ORIGINAL ARTICLE

Febuxostat versus Allopurinol For the Prevention and Treatment of Hyperuricemia in Chronic Myelogenous Leukemia with Hyperleucocytosis

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Abstract

The current study was undertaken to know whether febuxostat is superior to allopurinol in terms of efficacy and toxicity as hypouricemic agent in CML patients with hyperleucocytosis. 82 patients of CML with TLC>50000/cu.mm. were randomized to receive either febuxostat (40mg/day) or allopurinol (200-300 mg/day) beginning 2 days before starting hydroxyurea. Complete blood count, renal function tests, liver function tests, serum uric acid and LDH were done at baseline and 1 week after starting urate lowering therapy. The entire cohort, with median age of 40 years (range 13-82 years) comprised of 45 males and 37 females. There were 41 patients in each arm. Mean TLC at presentation was 1,63,622/ cu.mm. In our series, hyperuricemia was seen in 28% patients at presentation. The mean uric acid level at baseline (UA1) was 6.57(±1.55) mg/dl (range 2.6-11.5) and at 1 week post therapy (UA2) was 5.74(±1.29) mg/dl (range 2.9-9). There was no difference between the two groups receiving febuxostat or allopurinol in terms of UA1 and UA2 (p=1.89). The mean reduction in uric acid levels by febuxostat was found to be 1.022mg/dl (±0.69SD) as compared to 0.6512mg/dl (±0.61SD) with allopurinol and the difference was statistically significant(p=0.012). The study has shown that febuxostat (40mg/day) might be superior to allopurinol in quantitative reduction of serum uric acid over the period of initial one week of therapy in CML patients with hyperleucocytosis.

Key Words

Febuxostat, Allopurinol, Hyperuricemia, Chronic Myelogenous Leukemia

Introduction

Hyperuricemia is the hallmark of tumor lysis syndrome (TLS) which is the most dreaded complication of cancer treatment with high mortality ranging from 23% to 79% (1). TLS prophylaxis is the first priority, while starting treatment, especially for the cancers vulnerable to this complication. The risk of tumor lysis syndrome depends on host related factors like patient's age, renal function, liver function and disease related factors like tumor burden, histopathology, proliferation rate etc.(2). The key to TLS prophylaxis is the control of serum uric acid levels, hydration and urinary alkalinization (3). Allopurinol, a hypoxanthine analog, has been the standard of care for TLS prophylaxis for over four decades till it was replaced by rasburicase in high risk cases (4). Allopurinol is still used in low risk and intermediate risk cases for TLS prophylaxis because of its efficacy and low cost. The disadvantages of hypersensitivity reaction and hepatotoxicity while using allopurinol, more so in patients with renal dysfunction impels us to search for alternatives like febuxostat. Febuxostat is a non-purine xanthine oxidase inhibitor that does not need dose adjustment in mild to moderate renal dysfunction (5). For CML patients with high total leucocyte count (TLC), prophylactic therapy to lower uric acid levels is considered appropriate especially when serum LDH is elevated and this is supposed to reduce the likelihood of TLS (6). In the present study we randomized patients of chronic myeloid leukemia with hyperleucocytosis to receive TLS prophylaxis with allopurinol or febuxostat when starting treatment with hydroxyurea till the diagnosis is confirmed by Philadelphia chromosome. Hydroxyurea is an integral part of supportive therapy for CML patients presenting with leukocytosis and/or thrombocytosis. Similarly, allopurinol is also recommended for prevention of

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hyperuricemia and TLS in CML (7). Our aim was to find out whether febuxostat is superior to allopurinol in controlling serum uric acid levels and TLS prophylaxis in patients with CML with hyperleucocytosis.

Material and Method

We prospectively randomized 82 newly diagnosed patients of CML in chronic phase with TLC>50000/ cu.mm to receive allopurinol or febuxostat in addition to hydroxyurea and other medications as needed. The patients were enrolled from July, 2012 to June, 2015. All patients provided written informed consent for treatment after due approval. CML was suspected in patients with elevated WBC count with shift to left with basophilia and enlarged spleen. The diagnosis was confirmed by bone marrow aspiration cytology and cytogenetics and demonstration of BCR-ABL by FISH or PCR in all cases. The patients receiving drugs which can potentially increase uric acid levels were excluded from the study. Patients with severe renal or hepatic failure at presentation were also excluded. The febuxostat or allopurinol was started 2 days prior to starting hydroxyurea and continued for upto 2 consecutive weeks. The dose of allopurinol used was 300 mg/day and that of febuxostat was 40 mg/ day. In patients with deranged renal function, allopurinol dose was reduced to 200 mg/day. We monitored complete blood count, renal function test and liver function test, serum uric acid, LDH and serum electrolytes at baseline and at 7th day of therapy. During the study period patients were monitored for cardiac arrhythmias, seizures and renal insufficiency features. Hydroxyurea was given empty stomach daily by mouth, with the dose (40mg/kg/ /day) ranging from 1-3g per day in two divided doses. Hydroxyurea was stopped and imatinib started in BCR-ABL positive patients when the diagnosis was confirmed which usually takes 10 days in our hospital.

Statistical Analysis

All statistical analysis was performed using Microsoft Excel 2007 and SPSS version 17. Descriptive statistics were determined and Group comparison of uric acid levels pre-therapy and post-therapy was done using 2 sample't' tests.

Result

Patient Characteristics: The data of all 82 patients of chronic myeloid leukemia in chronic phase were analyzed (*Table 1*). There were 45 males and 37 females. There were 41 patients each in the febuxostat and allopurinol arm. The age ranged from 13 years to 82 years (median 40 years) for the whole cohort. 90% patients were symptomatic with anemia, generalized weakness, fever, splenomegaly and vision disturbances. Mean TLC at presentation was 1,63,622/cu.mm. Mean Hb was 8.25g%. Eight (9.76%) patients had severe anemia Hb<6g/dl at presentation. Mean LDH at presentation was 617 IU/ml. Baseline serum uric acid levels ranged from 2.6-11.5mg//dl (*Fig 1*). 22(26.83%) patients presented with serum creatinine >1.3mg/dl from the very beginning. 31(37.8%) patients presented with serum uric acid >7 mg/dl and 23(28.05%) presented with serum uric acid >7.5mg/dl.

Efficacy: The mean uric acid level at baseline (UA1) was 6.57mg/dl (±SD 1.55)[range 2.6-11.5] and at 1 week post therapy (UA2) was 5.74mg/dl (±SD 1.29)[range 2.9-9]. There was no difference between the two groups receiving febuxostat or allopurinol in terms of UA1 and UA2 (p=1.89) (*Fig.2 & 3*). Uric acid response rate (patients achieving serum uric acid levels<7.5mg/dl after therapy) was seen in 38 patients in febuxostat arm and in 39 patients in allopurinol arm. This difference was statistically not significant. When we analyzed the data for reduction in uric acid levels after 1 week of therapy with febuxostat or allopurinol, we found that febuxostat reduced serum uric acid more than allopurinol. The mean reduction in uric acid levels by febuxostat was found to be 1.022mg/dl(±0.69SD) as compared to 0.6512mg/ dl(±0.61SD) with allopurinol and the difference was statistically significant(p=0.012). Adverse effects: 3 patients received packed RBCs transfusion for severe anemia (Hb<6g/dl). SGOT and SGPT elevation was noticed in 4 patients in febuxostat and 5 patients in allopurinol arm. The liver enzyme elevation was less than thrice the upper limit of normal range (ULN) and drugs were not stopped. One patient developed generalized itching which was relieved with antihistamines and after stopping hydroxyurea.

Discussion

Generally CML in chronic phase is considered to be a low risk for TLS when compared with AML where incidence of TLS can be as high as 17% (Clinical TLS-5% and Laboratory TLS-12%). But presence of certain high risk features can predispose to TLS such as hyperleucocytosis, elevated serum LDH, massive splenomegaly, high serum creatinine and hyperuricemia at presentation. Hyperuricemia in CML patients is detected either at presentation or found in the first few weeks of starting treatment because of purine catabolism and rapid cell turnover. In our series hyperuricemia was seen in 28% patients at presentation. Several cases of TLS have been reported in CML patients after hydroxyurea and imatinib therapy (7, 8, 9). Therefore, a urate lowering therapy is needed before starting the definitive therapy (10). Febuxostat has emerged as a preferred uric acid lowering therapy for patients with

Table 1. Patient Characteristics

Variable	Total Group	Febuxostat Group	Allopurinol Group
Number Patients	82	41	41
Age years	13-82 (median 40)	18-75(40)	13-82(43)
Gender M:F	45:37	17:24	28:13
Hemoglobin	4-12.9	5-12.4	4-12.9
WBC count	56000-420000	80000-400000	56000-420000
Platelets	20000-656000	20000-656000	87000-450000
Urea	16-110	16-81	21-110
Creatinine	0.6-2.3	0.6-1.9	0.6-2.3
Uric acid1(Day1)	2.6-11.5	4.5-11.5	2.6-10.5
Uric acid2 (Day7)	2.9-9.0	3.3-8.9	2.9-9.0
UA difference (D1-D7)	-0.7-2.8	0-2.8	-0.7-2.3

Fig 1. Chart Line Diagram Showing Distribution of S. Uric Acid Level (y-axis) at Baseline (UA1) and 1-Week Post-Therapy (UA2) in the whole cohort (individual patients on x-axis)

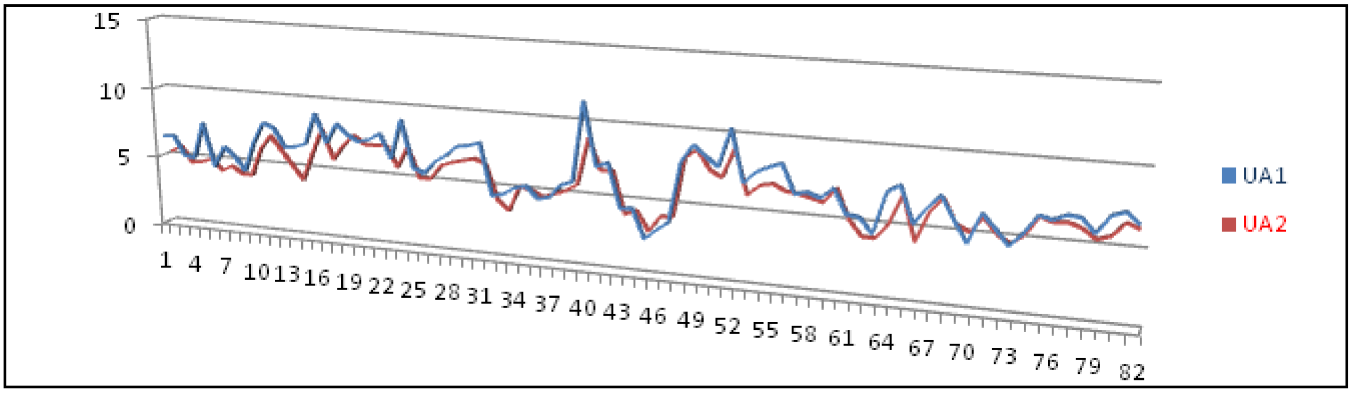
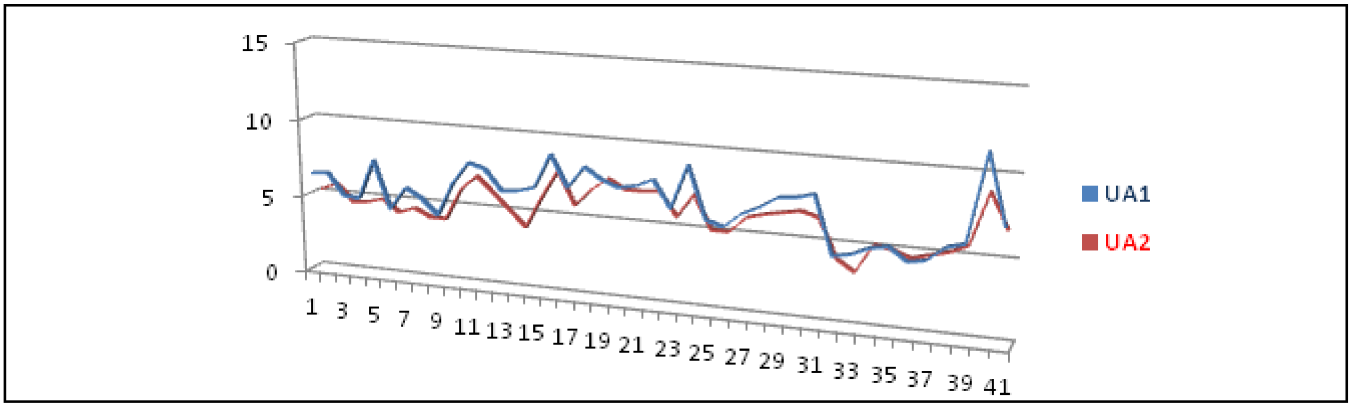
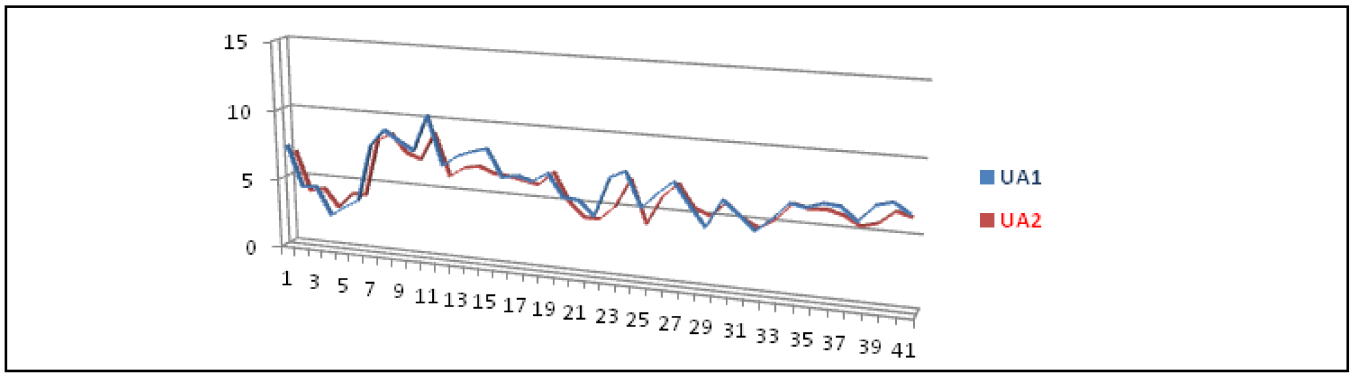


Fig 2. Chart Line Diagram Showing Distribution of S. Uric Acid level (y-axis) at Baseline (UA1) and 1-Week Post-Therapy (UA2) in the Febuxostat Arm (individual patients' x-axis)



gout and hyperuricemia especially when there is mild to moderate renal dysfunction or allopurinol intolerance. Cochrane Database Systematic Review analysis has shown it to be comparable to allopurinol in terms of efficacy with some advantages (11). Our study has shown that febuxostat (40mg/day) is better than allopurinol in reducing serum uric acid levels in CML patients with hyperleucocytosis and is effective in preventing tumor lysis syndrome in this clinical setting. Several studies have shown that febuxostat is equivalent to allopurinol in preventing TLS and hyperuricemia in adequate doses. We used the established dose of 40 mg /day for the purpose of reducing uric acid levels in selected CML patients. The CONFIRMS trial has already shown

Fig 3. Chart Line Diagram Showing Distribution of S. Uric Acid level (y-axis) at baseline (UA1) and 1-week Post-Therapy (UA2) in the Allopurinol arm (individual patients' x-axis).



febuxostat(80mg/day) to be safer and more effective in gout patients when compared with allopurinol(300mg/day) especially in the clinical scenario of mild to moderate renal impairment (12).

The FLORENCE study provides high quality evidence to support the use of febuxostat as hypouricemic agent for TLS prophylaxis in hematological malignancies. The FLORENCE trial confirms that serum uric acid control is superior with one fixed dose febuxostat (120mg/day) whereas renal function preservation and adverse events are comparable to allopurinol in hematologic malignancies at intermediate to high TLS risk.13 We need to test further higher dose of febuxostat (80mg/day) in CML patients with hyperuricemia at presentation to know whether it is superior to lower dose (40mg/day) and allopurinol in terms of efficacy and toxicity in the low risk setting of CML.

Conclusion

The study has shown that febuxostat (40mg/day) might be superior to allopurinol in quantitative reduction of serum uric acid over the period of initial one week of therapy in CML patients with hyperleucocytosis. It is equivalent to allopurinol in terms of safety and can replace the latter as a drug of choice for TLS prophylaxis in low and intermediate risk patients.

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