Original Article

Effect of Oral Allopurinol in Elevated Liver Enzyme Reduction in Pediatric Acute Lymphoblastic Leukemia During Maintenance Therapy

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Abstract

Background: Acute lymphoid leukemia (ALL) represents a prevalent form of cancer in pediatric populations. Mercaptopurine is one of the proposed treatments for these patients. This treatment may cause multiple side effects, including liver-related effects. Allopurinol has been proposed as a means to mitigate hepatotoxicity, but the previous studies in this regard remain scarce. This study aimed to investigate the effect of allopurinol on preventing increases in liver enzymes in children with ALL during the maintenance phase of drug treatment.

Materials and Methods: This is a double-blind clinical trial conducted on children with ALL receiving maintenance treatment with mercaptopurine during the maintenance phase of the disease. Patients were categorized into two groups. The initial cohort of 25 individuals was administered mercaptopurine tablets in combination with allopurinol tablets. The second group, comprising an equivalent number of patients, was administered mercaptopurine tablets and a placebo. Laboratory studies were evaluated. The patients' data were analyzed at the 0.05 significance level.

Results: The mean age in group A was 7.64 ± 3.78 years, while in group B it was 6.92 ± 3.19 years. In group A, the proportion of boys was 44%, whereas in group B, it was 72%. In both groups, the majority of patients tolerated less than 75 mg of mercaptopurine per body surface area, whereas, for methotrexate, most patients tolerated less than 20 mg per body surface area. Allopurinol significantly reduced mercaptopurine-induced hepatotoxicity in pediatric patients with ALL (P-value < 0.05). Allopurinol significantly reduced alanine transaminase (ALT) and aspartate aminotransferase (AST) levels compared to placebo (P-value<0.05). The intra-group analysis indicated that allopurinol significantly reduced enzyme levels over time (all P-values < 0.05).

Conclusion: Allopurinol reduces hepatotoxicity in ALL patients receiving mercaptopurine.

Keywords: Allopurinol, Mercaptopurine, Acute lymphoid leukemia, Pediatric

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Introduction

Acute lymphoblastic leukemia (ALL) is the predominant malignant condition in children and adolescents, with an annual incidence of roughly 3–4 cases per 100,000 individuals under 15 years of age. Multimodal chemotherapy is the cornerstone of contemporary treatment for ALL[1,2]. In consecutive randomized and prospective clinical trials, the prognosis of pediatric ALL has markedly improved. Presently, over 90% of all pediatric patients diagnosed with ALL achieve survival. Nonetheless, 15–20% of all patients ultimately experience a recurrence. Among these patients, 60–80% achieve complete remission (CR) with aggressive chemotherapy regimens[3-5].

Insufficient myelosuppression in patients on maintenance chemotherapy for ALL and juvenile lymphoma correlates with a heightened risk of relapse. Strategies to enhance myelosuppression during maintenance therapy have been documented. A first strategy involves augmenting the dosage of methotrexate (MTX) and 6-mercaptopurine (6-MP) to achieve the desired white blood cell count (WBC) or absolute neutrophil count (ANC) range[6-8]. 6-MP is a prodrug that is metabolized via multiple pathways, yielding both active and inactive metabolites. The6-MP or thiopurine methyltransferase (TPMT) intermediate can be methylated by TPMT, resulting in the formation of inactive 6-MMP, which is associated with hepatotoxicity[9].

Allopurinol, a xanthine oxidase inhibitor, is a urate-lowering medication used for the treatment of gout, the prevention of tumor lysis syndrome, and the prevention of calcium nephrolithiasis in individuals with hyperuricosuria[10]. Allopurinol alters6-MMP metabolism, reducing its methylation. Consequently, allopurinol has been administered concurrently with 6-MP in adults suffering fro6-MP-resistant inflammatory bowel disease. A uniform strategy has been proposed as the standard of care for all patients with acute hepatotoxicity. Nonetheless, the enduring efficacy of this method remains unverified[11-13]. This study aims to examine the impact of allopurinol on preventing increased liver enzyme levels in adolescents with acute lymphoblastic leukemia throughout the maintenance phase of pharmacotherapy.

Methods

This research was a double-blind clinical trial involving children diagnosed with ALL leukemia undergoing maintenance therapy with 6-MP at Loghman Hakim Hospital and Mofid Children's Hospital in 2024.

This study evaluated children aged 18 years and younger with ALL who were in the maintenance phase of ALL treatment. Exclusion criteria were severe myelosuppression following allopurinol administration (absolute neutrophil count <100 cells/m3)[14], a history of severe hypersensitivity to allopurinol, and a history of any underlying liver disease unrelated to the primary disease or chemotherapy agents.

Sample size was calculated based on the study by Topley et al. on hepatotoxicity rates in children with leukemia during the maintenance phase. So, with a 10% dropout rate, the sample size was calculated to be 25 individuals per group[15].

At the onset of the study, liver enzyme levels, including total and direct bilirubin, alanine transaminase (ALT), aspartate aminotransferase (AST), and a complete blood count (CBC), were assessed in all patients. The biomarkers were monitored biweekly during the initial month and subsequently monthly for 6 months. The patients were categorized into two groups. The control group (group A) included 25 patients who received mercaptopurine tablets according to the standard treatment protocol, based on their previous standard dosage and patient tolerance, targeting an absolute neutrophil count between 500 and 1500, along with a placebo. The intervention group (group B) comprised 25 patients who were administered mercaptopurine tablets following the established treatment protocol, which was based on their previous standard dosage and patient tolerance, targeting an absolute neutrophil count between 500 and 1500, along with allopurinol tablets at a dosage of 4 mg/kg/day or 100 mg daily for children weighing less than 30 kg. In cases where the absolute neutrophil count during childhood dropped below 500 without an identifiable cause, such as infection or inflammation, the administration of drug A or B was halted[14].

Allopurinol and placebo were prepared by Hakim Pharmaceutical Company in collaboration with the center's pharmacologist, coded as drug A or B. The drugs were packaged in identical cans at the pharmaceutical company and subsequently delivered to the researcher. Randomization was sequential and not truly random, with patients receiving treatment one after another. The treatment regimen did not influence the selection of drug A or B for the patient. During statistical analysis, a clinical pharmacology colleague decoded A and B, facilitating a comparison of the variables of interest between the two drug and placebo groups. No alterations were observed in the dosage of methotrexate (mg/m²) across any of the groups.

Patients underwent a 6-month follow-up period. The increase in liver enzymes was assessed using CTCAE grades in both groups. Additionally, a complete blood count was performed biweekly during the first month and subsequently monthly to evaluate neutropenia and myelosuppression, including anemia and thrombocytopenia. After six months, a comparison was conducted between the two groups. In the study, patients requiring a reduction in mercaptopurine dosage or discontinuation of treatment were identified based on the underlying causes, specifically hepatotoxicity or myelosuppression. The mercaptopurine dosage was adjusted to maintain the antileukemic effect by keeping the absolute neutrophil count within the range of 500 to 1500 cells per microliter, with the rationale for the dosage modification and its specific amount documented.

The assessment standards for mercaptopurine-induced hepatotoxicity were derived from the CTCAE table. The extent of liver damage was reported based on the frequency distribution of grades in both study arms. Grade 1 (mild) liver damage is characterized by an elevation of liver enzyme levels up to three times the normal range. Grade 2 liver damage, classified as mild to moderate, is characterized by liver enzyme levels elevated 3 to 5 times above normal. Grade 3 liver damage is characterized by elevated liver enzyme levels 5 to 20 times the upper limit of normal. Grade 4 liver damage is characterized by liver enzyme levels exceeding normal values by more than 20 time[16].

The criterion for early discontinuation of the study was the observation of severe adverse side effects in the intervention group.

Statistical analysis: Qualitative variables were presented as both raw and relative frequencies. Quantitative outcome variables were transformed into ordinal qualitative variables. The Mann-Whitney test compared the intervention and placebo groups. All analyses were conducted using SPSS 26.0. Statistical significance was defined as a p-value < 0.05.

Ethics committee approval was obtained by the Clinical Research Ethics Committee of Shahid Beheshti Medical University (IR.SBMU.MSP.REC.1401.261)

Results

This study assigned 25 patients to group A, receiving mercaptopurine and a placebo, and 25 patients to group B, receiving mercaptopurine and allopurinol. Table 1 presents the demographic, laboratory, and drug information of the patients categorized by group. The mean age in group A was 7.64±3.78 years, while in group B it was 6.92±3.19 years. In both groups, the majority of patients received less than 75 mg/m² of mercaptopurine. In comparison, most patients in both groups received less than 20 mg/m2 of methotrexate.

Table 2 presents the laboratory data following the initiation of treatment. The levels of liver enzymes showed significant differences between the two groups one month post-treatment initiation, and this disparity in ALT and AST levels persisted in subsequent months. Our findings indicate that allopurinol did not significantly alter the absolute neutrophil count during treatment (p-value: 0.191); however, AST and ALT levels decreased significantly during treatment (p-values <0.05). No significant changes were observed in any of these parameters during treatment in group B receiving allopurinol (all p-values > 0.05).

Discussion

This clinical trial showed that allopurinol can reduce mercaptopurine-induced hepatotoxicity in pediatric patients undergoing maintenance treatment for ALL. We found that allopurinol had no significant effect on ANC in these patients, but significantly reduced AST and ALT.

Table 1: Demographic, laboratory and drug information of patients by group.

		Type of drug	
		Mercaptopurine and placebo	Mercaptopurine and allopurinol
Age	mean	7.64	6.92
	Standad deviation	3.78	3.16
	median	7.00	6.00
	min	2.00	2.00
	max	17.00	15.00
Gender	Girl	14(56%)	7(28%)
	Boy	11(44%)	18(72%)
Amount of mercaptopurine	Full dose of 75 mg per body surface area	3(12%)	5(20%)
	Less than 75 ml per body surface area	22(88%)	19(76%)
	More than 75 ml per body surface area	0(0%)	1(4%)
Methotrexate dosage	Full dose of 20 mg per body surface area	7(28%)	10(40%)
	Less than 20 ml per body surface area	17(68%)	14(56%)
	More than 20 ml per body surface area	1(4%)	1(4%)
Absolute neutrophil count at baseline (before starting medication)	1500/ml ≤	13(52%)	16(64%)
	1000-1500/ml	7(28%)	2(8%)
	500-1000/ml	4(16%)	6(24%)
	≤ 500/ml	1(4%)	1(4%)
History of elevated liver enzymes before starting the drug	Yes	14(56%)	9(36%)
	No	11(44%)	16(64%)
Initial ALT level before starting medication	Normal	10(40%)	10(40%)
	Normal to 2.5 times greater	11(44%)	10(40%)
	2.5-5 times greater more than normal level	3(12%)	4(16%)
	5-20 times greater more than normal level	1(4%)	1(4%)
	more than 20 times greater more than normal level	0(0%)	0(0%)
Initial AST level before starting medication	Normal	14(56%)	13(52%)
	Normal to 2.5 times greater	10(40%)	10(40%)
	2.5-5 times greater more than normal level	1(4%)	1(4%)
	5-20 times greater more than the normal level	0(0%)	0(0%)
	more than 20 times greater more than normal level	0(0%)	1(4%)

Mercaptopurine (6-MP) has received approval from the Food and Drug Administration (FDA) for the treatment of acute lymphoblastic leukemia in both children and adults, used as part of combination therapy[17,18]. Patients may encounter adverse events during mercaptopurine treatment, which can be either dose-independent or dose-related. Allergic reactions, including nausea, fever, rash, flu-like symptoms, and arthralgia, are classified as non-dose-related symptoms that may necessitate changing the timing of administration to nighttime or discontinuing treatment. Adverse events associated with mercaptopurine may be dose-related and include jaundice, pancreatitis (3.3%), cytostatic suppression (2–15%), increased transaminases (30%), drug-induced hepatitis (0.3%), hepatotoxicity, veno-occlusive disease, leukopenia, and hepatic T-cell lymphoma[19, 20].

Table 2: Comparison of laboratory data after the start of treatment in the two groups.

	Type of drug			p-value
	Mercaptopurine and placebo	Mercaptopurine and allopurinol		
Pancytopenia after starting the drug	Yes	2(8%)	6(24%)	
	No	23(92%)	19(76%)	
Discontinuation of chemotherapy due to pancytopenia	Yes	2(8%)	6(24%)	
	No	23(92%)	19(76%)	
Absolute neutrophil count at baseline (before starting medication)	1500/ml ≤	13(52%)	16(64%)	0.68
	1000-1500/ml	7(28%)	2(8%)	
	500-1000/ml	4(16%)	6(24%)	
	≤ 500/ml	1(4%)	1(4%)	
Absolute neutrophil count two weeks after starting the drug	1500/ml ≤	18(72%)	13(52%)	0.18
	1000-1500/ml	3(12%)	7(28%)	
	500-1000/ml	3(12%)	2(8%)	
	≤ 500/ml	1(4%)	3(12%)	
Absolute neutrophil count one month after starting the drug	1500/ml ≤	18(72%)	8(32%)	0.02
	1000-1500/ml	3(12%)	11(44%)	
	500-1000/ml	4(16%)	5(20%)	
	≤ 500/ml	0(0%)	1(4%)	
Absolute neutrophil count two months after starting the drug	1500/ml ≤	19(76%)	17(68%)	0.54
	1000-1500/ml	3(12%)	4(16%)	
	500-1000/ml	3(12%)	4(16%)	
	≤ 500/ml	0(0%)	0(0%)	
Absolute neutrophil count three months after starting the drug	1500/ml ≤	16(64%)	13(52%)	0.26
	1000-1500/ml	8(32%)	8(32%)	
	500-1000/ml	1(4%)	2(8%)	
	≤ 500/ml	0(0%)	2(8%)	
Absolute neutrophil count four months after starting the drug	1500/ml ≤	20(80%)	16(64%)	0.11
	1000-1500/ml	5(20%)	3(12%)	
	500-1000/ml	0(0%)	6(24%)	
	≤ 500/ml	0(0%)	0(0%)	
Absolute neutrophil count five months after starting the drug	1500/ml ≤	19(76%)	14(56%)	0.12
	1000-1500/ml	5(20%)	8(32%)	
	500-1000/ml	1(4%)	3(12%)	
	≤ 500/ml	0(0%)	0(0%)	

Absolute neutrophil count six months after starting the drug	1500/ml ≤	19(76%)	14(56%)	0.12
	1000-1500/ml	5(20%)	8(32%)	
	500-1000/ml	1(4%)	3(12%)	
	≤ 500/ml	0(0%)	0(0%)	
Initial ALT level before starting medication	Normal	10(0%)	10(40%)	0.88
	Normal to 2.5 times greater	11(44%)	10(40%)	
	2.5-5 times greater more than normal level	3(12%)	4(16%)	
	5-20 times greater more than normal level	1(4%)	1(4%)	
	more than 20 times greater more than normal level	0(0%)	0(0%)	
ALT levels two weeks after starting the drug	Normal	10(40%)	13(52%)	0.3
	Normal to 2.5 times greater	11(44%)	10(40%)	
	2.5-5 times greater more than normal level	2(8%)	2(8%)	
	5-20 times greater more than normal level	2(8%)	0(0%)	
	more than 20 times greater more than normal level	0(0%)	0(0%)	
ALT level one month after starting the drug	Normal	5(20%)	17(68%)	0.000
	Normal to 2.5 times greater	13(52%)	7(28%)	
	2.5-5 times greater more than normal level	6(24%)	1(4%)	
	5-20 times greater more than normal level	1(4%)	0(0%)	
	more than 20 times greater more than normal level	0(0%)	0(0%)	
ALT levels two months after starting the drug	Normal	6(24%)	17(68%)	0.001
	Normal to 2.5 times greater	11(44%)	7(28%)	
	2.5-5 times greater more than normal level	6(24%)	0(0%)	
	5-20 times greater more than normal level	2(8%)	1(4%)	
	more than 20 times greater more than normal level	0(0%)	0(0%)	
ALT levels three months after starting the drug	Normal	7(28%)	21(84%)	<0.001
	Normal to 2.5 times greater	12(48%)	4(16%)	
	2.5-5 times greater more than normal level	6(24%)	0(0%)	
	5-20 times greater more than normal level	0(0%)	0(0%)	
	more than 20 times greater more than normal level	0(0%)	0(0%)	
ALT levels four months after starting the drug	Normal	6(24%)	23(92%)	<0.001
	Normal to 2.5 times greater	11(44%)	1(4%)	
	2.5-5 times greater more than normal level	8(32%)	1(4%)	
	5-20 times greater more than normal level	0(0%)	0(0%)	
	more than 20 times greater more than normal level	0(0%)	0(0%)	
ALT levels five months after starting the drug	Normal	7(28%)	22(88%)	<0.001
	Normal to 2.5 times greater	10(40%)	2(8%)	
	2.5-5 times greater more than normal level	8(32%)	1(4%)	

	5-20 times greater more than normal level	0(0%)	0(0%)	
	more than 20 times greater more than normal level	0(0%)	0(0%)	
ALT levels six months after starting the drug	Normal	7(28%)	22(88%)	<0.001
	Normal to 2.5 times greater	10(40%)	2(8%)	
	2.5-5 times greater more than normal level	8(32%)	1(4%)	
	5-20 times greater more than normal level	0(0%)	0(0%)	
	more than 20 times greater more than normal level	0(0%)	0(0%)	
Initial AST level before starting medication	Normal	14(56%)	13(52%)	0.69
	Normal to 2.5 times greater	10(40%)	10(40%)	
	2.5-5 times greater more than normal level	1(4%)	1(4%)	
	5-20 times greater more than normal level	0(0%)	0(0%)	
	more than 20 times greater more than normal level	0(0%)	1(4%)	
AST levels two weeks after starting the drug	Normal	15(60%)	18(72%)	0.41
	Normal to 2.5 times greater	9(36%)	6(24%)	
	2.5-5 times greater more than normal level	1(4%)	0(0%)	
	5-20 times greater more than normal level	0(0%)	1(4%)	
	more than 20 times greater more than normal level	0(0%)	0(0%)	
AST level one month after starting the drug	Normal	9(36%)	22(88%)	<0.001
	Normal to 2.5 times greater	12(48%)	3(12%)	
	2.5-5 times greater more than normal level	3(12%)	0(0%)	
	5-20 times greater more than normal level	1(4%)	0(0%)	
	more than 20 times greater more than normal level	0(0%)	0(0%)	
AST levels two months after starting the drug	Normal	7(28%)	20(80%)	<0.001
	Normal to 2.5 times greater	16(64%)	4(16%)	
	2.5-5 times greater more than normal level	1(4%)	1(4%)	
	5-20 times greater more than normal level	1(4%)	0(0%)	
	more than 20 times greater more than normal level	0(0%)	0(0%)	
AST levels three months after starting the drug	Normal	8(32%)	25(100%)	<0.001
	Normal to 2.5 times greater	15(60%)	0(0%)	
	2.5-5 times greater more than normal level	2(8%)	0(0%)	
	5-20 times greater more than normal level	0(0%)	0(0%)	
	more than 20 times greater more than normal level	0(0%)	0(0%)	
AST levels four months after starting the drug	Normal	11(44%)	24(96%)	<0.001
	Normal to 2.5 times greater	12(48%)	1(4%)	
	2.5-5 times greater more than normal level	1(4%)	0(0%)	
	5-20 times greater more than normal level	1(4%)	0(0%)	
	more than 20 times greater more than normal level	0(0%)	0(0%)	

AST levels five months after starting the drug	Normal	8(32%)	22(88%)	<0.001
	Normal to 2.5 times greater	12(48%)	2(8%)	
	2.5-5 times greater more than normal level	5(20%)	1(4%)	
	5-20 times greater more than normal level	0(0%)	0(0%)	
	more than 20 times greater more than normal level	0(0%)	0(0%)	
AST levels six months after starting the drug	Normal	8(32%)	22(88%)	<0.001
	Normal to 2.5 times greater	12(48%)	2(8%)	
	2.5-5 times greater more than normal level	5(20%)	1(4%)	
	5-20 times greater more than normal level	0(0%)	0(0%)	
	more than 20 times greater more than normal level	0(0%)	0(0%)	

Acute and chronic hepatotoxicity induced by mercaptopurine manifests in various forms. Acute liver injury typically presents as elevated liver enzymes, accompanied by fatigue and jaundice, occurring within one to six months of initiating treatment. The liver biopsy reveals a combination of hepatocellular and cholestatic injury characterized by cholestasis, focal hepatocellular necrosis, bile duct injury, and varying degrees of inflammation[19,20]. Allopurinol, a xanthine oxidase inhibitor, has been proposed in prior studies to mitigate mercaptopurine hepatotoxicity[21]. It is important to note that the majority of studies investigating the impact of allopurinol on mercaptopurine toxicity have focused on patients with inflammatory bowel disease, with limited evaluation in pediatric acute lymphoblastic leukemia[21-23].

This study demonstrates that allopurinol effectively mitigates the hepatotoxic effects of mercaptopurine in pediatric patients undergoing treatment for ALL. The research conducted by Kamojjala and Bostrom assessed the efficacy of allopurinol in mitigating the adverse effects of mercaptopurine in pediatric and adult patients diagnosed with ALL. Twenty-five patients with ALL undergoing maintenance therapy alongside allopurinol were examined. All participants experienced significant side effects from elevated 6MMP levels, including abdominal pain, nausea, vomiting, reduced appetite, hypoglycemia, fatigue, and hepatotoxicity. Furthermore, a considerable number exhibited facial rash. All patients experienced symptom resolution within a few weeks of initiating allopurinol treatment. No decrease was observed in absolute neutrophil count or hemoglobin levels. Platelet levels declined slightly, without necessitating any modification in treatment. Bilirubin levels returned to normal, and alanine aminotransferase significantly decreased to within normal ranges. All patients maintained allopurinol throughout the treatment period. The study concluded that allopurinol, in combination with a reduced dose of 6-MP, effectively mitigated side effects associated with 6-MP in ALL patients receiving maintenance chemotherapy [24]. Our study demonstrated that the addition of allopurinol to mercaptopurine therapy resulted in a significant reduction of liver enzymes.

Furthermore, allopurinol was more effective than placebo, resulting in a notable decrease in liver enzyme levels over time. Our study found that ANC did not exhibit a statistically significant reduction, either overall or over time. The findings of this study align with those reported by Kamojjala and Bostrom.

Vasta et al. reported that over 75% of patients with ALL or lymphoblastic lymphoma experienced toxicity related to 6-MP. Allopurinol was commenced in 12 out of 23 patients exhibiting overt toxicity. Allopurinol has been demonstrated to mitigate MP6-related toxicity[25]. The results of Vasta et al. align with the current study, confirming that allopurinol mitigates 6-MP hepatotoxicity.

Cohen et al. assessed the impact of 6-MP maintenance therapy in pediatric ALL. All thirteen patients received

allopurinol: nine due to hepatotoxicity, five for inadequate myelosuppression, and three for nonhepatic gastrointestinal toxicity. Allopurinol demonstrated good tolerability, with no notable adverse events reported. Patients with hepatotoxicity showed a notable decrease in transaminase levels after allopurinol initiation, with ALT decreasing by a mean of 22.1%. Conversely, individuals with insufficient myelosuppression demonstrated a significant rise in ANC, with a mean increase of 26.4%. The study concluded that allopurinol is a safe, feasible, and effective intervention during maintenance chemotherapy for ALL in patients with altered 6MP metabolism, which leads to toxicity or inadequate myelosuppression[26]. The present study offers advantages over the research conducted by Cohen et al., as it was a placebo-controlled clinical trial and involved a larger patient population. Our study demonstrated a reduction in hepatotoxicity following allopurinol administration in patients receiving mercaptopril treatment. Our study found no significant change in ANC overall, in contrast to the findings of Cohen et al. Consistent with the findings of Cohen et al., our study demonstrated that allopurinol, when combined with maintenance therapy for ALL, can mitigate hepatotoxicity in these patients.

Conclusion

Allopurinol significantly reduces AST and ALT in pediatric patients with ALL undergoing mercaptopurine treatment. The administration of this drug does not alter patient treatment; however, by mitigating liver toxicity, it prevents treatment discontinuation resulting from liver damage in these patients. Allopurinol may be prescribed to patients undergoing treatment who exhibit a significant elevation in liver enzymes.

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Conflict of interest

The authors further declare that they have no conflict of interest.

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