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Survival and Prognosis of Children and Adolescents with Hematological Malignancies with Liver Involvement Undergoing Chemotherapy

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ABSTRACT

Background and Objective: Liver disorders in hematological malignancies cause treatment delays and, as a result, disease recurrence. The aim of this study was to evaluate the survival and prognosis of children and adolescents with hematological malignancies and liver involvement after chemotherapy.

Methods: This cross-sectional study was conducted in the Hematology and Oncology Department of Mardani Azar Children's Hospital, Tabriz University of Medical Sciences, by reviewing the files of patients hospitalized from December 22, 2021 to December 22, 2023. The study included hospitalized children with hematological malignancies. Demographic information, treatment stage, and liver test results were recorded before and after chemotherapy. Survival modeling was performed from the time of diagnosis to the occurrence of outcomes, including relapse, disease remission, complete recovery, and mortality, using the Kaplan–Meier method. Data were statistically analyzed using SPSS 26. A value of $P<0.05$ was considered significant.

Findings: In this study, out of 150 patients, 55 (36%) had elevated liver enzyme levels. During the clinical and laboratory follow-up, one patient achieved complete recovery, 27 patients had remission, and 21 patients experienced relapse. The mortality rate was 1.9%. The survival rate among patients with liver damage was 87%. The survival probability for patients with liver damage was 0.95 after 7 months, 0.89 after 10 months, and decreased to 0.45 after 21 months.

Conclusion: The mortality rate was higher in patients whose treatment was discontinued due to prolonged elevation of liver enzymes than in those whose liver damage improved and who continued malignant treatment.

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Introduction

Different therapeutic interventions are used in cancer management. The use of chemotherapeutic drugs is generally associated with various side effects such as renal and hepatic disorders [1].

Overall survival in hematologic malignancies depends on the incidence of hepatic, cardiac, pulmonary and renal complications. Liver complications are a well-known cause of early and late mortality in patients with hematologic malignancies. Because most chemotherapeutic drugs are lipid-binding, they are easily absorbed by the liver and can cause liver damage. Up to 85% of patients undergoing chemotherapy develop hepatic steatosis. Steatohepatitis is a more serious event, especially if accompanied by elevated bilirubin levels [1-3].

In Drug-induced liver injury (DILI) (a general term) drug metabolism leads to liver injury in the form of oxidative stress, inflammatory damage, apoptosis, necrosis, or mitochondrial membrane destruction. Chemotherapy-induced liver injury (CILI) cannot be distinguished from other drugs that damage the liver by histological features [4].

Various drugs are used for treating hematological malignancies in children and adolescents. Most chemotherapeutic drugs, such as alkylating agents, antimetabolites, antitumor antibiotics, and immunotherapeutic agents, can cause liver complications. Liver injury in patients undergoing chemotherapy is detected by liver function enzyme tests [5-9].

The National Cancer Institute (NCI) has classified the severity of liver injury based on the elevation of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and γ-glutamyl transferase (GGT) [9].

The Drug Induced Liver Disease Network (DILI) suggested using clinical measures rather than laboratory values to define liver injury [10].

Imaging techniques can be used to diagnose chemotherapy-related liver injury. If liver disease occurs as an adverse effect of these agents, discontinuation or continuation of chemotherapy should be based on careful risk-benefit monitoring [6, 8].

Elevations in hepatic transaminases, alkaline phosphatase, and bilirubin have been reported in 30-60% of patients receiving asparaginase as part of multiagent therapy for acute lymphoblastic leukemia (ALL) [11].

Vincristine can cause transient elevations in aminotransferases. Despite its hepatic metabolism, no cases of severe hepatotoxicity have been reported with vincristine monotherapy [12].

Antitumor antibiotics include doxorubicin and daunorubicin. In a study of six patients with acute lymphoblastic leukemia who were receiving induction therapy with vincristine, prednisone, and doxorubicin, elevated AST, ALT, and bilirubin and steatosis were observed on liver biopsy, which was considered an unusual response [13].

The use of methotrexate as maintenance therapy in children with acute leukemia has been associated with liver fibrosis and cirrhosis. Methotrexate is rarely considered a hepatotoxin and can be administered with relative safety in cases with altered liver function [6, 14].

Combination chemotherapy uses multiple chemotherapeutic agents, each with a different mechanism of action and toxicity profile. However, along with the potential for increased tumor eradication, there is also the potential for increased toxicity. The addition of Mercaptopurine (MP-6) to doxorubicin for the treatment of patients with refractory leukemia is an example of this phenomenon [14].

Approximately 80% of DILI cases resolve spontaneously after discontinuation. In more severe cases, liver biopsy may be required to determine the type of injury and prognosis [15]. Unfortunately, some cases of DILI result in acute liver failure (ALF) with high mortality and require liver transplantation [16, 17].

Liver dysfunction is a common complication of chemotherapy for a variety of reasons and can lead to delay, dose reduction, or discontinuation of chemotherapy, ultimately leading to relapse of the malignancy and sometimes to fulminant hepatic failure. Liver complications in patients with malignancies undergoing chemotherapy have not been systematically investigated. The aim of this study was to evaluate survival and prognosis of children and adolescents with hematological malignancies with liver involvement undergoing chemotherapy at Mardani Azar Hospital in Tabriz.

Methods

Study design and sample selection

This cross-sectional study was conducted at the Hematology and Oncology Department of Mardani Azar Children's Hospital, affiliated with Tabriz University of Medical Sciences. We reviewed the medical records of pediatric patients diagnosed with hematological malignancies (ALL, acute myeloid leukemia [AML], and lymphoma) who were hospitalized between December 22, 2021, and December 22, 2023.

Eligibility Criteria

Patients hospitalized during the two-year study period who met the following criteria were included: aged between 2 and 18 years, diagnosed with hematological malignancies including ALL, AML, or lymphoma, and undergoing a chemotherapy regimen.

Patients were excluded based on the presence of significant underlying diseases such as infection, renal failure, or cardiac disease; primary liver malignancy or hepatic metastasis; any chronic liver disease, including infectious, anatomical, metabolic, endocrine, or autoimmune etiologies; concurrent use of hepatotoxic medications; or incomplete medical records.

Data collection

The collected data included patient demographics, type of malignancy, time of diagnosis, stage of treatment, drugs used in each stage of the chemotherapy regimen (such as methotrexate, vincristine, asparaginase, adriamycin, and cyclophosphamide) and their doses, as well as tests related to liver complications (AST, ALP, ALT, total and direct bilirubin) before and after administration of these drugs.

The normal upper limits according to the regional laboratories are as follows: AST: 40 IU/L, ALT: 55 IU/L, ALP: 350 IU/L, total bilirubin: 1.2 mg/dl, direct bilirubin: <0.2 mg/dL. If liver enzyme levels exceeded twice the maximum normal value, liver ultrasound and serology for viral hepatitis were performed.

Survival modeling was conducted by recording the patient's clinical and laboratory course from the time of diagnosis to the occurrence of outcomes including disease recurrence (lymphoblastic cells reappear in the bone marrow, confirmed by bone marrow aspiration), disease remission (no symptoms of leukemia and cancer cells in the bone marrow have decreased to undetectable levels), complete recovery (all symptoms of cancer have disappeared and cancer cells are no longer detectable in the bone marrow) and mortality using the Kaplan-Meier method.

The checklists were completed after Ethics Committee approval on behalf of the patients' parents. In accordance with the Declaration of Helsinki (Ethical Principles in Medical Research involving Human Subjects), only patients requiring treatment were included in the study, and no patient received treatment solely for the research project; therefore, so the intervention did not pose a risk to any individual. All information remained confidential and was not disclosed to any individual or legal entity. The tests, ultrasound examinations, and consultations with the Gastroenterology and Liver Service followed standard procedures for the treatment and follow-up of patients with liver complications, and no additional costs were incurred by the patients. The interests of the patients and the proper treatment of their diseases were prioritized, and the implementation of this project did not interfere with their care.

Statistical Analysis

Data were statistically analyzed using SPSS 26. Frequency (percentage) was used to describe qualitative data, and mean (standard deviation) was used for quantitative data if normally distributed, or median (25th and 75th percentiles) if not. The chi-square test and independent t-test were used to analyze data between two groups, and the Mann-Whitney test was used if data were not normally distributed. A value of $P<0.05$ was considered significant.

Results

In the present study, 150 patients with hematological malignancies undergoing treatment met the inclusion criteria. Of these 57 developed liver damage during treatment. Two patients were excluded due to incomplete file information, leaving 55 patients

included in the final analysis. Among these 55 patients, 36 (65.4%) were male and 19 (34.6%) were female. Twenty-four (43.7%) patients were in the preschool age group, 19 (34.5%) were in the elementary school age group, 10 (18.2%) were in the early adolescence age group, and 2 (3.6%) were in the late adolescence age group. The mean age was 15.8 years, and the mean weight was 27.29 kg. Of the 55 patients, 47 (85.4%) had a primary diagnosis of ALL, 4 (7.3%) had relapsed ALL, 3 (5.5%) had a primary diagnosis of AML, and 1 (1.8%) had relapsed lymphoma. All had liver enzyme elevations greater than twice the upper limit of normal (ULN). The patients received chemotherapy according to protocol, and one patient also received radiotherapy. Liver enzyme elevations greater than twice the ULN occurred in 41 (74.6%) patients during the induction phase, 8 (14.6%) during the consolidation phase, and 6 (10.8%) during the maintenance phase of treatment. In the study of liver and bile duct ultrasound following an increase in liver enzymes to more than twice the upper limit of normal (ULN), 39 patients were evaluated. The ultrasound was reported as normal in 37 patients, while steatosis was found in one (1.8%) patient and granuloma in another, which was identified as liver fibrosis on open liver biopsy. The prevalence of fibrosis among these patients was 0.9%, and no cases of liver cirrhosis were observed.

The severity of liver injury according to the NCI Common Toxicity Criteria for Adverse Events based on increases in liver enzymes (AST and ALT), was reported as mild in 5 (9.1%) patients, moderate in 23 (41.8%) patients, severe in 26 (47.3%) patients, and life-threatening in 1 (1.8%) patient. An analysis of the medications prescribed during the period of increased liver enzymes showed that vincristine was used in 46 (83.6%) cases, methotrexate in 44 (80%) cases, L-asparaginase in 20 (36.4%) cases, cytosar in 29 (52.7%) cases, doxorubicin and daunorubicin in 23 (41.8%) cases, and cyclophosphamide and ifosfamide in 1 (1.8%) case.

A comparison of liver enzyme values before and after the treatment process is shown in Table 1. The results indicated that the average AST value before treatment was 31.16 IU/mL, and after treatment it was 128.21 IU/mL, representing a significant increase of more than fourfold (p=0.001). The mean ALT value before treatment was 37.61 IU/mL and after treatment it was 236.70 IU/mL, representing a significant increase of more than 6 times (p=0.001). The changes in total bilirubin (Bill T) and direct bilirubin (Bill D) values before and after chemotherapy were also statistically significant (p=0.001). However, no significant difference was observed in serum albumin (Alb) and total protein values before and after treatment (p=0.2 and p=0.7, respectively).

An increase in liver enzymes to more than twice the ULN was mild and transient in 13 cases and did not lead to discontinuation of chemotherapy. In 33 patients, it led to temporary discontinuation of treatment until enzyme levels decreased. In 6 cases, it resulted in long-term discontinuation of chemotherapy; in 1 case, it led to a reduction in the drug dose; and in 2 cases, it led to a change in the chemotherapy drug. In 43 cases, the liver complication resolved, while in 12 cases, a long-term persistence of elevated liver enzymes was observed.

In the clinical and laboratory study of the patients, one patient achieved complete recovery from the underlying disease, as confirmed by BMA. Twenty-seven patients were in remission (confirmed by BMA), 21 patients experienced relapse, and 5 deaths were reported. The mortality rate among the patients was 1.9%. The outcomes of the patients after treatment are presented in Table 2.

To identify factors affecting patient survival, univariable Cox regression was first performed. Subsequently, multivariable Cox regression was used to adjust for confounding variables. Variables with a significance level less than or equal to 0.05 were included in the multivariable model. The results of the multivariable Cox regression analysis are shown in Table 3. The findings indicated that the survival rate in females was 0.08 times that of males (p=0.58).The survival of patients with AML and lymphoma was 1.02 times and 12.47 times that of patients with ALL, respectively; however, these relationships were not statistically significant (p=0.9 and p=0.9, respectively).

The survival of children and adolescents with hematological malignancies and liver involvement undergoing chemotherapy is shown in Figure 1. According to the results, the probability of survival was 0.95 after 7 months, 0.89 after 10 months, and decreased to 0.45 after 21 months.

Table 1. Liver enzyme values of patients before and after treatment

Variables	Before treatment	After treatment	p-value
AST (U/L)	31.16 ± 20.27	128.21± 91.28	0.001
ALT(U/L)	37.61 ± 31.37	236.70± 188.40	0.001
ALP(U/L)	368.6 ± 134.58	372.78 ± 156.26	0.8
Bill T(mg/dl)	0.84 ± 0.4	1.23 ± 0.67	0.001
Bill D (mg/dl)	27.0 ± 0.17	0.44 ± 0.30	0.001
Alb(g/dl)	4.40± 0.70	3.90 ± 0.58	0.2
Total Protein(g/dl)	5.84 ± 0.80	0.79 ±5.87	0.7

* Results are presented as mean ± standard deviation.

AST: aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; Bill T: Bilirubin total; Bill D: Bilirubin direct; Alb: Albumin.

Table 2. Outcome of the patients studied after treatment

Variable	Classification	Frequency	Percentage
Outcome	Complete recovery	1	1.8
	Disease remission	27	49.1
	Disease relapse	21	38.2
	Undetermined status	1	1.8
	Mortality	5	9.1

Table 3. Results of the multivariate Cox regression analysis

Variable	Classification	95% CI	p-value
Sex	Male	Reference	-
	Female	0.08(0 - 23)	0.58
Type of malignancy	ALL	Reference	-
	AML	1.02(0.7-5)	0.9
	Lymphoma	12.47(0.62-14)	0.9
Stage of treatment at the time of onset of elevated liver enzymes	Induction	Reference	-
	Fixation	12.47(0.95-20)	0.5
	Maintenance	1.31(0.67-8)	0.

ALL: Acute lymphocytic leukemia; AML: Acute myelogenous leukemi

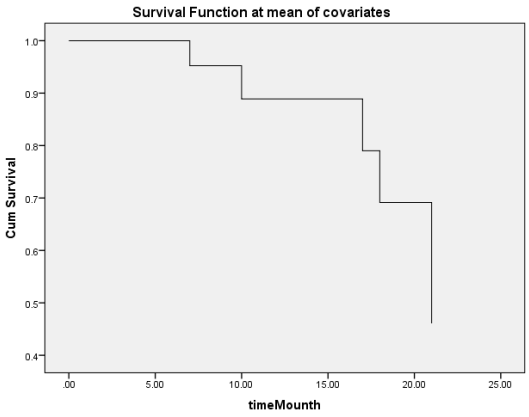

Figure 1. Survival of children and adolescents with hematological malignancies with liver involvement undergoing chemotherapy

Discussion

The aim of this study was to investigate the liver complications of patients with hematological malignancies undergoing chemotherapy and the impact of liver disorders on the duration of treatment, prognosis and patient survival such as complete

remission, disease recurrence and mortality. Chemotherapy-induced liver injury (CILI) is one of the important complications in patients with hematological malignancies. Available evidence has shown that most classes of chemotherapy can cause liver injury [1, 4, 18].

According to the results, of the 55 patients studied, 47 patients (85.4%) with a primary diagnosis of ALL, 4 cases (7.3%) with relapsed ALL, 3 patients (5.5%) with a primary diagnosis of AML, and 1 patient (1.8%) with relapsed Lymphoma had elevated liver enzymes greater than twice the ULN. Moreover, 41 patients (74.6%) in the induction phase of treatment, 8 cases (14.6%) in the consolidation phase, and 6 cases (10.8%) in the maintenance phase of treatment had an increase in liver enzymes more than twice the ULN. One patient (1.8%) had steatosis and one patient had liver fibrosis.

In a study conducted in 2024 by Reddy et al. on liver dysfunction during induction chemotherapy in children with ALL and lymphoblastic lymphoma and its impact on patient outcome, 142 children , aged 1 to 18 years were studied. According to the results of their study, 21.8% of children had liver dysfunction, 9.9% had increased ALT/AST, and 19% had increased bilirubin. Treatment protocol modification was performed in 14 of 31 patients with liver dysfunction. Mortality was significantly higher in children with hepatic dysfunction. The 5-year survival rates for patients with hepatic dysfunction were 59.93% and 72% for patients without hepatic dysfunction [19]. The aim, methodology, and results of the study by Reddy et al. were somewhat similar to ours, but the main difference was the 5-year survival rate in their study.

A study by Mekonnen et al. observed clinically significant hepatotoxicity in 15% of patients after chemotherapy [20]. Our study, similar to the Mekonnen study, showed that the mean AST values before treatment were 31.16 IU/mL and after treatment were 128.21 IU/mL, which was a more than four-fold increase. The mean ALT values before treatment were 37.61 IU/mL and after treatment were 236.70 IU/mL, which was a more than six-fold increase.

In a study conducted in 2020 by Akma et al. to investigate the effect of chemotherapy based on a standard protocol on liver function in children with acute lymphoblastic leukemia over a 12-month period, the results of their study showed that 4.5% of patients had an increase in SGPT, 50% had an increase in prothrombin, 43.2% had a decrease in albumin, and 20.5% had an increase in bilirubin. Comparison of liver function in children after chemotherapy during induction with pre-treatment function did not show any significant difference. This study concluded that current treatment for induction of remission of ALL does not cause any toxic effects on the liver. However, enzymes such as SGPT increase sharply during remission induction, but this is transient [21].

In our study, the increase in liver enzymes was similar to the study of Akma et al., but although the comparison of changes in total bilirubin (Bill T) and direct bilirubin (Bill D) between the times before and after chemotherapy was statistically significant, there was no significant difference in serum albumin (Alb) and total protein (Total Protein) and prothrombin time between the times before and after treatment.

In 2001, Meir et al. conducted a study of liver dysfunction after chemotherapy in 105 children with ALL. Liver function enzymes and viral hepatitis panel test results were evaluated. 54 children were Egyptian and 51 were Saudi. The prevalence of hepatitis (HBV and/or HCV) infection was significantly higher in Egyptian children (80%), and only 5 Saudi children had evidence of HBV exposure (9.8%). During the study, 22 Egyptian children and 4 Saudi children had at least one episode of elevated liver function enzymes 3 times or more above the upper limit of normal) [22].

In our study, in terms of examining the prescribed drugs of patients in the stage of increased liver enzymes, it was shown that in 46 cases (83.6%) vincristine, 44 cases (80%) methotrexate, 20 cases (36.4%) L-asparaginase, 29 cases (52.7%) cytosar, 23 cases (41.8%) doxorubicin and daunorubicin, and one case (1.8%) cyclophosphamide and ifosfamide were prescribed.

In 1994, Bessho et al. conducted a study of 27 children with ALL with elevated liver enzymes. Induction included prednisolone + vincristine in 16

patients, combined with doxorubicin in 4 patients, and combined with L-asparaginase in 7 patients. Elevated ALT (3 times the upper limit of normal) was reported in half of the patients. 3 months after completion of maintenance therapy, ALT levels normalized in all patients and remained within the normal range in all but 2 patients. Serum bilirubin, albumin, and prothrombin levels were normal in all patients [23].

The results of the Bessho study showed that doxorubicin was a potential liver-damaging drug in 17 patients, and in the study by Aviles et al., there was an association between doxorubicin administration and liver dysfunction in six ALL patients [23]. Also, in the study by Urrutia-Maldonado et al. in 2019, which investigated liver damage from oncological drugs in 22 children undergoing chemotherapy, it was observed that all children had a period of hepatotoxicity and methotrexate was reported to be the most common drug causing liver damage [7]. Also, the study by Shoaran et al., which investigated the relationship between liver complications of high-dose methotrexate with a ten-year follow-up. Although methotrexate was considered safe, they recommended that patients be followed for a long time, many years after discontinuation of treatment [24].

In our study, methotrexate was the likely causative drug in 32 cases, and in 8 cases, high doses were used. However, the follow-up of our patients was not ten years. The results of our study on the adjusted survival of patients showed that the probability of survival of patients after 7 months was 0.95, after 10 months it was 0.89, and finally after 21 months it decreased to 0.45.

In line with our study, in the study by Reddy et al., which was conducted in 2022 to investigate the prevalence of liver dysfunction during chemotherapy induction in patients with acute lymphoblastic leukemia and lymphoblastic lymphoma in 142 children, 31 children (21.8%) developed liver dysfunction, 14 (45.1%) patients had increased ALT/AST, and 27 (87%) patients had increased bilirubin. Fourteen of the 31 children with liver dysfunction required treatment. Death was more common in children with liver complications [25].

Limitation

The main limitation of this study was the short-term follow-up and the relatively small sample size.

Conclusion

The results of this study showed that in children and adolescents with hematological malignancies, AST and ALT levels increased significantly after chemotherapy compared to before treatment. The survival of patients who had elevated liver enzymes at the start of chemotherapy and were in the stabilization phase was 12.47 times that of patients in the induction phase. In contrast, the survival of those in the maintenance phase at the time of starting treatment for elevated liver enzymes was 0.31 times that of those in the induction phase. Finally, this study concluded that the survival probability of children with hematological malignancies and liver involvement decreased with increasing treatment time, from 0.95 at month 7 to 0.45 at month 21.

The main advantage of our study is the homogeneity of the patient race and the modeling of patient survival.

The present study recommends that prospective studies with larger study populations, multicenter designs, and different ethnicities would be helpful. In addition, long-term follow-up of patients could determine the long-term prognosis of the disease.

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Ethical Considerations

The ethics code for this study is IR.TBZMED.REC.1402.907, approved by the ethics committee of Tabriz University of Medical Sciences.

Authors' Contributions

All authors contributed to the research and writing of the article: Dr. Abbas Ali Hosseinpour Faizi served as research supervisor, Dr. Fateme Amri collected data, Dr. Saeed Dastagiri analyzed data, and Dr. Parviz Amri performed the final editing.

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Conflict of interest

The authors declare no conflicts of interest.

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