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Research Article

The role of ursodeoxycholic acid in the treatment of chemotherapy induced hepatotoxicity in the maintenance treatment of children with acute leukemia

Akut lösemili çocukların idame tedavisinde kemoterapiye bağlı hepatotoksisite tedavisinde ursodeoksikolik asitin rolü

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Abstract

Introduction: Chemotherapeutic agents used in the treatment of leukemia patients may cause toxic effects in the liver where they are metabolized. Ursodeoxycholic acid (UDCA) is used because of its hepatoprotective effect in the treatment of drug-induced liver toxicity. This study investigated the efficacy of UDCA use, despite the effect of UDCA on tumor cells being unknown, in the treatment of liver toxicity in pediatric patients on chemotherapy for leukemia.

Methods: Data from pediatric leukemia patients, who were on maintenance therapy and developed liver toxicity, were retrospectively analyzed. Patients were divided into three groups and the results were compared regarding development of liver toxicity. Patients who were not given UDCA and whose chemotherapy (CT) treatment was interrupted were defined as Group 1, patients who were given UDCA and whose CT was interrupted were defined as Group 2, and patients who were given UDCA and continued CT were defined as Group 3.

Results: The study cohort numbered 119 patients, of whom 64 were included in Group 1, 26 patients were in Group 2 and 29 patients were included in Group 3. The mean age of the patients was 6.29±3.03 years and 57.1% of them were male. In Group 1, alanine aminotransferase (ALT) decreased to <100 IU/L so UDCA was interrupted, and CT could be rechallenged in 85.9%, in Group 2 this proportion was 100%, and in 69.2% of patients in Group 3, respectively. While there was no significant difference between Group 1 versus Group 2 and Group 1 versus Group 3, a significant difference was found between Group 2 and Group 3 (p=0.005). There were no patients in any group with a bilirubin level of >3 mg/dL. Duration for normalization of ALT and aspartate aminotransferase levels were similar.

Conclusions: The most effective treatment for chemotherapy-induced liver toxicity in pediatric patients with leukemia seems to be to interrupt CT. It was noteworthy that UDCA administration without interruption of CT treatment, the source of the liver toxicity, was effective in 69.2% of patients. Further and comprehensive studies are needed to evaluate the role of UDCA in hepatoprotection in these patients.

Keywords: Ursodeoxycholic acid; leukemia; chemotherapy; hepatotoxicity

Öz

Giriş: Lösemi hastalarının tedavisinde kullanılan kemoterapötik ajanlar metabolize oldukları karaciğerde toksik etkilere neden olabilirler. Ursodeoksikolik asit (UDCA), ilaca bağlı karaciğer toksisitesinin tedavisinde hepatoprotektif etkisinden dolayı kullanılmaktadır. Çalışmamızda kemoterapi (KT) tedavisi devam eden lösemi tanılı çocuk hastalarda karaciğer toksisitesinin tedavisinde kullanılan ve tümör hücrelerine etkisi net olarak bilinmeyen ursodeoksikolik asidin etkinliği araştırıldı.

Yöntem: İdame tedavisi alan ve karaciğer toksisitesi gelişen pediatrik lösemi hastalarının verileri retrospektif olarak analiz edildi. Hastalar üç gruba ayrıldı ve sonuçlar karaciğer toksisitesi gelişimi açısından karşılaştırıldı. Ursodeoksikolik asit verilmeyen ve KT tedavisi kesilen hastalar Grup 1, UDCA verilen ve KT kesilen hastalar Grup 2, UDCA verilip KT' ye devam edilen hastalar Grup 3 olarak tanımlandı.

Bulgular: Çalışma grubu 119 hasta olup, bunlardan Grup 1' de 64, Grup 2' de 26 ve Grup 3' te 29 hasta yer aldı. Hastaların yaş ortalaması 6,29 ± 3,03 ve %57,1' i erkekti. Grup 1' deki hastaların %85,9' u, Grup 2' deki hastaların %100' ü, Grup 3' teki hastaların %69,2' sinin alanin aminotransferaz (ALT) seviyesi <100 düzeyine inerek UDCA verilmeyecek ve KT tedavisine devam edilecek duruma ulaşmıştır. Grup 1 ve Grup 2 ile Grup 1 ve Grup 3 arasında istatistiksel olarak anlamlı fark yok iken, Grup 2 ve Grup 3 arasında istatistiksel olarak anlamlı bir fark bulunmuştur (p=0,005). Hiçbir grupta bilirubin düzeyi >3 mg/dL olan hasta yoktu. Alanin aminotransferaz ve aspartat aminotransferaz değerlerinin normale dönme süreleri benzer bulundu.

Sonuç: Lösemi tanılı çocuk hastalarda kemoterapiye bağlı karaciğer toksisitesinin tedavisinde en etkili yol KT' ye ara vermek gibi görünmektedir. Karaciğer toksisitesinin kaynağı olan KT tedavisine ara vermeden UDCA uygulamasının hastaların %69,2' sinde etkili olması dikkat çekici bulunmuştur. Ursodeoksikolik asitin bu hastalarda hepatoproteksiyondaki rolünü değerlendirmek için, daha ileri ve kapsamlı çalışmalara gerek vardır.

Anahtar kelimeler: Ursodeoksikolik asit; lösemi; kemoterapi; hepatotoksisite.

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Key Points

1. The results of the present study indicated that interruption of chemotherapy (CT) seemed to be an effective and safe way to manage CT-induced liver toxicity.
2. It was noteworthy that ursodeoxycholic acid administration without interruption of CT treatment, the source of the liver toxicity, was effective in 69.2% of patients.
3. Duration for normalization of alanine aminotransferase and aspartate aminotransferase levels were similar.

Introduction

Chemotherapeutic agents used in the treatment of leukemia patients may cause toxic effects in the liver where they are metabolized. However, the extent of liver damage is variable [1]. There may be mild elevation in transaminases with an asymptomatic course or the elevation may reach toxic levels and require hospitalization. Reactions are generally dose independent and they may be unusual because of immunological mechanisms due to the nature of leukemia. Reducing the dose or discontinuation of drugs used in cancer treatment may result in reduced survival rates and so hepatotoxicity is an important concern in patients with leukemia [1-2].

Oral methotrexate (MTX) and oral mercaptopurine (MP) are used during maintenance treatment in acute lymphoblastic leukemia (ALL) in pediatric patients with leukemia while oral thioguanine (TG) and subcutaneous cytarabine are used in acute myelocytic leukemia (AML) [3-5]. Although the metabolism of the patients has a critical and complex role in the pharmacokinetics of all these agents, they may have toxic effects on the liver. Folic acid, which is decreased by the effect of MTX, may cause inappropriate DNA replication in hepatocytes. In this case, toxins accumulate in the liver, and liver enzyme levels rise [6]. The hepatotoxic metabolite 6-ethyl MP is produced in 15-20% of patients using MP [7]. TG may rarely be associated with significant hepatotoxicity [8]. Cytarabine has also been reported as a drug with a high potential for liver damage [9].

Ursodeoxycholic acid (UDCA) has been shown to increase bile flow and change the hydrophobicity index of the bile acid pool [10-12]. It is also used because of its hepatoprotective effect in the treatment of drug-induced liver toxicity. Studies have reported that UDCA reduces serum alanine aminotransferase (ALT) by 35% and aspartate aminotransferase (AST) by 33% [13-16]. In addition, the protective role of UDCA on cancer cells is also discussed [17]. In patients with leukemia the risk of multiplying cancer cells through the effects of UDCA on treatment efficacy is too great a risk. Furthermore, UDCA is not licensed for use in children. Efficacy and safety of UDCA in the pediatric age group is unknown but it has been reported that it can increase mortality, especially in the neonatal and infancy period [18-19].

Despite this, the use of UDCA is common in drug-induced hepatotoxicity in childhood leukemia. However, studies on the effectiveness of this drug are limited and the effect of UDCA on cancer cells is not clear. In this study, the efficacy of UDCA was examined, and the necessity of its use was investigated.

Methods

Pediatric patients with a diagnosis of leukemia, aged between 1-18 years, and who were on maintenance therapy managed by a single Pediatric Hematology and Oncology Clinic between 01.08.2020 and 01.08.2021 were included. All included patients had developed Stage ≥3 liver toxicity. Demographic and clinical data of the patients were obtained retrospectively from patient records. In terms of treatment protocols, ALL IC-BFM 2009 was used in 99.2% patients with ALL and AML BFM 2019 protocol was used in a single patient. Patients with ALL were treated with 6-MP (50 mg/m^2/day) and MTX (20 mg/m^2/week). Patients with AML received 6-TG (40 mg/m^2/day) and cytarabine (4 days a month, 40 mg/m^2/day) treatment regularly. Depending on the changes made in the treatment doses, the blood counts, liver function tests and bilirubin values of the patients were checked on average every two weeks or at least once a month.

Liver dysfunction was defined as an ALT value five times normal or >200 U/L and/or total bilirubin value three times normal or >3 mg/dL [20]. UDCA support was not given to all patients since the efficacy of UDCA was unproven. Therefore the patients were stratified into three groups based on interruption of chemotherapy (CT) and whether or not they received UDCA. In the first group (Group 1), patients had interrupted CT but did not receive UDCA. In Group 2 patients were given UDCA and CT was interrupted while in Group 3, patients received UDCA and CT was continued. Patients in Group 2 and 3 were given UDCA at a dose of 15 mg/kg/day. Liver function biomarkers were monitored weekly until the values ALT <100 U/L and/or bilirubin <2 mg/dL.

Patients with known viral/autoimmune/metabolic liver disease or a chronic disease other than leukemia, and patients who were given antibiotics, antipyretics and other drugs that may cause elevation in liver enzymes were excluded.

Ethical approval

This research was approved by Saglik Bilimleri University Cam and Sakura City Hospital Ethics Committee (Non-Invasive Clinical Research Ethics Committee Decision Form: 274/01.12.2021).

Statistical analysis

Data were analyzed with IBM SPSS, version 23 (IBM Inc., Armonk, NY, USA). Conformity to the normal distribution was evaluated using the Shapiro-Wilk test. The chi-square test was used to compare categorical variables according to groups, and multiple comparisons of ratios were analyzed with a Bonferroni corrected Z test. Kappa statistics were used to examine the concordance between ALT and AST. The Kruskal-Wallis test was used to compare white cell counts (WBC) according to treatment modalities, and multiple comparisons were analyzed with Dunn's test. The Friedman test was used to compare WBC values over time. Statistical significance was assumed when p <0.005.

Results

A total cohort size of 119 patients were identified, of whom 57.1% of the cases were male. The majority of patients (118, 99.2%) were diagnosed with ALL. The mean age was 6.29±3.03 years (Table 1).

Table 1. Identification of patients

Age, years		6.29 ± 3.03 S.D	
Sex, *n*	Female	51	42.9%
	Male	68	57.1%
Diagnosis, *n*	AML	1	0.8%
	ALL	118	99.2%

S.D: Standard deviation **ALL**: Acute lymphoblastic leukemia **AML**: Acute myelocytic leukemia

Group sizes were Group 1 n=64 (53.8%); Group 2 n=26 (21.8%); and Group 3 n=29 (24.4%) (Table 2).

Table 2. Treatment groups

	(n)	**(%)**
Group 1. UDCA-/CT-	64	53.8
Group 2. UDCA+/CT-	29	24.4
Group 3. UDCA+/CT+	26	21.8

UDCA: Ursodeoxycholic acid **CT**: Chemotherapy

The ALT level of 85.9% of the patients in Group 1, 100% of the patients in Group 2, and 69.2% of the patients in Group 3 decreased to <100 U/L when CT treatment could be continued. While there was no significant difference between these proportions in Group 1 vs Group 2 or Group 1 vs Group 3, a significant difference was found between Group 2 vs Group 3 (p=0.005). Normalization of ALT and AST levels in the three groups paralleled these proportions. There were no patients in any group with a bilirubin level of >3 mg/dL (Table 3).

Table 3. Comparison of AST and ALT parameters according to treatment

		Group 1 UDCA-/CT- n (%)	**Group 2** UDCA+/CT- n (%)	**Group 3** UDCA+/CT+ n (%)	n (%)	p*
AST	<100	55 (85.9)	29 (100)	18 (69.2)	102 (85.7)	
	>100	9 (14.1)ab	0a	8 (30.8)b	17 (14.3)	**0.005**
ALT	<100	55 (85.9)	29 (100)	18 (69.2)	102 (85.7)	**0.005**
	>100	9 (14.1)ab	0a	8 (30.8)b	17 (14.3)	

*Chi-square test, a-b: There is no difference between treatments with the same letter. **UDCA:** Ursodeoxycholic acid **CT**: Chemotherapy **AST**: Aspartate aminotransferase. **AST/ALT >100:** Liver toxicity persists. **ALT**: Alanine aminotransferase <100 and/or UDCA will not be given, and CT treatment will be continued.

However, a significant difference was found between the distributions within the groups for normalization of AST and ALT <100 U/L (p=0.042 and p=0.015, respectively). While 14.1% of the patients in Group 1 and 30.8% of the patients in Group 3 did not achieve ALT <100 U/L, the ALT value of all patients in Group2 decreased below 100 U/L (Table 4).

Table 4. Time to normalization of AST and ALT

	Time for: AST/ALT <100	**Group 1 UDCA-/CT- n (%)**	**Group 2 UDCA+/CT- n (%)**	**Group 3 UDCA+/CT+ n (%)**	**Total (%)**	**p****
AST	1 week	1 (1.6)	0 (0)	0 (0)	1 (0.8)	
	2 weeks	33 (51.6)	14 (48.3)	9 (34.6)	56 (47.1)	
	3 weeks	21 (32.8)	15 (51.7)	9 (34.6)	45 (37.8)	**0.042**
	AST>100	9 (14.1)ab	0 (0)a	8 (30.8)b	17 (14.3)	
ALT	1 week	0 (0)	0 (0)	0 (0)	0 (0)	
	2 weeks	34 (53.1) 21 (32.8)	14 (48.3) 15 (51.7)	9 (34.6)	57 (47.9) 45	
	3 weeks	9 (14.1)ab	0 (0)a	9 (34.6)	(37.8) 17	**0.015**
	ALT>100			8 (30.8)b	(14.3)	

Chi-square test, a-b: There is no difference between treatments with the same letter.** Time for patients with ALT>200 to reach ALT<100 and AST<100. **UDCA:** Ursodeoxycholic acid **CT**: Chemotherapy **ALT**: Alanine aminotransferase **AST**: Aspartate aminotransferase

The normalization times for ALT and AST were significantly similar (p<0.001) (Table 5).

Table5. Correlation between ALT and AST

	ALT		Test value	*p*
	<100	**>100**		
AST <100	102 (100)	0 (0)	1.000	**<0.001**
AST >100	0 (0)	17 (100)		

*Kappa statistical method. **ALT**: Alanine aminotransferase **AST**: Aspartate aminotransferase

Discussion

The published evidence concerning the use of UDCA in the treatment of liver toxicity due to CT in pediatric patients with leukemia is inconsistent and thus the use of this agent remains controversial, especially given its unproven potential to worsen the malignancy. In our study, the success of treatment was significantly better in patients who were given UDCA treatment when CT treatment was also interrupted. Positive results were obtained in 85% of the patients when only CT treatment was interrupted. In addition, it was noteworthy that UDCA administration without interruption of CT treatment, the source of the liver toxicity, was effective in 69.2% of patients. In the study of Uraz et al., it was reported that UDCA treatment protected against liver toxicity caused by MTX, that histologically-proven hepatocyte necrosis was prevented by UDCA treatment, and the authors concluded that UDCA had a hepatoprotective effect on MTX-induced liver damage [21]. In contrast, Bordbar et al. reported that UDCA had a minimal role in hepatoprotection in the treatment of MTX-induced liver injury in pediatric patients with ALL [22]. In the study of Mohammed Saif et al., 19 out of 39 (48.7%) pediatric patients diagnosed with ALL were given UDCA in conjunction with CT for six months, then UDCA was discontinued, and the patients were followed for another three months. In the control group, UDCA was not given to 20 patients for nine months. These authors reported that UDCA treatment was associated with a trend towards decreased liver transaminase levels when co-administered with chemotherapy [23].

Although the effect of UDCA in preventing drug-induced liver damage is controversial in childhood leukemia, it is equally important to consider that the effect of UDCA on the cancer cells is not fully understood. Little is known about the efficacy and safety of antioxidant use during chemotherapy [24]. There is some concern about the possible interaction of antioxidants with chemotherapy agents [25]. Furthermore, researchers have raised concerns about the safe use of antioxidants in cancer patients, as antioxidants can not only protect normal cells, but may also protect malignant cells from free radicals [26]. This effect has been documented previously from our clinic, which showed that UDCA did indeed protect cancer cells [16]. However, the effect of interrupting treatment on survival rates in cancer patients is also under scrutiny.

Although UDCA appears to be beneficial in the prevention and treatment of drug-induced liver injury, the evidence remains inconclusive [27]. However, the use of this agent, especially given that the effect of UFCA on cancer cells is not understood, is a risk that we believe should not be taken. The results of the present study indicated that interruption of CT seemed to be an effective and safe way to manage the CT-induced liver toxicity.

Limitations

The limitations of this study should be noted. These include the retrospective character and the limited number of patients, as the sample size was limited in order to reach a general conclusion.

Conclusion

The role of UDCA in the treatment of CT-induced liver toxicity in pediatric patients with leukemia remains controversial. More large, prospective, multicenter studies are needed to resolve this controversy.

Conflict of interest: The authors declare that they have no conflict of interest

Author Contributions		**Author Initials**
SCD	Study Conception and Design	OT, AA, HAS, DY, CB, ST
AD	Acquisition of Data	OT, HAS, ST, DY
AID	Analysis and Interpretation of Data	OT, CB, AA, ST, HAS, DY
DM	Drafting of Manuscript	OT, CB, AA
CR	Critical Revision	OT, CB, AA

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