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Effect of Allopurinol versus Urate Oxidase on Methotrexate Pharmacokinetics in Children with Newly Diagnosed Acute Lymphoblastic Leukemia

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Abstract

Background—Allopurinol and urate oxidase are both effective in preventing or treating hyperuricemia during remission induction therapy for lymphoid malignancies, but their effect on concomitant anticancer drug therapy has not been compared.

Methods—We compared plasma methotrexate pharmacokinetics in pediatric patients with newly diagnosed acute lymphoblastic leukemia who received concomitant allopurinol (n=20) versus non-recombinant or recombinant urate oxidase (n=96) during high-dose methotrexate administration before conventional remission induction therapy.

Results—The minimum plasma concentration of uric acid was significantly ($p<0.0001$) lower after treatment with urate oxidase as compared to allopurinol treatment. Methotrexate clearance was significantly higher (median, 117.1 vs. 91.1 ml/min/m², $p=0.019$) in patients receiving urate oxidase. A higher proportion of patients in the allopurinol group had elevated methotrexate plasma concentrations (36% vs. 7%, $p=0.003$), and experienced mucositis (45% vs. 16%, $p=0.003$) after methotrexate treatment than those in the rasburicase group.

Conclusions—The lower rate of methotrexate clearance in patients receiving allopurinol likely reflects a less potent hypouricemic effect of allopurinol, leading to precipitation of uric acid in renal tubules. Hence, during remission induction therapy for lymphoid malignancies, renally-excreted drugs should be monitored closely, especially in patients receiving allopurinol.

Keywords

methotrexate; acute lymphoblastic leukemia; hyperuricemia; allopurinol; urate oxidase

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Introduction

Patients with leukemia and lymphoma are at risk of hyperuricemia and tumor lysis syndrome before and during chemotherapy.(1;2) Hyperuricemia is caused by the rapid breakdown of nucleic acids released by tumor cell lysis. Uric acid is relatively soluble in plasma but is poorly soluble in acidic urine. As plasma uric acid concentration increases, uric acid is more likely to precipitate in the renal tubules and impair renal function.(3) Renal insufficiency caused by hyperuricemia may in turn reduce the clearance of renally-excreted anticancer drugs, thereby increasing the risk of toxicity. Historically, the standard prophylaxis or treatment of hyperuricemia in leukemia and lymphoma has included allopurinol, urinary alkalization, and vigorous hydration.(4–6) Allopurinol, a xanthine analogue, inhibits the enzyme xanthine oxidase, which catalyzes the hepatic conversion of hypoxanthine and xanthine to uric acid. Thus, allopurinol does not eliminate existing uric acid in plasma, which still needs to be excreted by the kidneys. Further, allopurinol increases the renal load of xanthine, which is less soluble than uric acid and can cause nephropathy.(7;8)

The enzyme urate oxidase is an alternative agent with a more rapid onset of action than allopurinol.(9–13) Urate oxidase is an endogenous enzyme in most mammals, but not in humans. Unlike allopurinol, urate oxidase converts uric acid to allantoin, a highly soluble metabolite that is readily excreted by the kidneys.(14) Non-recombinant urate oxidase derived from *Aspergillus flavus* has been used to treat hyperuricemia in France and Italy for more than 3 decades but is associated with acute hypersensitivity reactions in approximately 5% of patients.(10) The recombinant urate oxidase rasburicase is also very effective in the prevention and treatment of hyperuricemia, and is associated with less hypersensitivity reactions.(9;11–13)

The uric acid-lowering effect of allopurinol and rasburicase in children has been compared in a randomized study,(9) but the effect of these agents on concomitant anticancer chemotherapy has not been compared in adults or in children. Here we compare the clearance and the toxicity of the renally-excreted drug methotrexate in children with newly diagnosed acute lymphoblastic leukemia (ALL) who received either allopurinol or urate oxidase for the treatment or prophylaxis of hyperuricemia.

Materials and Methods

Patients

We reviewed the records of all patients with newly diagnosed ALL treated at St. Jude Children's Research Hospital between December 1991 and January 2006 to identify those who received allopurinol, non-recombinant urate oxidase, or recombinant urate oxidase immediately before, during, or within 48 hours after the start of high-dose methotrexate given in the "upfront window" before conventional remission induction therapy.

Chemotherapy

All patients in this study were treated on one of three Total Therapy ALL protocols (XIIIA, XIIIB and XV).(15–17) Patients or their parents or guardians (as appropriate) gave informed consent to participate in the treatment protocol. Each protocol and the study reported here were approved by the St. Jude Institutional Review Board. In the interest of comparability, we included in this analysis only patients who received intravenous high-dose methotrexate at the same dose and schedule (1 g/m² over 24 hours).

In Total XIIIA (December 1991–August 1994), patients received up-front single-agent therapy with intravenous high-dose methotrexate (1 g/m² over 24 hours). To prevent

methotrexate toxicity, all patients received hydration and alkalinization with NaHCO_3 . Leucovorin rescue was initiated at hour 48 from the start of methotrexate for a total of 5 doses at 5 mg/m^2 every 6 hours. Rescue was elevated per protocol if plasma methotrexate was $\geq 1.0 \text{ } \mu\text{M}$ at hour 44 from the start of methotrexate, and leucovorin was continued until the methotrexate plasma concentration was $<0.1 \text{ } \mu\text{M}$. Four days after up-front high-dose methotrexate, all patients started remission induction therapy with prednisone, vincristine, daunorubicin, L-asparaginase, etoposide, and cytarabine.(15)

In Total XIIIIB (August 1994–July 1998), patients received up-front window therapy with intravenous high-dose methotrexate (1 g/m^2 over 24 hours) immediately followed by intravenous mercaptopurine. To prevent methotrexate toxicity, all patients received hydration and alkalinization with NaHCO_3 . Leucovorin rescue was initiated at hour 48 from the start of methotrexate for a total of 5 doses at 10 mg/m^2 every 6 hours. Rescue was elevated per protocol if plasma methotrexate was $\geq 1.0 \text{ } \mu\text{M}$ at hour 44 from the start of methotrexate, and leucovorin was continued until methotrexate plasma concentration was $<0.1 \text{ } \mu\text{M}$. Conventional remission induction therapy with prednisone, vincristine, daunorubicin, L-asparaginase, etoposide, and cytarabine began 4 days after the start of up-front therapy.(16)

In Total XV, patients received up-front intravenous high-dose methotrexate (1 g/m^2) administered over 24 hours.(17) All patients received hydration and alkalinization with NaHCO_3 to prevent methotrexate toxicity. Leucovorin rescue was initiated at hour 44 from the start of methotrexate at a dose of 50 mg/m^2 , followed by 7 doses of 15 mg/m^2 leucovorin every 6 hours. Rescue was elevated per protocol if plasma methotrexate was $\geq 0.5 \text{ } \mu\text{M}$ at hour 42 from the start of methotrexate, and leucovorin was continued until methotrexate plasma concentration was $<0.1 \text{ } \mu\text{M}$. Four days later, all patients received conventional remission induction therapy that included prednisone, vincristine, daunorubicin, L-asparaginase, cyclophosphamide, mercaptopurine, and cytarabine.(17)

Prevention and Treatment of Hyperuricemia

Patients received either allopurinol or urate oxidase for the prevention or treatment of hyperuricemia. Allopurinol was used in the early cohort of patients when urate oxidase was not available and in the later cohort of patients if the individual had a history of atopic allergy, bronchial asthma, or glucose-6-phosphate dehydrogenase deficiency, conditions precluding the use of urate oxidase based on the protocol criteria. Allopurinol 100 mg/m^2 per dose was given orally three times a day. Non-recombinant urate oxidase (Uricozyme[®], Sanofi-Synthelabo Inc., Paris, France) was given as an intravenous 100 Units/kg dose once daily over 30 minutes. Recombinant urate oxidase (rasburicase, Sanofi-Aventis Inc., New York, NY) was given as an intravenous dose of 0.1 to 0.2 mg/kg per dose over 30 minutes one to two times per day. Allopurinol or urate oxidase dosing history was obtained from medical charts and was documented through pharmacy computer systems.

Laboratory Tests

Plasma uric acid concentration was measured daily by using a previously described assay. (10) To block degradation of uric acid *ex vivo* in patients receiving urate oxidase, we maintained the temperature of specimens at 0°C to 4°C during their collection, transport, and preparation. The uric acid assay lower limit of detection was 0.5 mg/dL . Complete blood cell counts with differential and serum creatinine, blood urea nitrogen, calcium, phosphorus, lactate dehydrogenase (LDH), potassium, and sodium assays were determined at least daily.

Toxicity

During up-front high-dose methotrexate therapy, adverse events were documented and graded prospectively using the National Cancer Institute Common Toxicity Criteria version 2.0. Adverse events considered in this analysis were those occurring within 14 days of high-dose methotrexate therapy and included renal and hepatic toxicity, and mucositis.

Analysis of Methotrexate Pharmacokinetics

In the Total XIII A and B protocols, blood samples were obtained for plasma methotrexate assay at 1, 6, 23, 44, and 68 hours after the start of the 24-hour methotrexate infusion. In the Total XV protocol, blood was drawn at 1, 4, 24, and 42 hours after the start of the 24-hour methotrexate infusion. Plasma methotrexate concentration was measured by fluorescence polarization immunoassay (TDx System; Abbott Laboratories, Abbott Park, IL). The plasma concentration-versus-time data for each methotrexate course were fit to a 2-compartment model by using a Bayesian estimation algorithm with pediatric population priors (18–20) as implemented in ADAPTII (Biomedical Simulations Resource, University of Southern California, Los Angeles, CA). The systemic clearance was calculated by multiplying the volume of distribution of the central compartment by the elimination rate constant.(21) For all patients, the plasma methotrexate concentration 42 hours after the start of the high-dose methotrexate infusion was estimated by using the concentration-versus-time data extrapolated from the estimated pharmacokinetic parameters.

Statistical Analysis

The Chi-square test, or Fisher's exact test for small sample size, was used to compare presenting features at diagnosis, the proportion of patients in each treatment group who had an hour-42 methotrexate concentration $\geq 0.5 \mu\text{M}$ (a value that indicates delayed methotrexate clearance and a requirement for additional intravenous fluids and leucovorin), and the incidence of toxicity in each treatment group. The Wilcoxon rank-sum test was used to compare the median plasma uric acid concentration, and serum creatinine and blood urea nitrogen values at baseline (i.e., before allopurinol or urate oxidase administration); the median percent change from baseline to post-treatment (with allopurinol or urate oxidase) values for plasma uric acid, serum creatinine, and blood urea nitrogen; and the median methotrexate clearance of the two treatment groups.

For statistical analysis, a uric acid concentration of 0.4 mg/dL was used in calculations if the concentration was below the lower limit of detection. If patients received allopurinol or urate oxidase before receiving high-dose methotrexate, baseline laboratory values were those determined in morning samples collected 2 days before the start of high-dose methotrexate. If patients received allopurinol or urate oxidase during the high-dose methotrexate infusion or within 48 hours of the start of the high-dose methotrexate infusion, baseline laboratory values were those determined in morning specimens collected 1 day before the start of high-dose methotrexate. The percent change of each value was calculated as (value post-treatment – baseline value/baseline value). For this calculation, the post-treatment value was the minimum value obtained during the 5 days following the start of the high-dose methotrexate infusion.

Results

A total of 116 patients received 24-hour high-dose methotrexate infusions and received treatment or prophylaxis for hyperuricemia. Twenty patients received allopurinol and 96 received urate oxidase (28 patients received non-recombinant urate oxidase and 68 received rasburicase). The demographic and clinical characteristics of these patients are summarized in Table 1. We found no significant differences between the two treatment groups in any of

the demographic variables. In the allopurinol treatment group, 9 patients were treated on the Total XIII A, 7 on the Total XIII B, and 4 on the Total XV protocol. In the urate oxidase treatment group, 29 patients were treated on the Total XIII B and 67 on the Total XV protocol. There were no significant differences in methotrexate clearance, plasma levels of uric acid or other indicators of tumor lysis among the three protocols in this study ($p>0.67$). Nine patients (45%) in the allopurinol treatment group and 37 patients (39%) in the urate oxidase treatment group were hyperuricemic at baseline.

Methotrexate clearance values in patients treated with allopurinol versus urate oxidase are depicted in Figure 1. The median (range) methotrexate clearance was 91.1 ml/min/m² (40.0 to 161.1 ml/min/m²) in patients receiving allopurinol versus 117.1 ml/min/m² (30.3 to 205.1 ml/min/m²) in those receiving urate oxidase ($p=0.019$). Seven of 20 patients (35%) receiving allopurinol versus 7 of 96 (7%) receiving urate oxidase had an hour-42 plasma methotrexate concentration $\geq 0.5 \mu\text{M}$ ($p=0.003$) and per Total XV protocol guidelines required an increased rescue dose of leucovorin.

Plasma uric acid was well-controlled in both treatment arms. Patients treated with urate oxidase had a significantly greater decrease in plasma uric acid concentration after treatment. The median decrease in uric acid was 89% (range, +150% to -96.5%) in the urate oxidase group and 63% (range, +24% to -96%) in the allopurinol group ($p = 0.0003$). The median minimum post-treatment plasma uric acid value was 0.4 mg/dL (range, 0.4 to 3.7 mg/dL) in the urate oxidase-treated patients versus 2.2 mg/dL (0.4 to 4.3 mg/dL) in the allopurinol-treated patients ($p = 0.0003$).

The median change from baseline value in serum creatinine ($p=0.77$) and BUN ($p=0.12$) did not differ significantly by treatment group. No patient in either treatment group required dialysis or hemofiltration, or experienced renal toxicity greater than grade 1. Grade 1 renal toxicity was observed in 3 patients (15%) in the allopurinol group vs. 3 patients (3%) in the urate oxidase group ($p=0.06$). The incidence of elevated bilirubin ($p=1.0$), or elevated SGPT or SGOT ($p=0.32$) did not differ significantly between the two treatment groups. However, 15 patients in the urate oxidase group (16%) versus 9 patients in the allopurinol group (45%) experienced mucositis ($p=0.003$).

We also compared data from patients in each treatment group to those from 191 patients enrolled on Total XIII A, XIII B, or XV who received methotrexate but did not require either allopurinol or urate oxidase. We found no difference in MTX clearance between patients in the urate oxidase treatment group and patients who received no allopurinol or urate oxidase ($p=0.088$). Among the 191 patients who received neither allopurinol nor urate oxidase, 38 (20%) patients experienced mucositis; this incidence of mucositis did not differ significantly from that in the urate oxidase treatment group ($p=0.38$).

Discussion

Hyperuricemia caused by tumor cell lysis can be life-threatening, requiring rapid and aggressive management to prevent acute renal failure. Here we have summarized the St. Jude experience with non-recombinant and recombinant urate oxidase versus allopurinol in patients newly diagnosed with ALL, and compared their effect on the clearance of methotrexate, a renally-excreted agent. Our finding that urate oxidase has a greater hypouricemic effect than allopurinol corroborates those of previous studies.(9;10) In our earlier study, we found a greater and more rapid decrease in blood uric acid levels in 134 children with acute leukemia and non-Hodgkin lymphoma who were treated with non-recombinant urate oxidase than in a similarly treated historical control group of 129 patients who had received allopurinol.(10) None of the patients treated with urate oxidase required

hemodialysis, whereas more than 20% of our patients with advanced-stage Burkitt lymphoma or leukemia treated historically with allopurinol did.(22;23) Similarly, only 2.6% of children with advanced-stage Burkitt lymphoma or leukemia who were treated on the French LMB 89 protocol and received non-recombinant urate oxidase required hemodialysis,(24) compared to 16% of patients who were treated with the identical chemotherapeutic regimen but received allopurinol on the UKCCSG 9003 protocol.(25) Subsequently, in a compassionate-use trial of rasburicase, Jeha and colleagues (26) found that 3% of 1069 rasburicase-treated adult and pediatric patients required hemodialysis, while at least 16% of historical control patients treated with other agents required hemodialysis.

Methotrexate is excreted primarily by the renal route. Renal dysfunction can cause delayed methotrexate elimination, which can result in a marked increase in hematological and nonhematological toxicity, and may delay subsequent therapy. In 1991, we began pharmacodynamic studies of methotrexate given before conventional remission induction therapy in patients with newly diagnosed ALL; allopurinol was initially used to prevent or treat hyperuricemia.(15–17;27) Because of the effects of allopurinol on purine biosynthesis, confounding our interpretation of the pharmacodynamics of methotrexate,(28) we replaced it with urate oxidase in 1994. However, some patients were not able to receive urate oxidase because of glucose-6-phosphate dehydrogenase deficiency or a history of severe allergy (exclusion criteria for urate oxidase treatment based on the protocol criteria), and therefore served as a comparison group in this study. We found that patients receiving allopurinol had a significantly lower median methotrexate clearance and were more likely to experience methotrexate-induced mucositis than were those receiving urate oxidase. The methotrexate clearance and the rate of mucositis in patients who received urate oxidase were actually comparable to those of patients who did not require urate oxidase or allopurinol. The decrease in methotrexate clearance in patients treated with allopurinol may be explained by a weaker hypouricemic effect of allopurinol, leading to precipitation of uric acid in renal tubules. Hence, during remission induction therapy for lymphoid malignancies, renally excreted drugs should be monitored closely, especially in patients receiving allopurinol for prophylaxis or treatment of hyperuricemia.

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References

1. Silverman P, Distelhorst CW. Metabolic emergencies in clinical oncology. *Semin Oncol.* 1989; 16:504–515. [PubMed: 2688110]
2. Jeha S. Tumor lysis syndrome. *Semin Hematol.* 2001; 38:4–8. [PubMed: 11694945]
3. Hogan DK, Rosenthal LD. Oncologic emergencies in the patient with lymphoma. *Semin Oncol Nurs.* 1998; 14:312–320. [PubMed: 9839344]
4. Krakoff IH, Meyer RL. Prevention of hyperuricemia in leukemia and lymphoma: use of allopurinol, a xanthine oxidase inhibitor. *JAMA.* 1965; 193:1–6. [PubMed: 14297704]
5. DeConti RC, Calabresi P. Use of allopurinol for prevention and control of hyperuricemia in patients with neoplastic disease. *N Engl J Med.* 1996; 274:481–486. [PubMed: 5904287]
6. Coiffier B, Altman A, Pui CH, Younes A, Cairo MS. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. *J Clin Oncol.* 2008; 26:2767–2778. [PubMed: 18509186]

7. Greene ML, Fujimoto WY, Seegmiller JE. Urinary xanthine stones--a rare complication of allopurinol therapy. *N Engl J Med.* 1969; 280:426–427. [PubMed: 5763090]
8. Andreoli SP, Clark JH, McGuire WA, Bergstein JM. Purine excretion during tumor lysis in children with acute lymphocytic leukemia receiving allopurinol: relationship to acute renal failure. *J Pediatr.* 1986; 109:292–298. [PubMed: 3461147]
9. Goldman SC, Holcenberg JS, Finklestein JZ, Hutchinson R, Kreissman S, Johnson FL, et al. A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis. *Blood.* 2001; 97:2998–3003. [PubMed: 11342423]
10. Pui CH, Relling MV, Lascombes F, Harrison PL, Struxiano A, Mondesir JM, et al. Urate oxidase in prevention and treatment of hyperuricemia associated with lymphoid malignancies. *Leukemia.* 1997; 11:1813–1816. [PubMed: 9369411]
11. Pui CH, Mahmoud HH, Wiley JM, Woods GM, Leverger G, Camitta B, et al. Recombinant urate oxidase for the prophylaxis or treatment of hyperuricemia in patients With leukemia or lymphoma. *J Clin Oncol.* 2001; 19:697–704. [PubMed: 11157020]
12. Pui CH, Jeha S, Irwin D, Camitta B. Recombinant urate oxidase (rasburicase) in the prevention and treatment of malignancy-associated hyperuricemia in pediatric and adult patients: results of a compassionate-use trial. *Leukemia.* 2001; 15:1505–1509. [PubMed: 11587206]
13. Coiffier B, Mounier N, Bologna S, Ferme C, Tilly H, Sonet A, et al. Efficacy and safety of rasburicase (recombinant urate oxidase) for the prevention and treatment of hyperuricemia during induction chemotherapy of aggressive non-Hodgkin's lymphoma: results of the GRAAL1 (Groupe d'Etude des Lymphomes de l'Adulte Trial on Rasburicase Activity in Adult Lymphoma) study. *J Clin Oncol.* 2003; 21:4402–4406. [PubMed: 14581437]
14. Pui CH. Rasburicase: a potent uricolytic agent. *Expert Opin Pharmacother.* 2002; 3:433–442. [PubMed: 11934348]
15. Pui CH, Mahmoud HH, Rivera GK, Hancock ML, Sandlund JT, Behm FG, et al. Early intensification of intrathecal chemotherapy virtually eliminates central nervous system relapse in children with acute lymphoblastic leukemia. *Blood.* 1998; 92:411–415. [PubMed: 9657739]
16. Pui CH, Sandlund JT, Pei D, Campana D, Rivera GK, Ribeiro RC, et al. Improved outcome for children with acute lymphoblastic leukemia: results of Total Therapy Study XIIIb at St Jude Children's Research Hospital. *Blood.* 2004; 104:2690–2696. [PubMed: 15251979]
17. Pui CH, Campana D, Pei D, Bowman WP, Sandlund JT, Kaste SC, et al. Treatment of childhood acute lymphoblastic leukemia without prophylactic cranial irradiation. *N Eng J Med.* in press.
18. Relling MV, Fairclough D, Ayers D, Crom WR, Rodman JH, Pui CH, et al. Patient characteristics associated with high-risk methotrexate concentrations and toxicity. *J Clin Oncol.* 1994; 12:1667–1672. [PubMed: 8040679]
19. Wall AM, Gajjar A, Link A, Mahmoud H, Pui CH, Relling MV. Individualized methotrexate dosing in children with relapsed acute lymphoblastic leukemia. *Leukemia.* 2000; 14:221–225. [PubMed: 10673736]
20. Evans WE, Relling MV, Rodman JH, Crom WR, Boyett JM, Pui CH. Conventional compared with individualized chemotherapy for childhood acute lymphoblastic leukemia. *N Engl J Med.* 1998; 338:499–505. [PubMed: 9468466]
21. Gibaldi, M.; Perrier, D. Multicompartment models. In: Gibaldi, M.; Perrier, D., editors. *Pharmacokinetics.* 2 ed. New York: Marcel Dekker, Inc.; 1982. p. 45-111.
22. Stapleton FB, Strother DR, Roy S III, Wyatt RJ, McKay CP, Murphy SB. Acute renal failure at onset of therapy for advanced stage Burkitt lymphoma and B cell acute lymphoblastic lymphoma. *Pediatrics.* 1988; 82:863–869. [PubMed: 3186376]
23. Bowman WP, Shuster JJ, Cook B, Griffin T, Behm F, Pullen J, et al. Improved survival for children with B-cell acute lymphoblastic leukemia and stage IV small noncleaved-cell lymphoma: a pediatric oncology group study. *J Clin Oncol.* 1996; 14:1252–1261. [PubMed: 8648381]
24. Patte C, Sakiroglu C, Ansoborlo S, Baruchel A, Plouvier E, Pacquement H, et al. Urate-oxidase in the prevention and treatment of metabolic complications in patients with B-cell lymphoma and leukemia, treated in the Societe Francaise d'Oncologie Pediatrique LMB89 protocol. *Ann Oncol.* 2002; 13:789–795. [PubMed: 12075750]

25. Atra A, Gerrard M, Hobson R, Imeson JD, Ashley S, Pinkerton CR. Improved cure rate in children with B-cell acute lymphoblastic leukaemia (B-ALL) and stage IV B-cell non-Hodgkin's lymphoma (B-NHL)--results of the UKCCSG 9003 protocol. *Br J Cancer*. 1998; 77:2281–2285. [PubMed: 9649146]
26. Jeha S, Kantarjian H, Irwin D, Shen V, Shenoy S, Blaney S, et al. Efficacy and safety of rasburicase, a recombinant urate oxidase (Elitek), in the management of malignancy-associated hyperuricemia in pediatric and adult patients: final results of a multicenter compassionate use trial. *Leukemia*. 2005; 19:34–38. [PubMed: 15510203]
27. Synold TW, Relling MV, Boyett JM, Rivera GK, Sandlund JT, Mahmoud H, et al. Blast cell methotrexate-polyglutamate accumulation in vivo differs by lineage, ploidy, and methotrexate dose in acute lymphoblastic leukemia. *J Clin Invest*. 1994; 94:1996–2001. [PubMed: 7525652]
28. Masson E, Synold TW, Relling MV, Schuetz JD, Sandlund JT, Pui CH, et al. Allopurinol inhibits de novo purine synthesis in lymphoblasts of children with acute lymphoblastic leukemia. *Leukemia*. 1996; 10:56–60. [PubMed: 8558939]

Figure 1.

Methotrexate clearance in patients who received allopurinol or urate oxidase immediately before, during, or within 48 hours after the start of high-dose methotrexate (1 g/m^2); clearance was higher in patients receiving urate oxidase ($p=0.019$, Wilcoxon rank-sum test). Each data point indicates the methotrexate clearance value of an individual patient; boxes include data between the 25th and 75th percentiles with bar indicating the median value, and whiskers indicate the minimal and maximal values excluding outliers.

Table 1

Baseline patient characteristics

	Treatment		P-value
	Allopurinol (n=20)	Urate Oxidase (n=96)	
Age at Diagnosis [n (%)]			
<1 year	0 (0)	2 (2.1)	0.85 ¹
1 to 9 years	14 (70.0)	68 (70.8)	
≥10 years	6 (30.0)	26 (27.1)	
Race [n (%)]			
White	18 (90.0)	70 (72.9)	0.40 ¹
Black	1 (5.0)	16 (16.7)	
Other	1 (5.0)	10 (10.4)	
Sex [n (%)]			
Male	10 (50.0)	51 (53.1)	0.81 ¹
Female	10 (50.0)	45 (46.9)	
WBC(× 10 ⁹ /L) [n (%)]			
< 50	11 (55.0)	62 (64.6)	0.45 ¹
≥50	9 (45.0)	34 (35.4)	
Immunophenotype [n (%)]			
B	16 (80.0)	81 (84.4)	0.74 ¹
T	4 (20.0)	15 (15.6)	
Uric Acid (mg/dL)			
Median	5.5	5.0	0.21 ²
Range	2.4–12.5	0.4–13.4	
Creatinine (mg/dL)			
Median	0.6	0.5	0.10 ²
Range	0.3–0.9	0.2–1.1	
BUN (mg/dL)			
Median	10.0	10.0	0.56 ²
Range	1.0–16.0	3.0–25.0	

¹ Chi-Square test or Fisher's exact test;² Wilcoxon rank-sum test