2.4)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; MD, mean difference; SUCRA, Surface Under the Cumulative RAnking curve. Comparisons should be read from left to right. The lower (i.e., more negative) the mean difference, the lower the area under the curve. An MD of less than 1 favors column-defining treatment.
deemed rasburicase as the treatment of choice for controlling sUA and preventing hyperuricemia. Two meta-analyses and several experts who evaluated previous preliminary clinical trials including compassionate use trials on TLS also recommend rasburicase. 

There is insufficient data to conclude on the effect of any of the treatments on the incidence of clinical TLS. The limited number of enrolled patients and small event rates may be underpowered to determine effectiveness, a limitation also observed by the authors. Similarly, another study failed to determine a difference in incidence of renal failure or those requiring renal replacement therapy between children given allopurinol or rasburicase due to small sample size. Vigilant monitoring of parameters of laboratory TLS is part of the standard of care thus once diagnosed, measures are taken to prevent progression to clinical TLS possibly explaining the low event rates.

All of the studies agreed that the majority of adverse events are attributable to the common toxicities of chemotherapy or underlying malignancy itself. Two studies in children support rasburicase as a safe drug ascribing adverse effects such as allergic reactions and methemoglobinemia might be more common for rasburicase than allopurinol, and clinicians should carefully weigh the risks and benefits. Furthermore, rasburicase was well-tolerated in both children and adults in a multicenter compassionate use trial with possible drug-related adverse events including allergic reactions being uncommon. However, it should not be given to patients with G6PD deficiency due to risk of hemolysis. In contrast, a meta-analysis in a pediatric population suggested that adverse effects such as allergic reactions and methemoglobinemia might be more common for rasburicase than allopurinol, and clinicians should carefully weigh the risks and benefits. On the other hand, the safety profile of allopurinol and febuxostat was comparable with increased liver function tests as the most common adverse effect. No severe adverse reactions were associated with administration of febuxostat among adults with active hematologic malignancies.

The authors acknowledge the limitations of the study. The small number of RCTs exploring the available pharmacotherapies for the prevention of TLS prove to be a limitation in drawing robust conclusions. The limited number of patients enrolled in the studies might overestimate treatment effects. Therefore, the SUCRA values and ultimately, the results of this study should be interpreted with caution. Also, the outcome measures investigated are surrogate markers and similar efficacy on hard outcomes such as need for renal replacement therapy and mortality should not be outright concluded. Finally, the doses of the treatments varied across different studies; this is a possible source of heterogeneity for the pairwise comparisons on AUC of sUA. While dosing was not taken into account in the analysis, it is important to note that dose-dependent effects may be possibly observed.

Based on the results and limitations, it is recommended that large-scale RCTs be done exploring the various aspects of prevention of TLS. While searching databases, it was noted that most RCTs found involved mixed or pediatric populations while most studies involving adult populations are prospective cohorts, case reports, or case series. Furthermore, hard outcomes such as mortality rate, acute renal failure needing renal replacement therapy, length of intensive care unit, or length of stay in the hospital should be investigated in future RCTs. Optimal hydration regimen, timing of initiation of TLS prophylaxis, and dose of rasburicase can also be looked into. More RCTs involving patients with solid tumors with high TLS risk (e.g., neuroblastoma, germ cell tumors, small cell lung carcinoma) should also be done.

Although results of this study suggest rasburicase is the most effective among the treatment groups compared, its unavailability locally and high cost may be prohibitive in clinical practice. However, a systematic review proposed that although rasburicase is expensive, findings that a single dose regimen do not compromise efficacy might mitigate this limitation. Furthermore, a pan-European cost-analysis study concluded that when total cost of medical care is considered, rasburicase is a cost-effective preventive treatment in children with acute myeloid leukemia, acute lymphoid leukemia, and non-Hodgkin leukemia and adults with acute lymphoid leukemia and non-Hodgkin leukemia. Therefore, once locally available and more affordable, rasburicase is recommended as a preventive monotherapy for TLS.

Conflict of Interest
None declared.

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