Impact of Delays in Therapy on Survival in Childhood Acute Lymphoblastic Leukemia: A Report from the LEARN Consortium

Ross Mangum, Tiffany M. Chambers, Andria Stevens, Robert C. Lynch, Evanette Burrows, Tamara P. Miller, Kelly D. Getz, Richard Aplenc, Philip J. Lupo, Maria Monica Gramatges, Michael E. Scheurer, Karen R. Rabin

Texas Children's Cancer and Hematology Centers, Houston, TX; Children's Hospital of Philadelphia, Philadelphia, PA

BACKGROUND

- Modern chemotherapy protocols for childhood acute lymphoblastic leukemia (ALL) attempt to balance treatment intensification for improved cure rates with efforts to minimize acute and long-term toxicities.
- This approach has led to significant improvement in relapse-free survival (RFS) and overall survival (OS).
- Treatment intensification is associated with increased myelosuppression and other infectious complications or end-organ damage that may result in prolonged treatment delays.
- Existing data focus on the prognostic impact of delays in diagnosis and/or treatment initiation.
- There is a paucity of data on the prognostic impact of delays during the intensive phases of therapy.
- This may create uncertainty and anxiety among patients, families, and medical providers.
- We sought to determine whether treatment-related toxicities leading to cumulative delays in therapy prior to maintenance contribute to worse outcomes.

PRIMARY OBJECTIVE

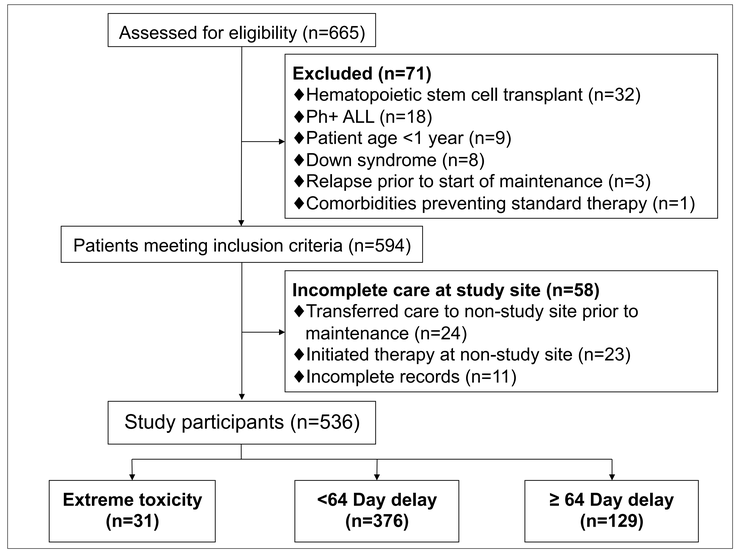
- The primary study objective was to assess the impact of treatment delays on RFS and OS.

METHODS

- We conducted a retrospective chart review of 536 pediatric patients treated for ALL from 2007 – 2015 at two quaternary academic children's hospitals in the LEARN (Leukemia Electronic Abstraction of Records Network) Consortium.
- 'Delay to maintenance' - the difference between the expected time (determined separately for each treatment protocol) and the actual time from the start of induction to the start of maintenance – was calculated for each patient.
- Patients were divided into quartiles based on duration of delay. The upper quartile - those with the longest delay - was compared with the lower three quartiles to assess for differences in RFS, OS, and a variety of host factors.
- 32 patients who experienced treatment-related toxicities requiring major alteration in therapy (e.g. substitution or omission of a treatment phase, transition to an alternative protocol, early termination of therapy) were categorized as "extreme toxicity" and analyzed separately.
- t-Test analysis was used to compare mean ages. Chi-square analysis was utilized for comparing differences in patient features by delay time and extreme toxicity status. Kaplan-Meier curves and log-rank tests of equality were used to compare survival rates between groups.

RESULTS

CONSORT Flow Diagram of Eligible Study Participants



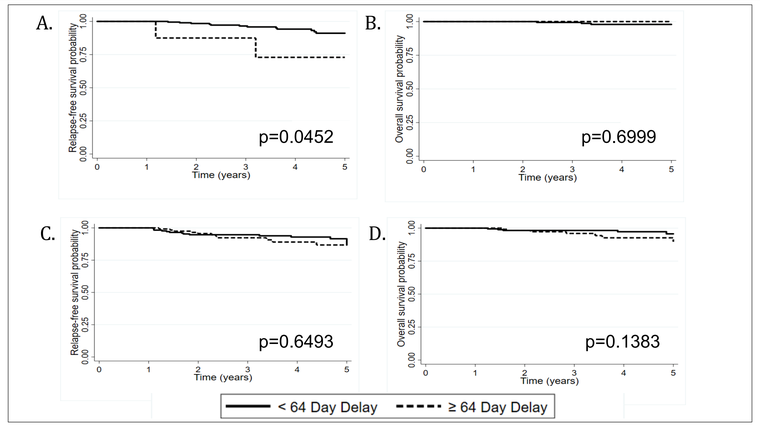
Patient Features Associated with Increased Delay to Maintenance

Table 1. Demographic and Clinical Factors According to Delay and Toxicity Status

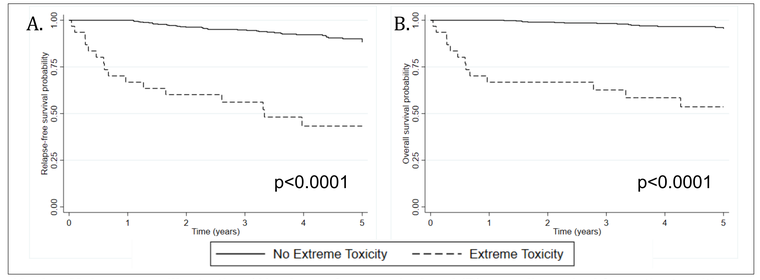
	Total N (%)	Lower 3 Quartiles Delay N (%)	Upper Quartile Delay N (%)	p-value	No Extreme Toxicity N (%)	Extreme Toxicity N (%)	p-value
N	**536**	**376**	**129**		**505**	**31**	
Race/Ethnicity							
NH White	252 (47.0)	189 (50.3)	56 (43.4)	**0.033**	245 (48.5)	7 (22.6)	**0.022**
Hispanic	186 (34.7)	120 (31.9)	49 (38.0)		169 (33.5)	17 (54.8)	
Black	52 (9.7)	40 (10.6)	7 (5.4)		47 (9.3)	5 (16.1)	
Asian/Other	46 (8.6)	27 (7.2)	17 (13.2)		44 (8.7)	2 (6.5)	
Hospital							
TCH	290 (54.1)	193 (51.3)	71 (55.0)	0.467	264 (52.3)	26 (83.9)	**0.001**
CHOP	246 (45.9)	183 (48.7)	58 (45.0)		241 (47.7)	5 (16.1)	
Gender							
Male	310 (57.8)	209 (55.6)	82 (63.6)	0.113	291 (57.6)	19 (61.3)	0.688
Female	226 (42.2)	167 (44.4)	47 (36.4)		214 (42.4)	12 (38.7)	
ALL Subtype							
B-cell	465 (86.8)	332 (88.3)	110 (85.3)	0.369	442 (87.5)	23 (74.2)	**0.034**
T-cell	71 (13.2)	44 (11.7)	19 (14.7)		63 (12.5)	8 (25.8)	
Treatment Intensity[a]							
Standard	215 (40.3)	203 (54.0)	8 (6.2)	**<0.001**	211 (41.8)	4 (14.3)	**0.004**
High	318 (59.7)	173 (46.0)	121 (93.8)		294 (58.2)	24 (85.7)	
Mean Age at Diagnosis, years (SD)	7.2 (4.9)	6.7 (4.7)	7.8 (5.0)	**0.0254**	7.0 (4.8)	11.8 (4.5)	**<0.0001**

Abbreviations: NH, Non-Hispanic; TCH, Texas Children's Hospital; CHOP, Children's Hospital of Philadelphia; ALL, Acute lymphoblastic leukemia; SD, Standard deviation; RSF, Relapse-free survival, OS, Overall survival. [a]Data missing on three patients with extreme toxicity

RESULTS (continued)



Kaplan-Meier curves demonstrating (A) relapse-free and (B) overall survival by delay status for patients receiving standard intensity therapy and (C) relapse-free and (D) overall survival by delay status for patients receiving high intensity therapy.



Kaplan-Meier curves illustrating (A) relapse-free survival and (B) overall survival for patients with and without extreme toxicity.

CONCLUSIONS

- There was no difference in 5-year RFS or OS between patients in the upper quartile, with delay to start of maintenance of ≥ 64 days, and patients in the other three quartiles.
- However, among patients who received standard intensity treatment, the 5-year RFS for patients in the upper quartile for delay was significantly lower at 70.9% compared to 91.0 % for patients in the lower three quartiles (Kaplan-Meier log-rank p=0.0452).
- Patients with extreme toxicity demonstrated a highly significantly inferior 5-year RFS (43.7% vs. 86.6%; Kaplan-Meier log-rank p<0.0001) and OS (51.9% vs. 95.0%; Kaplan-Meier log-rank p<0.0001) compared to the remainder of the cohort.

ACKNOWLEDGEMENTS

- This work has been supported by the St. Baldrick's Foundation with generous support from the Micaela's Army Foundation, and the Alex's Lemonade Stand Foundation.