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Febuxostat as a Prophylaxis for Tumor Lysis Syndrome in Children with Hematological Malignancies

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Abstract. *Aim: The aim of the present study was to determine if febuxostat could prevent tumor lysis syndrome (TLS) in children who received induction chemotherapy for hematologic malignancies. Patients and Methods: A retrospective analysis was performed in 45 pediatric patients with hematological malignancies who received febuxostat (10 mg daily, n=20) or allopurinol (300 mg/m^2 daily, n=25) as a prophylaxis for TLS. Results: A significant decrease of serum uric acid (UA) level was observed in patients with febuxostat over the first 2 days (6.6±3.8 mg/dl vs. 4.5±2.8 mg/dl, p<0.001). The febuxostat group also showed significant reduction of urinary UA/creatinine ratios during the first two days of treatment (0.98±0.85 vs. 0.51±0.26, p=0.010). No significant differences were observed between febuxostat-treated and allopurinol-treated patients regarding the percent change in serum UA level. Conclusion: Febuxostat had a notable effect in reducing serum UA level in children with hematological malignancies.*

Tumor lysis syndrome (TLS) is an oncological emergency that can occur following the treatment of hematologic cancers, and can result in life-threatening complications (1, 2). It is caused by the rapid destruction of tumor cells and the release of their contents into the systemic circulation, which can cause acute kidney injury, arrhythmias, seizures, and even death. Early identification of the risk for TLS and adequate prophylactic therapy are recommended (3, 4), and the control of serum uric acid (UA) level is a key component in its management (5). The current guidelines for the management of TLS include treatment with two hypouricemic agents: the conventional xanthine oxidase inhibitor allopurinol, and the recombinant urate oxidase rasburicase (3, 4).

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Febuxostat is a non-purine xanthine oxidase inhibitor that has more selective and potent activity than allopurinol (6). It has the advantage of not requiring for dose adjustments in patients with mild or moderate renal impairment (7). Previous studies in patients with gout have shown the superiority of febuxostat in reducing serum UA level compared with allopurinol (8, 9). A recent study of adult patients with hematologic malignancies at intermediate to high TLS risk showed that febuxostat was significantly more effective than allopurinol in controlling serum UA level as a means of TLS prevention (10). In children with cancer, however, there is little information on the role of febuxostat in the management of TLS. Thus, the aim of this retrospective single-center cohort study was to determine if febuxostat could prevent TLS in children who received induction chemotherapy for hematological malignancy.

Patients and Methods

Patients. A total of 45 consecutive children aged 5 to 15 years with hematologic malignancies, who received febuxostat or allopurinol for more than 7 days as a prophylaxis for TLS before and during induction chemotherapy at the Sapporo Hokuyu Hospital between January 2012 and December 2015, were enrolled in this study. Patients with clinical TLS at diagnosis and patients who required hemodialysis at diagnosis were excluded. Patients who received rasburicase prior to initiation of febuxostat or allopurinol were also excluded. Serum UA, potassium, phosphate, calcium, and creatinine values as well as urinary UA and creatinine values were prospectively monitored closely before and during induction therapy to assess TLS. Baseline characteristics of the patients, including demographic information and clinical information, were obtained from their medical records. Informed consent was obtained from the patients or their parents, and the study was approved by the Institutional Review Board of Sapporo Hokuyu Hospital.

Definitions. The diagnosis and classification of TLS were based on the Cairo-Bishop definition (11). Laboratory TLS was defined as the presence of two or more of the following criteria within 3 days before or 7 days after the initiation of induction therapy: (i) serum UA level >8.0 mg/dl or a 25% increase from baseline; (ii) serum potassium level >6.0 mEq/l or a 25% increase from baseline; (iii) serum phosphate level >6.5 mg/dl or a 25% increase from baseline;

Table I. *Patients characteristics*.

Characteristics	Febuxostat (n=20)	Allopurinol (n=25)	*p*-Value
Age(years),median (range)	13 (8-15)	12 (5-15)	0.62
Male/Female, n (%)	11 (55)/ 9 (45)	16 (64)/9 (36)	0.76
Diagnosis, n (%)			
ALL	13 (65)	15 (60)	0.84
AML	5 (25)	6 (24)	
Lymphoma	2 (10)	4 (16)	
Disease status, n (%)			
Newly diagnosed	15 (75)	22 (88)	0.44
Relapse	5 (25)	3 (12)	
TLS risk, n (%)			
Intermediate	9 (45)	12 (48)	1.0
High	11 (55)	13 (52)	
Initial laboratory values, median (range)			
WBC (109/l)	13.6 (1.4-335.3)	15.6 (1.4-218.3)	0.31
LDH (IU)	788 (123-16,432)	506 (162-9,809)	0.15
UA (mg/dl)	6.9 (2.4-15.3)	5.5(1.9-11.6)	0.12
Cr (mg/dl)	0.56 (0.33-1.11)	0.47 (0.28-0.95)	0.91

ALL, Acute lymphoblastic leukemia; AML, acute myeloid leukemia; Cr, creatinine; LDH, lactate dehydrogenase; TLS, tumor lysis syndrome; UA, uric acid; WBC, white blood cells.

(iv) serum corrected calcium level <7.0 mg/dl or a 25% decrease from baseline. Clinical TLS was defined as the presence of laboratory TLS and one or more of the following criteria: (i) serum creatinine level >1.5 times the upper limit of the age-appropriate normal range or the presence of oliguria; (ii) cardiac arrhythmia or sudden death caused by hyperkalemia; (iii) seizure or tetany caused by hypocalcemia. Risk classification for TLS was defined in accordance with TLS panel consensus (4).

Statistical analysis. Univariate analysis of the baseline characteristics was performed using the Mann-Whitney's *U*-test and unpaired *t*-test for quantitative variables, and using the chi-squared test and Fisher's exact test for qualitative variables. The changes in serum UA levels and urinary UA/creatinine ratio in the first 2 days, and those in serum creatinine levels in the first 7 days, were analyzed using the paired *t*-test. Percent changes in serum UA level, urinary UA/creatinine ratio, and serum creatinine level were compared between febuxostat-treated and allopurinol-treated patients by the unpaired *t*-test. The incidence of TLS was also compared between febuxostat-treated and allopurinol-treated patients by the Chi-squared test. The odds ratio (OR) for TLS and the 95% confidence interval (CI) were calculated for patients receiving febuxostat relative to those receiving allopurinol. *p*-Values less than 0.05 were considered statistically significant; all tests were two-tailed. All of the statistical analyses were conducted using EZR on R (The R Foundation for Statistical Computing) (12).

Results

During the study period, 20 (44%) patients received febuxostat (10 mg once daily) and 25 (56%) patients received allopurinol (300 mg/m^2 daily, divided into two or three doses). Induction chemotherapy was initiated at least 2 days after the first dose of xanthine oxidase inhibitor. All of the patients received routine TLS prophylaxis with hydration (2,400-3,000 ml/m^2/day) and xanthine oxidase inhibitors. The selection of xanthine oxidase inhibitor was determined by the attending physician. The baseline characteristics of the patients are shown in Table I. Of these 45 patients, 21 (47%) and 24 (53%) were classified as intermediate and high risk for TLS, respectively, and were distributed almost equally between the two groups (p=1.0). There were no significant differences in age and sex distribution between groups. Median serum lactate dehydrogenase and UA levels at diagnosis were higher in patients treated with febuxostat than in those treated with allopurinol, although these differences were not significant. Rasburicase (0.2 mg/kg/dose) was used in 10 (50%) of febuxostat-treated patients and 8 (32%) of allopurinol-treated patients (p=0.36) during induction chemotherapy.

Reduction in UA level. The mean serum UA level was significantly lower after the first 2 days of febuxostat treatment than that before administration (before: 6.6±3.8 mg/dl *vs*. after: 4.5±2.8 mg/dl, p<0.001). A significant decrease in serum UA level was also observed in patients with allopurinol in the first 2 days (5.9±2.1 mg/dl *vs*. 3.5±1.1 mg/dl, p<0.001). Similarly, both febuxostat and allopurinol groups showed a significant reduction in urinary UA/creatinine ratio during the first 2 days of treatment (febuxostat group, 0.98±0.85 *vs*. 0.51±0.26, p=0.010; allopurinol group, 0.79±0.41 *vs*. 0.51±0.39, p<0.001). A *post-*

Table II. *Percent changes in serum UA level, urinary UA/creatinine ratio, and serum creatinine level.*

Characteristics	Serum UA-change Days 0-2 (%)	*p*-Value	Urinary UA/Cr-change Days 0-2 (%)	*p*-Value	Serum Cr-change Days 0-7 (%)	*p*-Value
Overall						
Febuxostat (n=20)	–34.4±19.0	0.16	–31.6±19.6	0.60	–4.3±18.5	0.43
Allopurinol (n=25)	–42.1±14.1		–27.3±29.0		3.0±36.0	
TLS risk						
Intermediate						
Febuxostat (n=9)	–33.3±14.3	0.72	–22.8±14.0	0.84	3.5±10.3	0.079
Allopurinol (n=12)	–36.1±16.9		–19.4±40.1		–8.0±16.4	
High						
Febuxostat (n=11)	–35.3±23.3	0.13	–37.2±22.1	0.68	–10.7±22.3	0.14
Allopurinol (n=13)	–46.7±10.6		–33.8±16.2		13.1±47.2	
Initial UA (mg/dl)						
<6.5						
Febuxostat (n=9)	–41.1±14.8	0.95	–21.0±15.7	0.82	0.1±13.9	0.50
Allopurinol (n=17)	–40.6±16.9		–23.8±32.5		10.2±42.4	
≥6.5						
Febuxostat (n=11)	–28.5±22.1	0.069	–40.1±19.9	0.73	–7.8±22.4	0.61
Allopurinol (n=8)	–44.8±8.1		–36.5±19.9		–12.4±11.3	
Initial Cr (mg/dl)						
<0.50						
Febuxostat (n=9)	–38.8±17.9	0.98	–35.1±13.7	0.35	–4.1±13.0	0.63
Allopurinol (n=13)	–39.0±17.4		–20.8±37.6		–7.0±13.7	
≥0.50						
Febuxostat (n=11)	–30.6±21.2	0.059	–29.3±23.8	0.64	–4.3±23.4	0.29
Allopurinol (n=12)	–44.9±11.0		–33.7±18.6		13.8±50.0	

Cr, Creatinine; TLS, tumor lysis syndrome; UA, uric acid.

hoc power analysis was performed to determine the statistical power for each comparison, which showed that the statistical power was higher than the adequate power level of 0.80 in all these cases. The overall percent changes in serum UA level and urinary UA/creatinine ratio were not significantly different between febuxostat-treated and allopurinol-treated patients (Table II). Subgroup analyses of patients with initial serum UA level ≥6.5 mg/dl and patients with initial serum creatinine level ≥0.5 mg/dl showed that the mean percent reduction in serum UA level was greater in patients receiving allopurinol than in those receiving febuxostat, although no statistical significance was observed (Table II).

Change in serum creatinine level. No significant change was found in serum creatinine level after the first 7 days of febuxostat or allopurinol treatment compared to that before administration (febuxostat group, 0.59±0.19 [before] *vs*. 0.54±0.23 [after], p=0.46; allopurinol group, 0.53±0.14 [before] *vs*. 0.56±0.33 [after], p=0.55). There was no significant difference in percent changes in serum creatinine between the two treatment groups (Table II).

TLS incidence. Overall, 10 of 45 (22%) patients developed TLS. Of these 10 patients, 6 experienced laboratory TLS and 4 patients had clinical TLS. All but one patient with TLS met the study criterion for hyperphosphatemia. The second most common laboratory finding was hyperuricemia (70%). TLS was observed in five (25%) patients with febuxostat and five (20%) patients with allopurinol (p=0.73). The OR for TLS in patients receiving febuxostat relative to those receiving allopurinol was 1.3 (95% CI=0.33-5.5).

Discussion

We found that 10 mg daily febuxostat had a notable effect in reducing serum UA level in children with hematologic malignancies at intermediate to high risk for TLS. Because the control of serum UA level plays a critical role in the prevention of TLS, our findings suggest that febuxostat is a potent agent for TLS prophylaxis in children with cancer. To the best of our knowledge, the present study is the first to show the effectiveness of febuxostat in TLS prevention and to find a significant reduction in UA level in children who received chemotherapy.

Febuxostat was shown to significantly reduce serum UA level in previous studies in adult patients who received chemotherapy (13, 14). Moreover, a recent double-blind, randomized study comparing febuxostat with allopurinol in

adults with hematologic malignancies reported the higher efficacy of febuxostat in subgroups of patients with different baseline serum UA level, creatinine level, and TLS risk classification (10). It should be noted that patients in the latter study received 120 mg daily febuxostat, which was considerably higher than the dose given in previous studies (13, 14) and was 12 times higher than the dose given to patients in the present study with children. Although both febuxostat and allopurinol led to a significant reduction of serum UA level, this study did not show the superiority of febuxostat in overall or subgroup analyses. Our results suggest that 10 mg daily febuxostat may be too low to exert superior effects to allopurinol in TLS prevention in children. Because the present subgroup analyses of patients with higher initial serum UA level or higher initial serum creatinine level showed that the reduction in serum UA level was somewhat greater in patients receiving allopurinol, patients with those characteristics seemed to benefit from a higher febuxostat dose.

The development of TLS can lead to acute kidney injury by precipitation of uric acid, xanthine, and calcium phosphate crystals in renal tubules (15). Therefore, reduction of urinary UA levels is critical to prevent crystal-associated acute kidney injury. The present study provides the first description of the changes in urinary UA levels in patients who received febuxostat as prophylaxis for TLS. We found a significant decrease in the urinary UA/creatinine ratio during the first 2 days of febuxostat treatment. Similarly, febuxostat was shown to significantly reduce urinary UA in a recent study of patients with higher urinary UA excretion and calcium stones (16). Febuxostat is metabolized to inactive metabolites in the liver, obviating the need for specific kidney dosing (17). Furthermore, a higher renoprotective effect of febuxostat has been found in patients with chronic kidney disease compared with allopurinol (18). These findings support the use of febuxostat, particularly in patients at risk of TLS with impaired renal function.

The incidence of TLS in this study seems to be comparable to that in previous reports of children with hematologic malignancies (3, 4, 15). A comparison of TLS incidence is difficult, however, because there have been considerable differences in the definition of TLS and in chemotherapy regimens among previous studies (19). The most common laboratory finding among patients with TLS was hyperphosphatemia in this study. Our results suggest that hyperphosphatemia may become more important in the era of TLS prophylaxis with rasburicase and xanthine oxidase inhibitors. Initial phosphate levels were recently shown to be a risk factor for clinical TLS in a study of patients with leukemia and lymphoma at high risk for TLS (20).

This study had several inherent limitations. The primary limitation was the relatively small number of patients, which may have limited the power to detect statistical differences. Analysis of a single hospital-based population was also a major limitation, which makes it hard to predict whether the findings are common in all children who receive chemotherapy. Future studies with a prospective design and larger study population are needed to confirm the findings of the present study. The third notable limitation is that this study was not designed to determine the optimal dose of febuxostat in TLS prevention for children. Despite these limitations, the results of this study provide novel and clinically important information on the prevention of TLS in children.

In conclusion, febuxostat had a notable effect in reducing serum UA levels in children with hematological malignancies at intermediate to high TLS risk. There is a need for further studies to establish its optimal dose as prophylaxis for TLS in children.

Conflicts of Interest

The Authors declare that they have no conflict of interest.

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