

An investigation of toxicities and survival in Hispanic children and adolescents with ALL: Results from the Dana-Farber Cancer Institute ALL Consortium protocol 05-001

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Funding information

Grant sponsor: National Institutes of Health (R25 CA094061); Grant sponsor: St. Baldrick's Foundation (Supportive Care Research Award).

Presented in abstract form at the 56th American Society of Hematology Annual Meeting and Exposition, December 5–8, 2015, Orlando, FL, USA.

Abstract

Purpose: This study compared the relative incidence of treatment-related toxicities and the event-free and overall survival between Hispanic and non-Hispanic children undergoing therapy for acute lymphoblastic leukemia (ALL) on Dana-Farber Cancer Institute ALL Consortium protocol 05-001.

Patients and methods: Secondary analysis of prospectively collected data from a phase III multicenter study in children and adolescents of 1–18 years with previously untreated ALL.

Results: Between 2005 and 2011, 794 eligible patients enrolled on DFCI 05-001, 730 of whom were included in this analysis (19% [N = 150] Hispanic, 73% [N = 580] non-Hispanic). Hispanic patients were more likely to be ≥ 10 years of age (32% vs. 24%, $P = 0.045$) at diagnosis. Toxicity analyses revealed that Hispanic patients had significantly lower cumulative incidence of bone fracture ($P < 0.001$) and osteonecrosis (ON; $P = 0.047$). In multivariable risk regression, the risk of

ON was significantly lower in Hispanic patients ≥ 10 years (HR 0.23; $P = 0.006$). Hispanic patients had significantly lower 5-year event-free survival (EFS) (79.4%; 95% CI: 71.6–85.2) and overall survival (OS) (89.2%; 95% CI: 82.7–93.4) than non-Hispanic patients (EFS: 87.5%; 95% CI: 84.5–90.0, $P = 0.004$; OS: 92.7%; 95% CI: 90.2–94.6, $P = 0.006$). Exploratory analyses revealed differences between Hispanic and non-Hispanic patients in the frequency of common variants in genes related to toxicity or ALL outcome.

Conclusion: Hispanic children treated for ALL on DFCI 05-001 had fewer bone-related toxicities and inferior survival than non-Hispanic patients. While disease biology is one explanatory variable for outcome disparities, these findings suggest that biologic and non-biologic mechanisms affecting drug delivery and exposure in this population may be important contributing factors as well.

KEYWORDS

acute lymphoblastic leukemia, ethnicity, Hispanic, outcomes, survival, toxicities

1 | INTRODUCTION

Despite overall cure rates near 90% in childhood acute lymphoblastic leukemia (ALL), survival in Hispanic children and adolescents with ALL remains inferior to survival in non-Hispanic patients.^{1–4} These disparities are particularly striking in light of dramatic improvements in survival for all children with ALL over the past three decades.^{5,6} In a large retrospective analysis from 12 Children's Cancer Study Group ALL trials (1983–1995), 5-year event-free survival (EFS) was significantly lower in Hispanic children ($65.9 \pm 1.5\%$) when compared with 5-year EFS in white ($72.8 \pm 0.6\%$) and Asian children ($75.1 \pm 3.5\%$; $P < 0.001$).⁷ More recent studies, including a Surveillance Epidemiology and End Results investigation of survival trends in ALL (1995–2012), have revealed a persistent survival difference (5–15 percentage points) between Hispanic and non-Hispanic children.¹ The reasons for reduced survival in Hispanic children with ALL in North America are multifactorial and likely include both biologic and nonbiologic factors, such as differences in the frequency of high-risk leukemia subtypes, host pharmacogenomics, reduced access to care, and nonadherence to oral chemotherapy.⁸

Differences in survival outcomes between Hispanic and non-Hispanic patients with ALL have been described.^{1,9–11} Fewer studies have investigated whether the incidence of treatment-related toxicities (TRT) during ALL therapy varies by self-reported ethnicity, and none have described both survival and TRT in the same cohort.^{9,12,13} The development of serious TRTs may result in an inability to tolerate full-dose chemotherapy, and the consequent interruptions in planned therapy (treatment delays, dose reductions) could theoretically contribute to increased risk of relapse. Conversely, development of very few TRTs might indicate lower overall drug exposure, either due to genetic polymorphisms affecting drug metabolism or to non-biologic factors, such as chemotherapy nonadherence. We conducted an analysis of TRTs and survival in Hispanic and non-Hispanic children and adolescents undergoing treatment for newly diagnosed ALL on the Dana-Farber Cancer Institute ALL Consortium protocol 05-001 (DFCI 05-001).¹⁴ We sought to compare the relative incidence of TRTs, EFS, and overall survival (OS) between these two patient cohorts.

Because common genetic variants are associated with risk of TRT,^{15,16} we also explored whether the prevalence of these polymorphisms in our patient population differed by ethnicity.

2 | METHODS

2.1 | Patients and eligibility criteria

Children and adolescents aged 1–18 years with newly diagnosed ALL were enrolled on DFCI 05-001 at 11 sites in Canada and the United States including Puerto Rico. Patients whose ethnicity was documented at the time of study enrollment were eligible for inclusion in this analysis. The Institutional Review Board of each participating institution approved the original treatment protocol and informed consent was obtained from each patient's guardian. All enrolled patients with known ethnicity (Hispanic and non-Hispanic) were included in the induction toxicity analysis. Patients with a documented complete remission (CR), final risk group, and treatment assignment were included in postinduction treatment analyses. For the investigation of targeted genetic variants, patients who met the above criteria and who also had genomic DNA available for analysis were included.

2.2 | Ethnicity designation

Patient ethnicity (Hispanic or non-Hispanic) was documented at the time of study enrollment by a clinical research associate and was based on patient/parent report and/or patient's country of origin, as was the standard during the period in which the clinical trial was conducted.¹⁷ Ethnicity designation was guided by the national standards for the classification of federal data on race and ethnicity as defined by the Office of Management and Budget Statistical Policy Directive No. 15.¹⁸ Patients were categorized as underweight, normal, overweight, and obese based on body mass index (BMI). For outcome analyses, patients were categorized as obese (BMI \geq the 95th percentile for age and sex) versus not obese (BMI $<$ 95th percentile).

2.3 | Therapy

Details of the DFCI 05-001 treatment regimen have been previously published.¹⁴ In brief, all patients underwent multiagent remission induction followed by risk-adapted postinduction therapy based on final risk group assignment. Final risk group was based on age, presenting leukocyte count, immunophenotype, presence or absence of leukemia in the cerebrospinal fluid at diagnosis, leukemia-associated cytogenetic abnormalities, and end-induction levels of minimal residual disease (MRD). All patients were scheduled to receive 24 months of postinduction treatment. Patients were eligible to participate in a randomized comparison of intramuscular native *Escherichia coli* L-asparaginase and intravenous pegaspargase during postinduction treatment. Patients who declined to participate, and those enrolled onto the trial after the randomized comparison had met its target accrual, were directly assigned to receive native *E. coli* L-asparaginase.

2.4 | Toxicity assessment

Treatment-related toxicities were defined using Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 and included bone fracture (all grades), grade 2 or worse osteonecrosis (ON), grade 3 or worse infection (bacterial, fungal, viral, and/or pneumocystis pneumonia), and grade 2 or worse asparaginase-associated toxicities (allergy, pancreatitis, thrombosis, or bleeding).¹⁴ A diagnosis of bone fracture or ON required both clinical symptoms and radiographic confirmation. Study staff at each participating institution prospectively collected TRT data at the time of CR, every 3 months subsequently until treatment completion, and annually thereafter.

2.5 | Analysis of genetic variants

We conducted a secondary analysis of genomic data that were gathered for a separate correlative study looking at toxicities in the same study population. In this study, toxicities were not analyzed by ethnicity. Genomic DNA was isolated from peripheral blood collected after patients achieved CR. Nineteen candidate genetic variants were selected for investigation through a nonexhaustive literature review, with the following criteria: (1) variants present in genes related to pathways presumed to be relevant to TRT; (2) variants known to be associated with altered function of the gene product; and (3) variants with a population prevalence of at least 10%.^{15,16} Single nucleotide polymorphisms (SNPs) were detected using PCR-based allelic discrimination assays (Life Technologies, Grand Island, NY). The number of 28-bp repeats in the 5' untranslated region of the thymidylate synthase (TS) gene was determined by PCR-product length analysis, as previously described.¹⁵

2.6 | Statistical methods

Toxicity rates during induction and postinduction therapy were compared between groups with the Fisher's exact test. In patients who were assigned a final risk group after achieving CR, ON and bone fracture with follow-up information were analyzed within age subgroups (<10 years vs. ≥10 years). The cumulative incidences of ON and

fracture were estimated with the *cuminc* utility in the "cmprsk" package in R and were tested using the Gray test, with relapse and death in remission identified as competing risks. Time-to-event was calculated as the time (years) from remission date to the date of first event. If the bone event occurred in induction, it was considered an event at time 0. The cumulative incidence was also modeled in univariate and multivariable analyses using competing risks regression. Multivariable models were adjusted for sex, asparaginase randomization, and final risk group. The grouping used in modeling for final risk group classification varied by age due to the protocol definition of age >10 as high risk.¹⁴

OS and EFS were estimated with the Kaplan–Meier method and were compared between groups with the log rank test. OS was defined as the time from registration to death from any cause. EFS was defined as the time from registration to the first event of relapse, death, or second malignancy. Induction events, including death and/or failure to achieve CR, were considered events at time 0. Cox proportional hazards models were used to model OS and EFS by group univariately and were adjusted in multivariable analyses for diagnostic age, immunophenotype, white blood cell (WBC), obesity, and sex. In patients receiving a single full dose of IV pegaspargase, a Wilcoxon rank sum test was used to compare the serum asparaginase activity (SAA) between Hispanic and non-Hispanic patients at days 4, 11, 18, and 25 during induction.

The association between ethnicity group and SNPs were analyzed with the Fisher's exact test. A false discovery rate, using the method of Benjamini and Hochberg,¹⁹ was used to adjust for multiple comparisons. Comparisons $P_{\text{adjusted}} < 0.05$ were considered significant. Additionally, an exploratory analysis was conducted to assess the univariate association between SNPs and toxicity (overall infection, pancreatitis, thrombosis, and allergy) within the ethnicity group. The relationship between EFS and SNPs within these groups was also explored.

3 | RESULTS

3.1 | Patient characteristics

Between 2005 and 2011, 794 eligible children and adolescents (ages 1–18 years) enrolled on DFCI 05-001, 730 of whom had ethnicity documented (150 [19%] Hispanic, 580 [73%] non-Hispanic). When compared with non-Hispanic children, a higher percentage of Hispanic patients were ≥10 years at the time of diagnosis (32% vs. 24%, $P = 0.045$). A higher percentage of Hispanic patients were obese (20% vs. 12%, $P = 0.024$). There was no significant difference in the presence or absence of the following leukemia-associated cytogenetic characteristics: high hyperdiploidy (51–65 chromosomes), *BCR-ABL1*, *KMT2A (MLL)* rearrangement, hypodiploidy, and *iAMP21* by ethnicity (Table 1). Hispanic patients were significantly less likely to have the *ETV6-RUNX1* fusion ($P = 0.018$). Presenting leukocyte count, immunophenotype, National Cancer Institute risk group, final DFCI risk group, or assigned randomized treatment arm (Table 1) did not significantly differ by ethnicity.

TABLE 1 Demographic and clinical characteristics of study participants on DFCI 05-001

	Entire cohort (with ethnicity)		Ethnicity				P-value
	Number	%	Hispanic		Non-Hispanic		
			Number	%	Number	%	
Cohort size	730	100	150	100	580	100	-
Age, years							0.045
<10	545	75	102	68	443	76	
≥10	185	25	48	32	137	24	
White blood cell count (cells/ μ l)							0.57
<50,000	578	79	116	77	462	80	
≥50,000	152	21	34	23	118	20	
NCI risk group							0.19
Standard risk	445	61	84	56	361	62	
High risk	285	39	66	44	219	38	
Immunophenotype							0.58
T-cell	89	12	16	11	73	13	
B-cell	641	88	134	89	507	87	
Sex							0.52
Female	325	45	63	42	262	45	
Male	405	55	87	58	318	55	
Body mass index (n = 729)							0.053
Underweight	47	6	10	7	37	6	
Normal	468	64	83	55	385	66	
Overweight	112	15	26	17	86	15	
Obese	102	14	30	20	72	12	
Cytogenetics ^a							
<i>ETV6-RUNX1</i>	136	17	18	12	118	20	0.018
High hyperdiploidy (51–65 chromosomes)	184	25	45	30	139	24	0.14
Ph ^b (<i>BCR-ABL-1</i>)	19	3	4	3	15	3	1.00
<i>KMT2A(MLL)</i> -rearrangement	12	2	1	1	11	2	0.48
Hypodiploidy	10	1	1	1	9	2	0.70
iAMP21	12	2	1	1	11	2	0.48
Achieved complete remission	695	95	141	94	554	96	0.36
Final DFCI risk group ^b							0.81
Standard risk	370	54	71	51	299	54	
High risk	242	35	54	39	188	34	
Very high risk	62	9	12	9	50	9	
Ph ^b	16	2	3	2	13	2	
Asparaginase therapy ^b							0.75
Directly Assigned to IM <i>E. coli</i>	267	39	52	37	215	39	
Randomized to IM <i>E. coli</i>	205	30	40	29	165	30	
Randomized IV pegaspargase	218	32	48	34	170	31	

^an = 12 not screened for cytogenetics including *ETV6-RUNX1*, high hyperdiploidy, *KMT2A (MLL)*-rearrangement, hypodiploidy, and iAMP21.

^bAchieved a complete remission and assigned a postinduction asparaginase group.

NCI risk group: Standard risk (WBC <50,000 and age <10 years); high risk (WBC ≥ 50,000 or age ≥ 10 years).

NCI, National Cancer Institute; B-cell, B-cell acute lymphoblastic leukemia; T-cell, T-cell acute lymphoblastic leukemia; Ph+, Philadelphia chromosome positive ALL; iAMP21, intrachromosomal amplification of chromosome 21; IM *E. coli*: intramuscular *E. coli* asparaginase; IV Peg: IV pegaspargase.

TABLE 2 Treatment-related toxicities by ethnicity during induction and postinduction therapy

Induction toxicity	Entire cohort		Ethnicity				P-value
	Number	%	Hispanic		Non-Hispanic		
			Number	%	Number	%	
All	730	-	150	-	580	-	-
Infection	203	28	37	25	166	29	0.36
Bacterial	183	25	29	19	154	27	0.07
Fungal	30	4	8	5	22	4	0.36
Viral	5	<1	1	1	4	1	1.00
Opportunistic	3	<1	1	1	2	0	-
Asparaginase toxicity	47	6	10	7	37	6	0.85
Pancreatitis	17	2	6	4	11	2	0.13
Allergy	10	1	2	1	8	1	1.00
Thrombosis	20	3	2	1	18	3	0.40
Bone event	3	<1	3	1	0	0	-
Bone fracture	3	<1	3	1	0	0	-
Osteonecrosis	0	<1	0	0	0	0	-

Postinduction toxicity	Entire cohort		Ethnicity				P-value
	Number	%	Hispanic		Non-Hispanic		
			Number	%	Number	%	
All	690	-	140	-	550	-	-
Infection	220	32	44	31	176	32	0.92
Bacterial	158	23	30	21	128	23	0.74
Fungal	17	2	2	1	15	3	0.55
Viral	59	9	17	12	42	8	0.09
Opportunistic	21	3	1	1	20	4	0.10
Asparaginase toxicity	183	27	40	29	143	26	0.59
Pancreatitis	75	11	20	14	55	10	0.17
Allergy	63	9	14	10	49	9	0.74
Thrombosis	72	10	11	8	61	11	0.35
Bone event ^a	163	24	15	11	148	27	<0.0001
Bone fracture	131	19	11	8	120	22	<0.0001
Osteonecrosis	54	8	4	3	50	9	0.013

^aOnly includes bone toxicity on therapy.

3.2 | Treatment-related toxicities

3.2.1 | Infection

The overall rate of infection during the induction treatment phase was not significantly different between Hispanic and non-Hispanic patients (25 vs. 29%, $P = 0.36$). Hispanic patients trended toward having fewer bacterial infections than non-Hispanic patients (19 vs. 27%), but this difference was not statistically significant ($P = 0.07$) (Table 2). Postinduction infections were documented in 31% of Hispanic patients and in 32% of non-Hispanic patients ($P = 0.92$) (Table 2).

3.2.2 | Asparaginase-associated toxicities

The overall incidence of postinduction asparaginase-associated toxicities including allergy, pancreatitis and thrombosis, was not significantly different between Hispanic and non-Hispanic patients (Table 2). The rate of ON and fracture during postinduction therapy was lower in Hispanic patients ($P = 0.013$ and <0.0001 , respectively) (Table 2).

3.2.3 | Serum asparaginase activity

At least one induction SAA level was available in 318 patients. During remission induction, when all patients received a single dose of pegasparaginase, we did not observe differences between Hispanic and non-Hispanic patients in median SAA levels at 4, 11, 18, and 25 days after the dose (Supplementary Fig. S1).

3.2.4 | Osteonecrosis

Overall, the incidence of ON differed by age ($P < 0.0001$) with patients ≥ 10 years having more events. In patients ≥ 10 years of age, Hispanic ethnicity was associated with a significantly lower cumulative incidence of ON (hazard ratio, HR, [95% confidence interval], 0.28 [0.10–0.76]; $P = 0.013$; Fig. 1A). This result remained significant in multivariable modeling ($P = 0.006$; Table 3). In patients < 10 years of age there was no statistically significant difference in the rate of ON between Hispanic and non-Hispanic patients (0.61 [0.18–2.02];

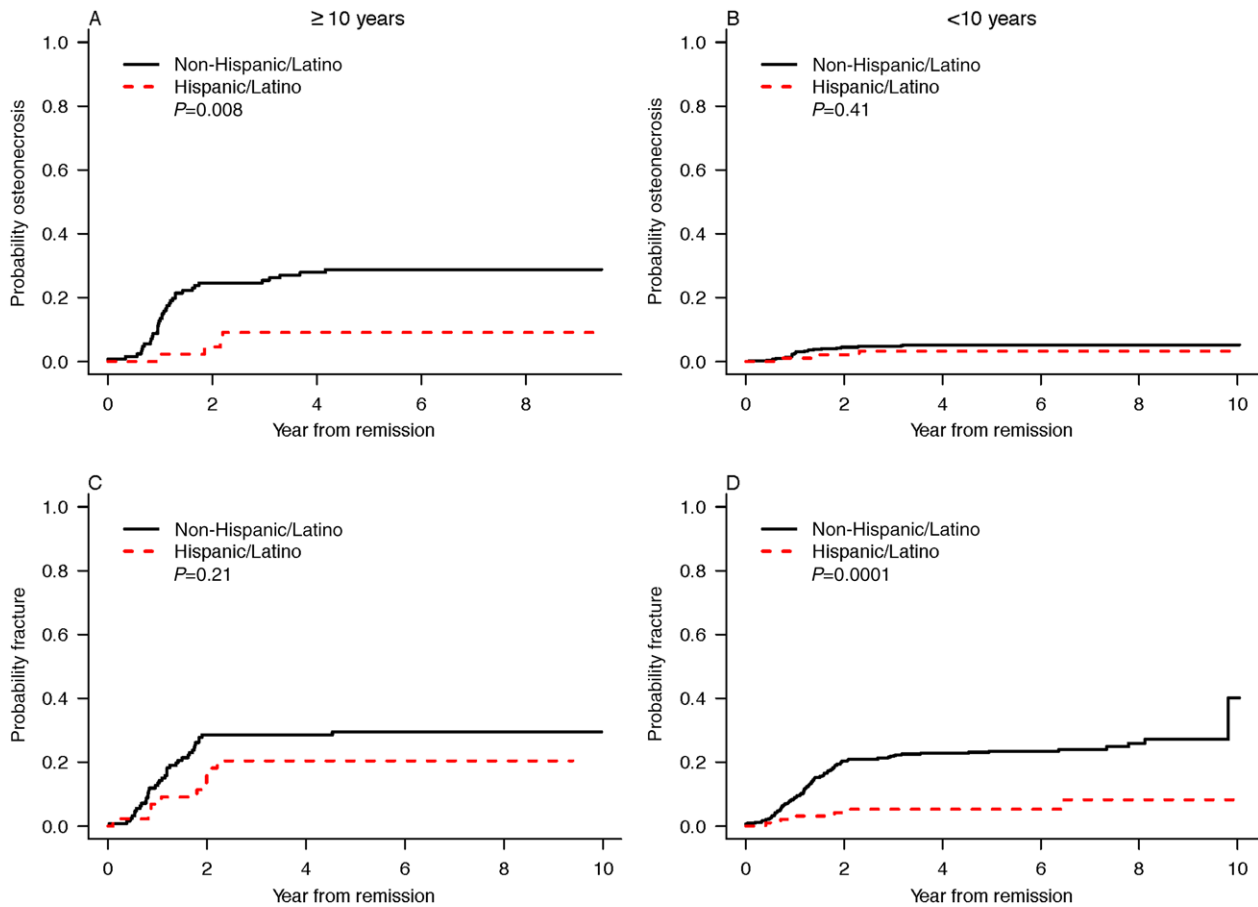


FIGURE 1 Probability of osteonecrosis and probability of fracture by age at diagnosis (<10 years vs. ≥ 10 years) in Hispanic and non-Hispanic patients: skeletal toxicity data are shown for (A) osteonecrosis in patients ≥ 10 years of age, (B) osteonecrosis in patients <10 years of age, (C) bone fracture in patients ≥ 10 years of age, and (D) bone fracture in patients <10 years of age

$P = 0.41$, Fig. 1B). Additionally, in competing risks regression there was no detectable difference in cumulative incidence of ON by obesity for each age group (Table 3). Analysis of SNPs revealed no significant difference between Hispanic and non-Hispanic patients in the frequency of the TS polymorphism, which we have previously shown is associated with risk of bone toxicity in this patient population.^{20,21}

3.2.5 | Fracture

In patients ≥ 10 years of age, there was no significant difference fracture incidence between Hispanic and non-Hispanic patients (HR 0.63 [0.31–1.28], $P = 0.20$ Fig. 1C). In children <10 years, cumulative incidence of fracture was significantly lower in the Hispanic group (0.24 [0.10–0.54], $P = 0.0006$; Fig. 1D). This remained significant in multivariable modeling ($P = 0.0003$; Table 3). In competing risks regression, there was no detectable difference in cumulative incidence of fracture by obesity for each age group (Table 3).

3.3 | Survival

The median follow-up time for those still alive was 6.12 years. Five-year OS was significantly lower in Hispanic patients (89.2% [82.7–93.4%]) vs. non-Hispanic patients (92.7% [90.2–94.6%]; $P = 0.006$; Fig. 2A). Five-year EFS was also significantly lower in Hispanic patients

(79.4% [71.6–85.2%]) vs. non-Hispanic patients (87.5% [84.5–90.0%], $P = 0.004$; Fig. 2B). While both cohorts had nearly identical CR rates (94–95%), a higher percentage of Hispanic versus non-Hispanic (13 vs. 9%) patients experienced disease relapse (Supplementary Table S1). There were no detectable differences in the site of relapse between groups (Supplementary Table S2). Of the B-ALL patients with a documented CR, there was no statistically significant difference in the proportion of patients with high end-induction MRD (defined as $\geq 10^{-3}$): Hispanic (11%) vs. non-Hispanic (9%), $P = 0.55$. Additionally, there was no difference in incidence of treatment-related mortality or in incidence of second malignant neoplasm between Hispanic and non-Hispanic patients. Ethnicity retained significance in multivariable Cox modeling for EFS ($P = 0.030$) when adjusting for age, WBC, sex, immunophenotype and obesity, and marginal significance ($P = 0.07$) in multivariable modeling for OS when adjusting for the same variables. In the multivariable models, obesity was significantly associated with OS ($P = 0.012$) but EFS ($P = 0.27$) (Table 4).

3.4 | Polymorphisms

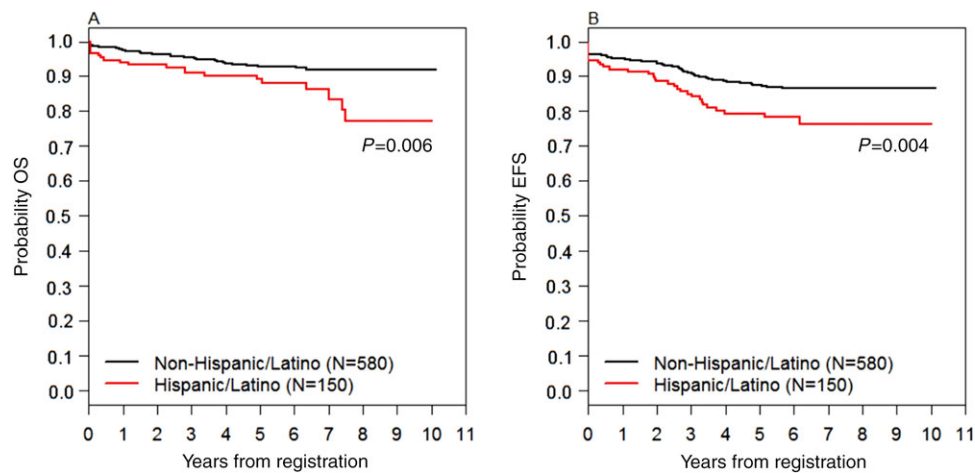
Genotyping data were available for 587 patients with ethnicity information, 574 of who received a final risk group classification (116 [20%] Hispanic, 458 [80%] non-Hispanic). After noting a difference

TABLE 3 Competing risks regression for skeletal toxicities by age subgroup and asparaginase treatment arm

	Bone fracture				Osteonecrosis			
	Univariate		Multivariable		Univariate		Multivariable	
	Hazard ratio [95% CI]	P-value	Hazard ratio [95% CI]	P-value	Hazard ratio [95% CI]	P-value	Hazard ratio [95% CI]	P-value
Age < 10 Years								
Hispanic versus non-Hispanic	0.24 [0.10–0.54]	0.0006	0.23 [0.10–0.51]	0.0003	0.61 [0.18–2.02]	0.41	0.59 [0.18–1.95]	0.39
Female versus male	1.25 [0.86–1.81]	0.25	1.25 [0.86–1.82]	0.23	0.35 [0.14–0.88]	0.025	0.34 [0.13–0.84]	0.020
Postinduction ASP								
Direct assignment versus not	0.96 [0.65–1.42]	0.86	0.97 [0.61–1.52]	0.88	1.92 [0.87–4.22]	0.11	1.79 [0.68–4.69]	0.23
IM <i>E. coli</i> versus not	1.09 [0.73–1.63]	0.67	1.03 [0.64–1.67]	0.90	0.58 [0.22–1.56]	0.28	0.90 [0.27–3.01]	0.86
SR versus not	0.95 [0.63–1.42]	0.80	0.96 [0.64–1.43]	0.83	1.64 [0.62–4.35]	0.32	1.79 [0.68–4.71]	0.24
Obese versus not	1.18 [0.69–2.03]	0.55	1.42 [0.82–2.47]	0.21	0.56 [0.13–2.4]	0.43	^a	^a
Age ≥ 10 years								
Hispanic versus non-Hispanic	0.63 [0.31–1.28]	0.20	0.62 [0.31–1.27]	0.19	0.28 [0.10–0.76]	0.013	0.23 [0.08–0.66]	0.006
Female versus male	0.99 [0.55–1.79]	0.98	0.91 [0.51–1.64]	0.76	0.61 [0.31–1.22]	0.16	0.49 [0.25–0.97]	0.042
Postinduction ASP								
Direct assignment versus not	0.72 [0.37–1.42]	0.35	0.80 [0.37–1.73]	0.57	0.34 [0.14–0.81]	0.015	0.32 [0.12–0.82]	0.020
IM <i>E. coli</i> versus not	1.53 [0.85–2.73]	0.15	1.38 [0.70–2.71]	0.35	1.66 [0.88–3.11]	0.12	1.14 [0.59–2.20]	0.70
VHR versus not	0.77 [0.28–2.14]	0.62	0.75 [0.27–2.07]	0.58	0.41 [0.10–1.72]	0.22	^a	^a
Obese versus not	1.21 [0.56–2.60]	0.63	1.31 [0.60–2.83]	0.50	0.42 [0.13–1.39]	0.16	^a	^a

^aDue to the small number of bone events ($n < 4$) not considered in multivariable modeling.

Direct assignment, directly assigned to receive native *E. coli* asparaginase; IM *E. coli*: intramuscular *E. coli* asparaginase; SR, standard risk; VHR, very high risk; ASP, asparaginase.

**FIGURE 2** Overall survival and event-free survival by ethnicity: (A) overall survival in Hispanic versus non-Hispanic patients and (B) event-free survival in Hispanic versus non-Hispanic patients

in bone toxicity between Hispanic and non-Hispanic patients, we tested whether there was also a significant difference in the prevalence of a polymorphism in TS known to be associated with bone toxicity.¹⁶ In addition, we tested whether there were disparities associated with ethnicity for 18 other TRT-related polymorphisms previously assessed in this cohort.¹⁵ Hispanic and non-Hispanic patients differed significantly in the proportion with the target genotype of four polymorphic genes: *MTHFR* A1298C (rs1801131; $P_{\text{adjusted}} = 0.001$), *SLCO2A1* ($P_{\text{adjusted}} = 0.003$), *IL1B* ($P_{\text{adjusted}} = 0.003$,

and *TCN2* ($P_{\text{adjusted}} = 0.002$) (Supplementary Table S3). Of these four polymorphisms, only *TCN2* was associated with both TRT and disease outcome. In Hispanic patients, having (vs. not having) the target *TCN2* genotype was associated with increased risk of induction infection (32 vs. 11%, $P = 0.010$). In the Hispanic cohort, the *TCN2* polymorphism was univariately associated with EFS within the Hispanic patient cohort. In multivariable modeling, *TCN2* was marginally associated with EFS (HR = 3.15, $P = 0.047$) (Supplementary Table S4).

TABLE 4 Cox proportional hazards univariate and multivariable models of overall survival (OS) and event-free survival (EFS) by ethnicity

	Univariate		Multivariable	
	Hazard ratio [95% CI]	P-value	Hazard ratio [95% CI]	P-value
Overall survival				
Hispanic versus non-Hispanic	2.06 [1.21–3.52]	0.008	1.67 [0.95–2.89]	0.07
Age ≥ 10 years versus < 10 years	1.62 [0.96–2.72]	0.07	1.41 [0.82–2.42]	0.21
WBC $\geq 50,000$ versus $< 50,000$	3.26 [1.97–5.38]	< 0.0001	3.61 [2.13–6.12]	< 0.0001
Female versus male	0.84 [0.51–1.40]	0.51	0.95 [0.57–1.60]	0.85
B-ALL versus T-ALL	1.07 [0.49–2.35]	0.87	2.03 [0.88–4.65]	0.09
Obese versus not obese	2.37 [1.34–4.20]	0.003	2.10 [1.18–3.76]	0.012
Event-free survival				
Hispanic versus non-Hispanic	1.82 [1.19–2.77]	0.005	1.61 [1.05–2.49]	0.030
Age ≥ 10 versus < 10 years	1.65 [1.10–2.46]	0.015	1.45 [0.96–2.20]	0.08
WBC $\geq 50,000$ versus $< 50,000$	2.44 [1.64–3.63]	< 0.0001	2.52 [1.64–3.85]	< 0.0001
Female versus male	0.87 [0.59–1.28]	0.48	0.96 [0.65–1.44]	0.85
B-ALL versus T-ALL	0.84 [0.48–1.47]	0.53	1.38 [0.75–2.53]	0.30
Obese versus not obese	1.46 [0.89–2.41]	0.13	1.33 [0.80–2.20]	0.27

BMI group was regrouped to obese versus not obese to account for overlap between obesity and overweight categories. No differences were seen with EFS. Adjusting for other variables, obesity remains significant and ethnicity is marginally significant.

WBC, white blood cell; B-ALL, B-cell acute lymphoblastic leukemia; T-ALL, T-cell acute lymphoblastic leukemia.

4 | DISCUSSION

This analysis of TRTs and survival from DFCI ALL 05-001 demonstrated that overall, Hispanic patients had lower rates of ON and fracture as well as reduced EFS and OS relative to non-Hispanic patients. The observation of both reduced toxicity and decreased survival in the Hispanic cohort suggests that host and/or environmental factors, rather than differences in leukemia biology alone, likely contributed to these outcomes.

In our Hispanic cohort, the lower incidence of skeletal toxicity is suggestive of reduced exposure to dexamethasone, which may be related to variations in medication adherence or to variations in disease biology or host pharmacogenomics. A potential mechanism of reduced dexamethasone exposure is oral chemotherapy adherence. Chemotherapy agents that need to be orally administered at home, including mercaptopurine and corticosteroid, are important components of the treatment regimen for children and adolescents with ALL.^{17,22} In a 2012 report from the Children's Oncology Group, Bhatia and colleagues found that patients who were $< 95\%$ adherent to mercaptopurine during maintenance therapy had a 2.5-fold higher risk of relapse than those who were $\geq 95\%$ adherent.²³ Further analyses revealed that Hispanic ethnicity, adolescent age ≥ 12 years, and low socioeconomic status were all associated with lower adherence.²³ Of interest, in patients with high adherence, Hispanic ethnicity was still associated with higher relapse rate. This further emphasizes the possibility that differential findings between Hispanic and non-Hispanic patients are likely driven in large part by biologic differences between groups, rather than only by differences in adherence. In 2012, Kawedia et al. reported that dexamethasone clearance may be higher in patients with anti-asparaginase antibodies. In that study, the increased clearance and/or the presence of the antibodies were associated with

a higher risk of relapse.²⁴ Although we did not prospectively assess asparaginase antibodies on the 05-001 study, we serially measured SAA in patients during treatment,²⁵ and demonstrated no differences in SAA between Hispanic and non-Hispanic patients, indicating similar exposure to this agent by the ethnic group.

Having identified reduced rates of ON in Hispanic patients, we were particularly interested in whether there were differences between cohorts in the frequency of an enhancer-repeat genotype (2R/2R) polymorphism in the *TS* gene.^{16,26} Our analysis did not identify a difference in prevalence of the 2R/2R *TS* polymorphism between Hispanic and non-Hispanic patients, suggesting that either untested germline genetic factors or other variables beyond genetic polymorphisms may have contributed to differences in skeletal toxicities.^{27–29} The incidence of ON was significantly different between Hispanic and non-Hispanic patients in the older (≥ 10 years of age) patients, and the incidence of fracture was significantly different between Hispanic patients and non-Hispanic patients in the younger (< 10 years of age) group. The association between older age and ON in ALL patients has been well documented, as has the association between fracture and younger age.^{30,31} To our knowledge, no published study has identified a clear explanation for this phenomenon. Possible mechanisms may include hormonal interactions related to older age, timing of skeletal development, and unidentified genetic predispositions. Further, while obesity is a known predictor of reduced bone mineral density in children without leukemia,³² it was not significantly predictive of either fracture or ON in our patient cohort and would not explain difference by age.

While host genetic variations likely play an important role in determining drug pharmacokinetics and pharmacodynamics, somatic abnormalities in leukemia cells are critical determinants of response and resistance to therapy as well. Differences in the frequency of prognostically significant subtypes of ALL between Hispanic and non-Hispanic

patients have been described, some of which could explain some of the outcome differences we observed.^{11,33} For example, we observed a significantly lower incidence of the favorable *ETV6-RUNX1* (*TEL/AML1*) fusion, in our Hispanic cohort, which may have contributed to a higher risk of relapse.³⁴

We^{15,16} and others^{20,35–40} have previously described associations between functional genetic polymorphisms and TRT or survival among children with leukemia and the prevalence of some of these polymorphisms is known to differ between ethnic groups.^{11,20,33,41–43} In exploratory analyses, we targeted a small subset of polymorphisms that were relatively common (population prevalence of at least 10%) and that could potentially impact either TRT or survival. We observed significant differences between Hispanic and non-Hispanic patients in the prevalence of four of the 19 polymorphisms analyzed (Supplementary Table 3); however, the clinical import of these germline genetic differences remains unclear. The *TCN2* rs1801198 polymorphism was more prevalent in Hispanic patients and was associated with inferior EFS within that cohort. This polymorphism was also associated with increased risk of induction infection in the whole study population, but there was no significant difference in infection rates between Hispanic and non-Hispanic patients; in fact, Hispanic patients tended to have fewer bacterial infections overall.

This study has some important limitations. First, the analysis of genetic polymorphisms was not prospectively designed or powered to detect associations between all polymorphisms and uncommon outcomes. Additionally, we did not analyze incidence of poor prognostic indicators, including *BCR-ABL1-like* subtype and deletions of the *Ikaros* (*IKZF1*) gene, both of which have been reported to be more common in Hispanic patients.^{36–38,41} These two features, which are frequently observed together, are independently associated with adverse outcomes in children with ALL. Thus, the inferior EFS and OS that we observed in Hispanic patients may be due to overrepresentation of these unfavorable biologic features within this population.⁴⁴ While these alterations may have contributed to survival differences by ethnicity, they would not explain the difference in TRTs.

There was not a standard approach to designating patient ethnicity at the time of study enrollment. Hispanic ethnicity as a single broad category does not delineate between different Hispanic/Latino groups (e.g., Cuban, Mexican, Puerto Rican, South or Central American, Spanish), each of which are known to have unique biologic and nonbiologic factors associated with disease outcome.⁴⁵ Because of sample size limitations, we did not analyze outcomes by combined race/ethnicity. We acknowledge there are more objective ways of classifying patients' ethnicity, for example by using genome-wide ancestry estimates. These methods, while precise in their characterization of genetic and biologic variation, are limited in their ability to account for sociocultural influences.^{45–48} For future studies, we will define both race and ethnicity using patient report, and will define genetic or biogeographical ancestry using modern genomic techniques.^{33,44} Comparing self-reported ethnicity to genetic ancestry will be an important part of investigating whether biology, sociocultural influences, or both are contributing to observed outcome differences between ethnically distinct populations.⁴⁹

5 | CONCLUSION

Hispanic children and adolescents enrolled on the DFCI 05-001 had significantly lower rates of skeletal toxicities as well as significantly lower EFS and OS compared to non-Hispanic patients. Hispanic patients were more frequently obese than non-Hispanic patients and obesity was associated with inferior OS, it did not explain differences in ON, fracture, or EFS by ethnicity. It is likely that the mechanisms behind our observations are a combination of biogeographical variables (i.e., inherited host genetic factors), gene–environment interactions, and sociocultural variables (i.e., early childhood exposures, baseline nutrition, health beliefs).^{50–52}

Other studies have compared self-defined ethnicity to genetic ancestry in childhood ALL, and have explored how these groups associate with relapse and adverse events.⁵³ Our combined analyses of disease outcomes and toxicity in a homogeneously treated patient population suggest that factors beyond genomics are involved. Considering the observation of both reduced toxicities and inferior survival in the Hispanic cohort, the possibility of suboptimal drug exposure in these patients likely deserves further inquiry. Thus, while differences in both host and leukemia biology are prognostically important, future studies will also focus on host pharmacogenomics, detailed analyses of nutrition status and obesity trends,⁵⁴ interpatient differences in biomarkers of drug exposure, frequency of drug interruptions for toxicity, and oral chemotherapy adherence.

CONFLICT OF INTEREST

L.B.S. has served on advisory boards for Sigma-Tau Pharmaceuticals and JAZZ Pharmaceuticals. All other authors declare no conflict of interest.

ACKNOWLEDGMENTS

The authors would like to thank the patients, families, physicians, nurses, research coordinators, and all others who participated in the data collection associated with this work. They would also like to thank the Dana-Farber Cancer Institute ALL Consortium for its contribution to this work.

The patients described in this report were enrolled at the following Dana-Farber Cancer Institute (DFCI) Acute Lymphoblastic Leukemia Consortium sites: DFCI/Boston Children's Hospital (Boston, MA), Columbia University Medical Center, Morgan Stanley Children's Hospital of New York-Presbyterian (New York, NY), Hospital Sainte Justine (Montreal, QC, Canada), Le Centre Hospitalier de L'Université Laval (Quebec City, QC, Canada), McMaster Children's Hospital (Hamilton, ON, Canada), San Jorge Children's Hospital (San Juan, PR), University of Rochester Medical Center (Rochester, NY), Hospital Ste. Justine (Montreal, Quebec, Canada), Hasbro Children's Hospital (Providence, RI), and Inova/Fairfax Hospital for Children (Falls Church, VA). This work was supported in part by funding from the National Institutes of Health (R25 CA094061) (to J.M.K.) and the St. Baldrick's Foundation (Supportive Care Research Award) (to P.D.C.). Clinical trial information for DFCI 05-001: ClinicalTrials.gov, number NCT00400946.

AUTHORS' CONTRIBUTIONS

Concept and design: J.M.K., P.D.C., T.M.B., K.E.S., L.B.S., and K.M.K.; provision of study materials or patients: L.B.S., U.H.A., P.D.C., L.A.C., K.M.K., C.L., J.-M.L., B.M., M.A.S., and J.J.G.W.; collection and assembly of data: J.M.K., P.D.C., T.M.B., K.E.S., L.B.S., and K.M.K.; data analysis and interpretation: J.M.K., P.D.C., T.M.B., K.E.S., Z.J., D.S.N., S.B., R.D., E.R., S.E.S., L.B.S., and K.M.K.; and manuscript writing and final approval of manuscript: all authors.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Kahn JM, Cole PD, Blonquist TM, et al. An investigation of toxicities and survival in Hispanic children and adolescents with ALL: Results from the Dana-Farber Cancer Institute ALL Consortium protocol 05-001. *Pediatr Blood Cancer*. 2018;65:e26871. <https://doi.org/10.1002/pbc.26871>