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Original Research Article

Evaluation of less treatment interruption of 6-Mercaptopurine by co-administration of ursodeoxycholic acid with chemotherapy in pediatric acute lymphoblastic leukemia

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ABSTRACT

Background: Ursodeoxycholic acid (UDCA), a bile acid, protects the liver through various mechanisms, including bile composition modulation and enhanced secretion. In ALL chemotherapy, 6MP is hepatotoxic, requiring dose reduction. UDCA is used to alleviate liver toxicity in ALL and other chronic cholestatic conditions. The study aims to evaluate the effectiveness of UDCA with chemotherapy in reducing 6MP treatment interruptions and its impact on treatment continuity in pediatric ALL.
Methods: This randomized controlled trial study conducted at the Department of Pediatric Hematology and Oncology, BSMMU in pediatric ALL patients during chemotherapy from September 2018 to August 2019. Fifty children aged 1 to 18 years with ALL were enrolled, half receiving UDCA alongside chemotherapy and the rest forming the control group. Serum hepatic transaminases, total bilirubin, and CBC were monitored every 14 days. Statistical analysis was performed using SPSS, with significance set at $p<0.05$.
Results: In this study of 50 pediatric ALL patients, there were no statistically significant age or gender differences between the "Case" (UDCA-treated) and "Control" groups. However, the UDCA group showed a significant decrease in abnormal liver function tests (32.0%) compared to controls (60.0%). Moreover, 6MP dose reduction was significantly lower in cases (4.0%) than controls (40.0%), indicating UDCA's potential hepatoprotective effects. Multivariate logistic regression revealed male gender and mean AST levels as significant factors associated with hepatotoxicity in pediatric ALL patients.
Conclusions: Co-administration of UDCA with chemotherapy demonstrates a significant effect in treatment interruption by hepatotoxic drug specially 6 MP in pediatric ALL patients.

Keywords: Ursodeoxycholic acid, Chemotherapy, Pediatric hematology and oncology

INTRODUCTION

Ursodeoxycholic acid (UDCA) is a dihydroxy (3a, 7bdihydroxy-5bcholan-24-oic acid) bile acid, which constitutes 4% of the total bile acid pool. Experimental evidence suggests three major mechanisms of action: protection of cholangiocytes against cytotoxicity of hydrophobic bile acids, resulting from modulation of the

composition of mixed phospholipid-rich micelles, reduction of bile acid cytotoxicity of bile and, possibly, decrease of the concentration of hydrophobic bile acids in the cholangiocytes; stimulation of hepatobiliary secretion, putatively via Ca2+ and protein kinase C-α-dependent mechanisms and/or activation of p38 and extracellular signal-regulated kinases (Erk) resulting in the insertion of transporter molecules (e.g., bile salt export pump and conjugate export pump) into the canalicular membrane of the hepatocyte and, possibly, activation of inserted carriers. UDCA also improves defective natural killer cell activity by inhibiting prostaglandin E2 synthesis and reducing peripheral eosinophilia.[1]

6-Mercaptopurine (6MP) in an orally daily regimen associated with weekly MTX is the backbone of maintenance chemotherapy for acute lymphoblastic leukemia (ALL). Hepatotoxicity produced by this drug includes both cholestatic and hepatocellular disease. Characteristic diagnostic profiles include prominently elevated serum bilirubin, typically between 3 and 7 mg/dl, accompanied by mild to moderate elevations in aminotransferases and alkaline phosphatase.[2,3] Due to its beneficial effects on the liver, UDCA is widely used in chronic cholestatic diseases such as primary biliary cirrhosis, primary sclerosing cholangitis, and drug-induced cholestasis; sometimes in non-cholestatic syndromes such as nonalcoholic steatohepatitis, alcoholic steatohepatitis, graft versus host disease and also sometimes in autoimmune hepatitis. To reduce hepatoxicity, measures are taken, such as reduction of drug dose, and holding the chemotherapeutic drug. Though these are the accepted measures to reduce drug toxicity these can increase the chance of relapse rate. To combat this challenge some hepatoprotective agents like ursodeoxycholic acid can play an important role.

Multi-agent systemic chemotherapy over a prolonged duration with antibiotics and blood product support was responsible for early improvements.[2] However, many of the chemotherapeutic agents used in the treatment of acute lymphoblastic leukemia are known to be hepatotoxic.[3] The spectrum of hepatotoxic effects is wide, including elevated liver function hepatocellular fibrosis.[4,5] Mercaptopurine may cause jaundice and ascites, L-Asperginase may produce toxic hepatitis with the fatty change, prednisolone may cause hepatomegaly with fatty infiltration and MTX may cause portal fibrosis. Continuous low dose oral MTX is said to cause more hepatic damage than the intermittent higher dose.[4] It has been found that 66.5% of children with ALL encountered higher liver toxicity at some point during their therapy.[6]

Objectives

The study aims to evaluate the effectiveness of UDCA with chemotherapy in reducing 6MP treatment interruptions and its impact on treatment continuity in pediatric ALL.

METHODS

This randomized controlled trial study was conducted at the department of pediatric hematology and oncology, BSMMU, spanning from September 2018 to August 2019. The focus of the research involved patients aged 1 to 18 years diagnosed with Acute Lymphoblastic Leukemia, specifically from the consolidation phase of therapy through the conclusion of the interim maintenance phase.

Sample size determination

Exact data on the hepatoprotective role of UDCA during chemotherapy among pediatric ALL in Bangladesh was not known but a study that was done earlier in abroad, it showed that after 6 months of UDCA therapy in case group average ALT was 30U/L with SD (standard deviation)13 and average ALT in the control group was 85U/L with SD (standard deviation) 977. So it was calculated using the following formula

$$n = \frac{(u + v)^2(\sigma_1{}^2 + \sigma_0{}^2)}{(\mu_{1-\mu_0})^2}$$

Where; n=Sample Size, u=1.96(fixed value), v=0.85(fixed value), u1 and u0 were the assumed population means for power and sample size calculations, $\mu_1 - \mu_0$was the difference between population means at which power and sample size calculations are made (μ_1=85, μ_0=30), σ_1 and σ_0 are the assumed population standard deviations for groups 1 and 2 respectively (σ_0=13, σ_1=97). Thus, Group sample sizes of 25 in each group and total sample size was 50.

Inclusion and exclusion criteria

The study's inclusion criteria encompassed individuals aged 1 to 18 years undergoing treatment for Acute Lymphoblastic Leukemia specifically from the Consolidation phase to the period preceding the initiation of the maintenance phase of chemotherapy. Conversely, exclusion criteria comprised children with ALL below 1 year and above 18 years, those with a history or evidence of medical conditions linked to chronic liver disease, and those with a previous history of ursodeoxycholic acid treatment.

Procedure

Newly diagnosed children with ALL aged 1 year to 18 years after successful completion of induction chemotherapy who got consolidation and interim maintenance phase of chemotherapy in the Department of Pediatric Hematology and Oncology, BSMMU were enrolled in this study. Informed written consent from the parent or guardian was obtained at the time of study enrollment. Data were collected using a preformed data collection sheet (questionnaire). Demographic data

regarding age, sex, socio-economic status, and family history of malignancy were collected from guardians or parents and medical records. Medical data regarding an initial presentation at diagnosis, risk stratification, type of treatment protocol, treatment starting date, and complications during treatment were compiled. Clinical information about pallor, temperature, pulse, blood pressure, respiratory rate, and other general and systemic clinical parameters were taken. Chemotherapy was given to all patients with acute lymphoblastic leukemia according to the UK ALL 2003 protocol after stratifying risk. Regimen-A was given to the standard risk group and Regimen-B was specified for the high-risk group.

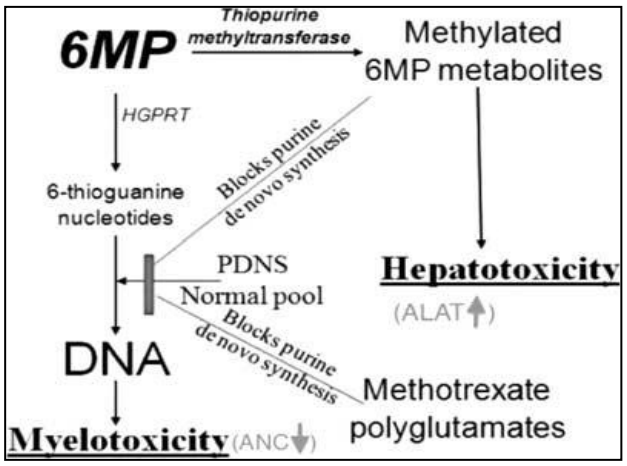

Figure 1: Mercaptopurine and MTX-induced hepatotoxicity.

The consolidation phase is the second phase which comprises 21 days for regimen A and 35 days for regimen B, and interim maintenance comprises 56 days. In the case of regimen, A, the chemotherapeutic agent used in this phase includes mercaptopurine (60 mg/m2/day) inj. cyclophosphamide (1000 mg/m2) inj. cytarabine (75 mg/m2/day), inj. vincristine (1.5 mg/m2), tab dexamethasone (10 mg/m2), IT or TIT methotrexate. However, in regimen B, another drug adriamycin (25 mg/m2) was given additionally. General supportive management like oral care, anal care, etc. were administered in all patients including oral cotrimoxazole during the whole study period along with chemotherapy. Parents or legal guardians of subjects who met the above-mentioned criteria were asked to sign an informed consent before conducting the study.

After recruitment, subjects were randomly divided into two groups according to the UDCA therapy as follows: UDCA Group: Patients who received UDCA concomitantly with chemotherapy for 77 days in regimen A and 91 days in regimen B, discontinued UDCA after this period. UDCA was given orally at a dose of 15 mg/kg/day in two divided doses with meals. Control Group: Patients who received chemotherapy without UDCA and were followed up for 77 days in regimen A and 91 days in regimen B. Studied children were tested every 14 days interval for serum hepatic transaminases - alanine transaminase (ALT) and aspartate transaminase (AST), total bilirubin (TB), and complete blood count (CBC) during the study period.

Patients who showed abnormal transaminases (ALT) level >3 times of upper normal limit (UNL) and AST level >3 times UNL and Total Bilirubin level >1.5 times of UNL according to common terminology criteria for Adverse Events (CTCAE) Version 5.0 throughout the study period were further evaluated. All patients were monitored for documented chemotherapy-related toxicities, particularly hepatotoxicity. All data were recorded systematically in the preformed data collection form. Statistical analyses were performed by using SPSS for Windows version 22.0, $p<0.05$ and a confidence interval set at 95% level were considered statistically significant.

RESULTS

Table 1 presents the distribution of study patients (n=50) categorized by age into three groups: 1-5 years, 6-10 years, and >10 years. Each age group is further divided into "Case" and "Control" with corresponding percentages. The p values are not provided for age groups, indicating perhaps that statistical significance was not observed. The (Table 1) also includes the total number of cases and controls, mean age with standard deviation, and age range for both groups. The mean ages for cases (4.80±2.25 years) and controls (5.90±3.13 years) show a numerical difference, but the p value (0.157) suggests that this difference is not statistically significant. The age range for cases is 1.17 to 11.0 years, and for controls, it is 2.10 to 14.0 years.

Table 1: Distribution of the study patients by age (n=50).

Age group (years)	Case, N (%)	Control, N (%)	P value
1-5	17 (68.0)	13 (52.0)	0.157
6-10	7 (28.0)	9 (36.0)	
>10	1 (4.0)	3 (12.0)	
Total	25 (100.0)	25 (100.0)	
Mean±SD	4.80±2.25	5.90±3.13	
Range	1.17-11.0	2.10-14.0	

Table 2 displays the distribution of study subjects (n=50) based on their sex, categorized into "Case" and "Control" groups. The number and percentage of males and females are provided for both groups, along with the total count. The p value of 0.077 indicates that the difference in the distribution of males and females between cases and controls is not statistically significant. The last row presents the male-to-female ratio, showing that in the case group, the ratio is 3.2:1, while in the control group, it is 1.1:1. The (Table 3) presents the comparison of altered liver function test results between the "Case" and "Control" groups, each consisting of 25 subjects. The

numbers and percentages of subjects with and without altered liver function tests are provided for both groups. The p value of 0.040s indicates a statistically significant difference in the prevalence of altered liver function tests between the two groups. Specifically, 32.0% of cases have altered liver function tests compared to 60.0% of controls. The majority of cases (68.0%) and a minority of controls (40.0%) do not exhibit altered liver function.

Table 2: Distribution of the study subjects by sex (n=50).

Sex	Case, N (%)	Control, N (%)	P value
Male	19 (76.0)	13 (52.0)	0.077
Female	6 (24.0)	12 (48.0)	
Total	25 (100.0)	25 (100.0)	
Male:Female ratio	3.2:1	1.1:1	

Table 3: Altered liver function test in both groups (n=50).

Altered liver function test	Case, N (%)	Control, N (%)	P value
Yes	8 (32.0)	15 (60.0)	0.040
No	17 (68.0)	10 (40.0)	
Total	25 (100.0)	25 (100.0)	

Table 4 presents the frequency of 6MP (6-mercaptopurine) dose reduction among the study participants, divided into "Case" and "Control" groups, each comprising 25 subjects. The (Table 4) reveals that 4.0% of cases experienced a dose reduction in contrast to 40.0% of controls, with a statistically significant p value of 0.002. Additionally, the duration of dose reduction is analyzed, showing that among cases, the reduction lasted for more than 15 days for the single subject affected, while in the control group, 60.0% had a reduction lasting less than 15 days and 40.0% for more than 15 days. However, the p value for this duration comparison is not statistically significant (0.251). The (Table 5) illustrates the distribution of adverse events among two groups, "Case" and "Control," each comprising 25 subjects. The adverse events include vomiting, diarrhea, abdominal pain, dyspepsia, and esophagitis. The (Table 5) shows that 8.0% of cases experienced vomiting compared to none in the control group, although the p value of 0.153 suggests that this difference is not statistically significant. Both groups had an equal incidence of diarrhea (8.0%), resulting in a p value of 1.000. The (Table 6) presents the results of a multivariate logistic regression analysis investigating the association of hepatotoxicity with various risk factors in children with Acute Lymphoblastic Leukemia. The (Table 6) includes variables such as age, sex (male), regimen, treatment interruption, mean ALT, mean AST, and mean bilirubin.

Table 4: Frequency of 6MP dose reduction in case and control group (n=50).

Parameters	Case, N (%)	Control, N (%)	P value
6MP dose reduction			
Yes	1 (4.0)	10 (40.0)	0.002
No	24 (96.0)	15 (60.0)	
Total	25 (100.0)	25 (100.0)	
Duration (days)	(N=1)	(N=10)	0.251
<15	0 (0.0)	6 (60.0)	
>15	1 (100.0)	4 (40.0)	

Table 5: Distribution of adverse events in two groups (n=50).

Adverse events	Case, N (%)	Control, N (%)	P value
Vomiting	2 (8.0)	0 (0.0)	0.153
Diarrhea	2 (8.0)	2 (8.0)	1.000
Abdominal pain	0 (0.0)	0 (0.0)	-
Dyspepsia	0 (0.0)	0 (0.0)	-
Esophagitis	0 (0.0)	0 (0.0)	-

The β values represent the regression coefficients, and the p values indicate the statistical significance of each variable. Odds Ratios (OR) are provided along with their corresponding 95% confidence intervals (CI), offering insights into the strength and direction of the associations. Notably, the male gender (p=0.048) and mean AST (p=0.037) show statistically significant associations with hepatotoxicity, with OR values of 4.965 and 1.078, respectively.

Table 6: Multivariate logistic regression analysis for the association of hepatotoxicity with risk factors in children with ALL.

Variables	β	P value	OR	95% CI for OR	
				Lower	Upper
Age (years)	0.197	0.167	1.218	0.921	1.611
Sex (male)	1.602	0.048	4.965	1.016	24.272
Regimen	0.407	0.632	1.502	0.284	7.933
Treatment interruption (yes)	1.083	0.227	2.953	0.510	17.086
Mean ALT	-0.003	0.853	0.997	0.967	1.028
Mean AST	0.075	0.037	1.078	1.005	1.157
Mean bilirubin	1.867	0.508	6.467	0.026	1617.922

DISCUSSION

This study was done to evaluate the role of UDCA in treatment interruption of hepatotoxic drug, especially 6MP. when given along with chemotherapy in the consolidation and interim maintenance phase of chemotherapy after successful completion of induction of remission in 50 patients with ALL aged between 1 to 18 years, among them 25 patients were in case group and 25 were in control group. Most patients were in the age group of 1-5 years (68% in the case and 52% in the control group) in this study found the highest incidence of ALL in children aged 1-4 years.[8] In this study, there was a male predominance with a male 76% in the case and 52% in the control group. Male predominance in acute lymphoblastic leukemia was also found in previously reported studies Sixty-five percent male in his study, as well as another study found incidence rates were higher in males.[8,9]

The beneficial action of UDCA may be related to its cytoprotective, antiapoptotic, membrane-stabilizing, antioxidative, and immunomodulatory effects.[10] In a study reported that 24.0% of patients of ALL needed 6MP drug interruption for up to one week, and 68.0% of patients had to discontinue 6MP for more than one week.[11] This finding was consistent with our study findings. In this study, 6MP drug interruption (dose modification) was done in 4% (1 patient out of 25) patients in the case group and 40% (10 patients out of 25) patients in the control group which was statistically significant (p=0.002). It signifies that UDCA has a significant hepatoprotective role against chemotherapeutics drugs especially 6MP. In a study reported that females are more vulnerable than men to the toxic effects of drugs in the liver but this finding was not consistent with our study finding. In this study, male sex had a significant association with raised mean AST, and age, regimen and treatment interruption had no significant association with hepatotoxicity.[12] In this study, two patients developed vomiting in the UDCA group and two patients in each group developed diarrhea managed in the outpatient department and did not require intensive treatment. These data support the suggestion that UDCA is safe when administered with chemotherapy in children with ALL reported by.[7] Chemotherapy toxicity becomes more frequent as the treatment is intensified, thus challenging the clinician with both diagnostic and therapeutic problems.[13] Liver function tests are transiently abnormal in the majority of children during maintenance of ALL, in the absence of other evidence of severe liver toxicity or viral hepatitis, it is generally not necessary to withhold or reduce the dose of continuation chemotherapy.[14] A study showed that ALL pediatric patients with mean ALT levels above the upper normal limit (40 IU/l) who were kept on therapy had a significantly lower risk of hematological relapse compared to other children.[15] 6-Thioguanine as maintenance treatment in childhood ALL has also been shown to cause hepatic veno-occlusive disease (VOD) usually mild and reversible on withdrawing 6-TG or replacing it with 6MP.[16]

Limitations

Limitations of current study were; the small size of the study population. Long-term follow-up for hepatotoxicity, time for the return to the normal level of altered liver functions, and liver function follow-up after stopping of UDCA were not evaluated.

CONCLUSION

Co-administration of UDCA with chemotherapy demonstrates a significant effect in treatment interruption of hepatotoxic drug especially 6MP in pediatrics ALL patients. Future studies with a larger sample size are necessary to confirm its efficacy/safety, the most effective dose, and its effect on relapse and leukemia-free survival.

Recommendations

Further study with a larger sample size and long-term follow-up are required to evaluate the effect of hepatotoxicity on the relapse rate of ALL patients due to 6MP drug interruption as well as the effect of UDCA on the reduction of drug interruption and relapse rate of ALL patients.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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