Efficacy of Febuxostat for the Prevention of Tumor Lysis Syndrome in Patients with Hematological and Soft Tissue Malignancies: A Meta-analysis

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Abstract

Introduction: Tumor lysis syndrome (TLS) is a therapy-related complication resulting from the rapid lysis of malignant cells post-treatment. The control of serum uric acid level plays a key role in its prevention, thus, allopurinol is used. Febuxostat is a novel xanthine oxidase inhibitor and there are currently no recommendations for using such in the prevention of TLS, hence, this study was conducted. This study aims to determine the efficacy of febuxostat in the prevention of TLS.

Methods: Extensive search for randomized controlled trials (RCT) focusing on the use of febuxostat in the prevention of TLS was done. Each article was appraised independently by the researchers. The data were analysed using Rev Man 5.3.

Results: Two trials were included in this review. The study results revealed that febuxostat, when compared to allopurinol, was able to decrease serum uric acid as hyperuricemia is the hallmark of TLS. This decrease in serum uric acid was consistent in both studies. Serum uric acid levels at the end of the treatment showed a standard mean difference of -1.09 (95% CI-1.29, -0.88, *p* for heterogeneity <0.01, *p* for effect <0.01, I^2 = 97%). The trend of both studies favored the efficacy of febuxostat. The adverse effects documented during the study period in both trials were mostly noted from the chemotherapeutic agents and none from the use of febuxostat.

Conclusion: Febuxostat was shown to be more effective than allopurinol in the prevention of TLS.

Keywords: febuxostat, prevention, tumor lysis syndrome, meta-analysis

Introduction

Tumor lysis syndrome (TLS) is an oncologic emergency arising from the rapid lysis of tumor cells post treatment and its deleterious effects to the already suffering body accumulates. TLS is commonly seen after chemotherapy for hematologic malignancies (42%),[1] specifically acute lymphoblastic leukemia (26.4%),[2] acute myeloid leukemia (20%),[3] and burkitt's lymphoma and is less commonly associated with chemotherapy of chronic leukemias and solid malignancies (16%).[3] TLS has also been reported in patients who underwent radiation therapy, dexamethasone treatment, thalidomide therapy, and newer chemotherapeutic agents including bortezomib and rituximab. Patients with comorbidities such as hypertension, diabetes mellitus, coagulopathies, chronic kidney disease also have increased risk of developing TLS.[4] Unfortunately, the incidence of TLS in the Philippines is understudied. US data showed 22% mortality,[2] and another study revealing 14.44%.[4]

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Tumor lysis syndrome (TLS) results from rapid release of intracellular material from lysing malignant cells. When clearance of these products by excretion is impaired and their serum burden increases, the clinical sequelae of TLS may occur. It is further described as a massive overload of potassium, phosphorus, and uric acid in the bloodstream plus hypocalcemia, potentially causing lethal cardiac arrhythmias and/or renal failure.[5] Although the rapid release of electrolytes from intracellular stores to the extracellular space can have fatal consequences, usual homeostatic mechanisms can often compensate for these shifts provided that kidney function remains robust.[6] Acute kidney injury (AKI) secondary to urate nephropathy is the central mechanism of TLS.[6] The liberation of potassium from lysing tumor cells can amount to a supraphysiologic potassium load, particularly in the case of hematologic malignancies with a large burden of disease. Among patients with chronic kidney disease (CKD) or AKI, potassium clearance is limited and the risk of clinically significant hyperkalemia is greatly increased. TLS can induce a large phosphorus load to the extracellular space. Similar to potassium, kidney elimination of phosphorus may be limited by AKI or preexisting CKD.

Accurate risk assessment is paramount to the prevention of TLS (See Appendix B). There is no universally accepted

system for classification and grading of TLS. However, current guidelines by the British Committee for Standards of Hematology adapts the definition of Cairo and Bishop made in 2004. According to them, TLS is defined as the presence of two or more laboratory derangements and at least one clinical finding. Laboratory parameters to diagnose TLS show a 25% increase from baseline of uric acid, potassium, and phosphorus and a 25% decrease of calcium between three days prior and seven days after cytotoxic therapy. Clinical findings mark the severity of TLS. These include the development of AKI, evidenced by increasing creatinine levels, cardiac arrhythmia, seizures marks the severity grading of TLS.[7]

The current guidelines for the management of TLS focuses on prevention, thus patient stratification is vital. Patients are assessed prior to initiation of cytotoxic therapy. Patients falling under low risk may only be observed and if need be, treatment may be initiated prior to the start of cytotoxic therapy. Intermediate risk patients should be adequately hydrated and maintained at approximately one to two times maintenance fluid levels, with a urine output goal of 80 to 100 mL/m^2/h. Intermediate risk patients are also started with Allopurinol 12-24 hours prior to cytotoxic therapy at an initial dose of 10 mg/kg/d divided every eight hours per orem (maximum, 800 mg/d) or 200-400 mg/m^2 /d in one to three divided dose.[8] Allopurinol acts as an inhibitor of the xanthine oxidase enzyme thereby preventing conversion of hypoxanthine to xanthine and xanthine to insoluble uric acid. Allopurinol use, however, has been limited by the development if severe hypersensitivity reactions and pre-existing kidney disease.[7] The use of recombinant urate oxidase such as rasburicase maybe initiated among low and intermediate risk patients who develop hyperuricemia during the course of chemotherapy. High risk patients should be managed with hydration as previously stated and rasburicase at 0.15 to 0.2 mg/kg once daily in 50 mL of normal saline as an IV infusion over 30 minutes for five days.[8] Rasburicase acts to convert the already insoluble uric acid to a much more soluble substance called allantoin. There are reported hypersensitivity reactions with intake of rasburicase in patients with history of atopy. It is also contraindicated in patients with G6PD as it may trigger hemolytic anemia.[8] Febuxostat is a novel xanthine oxidase inhibitor that does not appear to have the hypersensitivity profile of allopurinol. In addition, it is metabolized to inactive metabolites in the liver, obviating the need for specific kidney dosing.[6] To date, there are two studies comparing the efficacy of febuxostat to allopurinol in the prevention of TLS. That being said, this will be the first study to analyse the results from these randomized clinical trials, with a goal to provide a single conclusion that has a greater statistical power.

The main objective of this study is to determine the efficacy of febuxostat in the prevention of TLS in patients with hematologic malignancy and solid tumors. More specificly: (1) To determine the efficacy of febuxostat as a primary prevention for TLS in terms of lowering serum uric acid level; (2) To determine the adverse effects of febuxostat in the study population.

Methods

Study design

Meta-analysis was employed. Large electronic databases were searched for all available studies regarding the use of febuxostat in the prevention of TLS.

Search strategy

The researchers used large electronic databases such as Cochrane, EBSCO, Pubmed, ClinicalTrials.Gov, National Center for Biotechnology Information, and Science Direct for all available studies regarding the use of febuxostat in prevention of TLS. Other searches were done in Google scholar and if full text is not available, the corresponding authors were contacted through their e-mails. Keywords used were "febuxostat", "tumor lysis syndrome" and "randomized clinical trials". The search was without language limitation and up to January 2018. References of the retrieved articles and the review articles published by expert authors on the subject were also screened for eligible studies. The researchers applied the selection criteria and extracted the data independently.

Selection Criteria

Inclusion criteria

1. Participants with hematologic malignancies who were scheduled to receive their first cycle of chemotherapy;
2. Participants with solid tumor or bulky mass;
3. Patients who are at intermediate risk of TLS or a high risk of TLS;
4. Patients who were not scheduled to be treated with rasburicase;

Exclusion criteria

1. Patients diagnosed of TLS before receiving treatment;
2. Patients with history of allergic reaction to febuxostat;
3. Patients with significant renal dysfunction with an eGFR <30 mL/min/1.73 m^2;

Types of intervention

1. Treatment Group: febuxostat
2. Control Group: allopurinol

Types of outcome measures

Primary outcome - this study aims to determine if febuxostat can prevent the occurrence of TLS as indicated by a decreased in serum uric acid.

Secondary outcome - This study also intends to summarize the common side effects of febuxostat use.

Search methods for identification of studies

Extensive search using EBSCO, Pubmed, ClinicalTrials.Gov, National Center for Biotechnology Information, and Science Direct was done. The following search terms were entered;

1. "Febuxostat"
2. "Tumor Lysis Syndrome"
3. "Randomized clinical trial" was used to filter all related studies

Reference lists of relevant trials and related textbooks were reviewed.

Data collection and analysis

Eligible trials were searched through the electronic databases of EBSCO, Pubmed, ClinicalTrials.Gov, National Center for Biotechnology Information, and Science Direct to gather literatures relevant to this review. Table I presents the details on the specific search terms and combinations.

Each article was assessed and appraised independently by three reviewers in terms of validity, results and applicability. In the case of disagreement in the appraisal, the three researchers discuss the results so as to come up with a final appraisal. Trials that met the inclusion criteria were selected; otherwise, these studies were excluded.

The flow diagram for the study inclusion was shown in Figure 1. Utilizing five search engines, there was a total of eleven journals that were qualified based on the search terms used. Upon review of these eleven journals, eight journals were removed due to duplicate studies, leaving three records. No records were excluded after the initial round of screening. During the full-text assessment for eligibility, one study was removed because the study did not utilize allopurinol as a control drug or group. The two studies remaining were used and analysed for the meta-analysis. The data of the studies that met the inclusion criteria were analyzed using Review Manager version 5.3

Assessment of risk of bias in included studies

The reviewers utilized the PRISMA quality assessment checklist to evaluate bias in the included studies. Study evaluation included random sequence-generation, allocation concealment, baseline characteristics, eligibility criteria, blinding, use of intention-to- treat analysis, and completeness of follow-up. Biases in each trial were evaluated as adequate, partial, inadequate or unknown.

Table I. Search results from different electronic databases

Database	Keywords	Results
PubMed	febuxostat, tumor lysis syndrome, randomized clinical trial	3
EBSCO	febuxostat, tumor lysis syndrome, randomized clinical trial	2
ClinicalTrials.Gov	febuxostat, tumor lysis syndrome, randomized clinical trial	2
National Center for Biotechnology Information	febuxostat, tumor lysis syndrome , randomized clinical trial	2
Science Direct	Febuxostat, tumor lysis syndrome, randomized clinical trial	2
Total		11

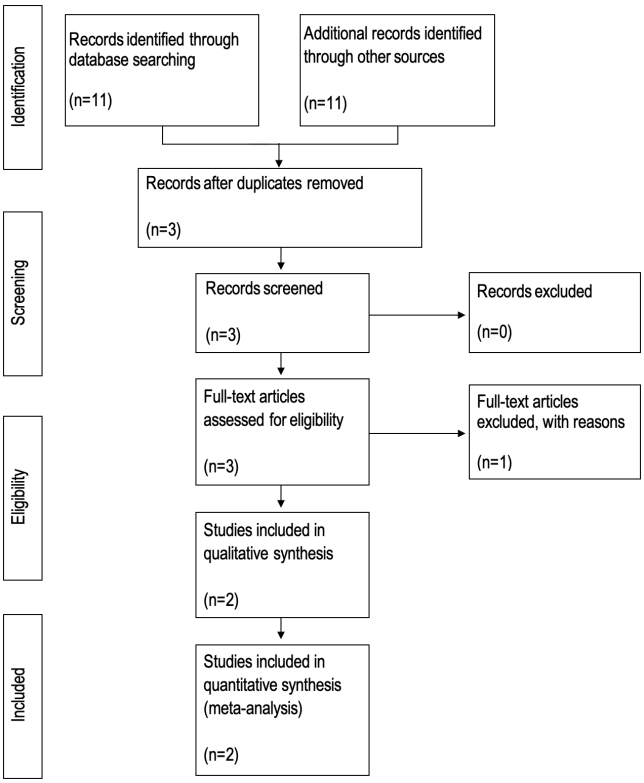

Figure 1. Flow diagram of included trials

Measures of treatment effect

Treatment effect was measured based on the outcome of interest in terms of standard deviation and means. The forest plot of the effects of the treatment groups was utilized to depict whether the overall results favored febuxostat or allopurinol. The nearer a study plot was to the line of null effect showed that the intervention being studied had no effect whatsoever. The side on which the standard mean difference of the study's result fell was the treatment the study showed to be favorable.

Data synthesis

Heterogeneity among the two studies was statistically treated by utilizing chi-square test with $p<0.50$ to indicate statistical significance. I^2 statistic was likewise used to quantify the magnitude of heterogeneity. The data extracted from individual studies were analyzed using Rev Man 5.3 and conclusion was eventually drawn after the data synthesis. Upon review, there was no reason for publication bias since both studies were non-sponsored by any company.

Definition of terms

Febuxostat: Febuxostat is an oral xanthine oxidase inhibitor used in this study as study treatment.

Allopurinol: Allopurinol is a xanthine oxidase (XO) inhibitor used in this study as control treatment.
Tumor Lysis Syndrome: Tumor Lysis Syndrome (TLS) is characterized by hyperuricemia, hyperkalemia, hyperphosphatemia, ang hypocalcemia and is caused by the destruction of a large number of rapidly proliferating neoplastic cells.[9]
Primary Prevention: It refers to the first level of health care. It means intervening before health effects occur.

Financing of project

The authors did not receive any grant from any funding agency in the public, commercial or not-for-profit organizations for this research.

Results

After an extensive search, two trials were included in this review.

Characteristics of included studies

Methods: Both studies that were selected for the review were randomized control trials that were published in English. The duration of the intervention was from two days before the initiation of chemotherapy until five to seven days done by Spina et al. and one day before the initiation of chemotherapy until at least six days after chemotherapy by Tamura et al.

Participants: It enrolled a total of 222 patients who were given febuxostat and 223 patients who were given allopurinol. Table I shows a summary of the baseline characteristics of these trials. All are randomized controlled trials (RCT) which utilized febuxostat versus allopurinol in the prevention of TLS.

Intervention:Both trials done were multicenter. The trial performed by Spina was in Italy and the intervention received by participants were febuxostat 120 mg orally once a day versus allopurinol 200 mg, 300 mg and 600 mg as decided by the investigator. The trial performed by Tamura was in Japan and the intervention received by the participants were febuxostat 60 mg orally once a day or 100 mg of allopurinol thrice a day (300 mg/day) except in patients with moderate or severe renal impairment who received allopurinol 100 mg twice daily (200 mg/day). (Table II)

Primary outcomes

In both studies, the primary outcome assessed was the change in serum uric acid from the baseline and after the last day of treatment.

Secondary and additional outcomes

Both studies evaluated the adverse effects, including the serious events that may have occurred during the trial. The adverse effects documented during the study period in the study by Tamura (2016) were mostly noted from the chemotherapeutic agents and none from the use of febuxostat, since both treatment groups (febuxostat and allopurinol) experienced similar adverse effects, which were identified to be leukopenia, neutropenia, and febrile neurtopenia. They were unable to isolate febuxostat as the cause of the adverse effects the participants experiences. No mortalities were noted as an outcome in any of the cases. Spina, et al. (2015) was able to identify the treatment emergent signs and symptoms in 11 patients in each study group. Diarrhea (1.2%), upper abdominal pain (0.6%), and nausea (0.6%) were gastrointestinal side effects that were seen in the febuxostat group. Cardiac disorders, such as left bundle branch block (0.6%) and sinus tachycardia (0.6%) were also noted for this group. Other signs and symptoms such as decreased appetite (0.6%), muscular weakness (0.6%), and haemorrhage (0.6%) were identified in the febuxostat group of this specific study

Figure 2 indicates that both studies showed a low overall risk of bias. They were able to report randomization, appropriate blinding among the participants, health care providers, investigators, and outcome assessors.

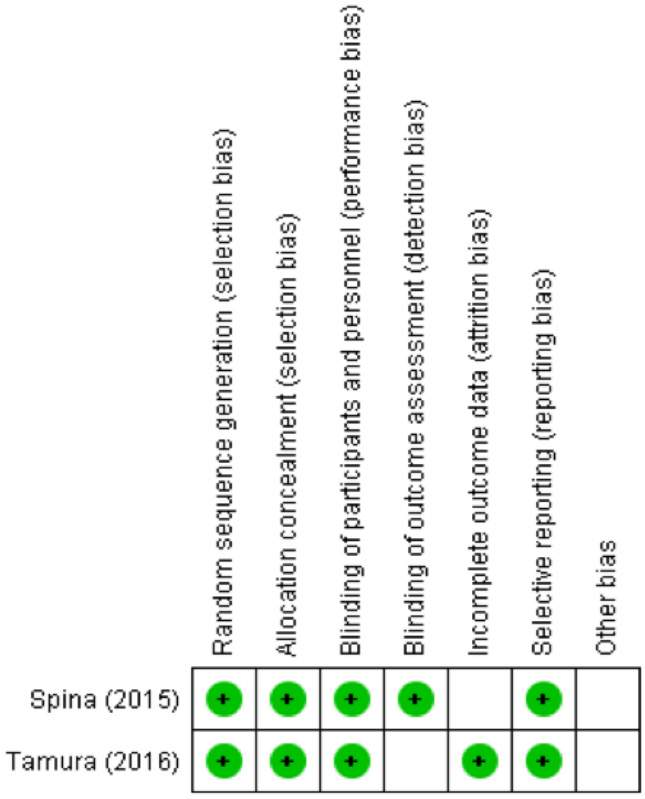

Figure 2. Quality measures of the RCT

Table II. Baseline characteristics of included trials

Trials	No. of patients	Design/ Setting	Intervention	Follow-up
1. Spina (2015)	Febuxostat group: 173 Allopurinol group: 173	Double-blind, multicenter	Febuxostat was administered 120mg orally once daily versus Allopurinol 200, 300 and 600 mg	None
2. Tamura (2016)	Febuxostat group: 49 Allopurinol group: 51	Open-label, multicenter	Febuxostat was administered 60mg orally once daily versus Allopurinol 300 or 200 mg/day	None

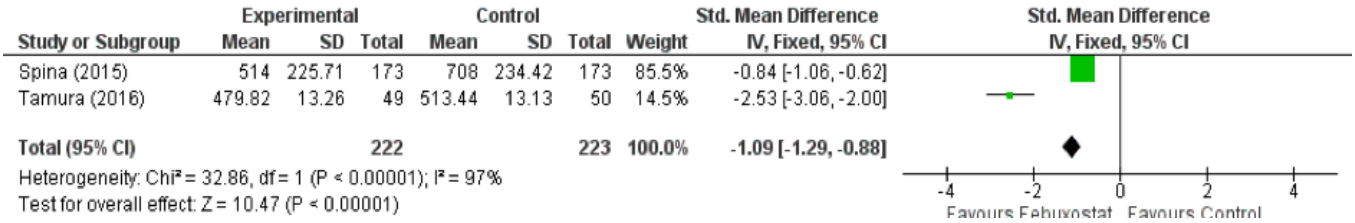

Figure 3. Efficacy of febuxostat in preventing TLS

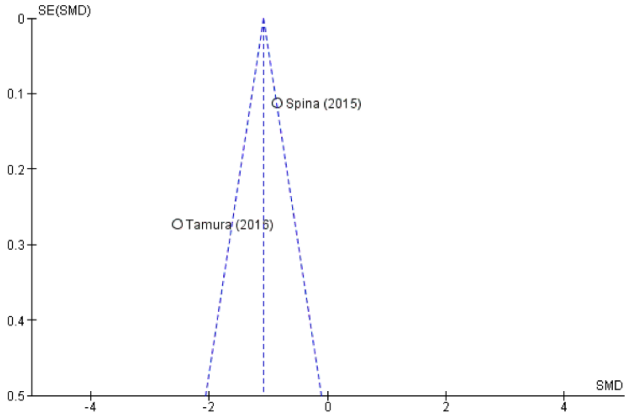

Figure 4. Funnel plot of studies investigating the prevention of TLS

Prevention of TLS

The study results revealed that febuxostat, when compared to allopurinol, was able to decrease serum uric acid, since hyperuricemia is one of the indicators of TLS. This decrease in serum uric acid was consistent in both studies (Spina, 2015; Tamura, 2016). The serum uric acid levels at the end of the treatment showed a standard mean difference of -1.09 (95% CI -1.29, -0.88, p for heterogeneity <0.01, p for effect <0.01, I^2 = 97%). The trend of both studies favored the efficacy of febuxostat.

It can be seen in Figure 3 that the confidence intervals of both studies did not cross the line of no effect, indicating that the serum uric acid levels had decreased further when febuxostat was used compared to allopurinol.

The funnel plot in Figure 4 suggests that there might be bias due to the imbalance in weight when comparing both studies, since the study by Spina, et al. (2015) held 85.5% of the study, while the study by Tamura, et al. (2016) only held 14.5% of the weight of the study.

Serum creatinine change

Spina, et al. (2015) found that there were no difference detected between the serum creatinine levels between the experimental drug, febuxostat, and the control drug, allopurinol, at the baseline and post-treatment evaluation at the end of the study. The data pointed to a nonsignificant difference in the effects on the serum creatinine levels for both drugs. This was similar to the study done by Tamura et al. (2016) where they stated that the serum creatinine or creatinine clearance in both treatment groups remained constant throughout the study, yielding a result indicating that febuxostat and allopurinol did not affect serum creatinine in the studied population.

Discussion

Tumor lysis syndrome (TLS) has been extensively discussed as a metabolic complication that ensues after the initiation of chemotherapy. This syndrome is composed of various metabolic abnormalities, such as hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. These metabolic abnormalities are a result of the rapid tumor cell lysis. The sudden onset of the different metabolic derrangements leads to severe renal and cardiac impairment, seizures, or even death.[10] Urate nephropathy was classically thought to be driven by the precipitation of uric acid crystals in the renal tubules, leading to micro-obstruction and decreased glomerular filtration rate (GFR). Uric acid also scavenges nitric oxide, which can lead to vasoconstriction and kidney ischemia. It is also proinflammatory in that vascular smooth muscle cells exposed to uric acid upregulate production of various cytokines, including monocyte chemoattractant protein-1 and tumor necrosis factor-α, which lead to white cell chemotaxis and tissue injury. Uric acid inhibits proximal tubular cell proliferation, potentially prolonging kidney injury once it occurs.[6] Hyperkalemia may present as muscle weakness and, if left untreated, it can lead to cardiac arrhythmia and death. Hyperphosphatemia leads to morbidity and mortality primarily through chelation with calcium, leading to hypocalcemia and the potential for calcium-phosphate salt deposition in soft tissues.[6]

Febuxostat was considered a novel and new nonpurine selective inhibitor of xanthine oxidase, which was seen to be more effective than allopurinol and prevented hyperuricemia in those with hematologic malignancies while seeking chemotherapeutic treatment and with a known intermediate risk at developing TLS.[11-13]

In the management of hyperuricemia, febuxostat was found to be more effective in lower doses compared to allopurinol. In a study by Hu and Tomlinson (2008), febuxostat given at 80mg lowered serum urates than allopurinol given at 300mg. It has also shown to be more well tolerated in long term treatment especially in patients who have experienced hypersensitivity or intolerance for allopurinol.[14]

Although side effects or adverse effects were not adequately isolated from both trials, due to the interference of the chemotherapeutic agents used, a literature review on febuxostat by Jordan and Gresser (2018) showed that it

is well tolerated in general. Febuxostat appeared to cause severe side effects less frequently than allopurinol, but was noted to cause side effects when the administered dose exceeded 120mg per day.[15]

Aside from the prevention of TLS and anti-hyperuricemic effects, febuxostat is shown to be more renoprotective than allopurinol as seen in a systematic review done by Kim, – (2017). It was stated in the study that the use of febuxostat increased eGFR in hyperuricemic patients with CKD and resistant to allopurinol.[16]

Limitations

The meta-analysis presented synthesizes the data found among two trials with a goal to estimate the ability of febuxostat to prevent TLS. The main limitation seen within this meta-analysis is that the sample size of participants, the dosage of febuxostat and the control drug, allopurinol, and the exact definition of outcomes were not uniform across both studies.

This study shows some limitations. There were only two trials that fit the inclusion criteria. This small number may not be fully representative of the comparison of efficacy between febuxostat and allopurinol. There was a large discrepancy between the sample sizes of both trials. This may have led to biases that may have occurred throughout the conduction of the trials, especially in the study with a smaller number of participants.

Conclusion

After the analysis of the two trials and review of other related studies, the evidence may point to febuxostat being more effective than allopurinol in the prevention of TLS. Febuxostat also appears to be more renoprotective than allopurinol, which is beneficial for patients already experiencing renal insufficiency.

More trials comparing febuxostat and allopurinol may be needed to further establish consistency in the efficacy of preventing TLS, especially in larger scales and in other types of malignancies that experience TLS during chemotherapy.

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Appendices

A. Risk of bias tables for the RCTs

Tamura 2015

Methods	Allopurinol-Controlled, Multicenter, Open-Label, Randomized, Parallel-Group Comparative Phase III Study
Participants	49 participants were given febuxostat and 51 participants were given allopurinol
Interventions	Febuxostat was administered 60 mg orally once daily (60 mg/day)
Outcomes	Febuxostat 60 mg/day resulted in decreased sUA and maintained low levels of sUA up to day 6 of treatment
Notes	

Risk of bias table

Bias	Author's judgment	Support for judgement
Random sequence generation (selection bias)	Low Risk	After enrollment, patients were randomly assigned in a 1:1 ratio to either the febuxostat or allopurinol group by Medidata Balance ® (Medidata Solutions, Inc., NY, USA).
Allocation concealment (selection bias)	Low Risk	Randomization was performed with a minimization method to minimize the imbalance of baseline sUA, TLS risk, and primary disease.
Blinding of participants and personnel (performance bias)	Low Risk	This is a double-blind study.
Blinding of outcome assessment (detection bias)	Low Risk	This is a double-blind study.
Incomplete outcome data (attrition bias)	Unclear Risk	
Selective reporting (reporting bias)	Low Risk	One patient in the allopurinol group was excluded from all analyses due to a lack of written consent. Eight patients (4 patients in each group) were excluded from PPS due to protocol violations which included concomitant use of a prohibited drug, low drug adherence rate, and missing important data.
Other bias	Unclear Risk	No noted other biases.

Spina 2015

Methods	Multicenter, Double-Blind, Randomized, Parallel-Group, Comparative Phase III Study
Participants	173 participants were given febuxostat and 173 participants were given allopurinol
Interventions	Febuxostat was administered 120 mg orally once daily
Outcomes	Febuxostat achieved a significant superior sUA control with one fixed dose in comparison to allopurinol with comparable renal function preservation and safety profile.
Notes	

Risk of bias table

Bias	Author's judgment	Support for judgement
Random sequence generation (selection bias)	Low Risk	Patients stratified by TLS risk (intermediate or high) and baseline sUA levels (≤7.5 or >7.5 mg/dl) were randomized to either arm at a 1:1 ratio, using a randomized block design.
Allocation concealment (selection bias)	Low Risk	Study treatment was blinded while daily dose depended on investigator's choice among low, standard and high containing either allopurinol 200, 300 and 600 mg, respectively, or fixed febuxostat 120 mg.
Blinding of participants and personnel (performance bias)	Low Risk	Study treatment was blinded while daily dose depended on investigator's choice among low, standard and high containing either allopurinol 200, 300 and 600 mg, respectively, or fixed febuxostat 120 mg. Randomization visit (day 1) assessments were considered as baseline; screening visit assessments, if carried out within 24 h before randomization, could be considered as baseline and not repeated.
Blinding of outcome assessment (detection bias)	Unclear Risk	
Incomplete outcome data (attrition bias)	Low Risk	Owing to missing values at baseline, one patient per arm was excluded from the analysis of AUC sUA; for the same reason, two patients allocated to allopurinol were excluded from that of serum creatinine change.
Selective reporting (reporting bias)	Low Risk	All patients but one in febuxostat arm underwent CT during the study.
Other bias	Unclear Risk	No noted other biases.

B. Risk stratification of tumor lysis syndrome[17]

Type of Cancer	High	Intermediate	Low
NHL	Burkitt's, lymphoblastic B-cell acute lymphoid leukemia	Diffuse Large B-cell lymphoma	Indolent NHL
Acute Lymphoid Leukemia	WBCC >/=100 x 10^9/L	WBCC >/=50-100 x 10^9/L	WBCC </=50 x 10^9/L
Acute Myeloid Leukemia	WBCC >/=50 x 10^9/L, monoblastic	WBCC >/=10-50 x 10^9/L	WBCC </=10 x 10^9/L
Chronic Lymphocytic Leukemia		WBCC >/=10-100 x 10^9/L; Treatment with fludarabine	WBCC </=10 x 10^9/L
Other hematologic malignancies (chronic myeloid leukemia and multiple myeloma) and solid tumors		Rapid proliferation with expected rapid response to therapy	Remainder of patients

Abbreviation: *NHL, Non-hodgkin Lymphoma; WBCC, White blood cell count*