A report from the Leukemia Electronic Abstraction of Records Network on risk of hepatotoxicity during pediatric acute lymphoblastic leukemia treatment

The objective of this work was to identify determinants of treatment-associated hepatotoxicity (TAH) in a diverse population of 782 children with acute lymphoblastic leukemia (ALL). Based on extracted electronic medical record data, nearly all subjects experienced mildly elevated hepatic laboratory values (HL), particularly those given high-intensity treatment. Furthermore, 15.9% of subjects experienced TAH in at least one post-induction treatment phase, which was associated with increased body mass index, but did not affect relapse-free survival.

While modern treatment for childhood ALL confers excellent survival,[1] 30-50% of children experience at least one serious adverse event during upfront ALL treatment.[2] TAH may be related to a number of ALL therapeutics, e.g., asparaginase, antimetabolites, and anthracyclines. The reported incidence of TAH in pediatric ALL is highly variable, likely due to inconsistent defining criteria and data-capturing methods.[3-10]

To comprehensively characterize the impact of ALL therapy on HL and the treatment phase-specific incidence of TAH, we leveraged data from the Leukemia Electronic Abstraction of Records Network (LEARN). LEARN is a multi-institutional collaboration and childhood leukemia data repository that includes comprehensive demographic, anthropometric, diagnostic, treatment, laboratory, and outcome data. Given evidence for racial and ethnic disparities in childhood ALL outcomes and survival[11] and the historic under-representation of children from minority groups in pediatric cancer trials,[12] LEARN was constituted by institutions with highly diverse patient populations. LEARN relies on automated extraction of electronic medical record data after manual input of basic data, an ascertainment method which significantly improves reporting accuracy of laboratory adverse events.[13] Here, we utilized LEARN data to assess HL changes by treatment phase and intensity, determining the incidence of TAH, its risk determinants, and its impact on patients' outcomes.

Our study utilized LEARN data from children (ages 1-21 years) diagnosed with ALL and treated at Texas Children's Cancer and Hematology Centers (TXCH) or the Children's Hospital of Philadelphia (CHOP) between 2006 and 2014. Children with infant ALL and Down syndrome were excluded, as were those who received part of their induction at another institution, did not complete induction, received non-standard agents or sequence of chemotherapy and/or a tyrosine kinase inhibitor, or underwent stem cell transplantation. Trained personnel manually populated a REDCap™ database with select data from the TXCH and CHOP electronic medical records, including date on diagnosis, dates of starting and ending chemotherapy courses, and risk stratification. Using the REDCap™ Application Programming Interface, we then auto-extracted demographic and laboratory data from each electronic medical record data warehouse. Manually-entered dates guided extraction by providing boundaries over which the data were extracted, enabling linkage of extracted data with a specific chemotherapy phase. Demographic data, disease characteristics, and HL were collected using a combination of targeted manual abstraction and extensive automated extraction from each institution's electronic medical records.

HL included alanine aminotransaminase, aspartate aminotransferase, and total and conjugated bilirubin, normed to the age-based upper limit of normal (ULN). TAH was determined by the following criteria: (i) grade 4 transaminitis by the Common Toxicity Criteria of Adverse Events (CTCAE) v5.0, defined as alanine aminotransaminase or aspartate aminotransferase >20xULN; (ii) grade 3 hyperbilirubinemia by the CTCAE, defined as total bilirubin >3xULN, or (iii) conjugated bilirubin ≥1.2 mg/dL. TAH was defined based on established Children's Oncology Group thresholds for dose modification considerations during ALL therapy. Each subject was categorized as having received high or standard-intensity treatment by phase, with high-intensity defined by inclusion of anthracycline (induction), cyclophosphamide (consolidation), and mercaptopurine (interim maintenance 1). Subjects were assigned final treatment intensity based on National Cancer Institute's diagnostic criteria and interim maintenance 1 treatment assignment.

Distributions of categorical characteristics and median age were compared by treatment intensity using χ^2 analyses and the Wilcoxon rank sum test, respectively. Median normed HL values were compared by treatment intensity for each treatment phase using the Wilcoxon rank sum test. Multivariable logistic regression models of factors influencing post-induction TAH and recurrent/persistent TAH (defined as TAH in 2 or more treatment phases) were performed. Cox regression models were used to calculate hazard ratios (HR) and 95% confidence intervals (95% CI) to compare overall and relapse-free survival in subjects with no TAH relative to those with any TAH, considered as a time-varying exposure introduced on the day of first documentation. All multivariable analyses were adjusted for treatment intensity, age at diagnosis, race/ethnicity, gender, body mass index, ALL immunophenotype, and end-induction minimal residual disease. Covariates were selected *a priori*, based on our hypotheses and clinical experience, and were included in all analyses. *P*-values <0.05 were considered statistically significant. Statistical analyses were performed using Stata 15.0 (StataCorp LP, College Station, TX, USA).

Of 921 eligible patients, 782 met the inclusion criteria. Demographic, diagnostic, and disease characteristics of included subjects are shown in Table 1 by induction treatment intensity. Approximately one-third were Latino, 9% Black, 5% Asian, and the remainder were White. Subjects assigned to high-intensity induction were more likely to be overweight or obese ($P<0.001$), possibly reflecting older mean age (10.6 years *vs.* 4.6 years). Data on end-induction minimal residual disease were available for 681 of 782 subjects, of whom 22% (n=149) were positive for minimal residual disease, representing 17% (n=60) of subjects given standard-intensity treatment and 29% (n=89) of those given high-intensity treatment.

A mean of 139.5 HL were obtained per subject. There were a greater number of HL for patients given high-intensity treatment than for those given standard-intensity treatment (148.9 *vs.* 129.3, $P<0.001$). The number of subjects analyzed per phase varied over time and by treatment intensity: induction, n=782; consolidation, n=691; interim maintenance 1, n=643; delayed intensification, n=625; interim maintenance 2, n=235; and maintenance, n=571. Over 80% of subjects had a HL >ULN during at least one treatment phase, with the values being mostly 1-3xULN (Figure 1A-D). Alanine aminotransaminase was the most consistently and markedly elevated HL throughout all phases (Figure 1A). Total and conjugated bilirubin remained within normal limits for

Table 1. Demographics and disease characteristics of the study cohort.

Characteristic	All subjects (n=782)	Assigned to standard intensity induction (n=419)	Assigned to high intensity induction (n=363)	*P*-value
Mean age (SD)	7.4 (4.9)	4.6 (2.3)	10.6 (5.2)	<0.001
Race/ethnicity				
Non-Latino-White	366 (46.8)	194 (46.3)	172 (47.4)	0.021
Latino	275 (35.2)	162 (38.7)	113 (31.1)	
Non-Latino-Black	68 (8.7)	26 (6.2)	42 (11.6)	
Asian	39 (5.0)	17 (4.1)	22 (6.1)	
Other	34 (4.3)	20 (4.8)	14 (3.9)	
Gender				0.010
Male	431 (55.1)	213 (50.8)	218 (60.1)	
Female	351 (44.9)	206 (49.2)	145 (39.9)	
BMI category*				<0.001
Not overweight or obese	509 (70.2)	293 (76.5)	217 (63.4)	
Overweight or obese	216 (29.8)	90 (23.5)	125 (36.6)	
ALL immunophenotype				<0.001
B-cell	712 (91.1)	419 (100.0)	293 (80.7)	
T-cell	70 (8.9)	0 (0.0)	70 (19.3)	
Minimal residual disease ^				<0.001
Positive	149 (21.9)	60 (16.4)	89 (28.3)	
Negative	532 (78.1)	306 (83.6)	212 (71.7)	

*Subject numbers dependent on documented/abstracted height & weight from diagnosis. ^Subject numbers dependent on documented minimal residual disease at end of induction. Standard intensity: standard, three-drug induction *versus* high intensity: four-drug Induction. SD: standard deviation; BMI: body mass index; ALL: acute lymphoblastic leukemia.

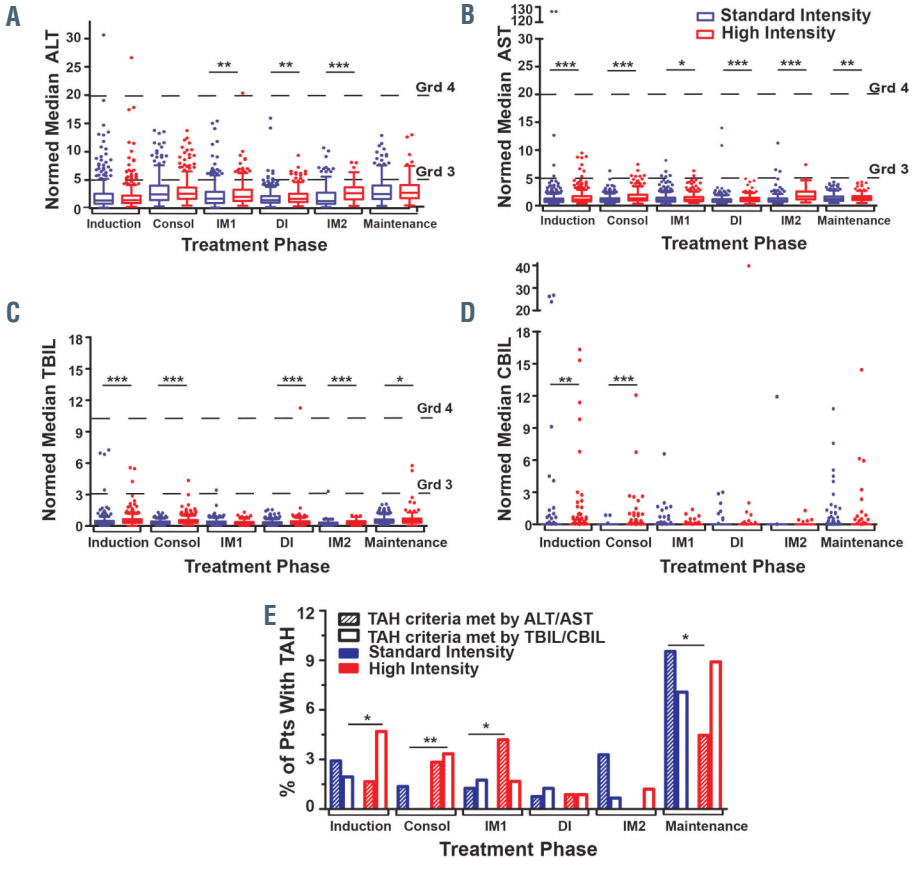

Figure 1. Trends in hepatic laboratory values, including treatment-associated hepatotoxicity, during acute lymphoblastic leukemia therapy by treatment intensity. (A-D) The normed median hepatic laboratory value (HL) of subjects by each HL are represented by box and whisker plots, with outliers shown in the dots, subjects given standard intensity treatment in blue, and those given high intensity treatment in red. (A) Normed median alanine aminotransaminase (ALT, SGPT). (B) Normed median aspartate aminotransaminase (AST, SGOT). (C) Normed median total bilirubin (TBIL). (D) Normed median conjugated bilirubin (CBIL). Dashed lines indicate thresholds of CTCAE v5.0 grading for grade 3 or grade 4 ALT, AST, or TBIL as follows: ALT/AST: Grd 3= 5-20x upper limit of normal (ULN), Grd 4= >20x ULN. TBIL: Grd 3= 3-10x ULN, Grd 4= >10x ULN. (E) Percentage of patients with treatment-associated hepatotoxicity (TAH) by treatment intensity over all courses of therapy. *P<0.05, **P=0.001-<0.01, ***P<0.001, comparing standard *vs.* high intensity groups. For (E), comparisons were made between TAH-ALT/AST of each intensity group (hashed bars) and between TAH-TBIL/CBIL of each intensity group (open bars) for each treatment phase. Consol: consolidation; IM1: interim maintenance 1; DI: delayed intensification; IM2i: interim maintenance 2.

nearly all subjects. Median HL were greater in the high-intensity than standard-intensity groups across all phases, with the differences being statistically significant for all phases (P<0.01) except delayed intensification and maintenance.

One hundred ten subjects (15.9%) experienced at least one episode of TAH after induction (Table 2). The majority of TAH events occurred during maintenance, and included both transaminitis and hyperbilirubinemia (Figure 1E). The presence of TAH was associated with being overweight/obese (odds ratio 1.7 [95% CI: 1.0-2.7], P=0.027). A minority of subjects (n=16, 2.3% overall) experienced recurrent/persistent TAH. Multivariable logistic regression did not identify patient characteristics associated with recurrent/persistent TAH in this small number of subjects (Table 2).

Time-varying Cox regression analyses identified risk factors associated with overall and relapse-free survival. The median follow-up was 3.4 years for overall survival and 3.1 years for relapse-free survival. TAH was not associated with relapse-free survival in adjusted analysis (HR=0.7, 95% CI: 0.2-2.3, P=0.543), although the follow-up was relatively short. Older age and positive minimal residual disease were associated with poorer relapse-free survival, and non-Latino Black patients also experienced poorer relapse-free survival, consistent with prior reports.[14] Because only three patients with TAH died, the study lacked power to assess the relationship between TAH and overall survival.

Here, we report the landscape of HL and TAH by treatment phase in a large, diverse, contemporary cohort of children with uniformly treated ALL. We show that mild elevations of hepatic transaminase levels are common throughout ALL therapy, particularly with high-intensity treatment. TAH is a rare outcome that is most common during maintenance, when therapy includes continuous antimetabolites. Our results provide reassurance that TAH-related dose modifications or delays in treatment are unlikely to have an impact on the risk of ALL relapse.

To date, the largest study assessing HL during childhood ALL therapy (n=262) found a higher risk for TAH among children ≥10 years and obese children (body mass index ≥95th percentile).[9] Our results confirm the association with body mass index in a larger, more diverse cohort but also provide reassurance that recurrent or persistent TAH is rare, and not predicted by known demographic or disease factors. Access to LEARN permitted novel examination of associations between TAH and treatment intensity by phase, rather than by protocol, showing a greater risk for TAH during the early phases of high-intensity treatment. While transaminitis is a recognized event during maintenance, we note that TAH-hyperbilirubinemia is also frequent, suggesting that both should be monitored. Recent recommendations to cap the PEG-asparaginase dose in obese patients and for those ≥22 years old may lead to a decrease in TAH in these at-risk populations.

The strengths of this study include the racial and ethnic diversity of the cohort, providing robust support that race and ethnicity do not independently predict TAH in childhood ALL. The use of automated HL extraction provides a more granular understanding of the impact of specific treatment blocks, minimizing abstraction error and reporting bias. Potential limitations include our inability to assess the impact on hepatic synthetic function and drug metabolism, as these assessments are not routinely obtained. Furthermore, determination of precise temporal trends with respect to the administration of specific chemotherapy agents and other concomitant medications was not possible from the data available. While our findings suggest an infrequent need for dose modifications due to TAH, dosing data were not available to con-

Table 2. Multiple logistic regression model for variables associated with treatment-associated hepatotoxicity.

Characteristic	TAH in any phase (n=110) OR (95% CI)	*P*-value	Recurrent/persistent TAH (n=16) OR (95% CI)	*P*-value
Treatment intensity				
Standard intensity	1.0 (REF)		1.0 (REF)	
High intensity	0.8 (0.5 -1.5)	0.515	3.9 (0.7-22.7)	0.125
Mean age	1.0 (1.0-1.1)	0.358	1.0 (0.9-1.2)	0.434
Race/ethnicity				
Non-Latino-White	1.0 (REF)		1.0 (REF)	
Latino	1.1 (0.7-1.8)	0.771	0.9 (0.3-3.1)	0.872
Non-Latino-Black	0.6 (0.2-1.6)	0.321	--	--
Asian	1.4 (0.6-3.5)	0.470	--	--
Other	0.4 (0.1-1.7)	0.211	1.2 (0.1-10.5)	0.878
Gender				
Male	1.0 (REF)		1.0 (REF)	
Female	0.9 (0.6-1.5)	0.774	1.2 (0.4-4.1)	0.755
BMI category*				
Not overweight or obese	1.0 (REF)		1.0 (REF)	
Overweight or obese	1.7 (1.1-2.8)	0.027	1.6 (0.5-5.5)	0.461
ALL immunophenotype				
B-cell	1.0 (REF)		1.0 (REF)	
T-cell	1.2 (0.5-2.6)	0.729	2.3 (0.5-10.1)	0.253
Minimal residual disease^				
Negative	1.0 (REF)		1.0 (REF)	
Positive	0.7 (0.4-1.3)	0.289	0.4 (0.1-1.9)	0.237

*Subject numbers dependent on documented/abstracted height & weight from diagnosis. ^Subject numbers dependent on documented minimal residual disease at the end of induction. TAH: treatment-associated hepatotoxicity; OR: odds ratio; 95% CI: 95% confidence interval; REF: reference; BMI: body mass index; ALL: acute lymphoblastic leukemia.

firm this observation. Last, the long-term impact of TAH on liver function could not be determined here.[15] Despite these limitations, our results provide novel insights regarding the impact of ALL treatment on HL and the risk of TAH in overweight/obese patients, providing guidance for future study designs that integrate potentially hepatotoxic novel therapeutics, and supporting further investigation of underlying pharmacogenomic contributors to TAH.

Joanna S. Yi,[1] Tiffany M. Chambers,[1] Kelly D. Getz,[2] Tamara P. Miller,[3] Evanette Burrows,[2] Marla H. Daves,[1] Philip J. Lupo,[1] Michael E. Scheurer,[1] Richard Aplenc,[2] Karen R. Rabin[1] and Maria M. Gramatges[1]

[1]Baylor College of Medicine, Texas Children's Cancer and Hematology Centers, Houston, TX; [2]University of Pennsylvania Perelman School of Medicine, Children's Hospital of Philadelphia, Philadelphia, PA and [3]Emory University School of Medicine, Children's Healthcare of Atlanta, Atlanta, GA, USA

Correspondence:

JOANNA S. YI - Joanna.yi@bcm.edu

doi:10.3324/haematol.2021.279805

Received: August 11, 2021.

Accepted: January 12, 2022.

Pre-published: January 27, 2022.

Disclosures: no conflicts of interest to disclose

Contributions: MMG, KRR, and RA conceptualized the study. KDG, TPM, EB, MHD, and RA abstracted the data. TMC and MES cleaned the data and performed all analyses with input from JSY, KDG, TPM, PJL, KRR, and MMG. JSY and MMG wrote the manuscript with significant editing from TMC, MES, and KRR.

Funding: the authors would like to thank the following funding sources: Alex's Lemonade Stand Foundation (ALSF) Epidemiology Award (to RA), ALSF Young Investigator Award (to KDG), St. Baldrick's Consortium Grant with generous support from the Micaela's Army Foundation (to PJL, KRR, and MES), Cancer Prevention and Research Institute of Texas #RP160771 (to MES), National Institutes of Health (NIH) National Cancer Institute (5K12CA090433-17, Principal investigator: Dr. Susan Blaney, support for JSY and 1P20CA262733-01, Principal investigators: Lupo and Rabin), NIH National Heart, Lung, and Blood Institute Career Development Award 5K01HL143153 (to KDG), and NIH National Cancer Institute Career Development Award K07CA211956 (to TPM)..

Data-sharing statement: data from LEARN may be accessed by investigators who submit an application that is reviewed and approved by the study team.

References

1. Hunger SP, Mullighan CG. Acute lymphoblastic leukemia in children. N Engl J Med. 2015;373(16):1541-1552.
2. Hough R, Vora A. Crisis management in the treatment of childhood acute lymphoblastic leukemia: putting right what can go wrong (emergency complications of disease and treatment). Hematology Am Soc Hematol Educ Program. 2017;2017(1):251-258.
3. Schmiegelow K, Pulczynska M. Prognostic significance of hepatotoxicity during maintenance chemotherapy for childhood acute lymphoblastic leukaemia. Br J Cancer. 1990;61(5):767-772.
4. Farrow AC, Buchanan GR, Zwiener RJ, et al. Serum aminotransferase elevation during and following treatment of childhood acute lymphoblastic leukemia. J Clin Oncol. 1997;15(4):1560-1566.
5. Adam de Beaumais T, Dervieux T, Fakhoury M, et al. The impact of high-dose methotrexate on intracellular 6-mercaptopurine disposition during interval therapy of childhood acute lymphoblastic leukemia. Cancer Chemother Pharmacol. 2010;66(4):653-658.
6. Segal I, Rassekh SR, Bond MC, et al. Abnormal liver transaminases and conjugated hyperbilirubinemia at presentation of acute lymphoblastic leukemia. Pediatr Blood Cancer. 2010;55(3):434-439.
7. McAtee CL, Schneller N, Brackett J, et al. Treatment-related sinusoidal obstruction syndrome in children with de novo acute lymphoblastic leukemia during intensification. Cancer Chemother Pharmacol. 2017;80(6):1261-1264.
8. Ebbesen MS, Nygaard U, Rosthoj S, et al. Hepatotoxicity during maintenance therapy and prognosis in children with acute lymphoblastic leukemia. J Pediatr Hematol Oncol. 2017;39(3):161-166.
9. Denton CC, Rawlins YA, Oberley MJ, et al. Predictors of hepatotoxicity and pancreatitis in children and adolescents with acute lymphoblastic leukemia treated according to contemporary regimens. Pediatr Blood Cancer. 2018;65(3):e26891.
10. Hashmi SK, Navai SA, Chambers TM, et al. Incidence and predictors of treatment-related conjugated hyperbilirubinemia during early treatment phases for children with acute lymphoblastic leukemia. Pediatr Blood Cancer. 2019;67(2):e28063.
11. Goggins WB, Lo FF. Racial and ethnic disparities in survival of US children with acute lymphoblastic leukemia: evidence from the SEER database 1988-2008. Cancer Causes Control. 2012;23(5):737-743.
12. Faulk KE, Anderson-Mellies A, Cockburn M, et al. Assessment of enrollment characteristics for Children's Oncology Group (COG) upfront therapeutic clinical trials 2004-2015. PLoS One. 2020;15(4):e0230824.
13. Miller TP, Li Y, Getz KD, et al. Using electronic medical record data to report laboratory adverse events. Br J Haematol. 2017;177(2):283-286.
14. Bhatia S, Sather HN, Heerema NA, et al. Racial and ethnic differences in survival of children with acute lymphoblastic leukemia. Blood. 2002;100(6):1957-1964.
15. Castellino S, Muir A, Shah A, et al. Hepato-biliary late effects in survivors of childhood and adolescent cancer: a report from the Children's Oncology Group. Pediatr Blood Cancer. 2010;54(5):663-669.