Impact of Race/Ethnicity and Language Preferences on Pediatric ALL Survival Outcomes

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Background

- Acute lymphoblastic leukemia (ALL) and acute lymphoblastic lymphoma (ALLy) are the most common pediatric malignancies, followed by brain tumors and lymphomas.
- Outcomes for patients with childhood leukemia and lymphoma have dramatically improved over the past 30 years, with exceptional 5-year survival rates of >90% in children and adolescents with newly diagnosed disease, improvements attributed to the use of multiagent systemic chemotherapy, development of broad-spectrum antibiotics to treat infectious complications, and enhanced availability of supportive blood products.
- Ethnic and racial disparities have recently been observed both in treatment-related toxicities and rates of long-lasting cure in childhood leukemia and lymphoma.
- Studies that investigating the combined impact of social demographic factors, cytogenetic mutations, and chemotherapy regimens on outcomes in ALL/ALLy patients are currently lacking.

Objective

- Our study sought to evaluate differences in cytogenetic mutations and common chemotherapy related toxicities among pre-B cell ALL/ALLy patients of different races/ethnicities to determine whether these predict for differential outcomes in all-cause overall survival.

Methods

- ***DESIGN***: Retrospective Cohort Study
- ***PARTICIPANTS***: 274 patients with pre-B cell acute lymphoblastic leukemia and acute lymphoblastic lymphoma
- ***SETTING***: within Montefiore Health System using Montefiore's Cancer Registry/Electronic Data Warehouse
  - Demographics, including self-reported race/ethnicity, BMI at diagnosis, ICD9 and ICD10 diagnosis codes, outpatient/inpatient prescription data, laboratory values, minimal residual disease (MRD), white blood cell count at diagnosis
  - Classified by following features
    - Presence of high-risk cytogenetics, MRD, administration of intensive chemotherapy
    - Complications including neuropathy, hypertension, diabetes, psychosis, febrile neutropenia, sepsis, pulmonary embolus, thrombosis, and pancreatitis
  - High-risk cytogenetics identified at Molecular Cytogenetics Laboratory at Albert Einstein College of Medicine and defined as hypodiploid status, *IKZF1* mutation, MLL rearrangement, and Ph-like genetic mutation
- ***ANALYSIS:*** Bivariate analyses using Chi-square tests, t tests, and ANOVA for normally distributed variables and non-parametric testing for variables not normally distributed
- Kaplan Meier method and log-rank test assessed all-cause mortality, overall survival
- Competing risk regression utilized to assess complication incidence with corresponding 95% confidence intervals by race/ethnicity
- Cox proportional hazard modeling to evaluate effect of race, ethnicity, and cytogenetics on vital status and multiple complications
  - A priori model included age at diagnosis in years and race and ethnicity
  - All additional variables that were associated with the outcome in univariate models ($p < 0.20$) were added using stepwise backward elimination
  - Final model including age at diagnosis, race/ethnicity, administration of intensive chemotherapy, preferred language, maximum glucose categories, ranging from normal to extreme elevations, hypertension

Results

- Hispanic patients were 78% less likely to die when compared with Non-Hispanic Black individuals (HR 0.22; 95%CI 0.07, 0.73)
- Spanish speakers were 2.91 times more likely to die compared to those who spoke English (HR 2.91; 95%CI 1.08, 7.82)
- Patients who developed hypertension during therapy were 11.65 times more likely to die when compared to those without hypertension (adjustedHR 11.65; 95%CI: 3.04, 44.62)

Table 1

Table 1. Demographics and Clinical Characteristics by Race and Ethnicity from Pediatric Hematologic Malignancies Cohort (PHMC) of 274 patients with Acute Lymphoblastic Leukemia and Lymphoma within Montefiore Health System (MHS)

Demographics	Hispanic (n=132)	Non-Hispanic Black (n=54)	Non-Hispanic White (n=25)	*p*-value
Age at diagnosis, years (median, IQR)	7.0 (3.6, 13.2)	8.1 (4, 15)	10.5 (5.4, 19.3)	0.06
Administration of Intensive Chemo, n (%)[a]	91 (69.0)	33 (61.1)	10 (40)	0.02
Follow up time, weeks (median, IQR)	218.7 (108.0, 445.0)	260.3 (82.9, 493.9)	124 (45.6, 312.1)	0.57
Time to diagnosis (mean±SD)[b]	8.2 ±21.4	9.0 ± 20.6	8.7 ±16.7	0.97
Female, n (%)	59 (44.7)	23 (42.6)	7.0 (28)	0.66
Body Mass Index, kg/m2 (IQR)	17.02 (15.27, 21.52)	16.63 (15.07, 20.55)	20.57 (15.26, 23.95)	0.40
Socioeconomic Status[c], median (IQR)	-3.4 (-6.5, -1.8)	-3.4 (-6.1, -1.2))	0.47 (-1.4, 0.93)	<0.0001
Preferred language spoken, n (%)				<0.0001
English/Other	87 (65.9)	52 (96.3)	25 (100)	
Spanish	46 (34.9)	2.0 (3.7)	0 (0)	
White Blood Count at Diagnosis, g/dL (median, IQR)	82.0 (18.0, 121.0)	81.5 (7.2, 112.0)	89.0 (49.0, 89.0)	0.92
Minimal Residual Disease[d], n (%)	11 (28.2)	7 (41.2)	0 (0)	0.44
High Risk Cytogenetics, n (%)	40 (46.0)	13 (41.9)	5.0 (55.6)	0.77

[a]Defined by Doxorubicin containing treatment strategies

[b]Time to diagnosis defined from first contact to diagnosis date

[c]SES was based upon the patient's census block group and is reported as a summary Z-score relative to the New York State mean using 6 variables (additional details within manuscript)

[d]Minimal Residual Disease at End of Induction therapy determined by Flow Cytometry testing at John Hopkins University

Table 2

Table 2. Within 274 patients in Pediatric Hematologic Malignancies Cohort (PHMC) within Montefiore Health System (MHS), Race/Ethnicity associated with decreased all-cause mortality, while Spanish Language, Hypertension, Diabetes, and Moderate to Severe Glucose Elevations associated with increased risk of death

	Observations, n	Deaths, n (%)	HR[1] (95% CI)	*p*- value	HR[2] (95% CI)	*p*- value
Age at diagnosis (years)	248		1.14 (1.09, 1.19)	<0.0001	1.15 (1.07, 1.25)	<0.0001
Diagnosis year	248		1.02 (0.97, 1.08)	0.47		
Race/Ethnicity						
Non-Hispanic Black	54	17 (31)	1.00 (ref)		1.00 (ref)	
Hispanic	132	18 (14)	0.49 (0.23, 1.08)	0.08	0.22 (0.07, 0.73)	0.01
Non-Hispanic White/Other	72	19 (26)	0.94 (0.43, 2.04)	0.87	0.38 (0.11, 1.37)	0.14
Administration of Intensive chemo[a]	248	25 (16)	0.62 (0.34, 1.13)	0.12	0.11 (0.03, 0.45)	0.002
Female Sex			0.62 (0.33, 1.18)	0.15		
Male	152	37 (24)				
Female	112	18 (16)				
Socioeconomic Status[b]	223		0.98 (0.89, 1.09)	0.76		
Insurance Status						
Private/Self Pay	85	14 (17)	1.00 (ref)			
Medicaid	189	41 (22)	2.98 (1.25, 7.08)	0.01		
Preferred language						
Spanish	69	19 (28)	2.24 (1.20, 4.18)	0.01	2.91 (1.08, 7.82)	0.04
English	205	36 (18)	1.00 (ref)		1.00 (ref)	
Body Mass Index (percentile, %)[c]	201		1.01 (1.00, 1.02)	0.23		
Max Glucose Categories						
Normal range (<250)	56	2 (4)	1.00 (ref)		1.00 (ref)	
Mild Elevation (250–499)	47	6 (13)	4.05 (0.82, 20.09)	0.09	8.95 (0.90, 89.40)	0.06
Moderate Elevation (500-749)	22	11 (50)	13.17 (2.73, 63.48)	0.001	28.69 (2.14, 385.24)	0.01
Extreme Elevation (>750)	139	36 (26)	7.51 (1.78, 31.66)	0.006	3.38 (0.41, 28.20)	0.41
Episodes of Hyperglycemia[d]	248		1.04 (1.02, 1.06)	<0.0001		
Minimal Residual Disease[e]	42	5 (25)	1.35 (0.66, 2.75)	0.41		
Presence of High Risk Genetics	146	11 (16)	1.15 (0.37, 3.63)	0.81		
Neutropenia[f]	248	32 (20)	1.17 (0.51, 2.67)	0.71		
Sepsis	248	32 (24)	1.89 (0.83, 4.32)	0.13		
Neuropathy	248	11 (26)	2.56 (1.06, 6.19)	0.04		
Hypertension[g]	248	24 (32)	3.17 (1.42, 7.07)	0.005	11.65 (3.04, 44.62)	<0.0001
Diabetes	248	18 (39)	3.49 (1.44, 8.46)	0.006		
Psychosis	248	4 (31)	1.24 (0.17, 9.22)	0.83		
Pancreatitis	248	11 (29)	0.97 (0.33, 2.85)	0.96		
Pulmonary Embolus	248	8 (89)	5.35 (1.82, 15.71)	0.002		
Deep Vein Thrombosis	248	4 (27)	did not converge	>0.99		
Cardiomyopathy	248	1 (33)	did not converge	>0.99		
Inflammatory Complications	248	36 (20)	1.07 (0.46, 2.50)	0.88		
Thrombosis	248	12 (43)	2.22 (0.83, 5.96)	0.11		

[1]Hazard Ratio (HR) and 95% Confidence Intervals (CI) Determined with Univariate Cox proportional hazard model

[2]Hazard Ratio (HR) and 95% Confidence Intervals (CI) Determined with Multivariate Cox proportional hazard model containing 251 observations

[a]Defined by Doxorubicin containing treatment strategies

[b]SES was based upon the patient's census block group and is reported as a summary Z-score relative to the New York State mean

mean using 6 variables (additional details within manuscript)

[c]as determined by World Health Organization (WHO) guidelines

[d]as determined by Glucose level ≥ 250 g/dL

[e]Minimal Residual Disease at End of Induction therapy determined by Flow Cytometry testing at John Hopkins University

[f]Neutropenia defined as Absolute Neutrophil Count ≤ 500 k/µL

[g]Hypertension defined as BP above 95% percentile for age

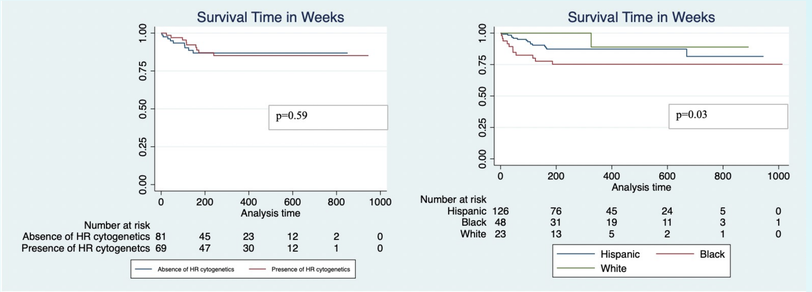
Model building with a priori inclusion of age at diagnosis ≤ 25 with all additional variables that were suggested to be associated

with the outcome in univariate models[2] ($p < 0.20$) added using stepwise backward elimination to build our final multivariate model.

Results

Figure 1

Figure 1. Within 274 patients in Pediatric Hematologic Malignancies Cohort (PHMC) within Montefiore Health System (MHS), Survival Time in Weeks Associated with Race/Ethnicity but not high-risk cytogenetics



Conclusions

- Hispanic patients had improved survival compared with Non-Hispanic Black patients
- Among Hispanic patients there was significant improvement in survival among English speakers compared to those with Spanish language preference.
  - Spanish speakers may be at a unique disadvantage when being treated for ALL/ALLy, possibly due to post-diagnosis disparities, including communication barriers with medical providers.
  - Improving their ability to understand various requirements in the treatment of ALL/ALLy, including medication recommendations, return to care precautions and treatment schedules for oral chemotherapy may impact survival.
- Hispanic pediatric patients are also more likely to receive intensive chemotherapy with doxorubicin at any point during therapy, despite the finding that multiple poor prognostic factors, including age at diagnosis, white blood cell count at presentation, MRD at end of induction chemotherapy, and presence of high-risk cytogenetic mutations happen with similar frequency between racial/ethnic groups
  - Administration of intensive chemotherapy including doxorubicin reduces mortality, as those receiving more of this chemotherapeutic have improved survival
- Limitations: the sample size and the total number of deaths in our study, only 56 total, was limited
  - Our study was only able to evaluate all-cause mortality due to limitations when reporting the cause of death within NDI
  - Missing cytogenetic data represents a potential limitation of the study, as this aspect of the study may have been underpowered, with limited information available regarding the cytogenetic mutations in our cohort, with model sizes decreased due to less data available on presence or absence of cytogenetic mutations
- Our study emphasizes the need to further study this unique population to understand what places them at greater risk of death and chemotherapy complications from treatment of pediatric ALL/ALLy.

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No Conflicts of Interest to declare

Acknowledgements

The research described was supported by NIH/National Center for Advancing Translational Science (NCATS) Einstein-Montefiore CTSA Grant Number UL1TR001073 and CHAM Fellow Research Award