



Hepatic Dysfunction during Induction Chemotherapy in Children with Acute Lymphoblastic Leukemia and Lymphoblastic Lymphoma and Its Effects on Subsequent Therapy and Outcome

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Abstract

Introduction The overall survival rate for childhood acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) has shown tremendous growth in the recent years. Hepatic dysfunction is one of the complications seen during therapy and can add to the underlying morbidity of the disease, delay in chemotherapy, modification of drugs, and rarely fulminant hepatic failure.

Objective This article aims to find out the prevalence of hepatic dysfunction during induction chemotherapy for ALL and LBL.

Materials and Methods This was a retrospective study, where the data of all children between 1 and 18 years of age with ALL and LBL treated at our center as per the UK-ALL 2003 protocol between December 2013 and December 2021 have been included from the medical records. Hepatic dysfunction was defined as grade 3 and 4 alanine transaminase (ALT) and aspartate transaminase (AST) levels as per Common Terminology Criteria for Adverse Events v5.0 and hyperbilirubinemia as ≥ 1.4 mg/dL as the chemotherapy modification begins at this cutoff. Data from children with hepatic dysfunction was compared with those without hepatic dysfunction using chi-squared test and Student's *t*-tests. Those variables with a *p*-value of < 0.2 were analyzed with multivariate regression analysis. Kaplan–Meier survival estimates were used to calculate the event-free survival (EFS).

Results A total of 142 children were included in the study. Thirty-one (21.8%) children developed hepatic dysfunction, 14 (9.9%) of them with ALT/AST elevation and 27 (19%) with bilirubin elevation. Weight (mean 25 ± 13.5 , *p* 0.01), body surface area (mean 0.87 ± 0.29 , *p* 0.02), and National Cancer Institute high risk (*p* 0.005) were associated with hepatic dysfunction in univariate analysis but none of them were significant in multivariate regression analysis. Treatment modification was required in 14/31 children with hepatic dysfunction. Death in induction was more among children with hepatic dysfunction (*p* < 0.001). There was no significant impact on minimal

Keywords

- ▶ acute lymphoblastic leukemia
- ▶ lymphoblastic lymphoma
- ▶ hyperbilirubinemia
- ▶ chemotherapy

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residual disease outcomes. Five-year EFS (death or relapse) was $59.93 \pm 9\%$ in children with hepatic dysfunction as opposed to $72 \pm 5.0\%$ in those without hepatic dysfunction (95% confidence interval, $p = 0.07$).

Conclusion One in five children with ALL and LBL on induction therapy developed hepatic dysfunction. Almost half of those with hepatic dysfunction required chemotherapy modifications.

Introduction

Acute lymphoblastic leukemia (ALL) is the most common cancer affecting children, accounting for 30% of all malignancies.¹ The overall survival rate for childhood ALL has shown tremendous growth in the past two decades due to the introduction of evidence-based risk-stratified protocols and improved supportive care.^{2,3} Lymphoblastic lymphoma (LBL) is a rare aggressive neoplasm developing from B/T cell precursor cells predominantly in children and young adults. International standards currently recommend treatment as per intensive pediatric lymphoblastic leukemia protocols with an improved survival rate of almost 90% in children.⁴ Remission induction is a major block of chemotherapy, and several complications are known to occur during this phase—febrile neutropenia, sepsis, bleeding, anemia, gastrointestinal disturbances, hepatic dysfunction, pancreatitis, venous thrombosis, etc.⁵ Hepatic dysfunction could be due to leukemic infiltrates in the liver, nonalcoholic steatohepatitis, sepsis, hepatotropic viral infections, therapy-related toxicity seen due to asparaginase, rarely hyperinflammatory syndromes like hemophagocytic lymphohistiocytosis (HLH), and indirect hyperbilirubinemia due to underlying genetic syndromes like Gilbert's syndrome.⁶ Hepatic dysfunction can contribute to morbidity by adding on to the underlying disease, delaying chemotherapy, dose modifications of chemotherapeutic agents, and rarely can cause mortality due to fulminant hepatic failure. This study was intended to find out the prevalence of hepatic dysfunction during induction therapy and its risk factors and effects on therapy and outcome.

Materials and Methods

This was a retrospective data analysis of all the children with ALL and LBL admitted to our center between December 2013 and December 2021. Children between 1 and 18 years of age with ALL or B/T cell LBL who underwent induction therapy at our center as per The UK-ALL 2003 protocol, which is the standard of care at our center, were included in the study.^{7,8} Those children who were started on different chemotherapy protocols were excluded.

Remission Induction Therapy

Children with B-ALL and National Cancer Institute (NCI) standard risk (i.e., age 1–10 years with leucocyte count less than $50,000 \text{ cells/mm}^3$) were given three-drug induction

(regimen A) with dexamethasone, vincristine, and asparaginase. Children with B-ALL and NCI high risk (age > 10 years and/or leucocyte count more than $50,000 \text{ cells/mm}^3$) and all the children with T-ALL and B/T LBL were given four-drug induction (regimen B) with dexamethasone, vincristine, daunorubicin, and asparaginase. Intrathecal methotrexate therapy was given as per the protocol. All the children on regimen B chemotherapy received oral antifungal prophylaxis with voriconazole (9 mg/kg/dose, twice a day) with temporary interruptions during vincristine administration. All the children were on oral cotrimoxazole 2 days a week as anti-*Pneumocystis jirovecii* prophylaxis. The duration of induction therapy lasted for 5 weeks.^{7,8}

Data Collection

The patient case notes from the medical records department, hospital laboratory reports track-care system, and oncology database were reviewed. The demographic data like age and sex; disease-related data like B/T cell disease, central nervous system disease status, and risk stratification (NCI standard risk/high); blood tests like white blood cell counts, lactate dehydrogenase (LDH) levels, and uric acid levels at presentation, viral serology (human immunodeficiency virus and hepatitis B for all patients), and liver function tests throughout the induction; treatment-related data like the type of asparaginase used, drug modifications—delay or dose reductions if any; induction outcomes (end of induction minimal residual disease [MRD]); number of deaths; and relapse and survival data (from beginning of therapy to last follow-up/death/relapse) were collected in a standard pro forma.

Definition of Hepatic Dysfunction

Though not all hepatic dysfunctions were due to drug toxicity, we used Common Terminology Criteria for Adverse Events (CTCAE) cutoffs to define hepatic dysfunction to maintain uniformity.⁹ Hepatic dysfunction was defined as grade 3 (> 5 to $20 \times$ the upper limit of normal [ULN]) and grade 4 (> $20 \times$ the ULN). Alanine transaminase (ALT) and aspartate transaminase (AST) levels as per CTCAE v5.0 and hyperbilirubinemia as $\geq 1.4 \text{ mg/dL}$ (CTCAE mentions grade 2 as $1.5\text{--}3 \times$ the ULN, grade 3 as $3\text{--}10 \times$ the ULN, grade 4 as $>10 \times$ the ULN) as the chemotherapy modifications begin at this cutoff as per the UK-ALL 2003 protocol.⁷ Liver function tests were done in all the patients at presentation and as required throughout the induction—before administering vincristine, clinical icterus, or septicemia.

Table 1 Distribution of patients between hepatic dysfunction and no hepatic dysfunction and multivariate regression analysis

Parameter	Hepatic dysfunction, yes		Hepatic dysfunction, no		RR (95% CI)	Adjusted <i>p</i> -value
	<i>n</i>	%	<i>n</i>	%		
Age groups (y)						
Up to 10	22	19.0	94	81.0	1	0.80
> 10	9	34.6	17	65.4	0.89 (0.33–2.4)	
Diagnosis						
B cell ALL	22	18.6	96	81.4	0.83 (0.39–1.74)	0.61
T cell ALL	7	35.0	13	65.0	1	
B lymphoblastic lymphoma	1	50.0	1	50.0	1.6 (0.47–5.3)	0.46
T Lymphoblastic lymphoma	1	50.0	1	50.0	1.28 (0.33–5.1)	0.72
NCI risk						
Standard risk	9	12.3	64	87.8	1	0.11
High risk	22	31.9	47	68.1	2.0 (0.85–4.9)	
BSA					1.9 (0.39–9.6)	0.41

Abbreviations: ALL, acute lymphoblastic leukemia; BSA, body surface area; CI, confidence interval; NCI, National Cancer Institute; RR, relative risk.

Statistical Analysis

Data were entered in Microsoft Excel and analyzed using IBM SPSS statistics for Windows, Version 25.0. Demographics and treatment regimens were reported using descriptive statistics (tabulations, mean, median). Data from children with hepatic dysfunction was compared with those without hepatic dysfunction. Age, sex, type of ALL/LBL, NCI risk status, MRD status, and deaths were assessed using chi-squared tests. Body weight, body surface area (BSA), LDH, and uric acid parameters were assessed using Student's *t*-tests. Those variables with a *p*-value of < 0.2 were analyzed with multivariate regression analysis. Kaplan–Meier survival estimates were used to calculate the event-free survival (EFS) where death or relapse were considered as events. A *p*-value of less than 0.05 was considered as significant.

Ethics: The study was approved by the institutional ethics committee with number 05- 2022/194 on May 19, 2022. The study was performed in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Results

A total of 161 children were treated at our center between December 2013 and December 2021, of which 142 children underwent induction chemotherapy at our center as per the UK-ALL 2003 protocol and were included in the study. Out of 142, 118 (83%) children had B cell ALL, 20 (14%) had T cell ALL, 2 (1.4%) had B-LBL, and 2 (1.4%) had T-LBL. Ninety-three (65.4%) were boys and 49 (34.5%) were girls.

Seventy-three (51.4%) out of 142 children were categorized as standard risk and received three-drug induction, whereas 69 (48.2%) children were under the high-risk category and received four-drug induction.

Thirty-one (21.8%; 95% confidence interval [CI] 15.3–29.5) children developed hepatic dysfunction during induction chemotherapy as per the defined criteria which included 11 girls (22.5%) and 20 boys (21.5%; *p* = 0.9). Among the children under the age group of less than 10 years, 22 (19%) developed hepatic dysfunction (B-ALL 15, T-ALL 5, B-LBL 1, and T-LBL 1) as opposed to 9 (34.6%; B-ALL 7, T-ALL 2) children among those above 10 years of age (*p* = 0.08) (► **Table 1**).

Sixty-four patients (45%) received L-asparaginase and 10 (15.6%) of them developed hepatic dysfunction, whereas 67 (47.2%) patients received pegylated asparaginase and 18 (26.9%) of them developed hepatic dysfunction. Ten patients (7%) received both molecules of asparaginase at different time periods of induction and 2 (20%) developed hepatic dysfunction (*p* 0.29).

Seven (7/31; 22.5%) of them had hepatic dysfunction at presentation, of whom one patient with T-ALL presented with acute liver failure and hepatic encephalopathy—AST 3463 U/L, ALT of 1878 U/L, and total bilirubin/direct bilirubin (TB/DB) of 14.24/11.25 mg/dL. Two (2/31; 6%) of them had hepatic dysfunction in the first week of induction and five (5/31; 16.1%) each during the second and third weeks of induction therapy. Twelve (12/31; 38.7%) of them had hepatic derangements toward the end of induction between days 25 and 35.

Body weight, BSA, LDH levels, uric acid levels, and white blood counts at presentation are mentioned in ► **Table 2**—weight and BSA were significantly high in patients with hepatic dysfunction. But none of these parameters proved

Table 2 Table showing mean values of weight, BSA, LDH, uric acid, and WBC at presentation in two groups

Parameter	Hepatic dysfunction, yes		Hepatic dysfunction, no		p-Value
	Mean	SD	Mean	SD	
Weight	25.5	13.5	18.5	10.5	0.01
BSA	0.87	0.29	0.73	0.26	0.02
LDH	985	955.3	1074.4	1476.6	0.7
Uric acid	5.2	3.7	5.1	4.9	0.85
WBC at presentation	80316	145391	46068	81883	0.21

Abbreviations: BSA, body surface area; LDH, lactate dehydrogenase; SD, standard deviation; WBC, white blood cells.

to be significant risk factors for the development of hepatic dysfunction on multivariate analysis (►Table 1).

Among the 31 children with hepatic dysfunction, chemotherapy modification in terms of dose alteration or delay in administration was required in 14 (53.9%) children. Chemotherapy drug doses were modified in five children and a single dose of chemotherapy was omitted in four children in view of high bilirubin. Four children had a delay in administration of scheduled doses (average duration of 12.5 days) and in one child there was both delay in administration of chemotherapy as well as omission of doses.

►Table 3 contains the data regarding the number of children in each category of hepatic dysfunction and their mean ages and ►Table 4 contains the mean values of TB, DB, AST, and ALT.

Induction outcomes were measured in terms of end-of-induction MRD status. Out of 138 ALLs, MRD data was available for 123 patients (11 induction deaths, MRD data was not available for 4 patients)—20 in hepatic dysfunction and 103 in the group without hepatic dysfunction. Among the 20 children with hepatic dysfunction, 18 (90%) were MRD negative (< 0.01%), and 2 (10%) were MRD positive (> 0.01%),

Table 3 Distribution of patients among various subgroups of hepatic dysfunction, their mean ages, and number of children requiring chemotherapy modifications in each subgroup

Deranged parameters	Number (%)	Age (median ± SE)	Dose modification or delay, n (%)
Hepatic dysfunction	31 (21.8)	6 ± 0.86	14 (45.1)
AST/ALT elevation irrespective of TB/DB	14 (9.9)	5.5 ± 1.3	5 (35.7)
Isolated AST/ALT	4 (2.8)	3.75 ± 1.8	—
TB/DB elevation irrespective of AST/ALT	27 (19.0)	7 ± 0.94	12 (44.4)
Isolated TB/DB elevation	17 (12.0)	7 ± 1.2	7 (41.1)

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; DB, direct bilirubin; SE, standard error; TB, total bilirubin.

Table 4 Average values of various hepatic parameters

	Mean	SD	Median	Range (Q1–Q3)
AST (U/L)	197.3	634.3	0	0–202
ALT (U/L)	207.1	396.2	0	0–312
TB (mg/dL)	4.3	3.6	3.4	1.9–6.1
DB (mg/dL)	3.3	3.2	2.4	1.0–4.7
Age in years	7.6	4.8	6	3.5–11

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; DB, direct bilirubin; SD, standard deviation; TB, total bilirubin.

whereas in the group with no hepatic dysfunction, 83 (80.6%) children had negative MRD and 20 (19.4%) children had positive MRD ($p = 0.31$). Among 18 children with a negative MRD in the hepatic dysfunction group, 8 received three-drug induction, and 10 received four-drug induction. Two patients who were MRD positive in the hepatic dysfunction group received four-drug induction.

A total of 37/142 (26%) children died in this cohort until the period of data collection—11/37 (29.7%) were during induction. Among the hepatic dysfunction group, 11/31 (35.4%) children died and 8/11 (72.7%) of them were during induction as opposed to 26/111 (23.4%) deaths among the group without hepatic dysfunction and 3/26 (11.5%) among them were during induction ($p < 0.001$). In the hepatic dysfunction group, 7/8 induction deaths were due to sepsis—2 children had multidrug-resistant (MDR) Gram-negative septicemia, 4 of them had MDR Gram-negative sepsis along with candida species infection, and 1 had culture-negative sepsis. Hepatic dysfunction in this set of children was preceded by sepsis. Acute liver failure at presentation was the cause of death in one child with T-cell ALL. Three other children died at later stages of treatment—two children died during maintenance chemotherapy—a 22-month-old child with chronic norovirus infection, a 10-year-old child with refractory congenital HLH (UNC13D defect), and another child died during consolidation therapy with septicemia.

Out of 23 patients who were alive at the end of induction in the hepatic dysfunction group, the data regarding the number of days taken for the resolution of dysfunction was available for only 18 patients, ranging from 5 to 45 days, with a median of 9.5 days.

In this cohort of 142 patients, a total of 15 children had a relapse of their disease until the time of data collection. None among the children with hepatic dysfunction had a relapse. Five-year EFS (death or relapse) was $59.93 \pm 9\%$ (95% CI: 40.2–75) in children with hepatic dysfunction as opposed to $72 \pm 5.0\%$ (95% CI: 59.1–78.8) in those without hepatic dysfunction (95% CI, $p = 0.07$) (► Fig. 1).

Discussion

Hepatic dysfunction during induction therapy was observed in 1 in 5 children at our center with a prevalence of 21.8% as opposed to a study by Denton et al where 6.8% hepatic dysfunction was seen during induction chemotherapy as per the Children's Oncology Group (COG) style modified Berlin-Frankfurt-Munich protocol.¹⁰ Hashmi et al reported a 4% incidence of conjugated hyperbilirubinemia during early phases of chemotherapy as per the COG guidelines and 3.2% had transaminitis, whereas hyperbilirubinemia prevalence was 19% in our cohort and 9.9% had transaminitis.¹¹ These varying data from different centers could be attributed to the ethnicity and genetic makeup of the study population, variations in protocols, drug toxicity, and infection rates.

In our study, 4.9% of children (i.e., 7 out of 142) had hepatic dysfunction at presentation, of whom one child had fulminant hepatic failure and died on day 1 of induction. Fulminant hepatic failure has been reported at presentation in the past

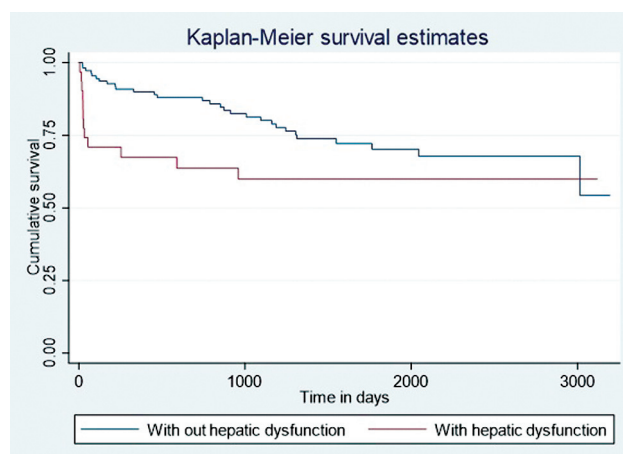


Fig. 1 Event-free survival in patients with hepatic dysfunction versus no hepatic dysfunction.

and was predominantly associated with poor outcomes.^{12–14} In a study by Segal et al, 34% of children had elevated transaminases and 3.4% had hyperbilirubinemia at presentation.¹⁵ This was attributed to the leukemic infiltrates in the liver and was substantiated by the findings of a significant association of hepatitis at presentation in patients with high leucocyte count, elevated LDH, and uric acid indicating an increased tumor burden. They treated these patients with a short course of steroids prior to the beginning of induction therapy. But in our cohort, we did not use any prephase steroids.

While obesity and age more than 10 years were noted to be significant predictors of hepatic derangement in earlier reported studies, none of them were significant on multivariate analysis in our cohort.^{10,11}

Though septicemia, HLH, leukemic infiltrates, and drugs are known causes of hepatic dysfunction and were evidenced in our study it was difficult to ascertain specific causes due to the retrospective nature of the study and lack of a structural workup. Mekonnen and Wondmeneh reported an incidence of moderate drug-induced hepatotoxicity to be 15% during ALL induction therapy.¹⁶ While the drugs commonly used in induction specially asparaginase can cause hepatic dysfunction, voriconazole used for antifungal prophylaxis in regimen B can also cause hepatic derangements making the cause-effect association more difficult in a retrospective setting.

Induction mortality in those who developed hepatic dysfunction is high compared to those who did not ($p < 0.001$). Septicemia was the cause of mortality in all but one case in this group.

Chemotherapy modifications due to hepatic dysfunction were done as per the UK-ALL 2003 protocol. In our cohort, close to 1 in 2 children with hepatic derangements during induction therapy (14/31) required some form of chemotherapy modification—delay/reduction in dose/omission. This was very high as compared to the cohort by Denton et al where 1 in 6 children with induction toxicity (hepatic + pancreatic) required drug modifications.¹⁰ They did not observe any effect on overall survival due to drug modifications. The 5-year EFS in our cohort was lower in patients with hepatic dysfunction compared to no hepatic dysfunction

($p=0.07$) as opposed to Denton et al where treatment-related toxicity did not affect the EFS.¹⁰ Sepsis-related induction deaths must have contributed to this dismal EFS in our patients with hepatic dysfunction.

Though the MRD outcomes in both the groups were not statistically different and there were no relapses in the hepatic dysfunction group, these must be interpreted with caution as the induction mortality was high in the hepatic dysfunction group.

A large prospective study with a structured workup for ascertaining specific causes for deranged hepatic functions will provide more comprehensive data and should be considered.

Conclusion

One in five children with ALL and LBL had hepatic dysfunction during induction therapy. Induction mortality is high in those with hepatic dysfunction compared to those with normal liver function, with sepsis being the most common cause of death in our settings. It is difficult to ascertain the cause of hepatic dysfunction in a retrospective study due to multiple confounding factors. Though modifications due to hepatic dysfunction did not seem to affect the induction outcomes in the hepatic dysfunction group, this should be interpreted with caution due to the high induction mortality in that group and the small sample size.

Patient Consent

Authorship

The manuscript has been read and approved by all the authors, that the requirements for authorship have been met, and each author believes that the manuscript represents honest work.

Authors' Contributions

N.A.R.: Contributed to conception of design, literature search, data collection, data and statistical analysis, manuscript writing, editing, and manuscript review.

K.R.: Contributed to data collection, literature search, and manuscript review.

H.P.L.: Contributed to conception of design, data and statistical analysis, manuscript editing, and manuscript review.

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Conflict of Interest

None declared.

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