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Incidence and predictors of treatment-related conjugated hyperbilirubinemia during early treatment phases for children with acute lymphoblastic leukemia

Saman K. Hashmi[*,1], **Shoba A. Navai**[*,1], **Tiffany M. Chambers**[1], **Michael E. Scheurer**[1], **M. John Hicks**[2], **Rachel E. Rau**[1], **Maria M. Gramatges**[1]

[1]Department of Pediatrics, Section of Hematology and Oncology, Baylor College of Medicine, Houston, TX

[2]Department of Pathology and Immunology, Baylor College of Medicine, Houston, TX

Abstract

Conjugated hyperbilirubinemia (CHB) and liver transaminase elevation are known complications of acute lymphoblastic leukemia (ALL) therapy, but host risk factors are poorly understood. Among 373 children diagnosed with ALL between 2011–2016, clinically significant CHB and transaminase elevation were observed in 15 (4.0%) and 12 (3.2%) children, respectively, during Induction and Consolidation. Body-mass-index ≥95th percentile (OR 9.20, CI 2.56–32.96) was the only host factor independently associated with CHB, and no host factors were associated with transaminase elevation. Obese patients warrant closer monitoring of hepatic function to facilitate early intervention prior to the development of severe, adverse hepatic events.

Keywords

Hyperbilirubinemia; pediatric; acute lymphoblastic leukemia; hepatotoxicity; obesity

INTRODUCTION

Despite survival rates exceeding 90%,[1] augmented therapeutic intensity to improve outcomes for higher risk pediatric acute lymphoblastic leukemia (ALL) increases risk for treatment-related complications. Children's Oncology Group (COG) protocols suggest assessing hepatic function prior to each chemotherapy cycle, with the need for more frequent assessment left to provider discretion. Well-established risks for drug-induced hepatotoxicity include female sex, obesity, malnutrition, and pre-existing liver disease such as non-alcoholic fatty liver disease (NAFLD); risk may be further moderated by genetic variability.[2] In a single-institution study conducted in a pediatric ALL population, treatment-related hepatotoxicity was associated with obesity and age ≥10 years.[3] In that study, hepatotoxicity

Corresponding author: Maria M. Gramatges, MD, PhD, Address: 1102 Bates Ave, Suite 1200, Houston, Texas 77030, Phone: 832-824-4678 Fax: 832-825-4651 gramatge@bcm.edu.

*Authors contributed equally

Conflict of Interest

The authors have no conflict to declare.

was defined by the Common Terminology Criteria for Adverse Events (CTCAE) as grade 3 or higher conjugated or unconjugated hyperbilirubinemia and grade 4 or higher transaminitis, definitions that do not directly correspond with dose modification criteria noted in COG clinical trials.

Here, we aimed to identify host risk factors predictive of early ALL treatment-related hepatotoxicity, focusing on conjugated hyperbilirubinemia (CHB) and elevated liver transaminases (TA) that met thresholds for dose-limiting toxicity during early treatment phases. Characterization of host factors associated with dose-limiting toxicities may identify patients that benefit from more frequent screening, thereby facilitating early detection and intervention.

METHODS

We reviewed medical records from patients diagnosed with ALL between 1–21 years of age and treated at Texas Children's Cancer Center between 2011–2016. Infants <12 months at diagnosis, those with Philadelphia chromosome-positive ALL, and those with Down syndrome were excluded due to differences in upfront therapy and susceptibility to therapy-related toxicities. Patients who presented in liver failure (n=1) and those who died in Induction from non-hepatotoxicity related causes were excluded (n=3). All patients were treated on, or in accordance with the standard arm of, contemporary COG protocols AALL0331, AALL0232, AALL0932, AALL1131, AALL0434, and AALL1231.

Significant, treatment-related CHB and TA elevation were defined as conjugated bilirubin ≥1.2 mg/dL, and alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >20x upper limit of normal (Grade 4 toxicity, CTCAE v5.0), definitions that represent thresholds for dose modification during these phases of treatment in COG ALL protocols. For all patients diagnosed between 2011–2016, demographic and clinical data including age, sex, self-described ethnicity, body mass index (BMI) and percentile for age and sex at diagnosis, Induction and post-Induction regimens, and bone marrow minimal residual disease at end of Induction were abstracted from the medical record. For patients who developed hepatotoxicity during Induction or Consolidation, additional data including comorbidities, concurrent infections, and vital status were also abstracted.

Statistical analyses were performed using Stata 14.0 (StataCorp LP, College Station, TX). Age was analyzed as a continuous variable, whereas BMI was categorized as $<95^{th}$ percentile or $\geq 95^{th}$ percentile. Subjects <2 years old (n=8) and >20 years old (n=1) were excluded from the BMI analysis given the lack of normative data. Features of cases with and without CHB or elevated TA were compared using the Wilcoxon rank sum test (for median age) and chi-square test for the remaining covariates. Univariable and multivariable logistic regression analyses were performed with a level of significance denoted by $p < 0.05$.

RESULTS

Of the 373 patients meeting inclusion criteria, 15 (4.0%) had CHB and 12 (3.2%) had elevated TA during Induction or Consolidation: 8 had isolated CHB, 5 had isolated elevated TA, and 7 had both CHB and elevated TA. There were no significant differences in the

distribution of patient demographics, diagnosis, and treatment factors for those with and without elevated TA. Compared with those without CHB, patients with CHB were more likely to have the following characteristics: older age (p=0.0001), Hispanic ethnicity (p=0.044), BMI ≥95th percentile (p<0.001), treatment with four-drug Induction that included anthracycline (p=0.002) (Table 1). We then conducted a multivariable logistic regression to investigate the association between these host and treatment factors and CHB, showing BMI ≥ 95th percentile as the only independent predictor of CHB (p=0.001) (Table 2). To investigate if associations with BMI extended to patients designated as overweight, we tested the impact of overweight/obese status (BMI ≥85th percentile) on risk for CHB, but associations observed in univariable analysis did not persist after multivariable analysis (p=0.059), suggesting that this association is limited to patients in the highest BMI range. Although age was not significant in our original multivariable model (p=0.064), expanding the BMI cutoff to the 85th percentile strengthened the effect of age (p=0.039, Supplemental Table 1). However, when we conducted these analyses with age as a dichotomous variable (<15 vs. 15–21 years), BMI ≥ 95th percentile remained highly significant (p<0.001), but age was no longer a contributing factor (p=0.384).

Clinical presentation of CHB most often included abdominal pain and jaundice. Concurrent evidence for hepatic dysfunction was common, including coagulopathy and hypoalbuminemia, as were concomitant infections (n=7) and steroid-induced, insulin-dependent diabetes (n=10; Supplemental Tables 2 and 3). All patients evaluated with abdominal ultrasound (n=13) had hepatomegaly with increased echogenicity. Nine patients (60%) presented with CHB between days 15 and 22 of Induction. The median time to CHB resolution was 14 days (range 2–44 days). Five underwent liver biopsy, all with evidence of canalicular and hepatocellular cholestasis, micro- and/or macrovesicular steatosis, and varying degrees of portal and peri-portal fibrosis (Supplemental Figure 1). Twelve had chemotherapy dose modifications or delays due to hepatotoxicity, and two high risk patients were subsequently given a standard COG consolidation as a result of toxicities experienced during Induction (Supplemental Table 2). Per institutional practice, most were treated with ursodiol (n=11, 73%). Seven (47%) experienced CHB recurrence post-Consolidation. Five did not survive, but none had deaths directly related to hepatotoxicity (sepsis in Delayed Intensification, n=1; sepsis in relapse, n=1, relapsed disease, n=1, encephalopathy post bone marrow transplant, n=2).

DISCUSSION

In this study, 20/373 (5.4%) of ALL patients developed hepatotoxicity that met criteria for chemotherapy dose modification during Induction and Consolidation. This observation is similar to the rate of early hepatotoxicity observed in a prior study,[3] which was also conducted in a predominantly Hispanic population. In that study, 4.9% of patients had hyperbilirubinemia (conjugated and unconjugated) during Induction, comparable to the 4.0% frequency of CHB we observed during Induction and Consolidation. Although in that study both age and obesity contributed to risk for hepatotoxicity, we observed a considerably stronger effect of BMI on CHB than we did for age, with BMI ≥ 95th percentile consistently associated with CHB.

Hepatic histopathologic findings of diffuse macrosteatosis are characteristic of non-alcoholic steatohepatitis (NASH), a subset of NAFLD.[4] The relationship we observed between obesity and CHB suggests underlying NAFLD, an indicator of metabolic syndrome, as a potential contributing factor. Further, the detection of portal fibrosis in patients with CHB, a characteristic seen in advanced NASH, also suggests that baseline hepatic damage may impact CHB risk. Although hepatic microsteatosis may be seen in NAFLD, the diffuse microsteatosis observed in our patients with CHB is more characteristic of an acute toxin- or medication-induced liver injury,[4] as described in asparaginase-induced liver disease.[5] The universal administration of asparaginase did not permit assessment of the impact of this agent on CHB risk. However, the majority of cases presented with CHB between 11 and 18 days after pegaspargase, within the expected timeframe for this known drug-related complication.[6,7] Notably, of the three non-obese cases with CHB, one was a patient with T-ALL who received two doses of asparaginase in Induction as per AALL1231. Unlike in some adult ALL protocols,[8] most pediatric consortium trials, including COG trials, do not cap pegaspargase doses. However, doses in excess of 3,750 IU have been associated with an increase in adverse events in pediatric cohorts, including increased total and direct bilirubin.[9] As such, there is support for capping pegaspargase dosing at one vial (3,750 IU) in at-risk populations.[10]

Treatment for therapy-related CHB is variable and there are no evidence-based guidelines. Ursodiol is a bile acid commonly used for treatment of primary biliary cirrhosis or gallstones but has off-label applicability for treating CHB.[11] A pilot study conducted in pediatric ALL demonstrated tolerability of ursodiol and a trend towards hepato-protective effect.[12] There are also reports of pegaspargase-related hyperbilirubinemia successfully treated with vitamin B complex and levocarnitine in pediatric ALL,[13] and of the use of milk thistle to treat hepatoxicity, though the results of the latter trial failed to demonstrate benefit.[14]

Limitations to our study include a lower than expected number of affected cases that may have precluded the detection of subtle risk factors and the possibility that CHB or elevated TA were not detected due to infrequent monitoring in the absence of clinical symptoms. Due to inconsistent availability of genetic material, we were unable to evaluate the impact of genetic variation on risk, e.g. the previously reported association between *PNPLA3* rs738409 and fatty liver disease and risk for TA elevation early in pediatric ALL therapy.[15] Larger, prospective studies are needed to inform considerations of introducing dose modification criteria for asparaginase, evaluating the efficacy of prophylactic and therapeutic interventions for CHB, and assessing genetic contributions to this outcome.

The results of this study support consideration of closer monitoring of liver function in obese children diagnosed with ALL. Nearly half of our cases who developed CHB experienced recurrence later in therapy, so that early presentation implicates later morbidity and the need for monitoring beyond ALL Consolidation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Abbreviations

ALL	Acute lymphoblastic leukemia
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AYA	Adolescent and young adult
BMI	Body mass index
CHB	Conjugated hyperbilirubinemia
CI	Confidence interval
COG	Children’s Oncology Group
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
OR	Odds ratio
TA	Liver transaminases

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Table 1.

Distribution of patient demographic and disease characteristics in Induction and Consolidation

	Conjugated hyperbilirubinemia (n=15)	No conjugated hyperbilirubinemia (n=358)	*P* value
Median Age in Years (IQR)	14.0 (10.9–15.5)	6.3 (3.5–11.9)	**0.0001**
Ethnicity, n (%)			**0.044**
Hispanic	12 (80.0)	192 (53.6)	
Non-Hispanic	3 (20.0)	166 (46.4)	
Sex, n (%)			0.901
Male	9 (60.0)	209 (58.4)	
Female	6 (40.0)	149 (41.6)	
BMI at Diagnosis, n (%)			**<0.001**
<95th Percentile	4 (26.7)	282 (84.4)	
≥95th Percentile	11 (73.3)	52 (15.6)	
ALL Induction Type, n (%)			**0.002**
Three-drug induction[1]	1 (6.7)	169 (47.2)	
Four-drug induction[2]	14 (93.3)	189 (52.8)	
MRD Status (NCI HR B-ALL patients only)			0.759
<0.01%	10 (76.9)	96 (71.1)	
≥0.01%	3 (23.1)	39 (28.9)	

[1]Three-drug induction includes oral dexamethasone, intravenous vincristine, and intramuscular or intravenous pegaspargase

[2]Four-drug induction in oral dexamethasone (age <10 years) or prednisone (age ≥10 years), intravenous vincristine, and intramuscular or intravenous pegaspargase, and intravenous daunorubicin

Table 2.

Multiple logistic regression model for variables associated with CHB in Induction or Consolidation

	Conjugated hyperbilirubinemia	
	Adjusted OR (95% CI)	***P***
Age	1.20 (0.99–1.44)	0.064
BMI at diagnosis		
<95th Percentile	1.00 (REF)	1.00
≥95th Percentile	9.20 (2.56–32.96)	**0.001**
Ethnicity		
Non-Hispanic	1.00 (REF)	1.00
Hispanic	1.78 (0.43–7.39)	0.426
Sex		
Male	1.00 (REF)	1.00
Female	1.91 (0.55–6.57)	0.306
ALL Induction Type		
Three-drug induction[1]	1.00 (REF)	1.00
Four-drug induction[2]	3.04 (0.26–35.59)	0.375

[1]Three-drug induction includes oral dexamethasone, intravenous vincristine, and intramuscular or intravenous pegaspargase

[2]Four-drug induction in oral dexamethasone (age <10 years) or prednisone (age ≥10 years), intravenous vincristine, and intramuscular or intravenous pegaspargase, and intravenous daunorubicin