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Allopurinol use during pediatric acute lymphoblastic leukemia maintenance therapy safely corrects skewed 6-mercaptopurine metabolism, improving inadequate myelosuppression and reducing gastrointestinal toxicity

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Abstract

Background: Inadequate myelosuppression during maintenance therapy for acute lymphoblastic leukemia (ALL) is associated with an increased risk of relapse. One mechanism is skewed metabolism of 6-mercaptopurine (6MP), a major component of maintenance therapy, which results in preferential formation of the hepatotoxic metabolite (6-methyl mercaptopurine [6MMP]) with low levels of the antileukemic metabolite, 6-thioguanine nucleotides (6TGN). Allopurinol can modify 6MP metabolism to favor 6TGN production and reduce 6MMP.

Methods: Patients in maintenance were considered for allopurinol treatment who had the following features: (a) Grade ≥3 hepatotoxicity; (b) Grade ≥2 nonhepatic gastrointestinal (GI)

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Gordon Cohen and Stacy Cooper contributed equally to this work and share first authorship.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

LINKED CONTENT

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

CONFLICT OF INTEREST

After completion of this data collection, Edward Allan Sison became an employee of Covance Inc., and after completion of the data collection and data analysis, Gordon Cohen became an employee of Astra Zeneca.

toxicity; or (c) persistently elevated absolute neutrophil count (ANC) despite >150% protocol dosing of oral chemotherapy.

Results: From 2013 to 2017, 13 ALL patients received allopurinol: nine for hepatotoxicity, five for inadequate myelosuppression, and three for nonhepatic GI toxicity (four met multiple criteria). Allopurinol was well tolerated, without significant adverse events. Allopurinol resulted in a significant decrease in the average 6MMP/6TGN ratio (mean reduction 89.1, $P = .0001$), with a significant increase in 6TGN (mean 550.4, $P = .0008$) and a significant decrease in 6MMP (mean 13 755, $P = .0013$). Patients with hepatotoxicity had a significant decrease in transaminase elevation after starting allopurinol (alanine transaminase [ALT] mean decrease 22.1%, $P = .02$), and all with nonhepatic GI toxicity had improved symptoms. Those with inadequate myelosuppression had a significant increase in the time with ANC in goal (mean increase 26.4%, $P = .0004$).

Conclusions: Allopurinol during ALL maintenance chemotherapy is a safe, feasible, and effective intervention for those who have altered metabolism of 6MPcausing toxicity or inadequate myelosuppression.

Keywords

allopurinol; leukemia; mercaptopurine

1 INTRODUCTION

Inadequate myelosuppression for patients during maintenance chemotherapy for treatment of pediatric acute lymphoblastic leukemia and lymphoma (ALL) has been associated with an increased risk of relapse.[1] Strategies have been adapted to improve therapeutic myelosuppression during maintenance therapy in the Children's Oncology Group (COG) and other large cooperative groups. One of the primary approaches has been to increase dosing of methotrexate (MTX) and 6-mercaptopurine (6MP) to a target white blood cell count (WBC) or absolute neutrophil count (ANC) range.[2–5] In current COG upfront ALL clinical trials, doses of MTX and 6MP are systematically increased during maintenance chemotherapy until an ANC of 500–1500/μL is achieved.

While most patients are able to achieve this goal range, a substantial proportion has difficulty maintaining ANC within this goal range. This can be due to multiple factors such as noncompliance, poor gastrointestinal (GI) absorption of chemotherapy, GI or hepatic toxicity (including nausea/vomiting, hyperbilirubinemia, and elevations in transaminase levels), and abnormal metabolism of 6MP resulting in inadequate suppression of ANC despite very high doses of drug. With these higher doses of chemotherapy, increased toxicity often occurs as well, limiting the ability to further increase doses if needed.

Mercaptopurine is metabolized by multiple enzymes including thiopurine methyltransferase, xanthine oxidase, hypoxanthine-guanine phosphoribosyltransferase, and others. The ultimate antileukemicmetabolite is 6-thioguanine nucleotides (6TGN).[6] This metabolite is incorporated into DNA and thought to be the main driver of 6MP-induced myelosuppression. It is also believed to correlate with the antileukemic activity of 6MP,

with multiple studies showing an association between higher levels of 6TGN and reduced risk of relapse for pediatric ALL patients.[7,8] However, other 6MP metabolites are also produced, which are not believed to substantially contribute to the efficacy of 6MP, such as 6-thiouric acid metabolites. 6-Methyl mercaptopurine (6MMP) is associated with GI and hepatic toxicity.[9,10] Some patients have skewed metabolism of 6MP to preferentially form 6MMP, with only minimal production of 6TGN.

One strategy to alter skewed metabolism of 6MP that disproportionately favors 6MMP is the use of allopurinol, a xanthine oxidase inhibitor. By inhibiting this key enzyme in the 6MP metabolic pathway, numerous studies have shown that 6MP is preferentially metabolized to its therapeutically active metabolite, 6TGN, and away from its toxic metabolite 6MMP.[11–16] In fact, allopurinol has been used successfully for more than 30 years in patients taking 6MP for Crohn's disease or other GI autoimmune diseases to reduce hepatic toxicity from the 6MP and improve efficacy.[15–16] There have also been case reports of successful allopurinol use in pediatric ALL to alter skewed 6MP metabolism in patients with very elevated 6MMP levels and clinical manifestations of hypoglycemia, pancreatitis, and hepatotoxicity, and report of a single ALL patient with inadequate myelosuppression that was improved with the addition of allopurinol.[12–14]

At our institution, we have used allopurinol for pediatric patients with difficulty achieving therapeutic myelosuppression and/or those with GI toxicity attributed to mercaptopurine (both hepatic and nonhepatic toxicity). Herein, we report the safety and efficacy of allopurinol for these pediatric patients with gastrointestinal toxicity and/or inability to achieve adequate myelosuppression during maintenance therapy.

2 | METHODS

2.1 | Data collection and outcome measures

This was a retrospective chart review of pediatric oncology patients at Johns Hopkins Children's Center from 2013 to 2017. During this time, a pilot study of the addition of allopurinol for skewed metabolism of 6MP for ALL patients in maintenance was designed, and was approved and opened in January 2014. Prior to its activation, our institution began to treat patients according to the strategy within the details of the protocol as it was developed, and this manuscript represents the retrospective clinical observations of all the patients identified in the chart review who were treated with allopurinol during this period.

This study was approved by the Johns Hopkins Institutional Review Board (IRB00084984). Data were extracted from the electronic medical record used by Johns Hopkins Hospital, EPIC, for each patient from the beginning of maintenance chemotherapy to end of chemotherapy or December 2017, whichever came first. The primary outcome measure was the duration of ANC in range before and after allopurinol treatment. Additionally, we investigated changes in liver enzymes alanine transaminase (ALT) and aspartate transaminase (AST), direct bilirubin, gastrointestinal adverse effects, 6MMP and 6TGN levels, and the ratio of 6MMP/6TGN. The study hypothesized that the addition of allopurinol to 6MP would improve inadequate myelosuppression as evidenced by an

improvement in ANC within range, as well as a decrease in hepatic and gastrointestinal toxicity.

2.2 Subject inclusion

All patients at our institution with B lymphoblastic lymphoma (B-ALL) or T lymphoblastic lymphoma (T-ALL) were considered for the addition of allopurinol therapy in maintenance. Our institution treats approximately 40 children per year with B-acute lymphoblastic leukemia/lymphoma and T-acute lymphoblastic leukemia/lymphoma, and upfront therapy uses COG protocols. All patients included in this study were treated as per COG protocols, specifically AALL0932 for average-risk B-ALL, AALL1131 for high-risk/very high risk B-ALL, and AALL1231 for standard/intermediate-risk T-ALL.

Indications for the addition of allopurinol therapy were defined as part of our emerging clinical guidelines at our institution, to mirror the criteria in the pilot study as mentioned above. As no clear guidelines yet existed to define those ALL patients who may benefit from allopurinol, we chose strict criteria to define the patient population we felt would be most likely to benefit. These criteria were chosen as surrogates to identify patients who clearly demonstrated a propensity to metabolize 6MP to 6MMP, as well as unambiguous evidence of inadequate myelosuppression or significant hepatotoxicity/gastrointestinal toxicity. To be considered for the addition of allopurinol therapy, acute lymphoblastic leukemia/lymphoma patients in maintenance must have shown laboratory evidence of abnormal 6MP metabolism with a 6MMP/6TGN ratio of >40 and elevated 6MMP levels (≥12 000/8 × 10^8 RBC) within 21 days prior to starting allopurinol. Additionally, patients needed to meet at least one of the following criteria: (a) elevated ANC (≥1500/mm^3) for ≥6 weeks despite 150% protocol doses of 6MP (112.5 mg/m^2/dose daily) and methotrexate (30 mg/m^2/dose once weekly); (b) hepatic toxicity (ALT ≥five times upper limit of normal (ULN) or AST ≥five times ULN, or direct bilirubin ≥five times ULN); or (c) Grade ≥2 nonliver GI toxicity (abdominal pain, nausea, vomiting, anorexia, pancreatitis, etc). Toxicity was graded based on Common Terminology For Common Adverse Events (CTCAE v4.0). Patients were excluded from allopurinol therapy if they had allergy to allopurinol, active relapse of ALL or lymphoblastic lymphoma, known history of chronic liver disease (except Gilbert syndrome), or were pregnant/breastfeeding women. No patients were excluded for any of these reasons, and no patients were treated with allopurinol who did not meet these criteria during this time at our institution.

2.3 Study procedures

Allopurinol was dosed daily at 50 mg for patients ≤30 kg and 100 mg for patients >30 kg, given at the same time as the 6MP. 6MP was given at any time most convenient for the patient and caregiver, ideally the same time each day. Upon starting allopurinol, the patient's prior 6MP dosing was reduced by 50% (and MTX remained at the same dose prior to starting allopurinol). Weekly complete blood count with differential and comprehensive metabolic panel were obtained, with 6MMP and 6TGN metabolites drawn at baseline, week 3 and 9 of allopurinol therapy. As per COG protocols, ANC goal range was defined as 5001500/μL, and LFT goal range was defined as <5× ULN. Dose escalation guidelines for standard ALL maintenance therapy were followed. For ANC <500/μL and/or platelets

<50/μL, allopurinol, 6MP, and MTX were held until counts recovered, and then restarted at the same allopurinol dose but at 50% dosing of both 6MP and MTX.

2.4 Data analysis

Data analysis was conducted using STATA 15.0 and MS Excel 2016. Paired *t*-tests were used to compare each outcome before allopurinol was added versus after allopurinol was added. Longitudinal data analysis was conducted using logistic mixed effects models.[17]

3 | RESULTS

3.1 | Patient characteristics

Thirteen patients were treated with allopurinol during maintenance chemotherapy, approximately 10% of our institutional population, and summary characteristics of each patient are given in Table 1. Among the 13 patients, nine were male and four female; 10 had B-ALL and three had T-ALL; eight were under 10 years of age and five were over 10 years of age. Patients had different indications for initiation of allopurinol: nine patients for hepatotoxicity, five patients for difficulty maintaining ANC in goal range, and three for nonliver-related GI toxicity. It should be noted that some patients met multiple criteria (Table 1). As of December 2017 when this analysis ended, among the 13 patients, nine had completed chemotherapy and four were still receiving therapy (Figure 1). The average duration of therapy with allopurinol was 58 weeks, with a median of 49 weeks (range 12–112 weeks). All patients continued on allopurinol for the duration of the remainder of maintenance therapy, with no patients stopping allopurinol for toxicity or intolerability.

3.2 Neutrophil count analysis

Analyzing specifically the five patients started on allopurinol due to inadequate myelosuppression, there was a significant improvement in the percentage of weeks that patients maintained ANC within goal range (500–1500 μL) once started on allopurinol (mean weeks preallopurinol 10%, mean weeks with allopurinol 36.4%, mean difference $P = .0004$) as shown in Figure 2. For all 13 patients, there was no significant increase in the percentage of time that patients were in goal range ANC after patients started allopurinol (mean difference between postallopurinol and preallopurinol 6.8%, $P = .325$; Table 2).

Longitudinal data analysis shows that the odds of ANC being in goal range with allopurinol compared to before initiation of allopurinol when adjusted for age, sex, WBC, and time is 1.3 times higher for all 13 patients, which is not statistically significant ($P = .41$), but 2.9 times higher among the five patients who had inadequate myelosuppression, which is statistically significant ($P = .01$), as shown in Table 3. After allopurinol, the average doses of 6MP and MTX were reduced by 43% ($P < .0001$) and 20% ($P = .0692$), respectively. Thus, allopurinol use is associated with improved ability to maintain ANC with goal range among patients with inadequate myelosuppression.

3.3 Reduction in hepatic and GI toxicity

For the nine patients treated with allopurinol for hepatic toxicity, there was a significant increase in the percentage of time that patients were in goal range for ALT after patients

started allopurinol (mean difference 22.1%, $P = .02$) as well as a significant increase in the percentage of time that these patients were in goal range for AST (mean difference 6.0%, $P = .01$), as shown in Table 2 and Figure 3. Longitudinal data analysis shows that the odds of being in goal range ALT (<5× ULN) with allopurinol compared to prior to initiation of allopurinol when adjusted for age, sex, WBC, and time was 6.1 times higher for all 13 patients and 7.1 times higher among the nine patients who had hepatotoxicity, and both these odds ratios were statistically significant ($P < .0005$). The odds of being in goal range AST with allopurinol compared to without allopurinol when adjusted for age, sex, WBC, and time was 3.3 times higher for all 13 patients, which was not statistically significant ($P = .061$), but 4.4 times higher among the nine patients who initially had hepatotoxicity, which was statistically significant ($P = .021$), as shown in Table 3. Accordingly, allopurinol use is strongly associated with an improvement in hepatotoxicity during ALL maintenance chemotherapy in patients with skewed mercaptopurine metabolism.

Two patients with nonhepatic GI symptoms were started on allopurinol for pancreatitis, a rare but possible adverse effect during maintenance therapy that has been attributed to both 6MP and steroids. For both patients, no further episodes were seen after starting allopurinol for the duration of maintenance. The other patient with nonhepatic severe GI toxicity was started for persistent nausea and emesis despite maximized antiemetic therapy, which also resolved with the addition of allopurinol.

3.4 Metabolite ratio analysis

There was a significant decrease in the average 6MMP/6TGN ratio after allopurinol was added compared to before allopurinol (mean preallopurinol 111.7, mean postallopurinol 22.6, mean decrease 89.1, $P = .0001$) and this was attributable to a significant increase in 6TGN (mean preallopurinol 251.4 pmol/8 × 10^8 RBC, mean postallopurinol 801.8 pmol/8 × 10^8 RBC, mean increase 550.4 pmol/8 × 10^8 RBC, $P = .0008$) and a significant decrease in 6MMP levels (mean preallopurinol 24 810 pmol/8 × 10^8 RBC, mean postallopurinol 11 055 pmol/8 × 10^8 RBC, mean decrease −13 755 pmol/8 × 10^8 RBC, $P = .0013$), as shown in Table 2.

3.5 Safety analysis

There was no significant difference in the percent of time that patients experienced ANC <500 after allopurinol was added (mean difference in time of neutropenia with ANC <500 between preallopurinol and postallopurinol 3.1%, $P = .08$; Table 2). Longitudinal data analysis shows that the odds ratio for being neutropenic with allopurinol compared to without allopurinol when adjusted for age, sex, WBC, and time is 0.78, and this is not statistically significant ($P = .47$), suggesting that there is no significant increase in neutropenia upon the addition of allopurinol (Table 3). Additionally, none of the patients were admitted for fever and neutropenia while on allopurinol, or had any other unexpected admissions. No other significant side effects were seen that could be attributed to allopurinol, including no incidence of rash, diarrhea, or elevated creatinine (the most common adverse reactions reported with allopurinol).

4 DISCUSSION

Our experience with incorporation of allopurinol to improve therapeutic myelosuppression and reduce GI toxicity during pediatric ALL maintenance therapy is the largest series to date, and is the first to demonstrate a statistically significant benefit of allopurinol use in this patient population. Other case reports have shown benefits in reducing hepatotoxicity[12] and a single patient has been reported with improvement in the ability to achieve target ANC ranges during maintenance,[13] but ours is the first to do so in a larger patient cohort, for both indications, with uniform treatment parameters.

Despite the small sample size, our results show that allopurinol can be administered safely over a prolonged duration to pediatric ALL patients during maintenance therapy. There were no significant adverse events experienced by these patients, and with all patients able to remain on allopurinol for the duration of the remainder of maintenance, without any patient stopping for toxicity or inability to tolerate the medication. Specifically, these patients had no admissions for fever and neutropenia, no infections requiring antibiotics otherwise, and no significant increase in incidence of severe neutropenia.

Analysis of the 6MP metabolites demonstrated that the addition of allopurinol was shown to cause a statistically significant decrease in the ratio of 6MMP/6TGN, with an associated significant decrease in 6MMP levels and increase in 6TGN levels. This suggests that allopurinol shifts the metabolism of 6MP to produce an increased amount of the active metabolite 6TGN and decreased amount of the toxic metabolite 6MMP.

Furthermore, allopurinol was effective in providing therapeutic myelosuppression and reducing hepatotoxicity, with statistically significant, clinically meaningful effects that were nearly universal in this patient cohort. For those started on allopurinol for elevated transaminases, eight of nine experienced a drop in transaminase levels following the addition of allopurinol. For the five patients started on allopurinol for inadequate myelosuppression, all patients experienced an increased amount of time in therapeutic goal ANC range. Our results were consistent across nearly all patients studied, and strengthens our confidence that we have identified a pediatric ALL population that can benefit from allopurinol therapy.

Another potential benefit of allopurinol is a lower exposure to chemotherapy during maintenance therapy. The lower 6MP doses are partly driven by the 50% mandated decrease in 6MP dose upon starting allopurinol. Further, and perhaps just as importantly, MTX doses trended lower as well. This suggests that efficacy of ALL maintenance chemotherapy can be enhanced and major toxicities can be decreased with a lower exposure to cytotoxic chemotherapy when given in combination with allopurinol.

A key question that remains in the use of allopurinol in pediatric ALL is the ideal patient population that would benefit. While no evidence-based guidance existed to define these patients, criteria were chosen to define the patients who were most likely to benefit from the addition of allopurinol. Specifically, we used a 6MMP/6TGN ratio of >40, a level based on anecdotal experience and review of prior patients with metabolite levels available. This is consistent with the rationale that elevated 6MMP levels are more closely associated with patients at risk for thiopurine toxicity, and low 6TGN levels seem to be associated

with a poorer therapeutic effect. This was supported in prior studies of IBD patients using thiopurines. The rationale for using the cut-off level of 40 versus another level was based on early anecdotal experience and it may not represent the optimal ratio.

There have been prior clinical trials that have captured the levels of 6MMP and 6TGN metabolites in pediatric ALL patients on clinical trials, including POG 9605 and CCG 1922/B925. However, comparisons of these ratios to associated myelosuppression and toxicity are yet to be published. We hope to evaluate data from larger studies such as those mentioned above to determine whether patients with even lower 6MMP/6TGN ratios could benefit from allopurinol treatment.

The limitations of this study are that it is retrospective, single institution, and with a relatively small number of patients. We are leading an ongoing multiinstitutional prospective clinical trial enrolling pediatric ALL patients with skewed metabolism for the same indications studied in this retrospective analysis. If these prospective data confirm our institutional results presented here, we anticipate this may support the incorporation of allopurinol in cooperative group trials to more rigorously test the efficacy and safety in ALL maintenance therapy, and ultimately demonstrate an associated decrease in the relapse rate for these patients. Ultimately, a large, national clinical trial of ALL that incorporates the addition of allopurinol for patients with evidence of skewed metabolism of 6MP would have the potential to demonstrate an improvement in relapse rate.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations:

6MMP	6-methyl mercaptopurine
6MP	6-mercaptopurine
6TGN	6-thioguanine nucleotides
ALL	acute lymphoblastic leukemia
ALT	alanine transaminase
ANC	absolute neutrophil count
AST	aspartate transaminase
COG	Children’s Oncology Group
GI	gastrointestinal
MTX	methotrexate
ULN	upper limit of normal
WBC	white blood cell count

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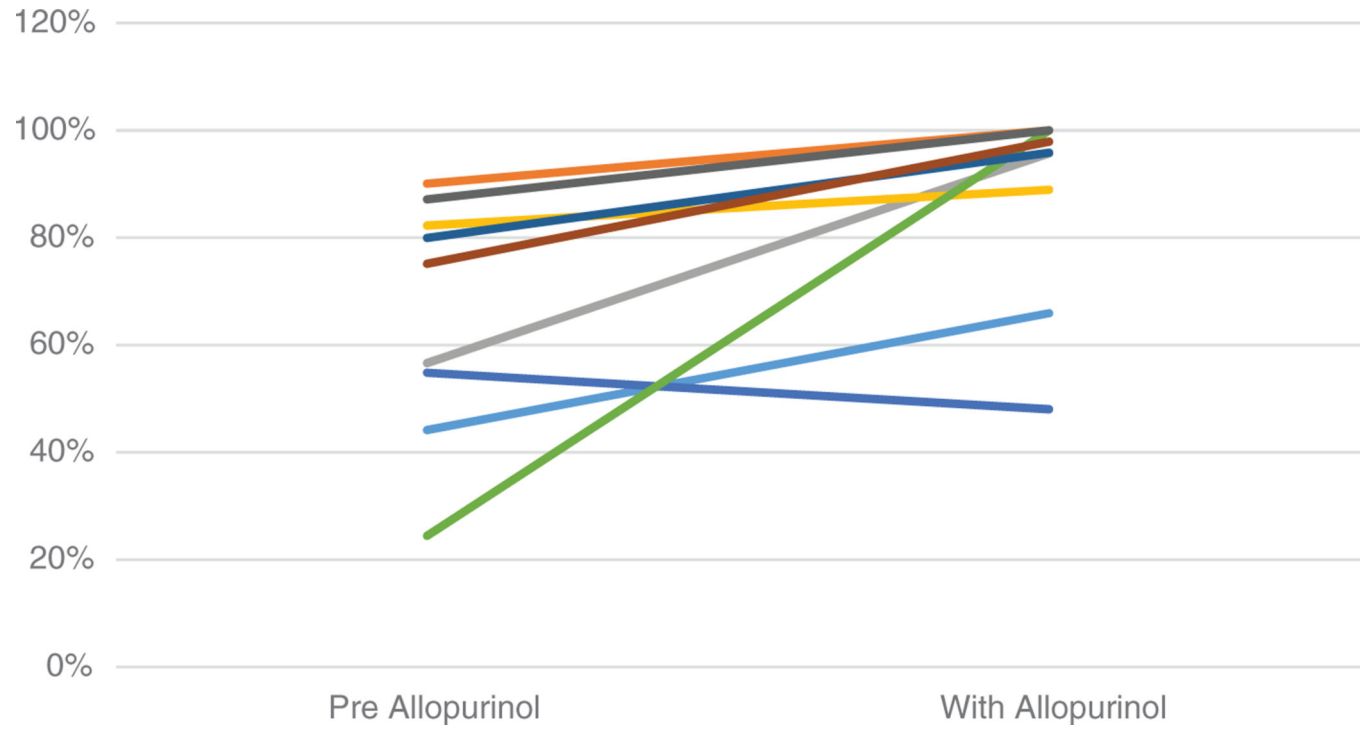

FIGURE 1.
Duration of time on allopurinol during maintenance therapy for each patient

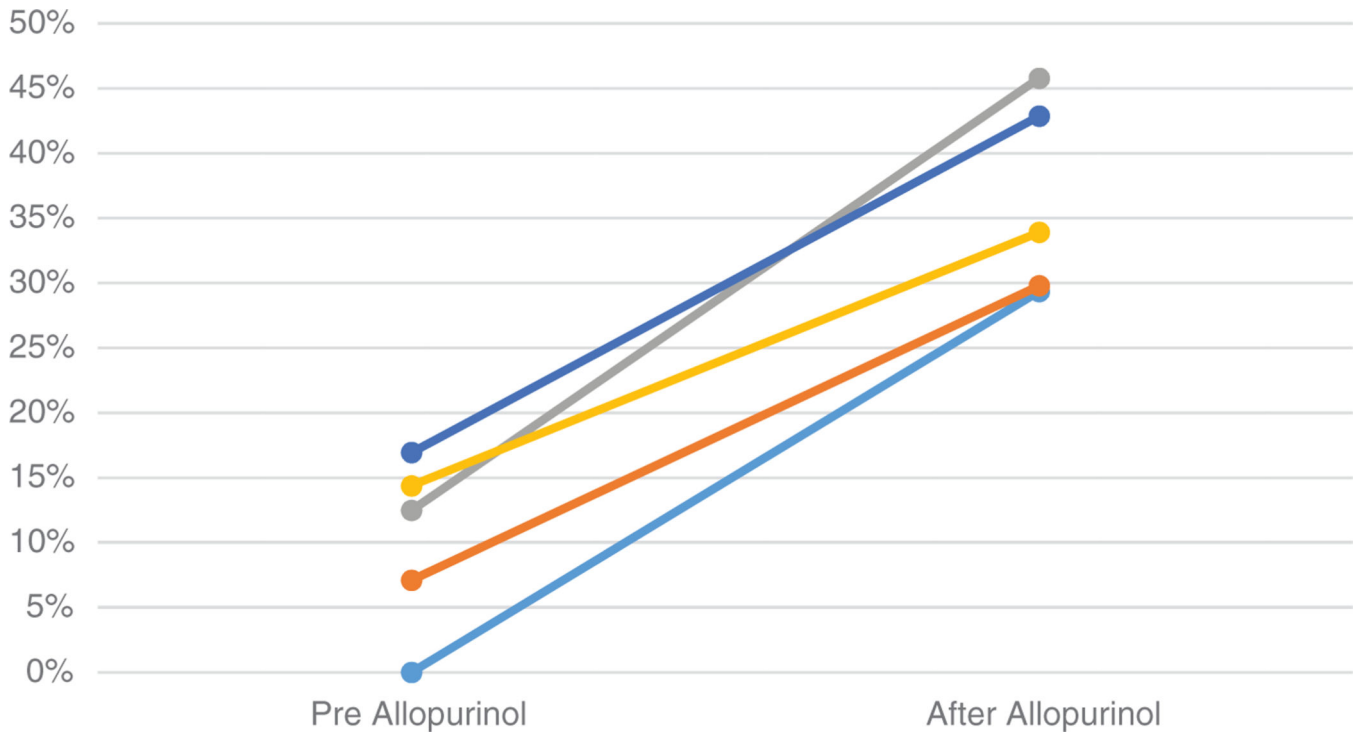

FIGURE 2.

Effect of allopurinol on absolute neutrophil count (ANC) among patients enrolled for inability to suppress ANC: there was a significant increase in the percentage of weeks that patients maintained ANC within goal range (500–1500 μL) once started on allopurinol

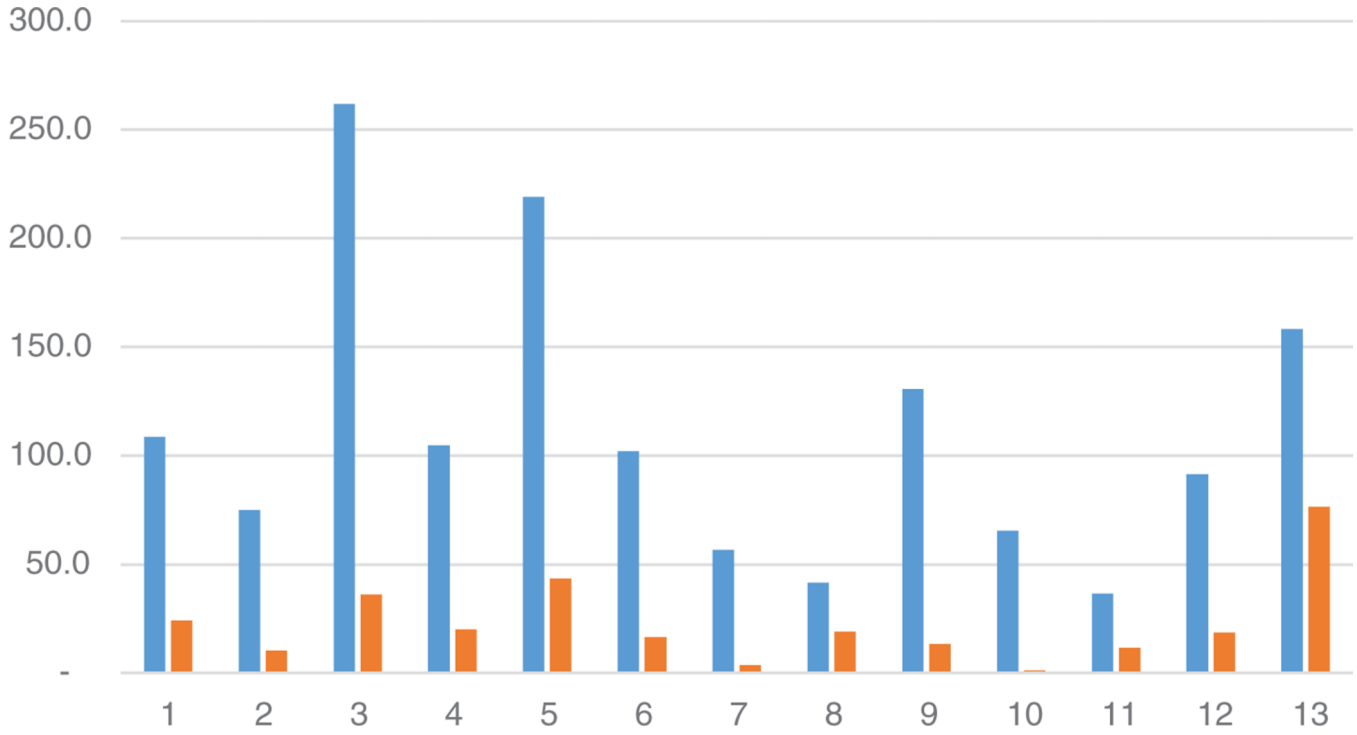

FIGURE 3.

Effect of allopurinol on alanine transaminase (ALT) among patients enrolled for hepatic toxicity: there was a significant increase in the percentage of time that patients were in goal ALT after patients started allopurinol

TABLE 1

Characteristics of each patient (total n = 13) summarized by age, sex, white blood cell count (WBC) at diagnosis, acute lymphoblastic leukemia (ALL) risk group, and indication for entering allopurinol study

Characteristics	Number of patients (% of patients)
Age at diagnosis	
Less than 10 years	8 (62)
More than 10 years	5 (38)
Immunophenotype	
B-ALL	10 (77)
T-ALL	3 (23)
Sex	
Male	9 (69)
Female	4 (31)
ALL risk group	
Average risk B-ALL	6 (46)
High-risk or very high risk B-ALL	4 (31)
Standard risk T-ALL	1 (8)
Intermediate risk T-ALL	2 (15)
Indication for initiation of allopurinol	
Hepatic toxicity	9 (69)
Inadequate myelosuppression	5 (38)
Gastrointestinal symptoms (eg, pancreatitis, persistent nausea, and vomiting)	4 (31)

Note. Some patients had multiple indications for entering the study.

TABLE 2

Mean differences in goal outcomes between postallopurinol and preallopurinol using paired *t*-tests with 95% confidence interval in parantheses (*P*-values and degrees of freedom are also given)

Outcome variables	Mean value preallopurinol	Mean value postallopurinol	Mean difference between postallopurinol and preallopurinol (95% confidence interval)	*P*-value
Percentage of weeks in goal ALT (<5× ULN) (all; n = 13)	73.1	90.2	17.2 (4.5, 29.8)	.012
Percentage of weeks in goal ALT (<5× ULN) (hepatotoxic cohort; n = 9)	66.1	88.0	22.0 (3.7, 40.2)	.024
Percentage of weeks in goal AST (all; n = 13)	95.1	98.3	3.3 (−0.2, 6.1)	.061
Percentage of weeks in goal AST (hepatotoxic cohort; n = 9)	92.9	98.3	5.4 (1.2, 9.6)	.018
Percentage of weeks in goal ANC (all; n = 13)	24.6	31.1	6.8 (−7.6, 21.1)	.325
Percentage of weeks in goal ANC (inadequate myelosuppression cohort; n = 5)	10.2	36.3	26.2 (19.4, 32.9)	.0004
Percentage of weeks neutropenic with ANC < 500 (all; n = 13)	3.4	6.5	−3.1 (−0.4, 6.7)	.081
Average 6MMP (all; n = 13)	810	055	−13 755 (−6582, −20 927)	.0013
Average 6TGN (all; n = 13)	251.4	801.8	+550.4 (766.2, 334.6)	.0001
Average ratio of 6MMP/6TGN (all; n = 13)	111.7	22.6	−89.1 (−55.0, −123.3)	.0001

TABLE 3

Odds ratios of outcomes comparing pre- and postallopurinol using mixed effects modeling

Outcome variables	Odds ratio (95% confidence interval)	*P*-value
Goal ALT (<5× ULN), all patients	6.1 (3.2, 11.4)	<.00001
Goal ALT (<5× ULN), hepatotoxic cohort	7.1 (3.3, 15.6)	<.00001
Goal AST (<5× ULN), all patients	3.3 (−0.2, 6.1)	.0613
Goal AST (<5× ULN), hepatotoxic cohort	4.4 (1.2, 15.4)	.021
Goal ANC (500–1500/μL), all patients	1.3 (0.7, 2.2)	.405
Goal ANC (500–1500/μL), inadequate myelosuppression cohort	2.9 (1.3, 6.5)	.01
Neutropenia (ANC < 500/μL), all patients	0.78 (0.39, 1.55)	.47

Note. Each model was adjusted for age at diagnosis, sex, WBC at diagnosis, and time in weeks; 95% confidence interval of odds ratios are provided in parentheses.