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ORIGINAL REPORT

Nonadherence to Oral Mercaptopurine and Risk of Relapse in Hispanic and Non-Hispanic White Children With Acute Lymphoblastic Leukemia: A Report From the Children's Oncology Group

Smita Bhatia, Wendy Landier, Muyun Shangguan, Lindsey Hageman, Alexandra N. Schaible, Andrea R. Carter, Cara L. Hanby, Wendy Leisenring, Yutaka Yasui, Nancy M. Kornegay, Leo Mascarenhas, A. Kim Ritchey, Jacqueline N. Casillas, David S. Dickens, Jane Meza, William L. Carroll, Mary V. Relling, and F. Lennie Wong

Smita Bhatia, Wendy Landier, Muyun Shangguan, Lindsey Hageman, Alexandra N. Schaible, Cara L. Hanby, and F. Lennie Wong, City of Hope, Duarte; Andrea R. Carter, David Geffen School of Medicine, University of California, Los Angeles; Jacqueline N. Casillas, University of California, Los Angeles; Leo Mascarenhas, University of Southern California Keck School of Medicine, Children's Hospital Los Angeles, Los Angeles, CA; Wendy Leisenring, Fred Hutchinson Cancer Research Center, Seattle, WA; Yutaka Yasui, University of Alberta, Edmonton, Alberta, Canada; Nancy M. Kornegay and Mary V. Relling, St Jude Children's Research Hospital, Memphis, TN; A. Kim Ritchey, Children's Hospital of Pittsburgh, University of Pittsburgh Medical Center, Pittsburgh, PA; David S. Dickens, Spectrum Health at Butterworth Campus, Grand Rapids, MI; Jane Meza, University of Nebraska Medical Center, Omaha, NE; and William L. Carroll, New York University Cancer Institute, New York, NY.

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Corresponding author: Smita Bhatia, MD, MPH, City of Hope, 1500 East Duarte Rd, Duarte, CA 91010-3000; e-mail: sbhatia@coh.org.

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ABSTRACT

Purpose
Systemic exposure to mercaptopurine (MP) is critical for durable remissions in children with acute lymphoblastic leukemia (ALL). Nonadherence to oral MP could increase relapse risk and also contribute to inferior outcome in Hispanics. This study identified determinants of adherence and described impact of adherence on relapse, both overall and by ethnicity.

Patients and Methods
A total of 327 children with ALL (169 Hispanic; 158 non-Hispanic white) participated. Medication event-monitoring system caps recorded date and time of MP bottle openings. Adherence rate, calculated monthly, was defined as ratio of days of MP bottle opening to days when MP was prescribed.

Results
After 53,394 person-days of monitoring, adherence declined from 94.7% (month 1) to 90.2% (month 6; $P < .001$). Mean adherence over 6 months was significantly lower among Hispanics (88.4% *v* 94.8%; $P < .001$), patients age ≥ 12 years (85.8% *v* 93.1%; $P < .001$), and patients from single-mother households (80.6% *v* 93.1%; $P = .001$). A progressive increase in relapse was observed with decreasing adherence (reference: adherence ≥ 95%; 94.9% to 90%: hazard ratio [HR], 4.1; 95% CI,1.2 to 13.5; $P = .02$; 89.9% to 85%: HR, 4.0; 95% CI, 1.0 to 15.5; $P = .04$; < 85%: HR. 5.7; 95% CI, 1.9 to 16.8; $P = .002$). Cumulative incidence of relapse (± standard deviation) was higher among Hispanics (16.5% ± 4.0% *v* 6.3% ± 2.2%; $P = .02$). Association between Hispanic ethnicity and relapse (HR, 2.6; 95% CI, 1.1 to 6.1; $P = .02$) became nonsignificant (HR, 1.8; 95% CI, 0.6 to 5.2; $P = .26$) after adjusting for adherence and socioeconomic status. At adherence rates ≥ 90%, Hispanics continued to demonstrate higher relapse, whereas at rates < 90%, relapse risk was comparable to that of non-Hispanic whites.

Conclusion
Lower adherence to oral MP increases relapse risk. Ethnic difference in relapse risk differs by level of adherence—an observation currently under investigation.

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy.[1] Although a majority of children with ALL enter remission after induction, 20% relapse within 5 years.[2] Furthermore, Hispanics have significantly inferior outcomes compared with non-Hispanic whites,[3] a difference not entirely explained by clinical[3] or genetic factors.[4,5] Durable remissions require a 2-year maintenance phase that includes oral mercaptopurine (MP).[6,7] Low erythrocyte levels of the MP metabolite (thioguanine nucleotide [TGN]) correlate with relapse.[8] Significant interpatient variability in TGN levels has been observed,[9] even after adjusting for inherited differences in thiopurine methyltransferase (TPMT) activity,[9] and could be the result of failure to adhere to prescribed therapy.[10] Lack of adherence to oral MP has been reported in children with ALL.[10-12] However, reports on nonadherence have relied on small cohorts of patients and been based largely on self-report. Furthermore, the impact of

nonadherence on relapse is not known. Finally, the role of nonadherence in explaining the observed ethnic difference in relapse remains unexplored.

We hypothesized that nonadherence to oral MP during maintenance would result in low systemic exposure to oral MP, thus increasing the risk of relapse. Furthermore, given the influence of sociodemographic factors on medication adherence in nononcologic populations,[13-15] we hypothesized that ethnic differences in adherence would contribute to the inferior outcome in Hispanics. We tested this hypothesis by: measuring adherence to oral MP in Hispanic and non-Hispanic white children receiving maintenance therapy for ALL, and examining sociodemographic determinants of adherence; determining the impact of adherence on risk of relapse in the entire cohort and among Hispanics and non-Hispanic whites; and examining the extent to which adherence to oral MP explained ethnic difference in relapse.

PATIENTS AND METHODS

Study Participants

Participating institutions (Appendix, online only) contributed patients after obtaining approval from local institutional review boards for the study. Written informed consent/assent (in English or Spanish) was obtained from all participating patients and/or parents or legal guardians. Eligibility criteria included diagnosis of ALL at age $\leq$ 21 years; in first continuous remission; belonging to one of two self-reported ethnic/racial groups (Hispanic or non-Hispanic white); and receiving maintenance chemotherapy that included self- or parent- or caregiver-administered oral MP. Rationales for inclusion and exclusion criteria are described in Appendix Table A1 (online only).

Measurement of Adherence

The study called for 6 months of adherence monitoring (study design illustrated in Appendix Fig A1, online only) using an electronic monitoring device (MEMS TrackCap; Aprex Corporation, Union City, CA). The MEMS cap uses microelectronic technology to record date and time of each pill bottle opening (Appendix Fig A2, online only). Patients/parents were informed about the purpose of MEMS and were instructed to take all doses of MP from the MEMS bottle. No compensation was provided for study participation. At the end of 6 months, data were downloaded (data download example illustrated in Appendix Fig A3, online only).

Erythrocyte TGN levels in pmol/8 $\times$ 10^8 erythrocytes were measured every month for the 6-month study period (Appendix Fig A1, online only) to demonstrate that MEMS bottle openings were accompanied by MP ingestion.[16] TGN levels reflect chronic systemic exposure to MP over the past 30 days and therefore depend on the prescribed dose, adherence, and inherited variability in TPMT activity. TPMT activity was measured at least 90 days after red cell transfusion.[17] Patients with TPMT activity $\geq$ 15th percentile for the cohort were assumed to have homozygous wild-type genotype based on known frequency of variant alleles.[7,9,17,18]

Demographic Questionnaire

A demographic questionnaire elicited self-reported information regarding parents' education, annual household income, number of adult caregivers, and race/ethnicity. Hispanics included patients of Mexican, Mexican-American, Chicano, Cuban, Puerto Rican, or other Spanish/Hispanic/Latino ethnicities, whereas non-Hispanic whites included patients of European, North African, or Middle Eastern ancestry.

Health Care Provider Reports

Participating institutions submitted monthly reports for each patient, detailing prescribed MP dose for each day of the preceding month and dates when the prescriber held MP for toxicity or illness. After completion of the 6-month adherence monitoring, participating institutions submitted biannual clinical status reports, detailing dates of last visit, relapse, or death and cause of death (if applicable) during the interim period.

Statistical Analyses

Adherence to oral MP. Adherence rate was defined as the ratio of the number of days with MEMS cap openings (X) to the number of days MP was prescribed (N), reported as a percentage (X/N $\times$ 100). Days when MP was withheld by the prescriber were removed from the denominator (N). Adherence rate was computed for each of the 6 months of adherence monitoring. Longitudinal binomial regression was conducted using generalized estimating equation methods by modeling monthly adherence rate as an unstructured mean model using five indicator variables of time for the 6 study months. Time in months was also treated as a continuous variable to explore temporal trends in adherence rate. Compound symmetry was assumed as the working correlation matrix over time.[19] Covariates considered for adjustment included those hypothesized to be predictors of adherence (sex, age at study participation [$<$ 12 *v* $\geq$ 12 years], ethnicity [non-Hispanic whites *v* Hispanics], family structure [multiple caregivers *v* single mother], annual household income [$\geq$ \$20,000 *v* $<$ \$20,000], parental education [$>$ high school *v* $\leq$ high school], time since start of maintenance, National Cancer Institute [NCI] risk classification [based on age at diagnosis and presenting white cell count],[20] blast chromosomal abnormalities,[21] and MP dose-intensity). MP dose-intensity was defined as the ratio of MP dose actually prescribed to the planned protocol dose of 75 mg/m^2/d for the entire 6 months of adherence monitoring. Detailed definition of these variables is provided in the Appendix (online only). A relationship between MEMS-based adherence and erythrocyte TGN levels was sought using generalized estimating equation for normally distributed data by determining the association between the square root of TGN levels and MP dose-intensity–adjusted MEMS-based adherence rate.

Adherence to oral MP and risk of relapse. All patients were in complete continuous first remission at entry into the adherence-monitoring study. Cumulative incidence of first relapse (at any site) was calculated, treating death as competing risk.[22] Cox proportional hazards regression models were constructed to understand the impact of adherence on relapse. The following variables were included in the model: sex, ethnicity, parental education and annual household income, NCI risk classification, blast chromosomal abnormalities, TPMT activity (low/absent *v* normal), MP dose-intensity, time from ALL diagnosis to entry into adherence study, and adherence rate. Adherence rate was treated as a time-varying covariate, updating the rate each month by cumulating the values of X and N. The overall 6-month adherence rate was used for maintenance remaining after completion of adherence study. Adherence rate was categorized as: $\geq$ 95%, 94.9% to 90%, 89.9% to 85%, and $<$ 85%. Proportional hazards assumption, examined by testing the interaction of adherence rate with time, was nonsignificant ($P = .81$).

Adherence to oral MP and ethnic difference in risk of relapse. To test the hypothesis that MP adherence contributed to ethnic difference in relapse risk, Cox regression was performed with variables organized into four conceptual models. Model 1 included the clinical variables known to be associated with relapse (sex, NCI risk classification, blast chromosomal abnormalities, TPMT activity [low/absent *v* normal], MP dose-intensity, ethnicity, and time from ALL diagnosis to entry into adherence study). Model 2 added adherence rate to model 1. Model 3 replaced adherence in model 2 with parental education and annual household income. Finally, model 4 included all variables in models 1, 2, and 3.

Modifying effect of ethnicity on adherence-associated relapse. Relapse risk among Hispanics and non-Hispanic whites was examined for varying categories of adherence ($\geq$ 95%, 94.9% to 90%, 89.9% to 85%, and $<$ 85%); non-Hispanics whites with adherence rate $\geq$ 95% served as referent group. Next, the modifying effect of ethnicity on relapse was examined by stratifying on categories of adherence.

All missing data were addressed with multiple imputation (Appendix, online only).[23] PROCs GENMOD, LIFETEST, PHREG, MI, and MIANALYZE of SAS 9.1 (SAS Institute, Cary, NC) were used for analysis (Appendix, online only). Two-sided tests with $P < .05$ were considered statistically significant.

Table 1. Demographics and Clinical Characteristics of the Study Participants

Characteristic	Entire Cohort No.	Entire Cohort %	Non-Hispanic Whites No.	Non-Hispanic Whites %	Hispanics No.	Hispanics %	*P*
Cohort size	327	100	158	48.3	169	51.7	—
Age, years							.91
Median	4.0		4.5		4.0		
Range	1-19		1-19		1-18		
Age at study participation, years							.85
Median	6.0		6.0		6.0		
Range	2-20		2-20		2-20		
Male sex	218	66.7	104	65.8	114	67.5	.75
WBC count at diagnosis ≥ 50,000/μL	61*	18.8*	31	19.6	30*	18.0*	.70
High-risk disease (NCI criteria)	124*	38.2*	63	39.9	61*	36.5*	.53
Cytogenetics							
Unfavorable†	15*	4.9*	9*	6.0*	6*	3.8*	.37
Favorable†	135*	43.8*	64*	42.7*	71*	44.9*	.69
Daily MP dose-intensity‡							.18
Mean	82.3		80.6		83.8		
SD	21.3		21.4		21.2		
TPMT activity							.16
Median	17.4*		17.9*		17.1*		
Range	0.5-31.4*		0.5-31.4*		7.7-26.9*		
Person-days of adherence monitoring	53,394		26,123		27,271		—
Annual household income < $20,000	83*	26.5*	10*	6.5*	73*	45.6*	< .001
Paternal education ≤ high school	159*	50.2*	42	26.6	117*	73.6*	< .001
Maternal education ≤ high school	140*	43.6*	32	20.3	108*	66.3*	< .001
Parental education ≤ high school	127*	39.4*	24	15.2	103*	62.8*	< .001
Single mother	36*	11.2*	10	6.3	26*	15.8*	.007
Monolingual, Spanish speaking	79*	24.2*	NA	NA	79*	47.0*	—
Time from start of maintenance to study entry, years							.65
Median	0.8		0.8		0.9		
Range	0.2-2.2		0.2-2.1		0.2-2.2		
Time from diagnosis to study entry, years							.56
Median	1.6		1.6		1.6		
Range	0.9-3.0		0.9-2.9		0.9-3.0		
Length of follow-up from diagnosis, years							< .001
Median	5.3		5.9		4.6		
Range	1.3-10.3		1.5-10.3		2.0-10.1		
Length of follow-up from study entry, years							< .001
Median	3.7		4.3		2.9		
Range	0.4-8.8		0.4-8.1		0.4-8.8		
Length of follow-up from study exit, years							< .001
Median	3.3		3.8		2.4		
Range	0-8.5		0-8.0		0-8.5		
Relapse	27	8.3	8	5.1	19	11.2	.04

Abbreviations: MP, mercaptopurine; NA, not applicable; NCI, National Cancer Institute; SD, standard deviation; TPMT, thiopurine methyltransferase.

*Statistics were calculated for this table by excluding patients with missing values for the characteristics.

†Unfavorable chromosomal abnormalities included t(9;22), t(4;11), hypodiploidy, or extreme hypodiploidy; favorable cytogenetics included one or more of the following: t(12;21), hyperdiploidy, trisomy 4 and 10, or trisomy 4, 10, and 17.

‡MP dose-intensity: mean MP dose (mg/m^2 body surface area) prescribed over the No. of days that the drug was prescribed divided by the planned daily protocol dosage (75 mg/m^2).

RESULTS

Patient Characteristics

Three hundred twenty-seven patients (169 Hispanics; 158 non-Hispanic whites) contributed 53,394 person-days for MP adherence monitoring. This sample size provided adequate power to address the proposed aims (Appendix, online only). All patients received treatment according to Children's Oncology Group therapeutic protocols (Appendix Table A2, online only). The distribution of Hispanics and non-Hispanic whites on low/standard-risk and high-risk protocols was comparable (Appendix, online only). Hispanic and non-Hispanic white participants were also comparable with respect to disease characteristics, MP dose-intensity, and TPMT activity (Table 1). However, Hispanics were more likely to report lower household income (< $20,000: 73 [45.6%] *v* 10 [6.5%]; *P* < .001), lower levels of parental education (≤ high school: 103 [62.8%] *v* 24 [15.2%]; *P* < .001), and higher prevalence of households with single mothers (26 [15.8%] *v* 10 [6.3%]; *P* = .007).

Adherence to Oral MP

Adherence to oral MP declined with time on study from 94.7% at the end of month 1 to 90.2% at the end of month 6 (*P* < .001; linear trend *P* = .001; Fig 1A). Multivariate analysis (Table 2) revealed Hispanic ethnicity (adjusted adherence rate: 88.4% *v* 94.8%; *P* < .001; Fig 1B), age ≥ 12 years at study entry (85.8% *v* 93.1%; *P* < .001; Fig 1C), and single-mother households (80.6% *v* 93.1%; *P* = .001; Fig 1D) to be associated with lower adherence. Sex (*P* = .51), parental education (*P* = .41), and annual household income (*P* = .93) did not influence adherence. Among patients with normal TPMT activity,

Table 2. Variables Associated With Adherence to Oral Mercaptopurine (N = 327)

Variable	Parameter Estimate*	95% CI	Estimated Adherence (%)	*P*
Intercept	3.85	3.34 to 4.35	—	< .001
Time on study, months				< .001
1	—		94.7	—
2	−0.29	−0.46 to −0.13	93.1	< .001
3	−0.41	−0.61 to −0.22	92.5	< .001
4	−0.52	−0.71 to −0.32	91.6	< .001
5	−0.59	−0.81 to −0.37	91.0	< .001
6	−0.66	−0.89 to −0.43	90.2	< .001
Age at study participation, years				< .001
< 12	—		93.1	
≥ 12	−0.81	−1.28 to −0.34	85.8	
Household structure				.001
Multiple caregivers	—		93.1	
Single mother	−0.86	−1.39 to −0.33	80.6	
Ethnicity				< .001
Non-Hispanic whites	—		94.8	
Hispanics	−0.86	−1.20 to −0.52	88.4	

NOTE. All models were adjusted for time from initiation of maintenance to study entry. Other variables examined but not found to be significantly associated with adherence included: sex (*P* = .51), National Cancer Institute criteria for disease risk (*P* = .44), chromosomal abnormalities (*P* = .51), parental education (*P* = .41), and annual household income (*P* = .93).

*More negative values of the parameter estimates indicate worse adherence rate when compared with the referent level, which is indicated by —.

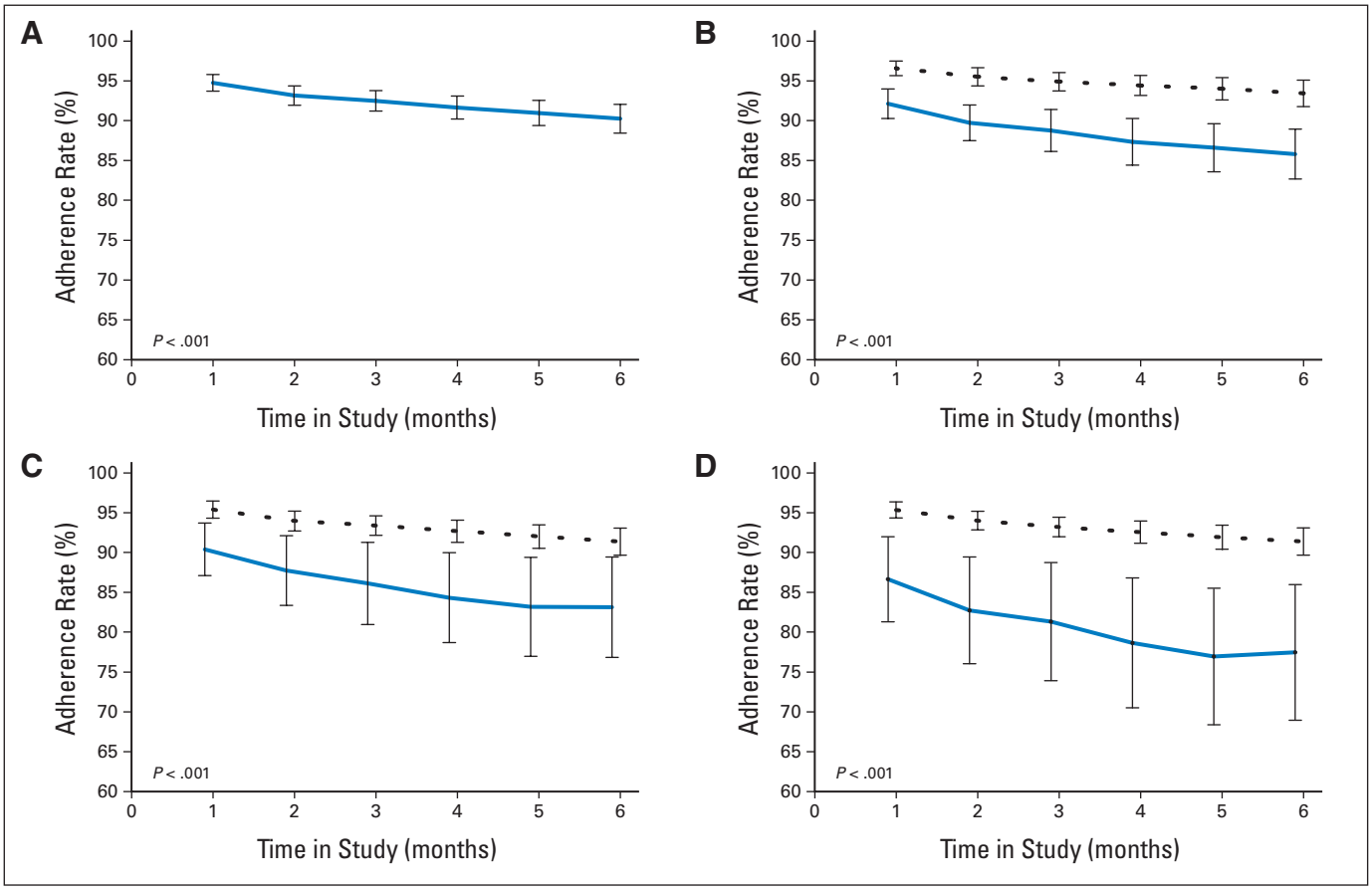

Fig 1. Adherence rates (A) for the entire cohort over the 6 months of observation, (B) over time according to ethnicity (solid and dashed lines represent estimated values for Hispanics and non-Hispanic whites, respectively), (C) over time according to age at study participation (solid and dashed lines represent estimated values for older [age ≥ 12 years] and younger [age < 12 years] patients, respectively), and (D) over time according to family structure (single mother *v* multiple caregivers; solid and dashed lines represent estimated values for single-mother and multiple-caregiver households, respectively). In each panel, 95% CIs of model estimates are presented on the plots.

each 1% increase in MEMS-measured adherence was associated with an 11.1-unit (pmol/8 × 10^8 erythrocytes) increase in MP dose-intensity–adjusted TGN levels ($P < .001$).

Adherence to Oral MP and Risk of Relapse

With a median follow-up of 3.7 years (range, 0.4 to 8.8 years) from adherence study entry, 27 patients experienced relapse of their primary disease, and three patients died (second malignancies [n = 2]; relapse [n = 1]); the remainder were alive and in complete remission at last contact. The cumulative incidence of relapse (± standard deviation) for the entire cohort was 11.0% ± 2.1% at 4 years from adherence study entry. The median adherence rate over 6 months was significantly lower among those who relapsed (88.2%) compared with those who remained in complete continuous remission (96.2%; $P = .001$). After adjusting for sex, NCI risk classification, blast chromosomal abnormalities, MP dose-intensity, TPMT activity, ethnicity, time from diagnosis to adherence study entry, parental education, and household income, there was a progressive increase in risk of relapse with decreasing levels of adherence (reference: adherence ≥ 95%; 94.9% to 90%: HR, 4.1; 95% CI, 1.2 to 13.5; $P = .02$; 89.9% to 85%: HR, 4.0; 95% CI, 1.0 to 15.5; $P = .04$; < 85%: HR, 5.7; 95% CI, 1.9 to 16.8; $P = .002$; overall $P = .01$; $df = 3$; Table 3; model 4).

Clinically relevant adherence. Nonadherence forms a continuum from the occasional missed dose to total refusal, creating a need to identify a clinically relevant level of adherence below which the risk of relapse is unacceptable. Using data from Table 3, model 4, we identified adherence rate < 95% to be associated with increased risk of relapse. Using this definition, 44% of the study participants were identified as nonadherent. The cumulative incidence of relapse (± standard deviation) was significantly greater among nonadherent patients (17.0% ± 3.7%) compared with adherent patients (4.9% ± 1.9%; $P = .001$; Fig 2A). The median absolute neutrophil count (MP dose-intensity adjusted) during the 6 months of adherence monitoring was significantly higher among the nonadherent patients (2.3 *v* 2.1; $P < .04$). After adjusting for all relevant prognosticators, nonadherent patients were 2.5-fold more likely to relapse (95% CI, 1.8 to 11.6; $P = .002$) compared with adherent patients. Finally, the adjusted risk of relapse attributable to nonadherence was 58.8%.[24]

Adherence to Oral MP and Ethnic Difference in Risk of Relapse

The cumulative incidence of relapse (± standard deviation) at 4 years was significantly higher among Hispanics (16.5% ± 4.0%) compared with non-Hispanic whites (6.3% ± 2.2%; $P = .02$; Fig 2B). To understand the contribution of adherence to ethnic difference in relapse risk, variables were introduced into the regression analysis

Table 3. Cox Regression Analysis for Determinants of Relapse Risk in Children With ALL

Variable	Model 1			Model 2			Model 3			Model 4		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
NCI criteria for disease risk												
Standard	1.0			1.0			1.0			1.0		
High	1.9	0.8 to 4.3	.13	1.6	0.7 to 3.8	.24	2.0	0.9 to 4.6	.10	1.7	0.8 to 4.0	.20
Sex												
Male	1.0			1.0			1.0			1.0		
Female	1.0	0.4 to 2.4	.95	1.1	0.5 to 2.7	.78	1.0	0.4 to 2.4	.94	1.1	0.5 to 2.8	.76
MP dose-intensity												
Per unit increase	1.0	0.99 to 1.02	.68	1.0	0.98 to 1.01	.62	1.0	0.99 to 1.02	.53	1.0	0.98 to 1.02	.81
TPMT activity												
Normal	1.0			1.0			1.0			1.0		
Low	0.9	0.3 to 3.2	.91	0.8	0.2 to 3.1	.76	0.9	0.2 to 3.2	.89	0.8	0.2 to 3.1	.75
Ethnicity												
Non-Hispanic whites	1.0			1.0			1.0			1.0		
Hispanics	**2.6**	**1.1 to 6.1**	**.02**	2.3	0.9 to 5.7	.07	2.1	0.8 to 5.7	.14	1.8	0.6 to 5.2	.26
Adherence to oral MP*												
≥ 95%				1.0						1.0		
94.9% to 90%				**4.0**	**1.2 to 13.2**	**.02**				**4.1**	**1.2 to 13.5**	**.02**
89.9% to 85%				**3.6**	**1.0 to 13.5**	**.05**				**4.0**	**1.0 to 15.5**	**.04**
< 85%				**5.5**	**1.9 to 16.2**	**.002**				**5.7**	**1.9 to 16.8**	**.002**
Parental education												
> High school							1.0			1.0		
≤ High school							1.6	0.6 to 4.0	.35	1.8	0.7 to 4.4	.23
Annual household income												
≥ $20,000							1.0			1.0		
< $20,000							1.0	0.4 to 2.5	.99	0.9	0.4 to 2.3	.85

NOTE. Adjusted for chromosomal abnormalities and time from diagnosis to study entry. Bold font indicates significance.
Abbreviations: ALL, acute lymphoblastic leukemia; HR, hazard ratio; MP, mercaptopurine; NCI, National Cancer Institute; TPMT, thiopurine methyltransferase.
**P* values for overall effect of adherence are .02 and .01 for models 2 and 4, respectively.

serially (Table 3). In model 1, after adjusting for conventional prognosticators (sex, NCI risk classification, blast chromosomal abnormalities, MP dose-intensity, TPMT activity) and time from diagnosis to study entry, Hispanic ethnicity was significantly associated with relapse risk (HR, 2.6; 95% CI, 1.1 to 6.1; $P = .02$). Adding adherence to the model (model 2) partially mitigated the association between ethnicity and relapse risk (HR, 2.3; 95% CI, 0.9 to 5.7; $P = .07$). Replacing adherence with parental education and income (model 3) also mitigated the association between ethnicity and relapse risk (HR, 2.1; 95% CI, 0.8 to 5.7; $P = .14$). Finally, inclusion of adherence, parental

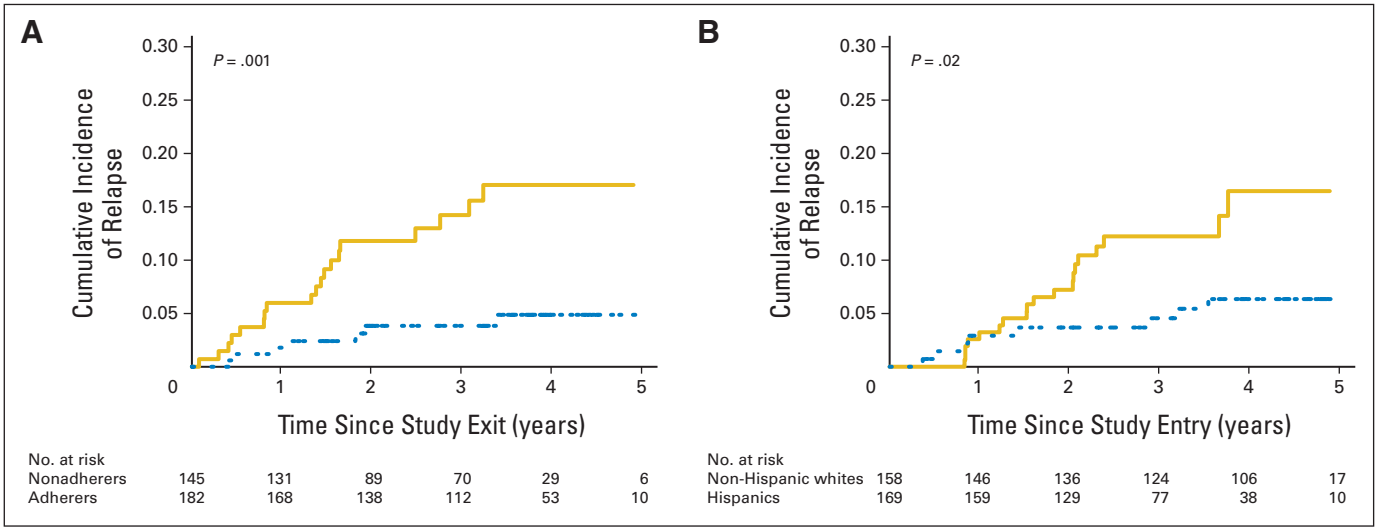

Fig 2. Cumulative incidence of relapse in a cohort of 327 children with ALL according to (A) adherence to oral mercaptopurine (solid and dashed lines represent nonadherers [< 95%] and adherers [≥ 95%], respectively) and (B) ethnicity (solid and dashed lines represent Hispanics and non-Hispanic whites, respectively).

Table 4. Relapse Risk in Children With ALL: Interaction Between Ethnicity and Adherence

Adherence	Risk of Relapse for All Patients*			Risk of Relapse by Ethnicity, Stratified by Adherence Level†		
	HR	95% CI	*P*	HR	95% CI	*P*
≥ 95%						
Non-Hispanic white	1.0		—	1.0		—
Hispanic	5.3	0.6 to 49.2	.14	5.3	0.6 to 49.2	.14
90% to 94.9%						
Non-Hispanic white	2.8	0.2 to 45.7	.46	1.0		—
Hispanic	29.7	3.0 to 291.5	.004	10.5	1.1 to 102.3	.04
85% to 89.9%						
Non-Hispanic white	13.6	1.2 to 154.1	.03	1.0		—
Hispanic	12.6	1.0 to 162.6	.05	0.9	0.1 to 7.8	.94
< 85%						
Non-Hispanic white	30.9	3.3 to 286.9	.003	1.0		—
Hispanic	16.5	1.8 to 148.7	.01	0.5	0.1 to 2.9	.37

NOTE. Adjusted for National Cancer Institute criteria of disease risk, sex, mercaptopurine dose-intensity, parental education, annual household income, blast chromosomal abnormalities, and time from diagnosis to adherence study entry.
Abbreviations: ALL, acute lymphoblastic leukemia; HR, hazard ratio.
*Reference group: non-Hispanic whites with adherence ≥ 95%.
†Reference group: non-Hispanics whites for the corresponding adherence level.

education, and income to model 1 further mitigated the impact of ethnicity on relapse risk (Hispanics: HR, 1.8; 95% CI, 0.6 to 5.2; $P = .26$). Of note, the association between adherence and relapse remained similar in models 2 and 4, whereas the association between education/income and relapse were never statistically significant (model 3 or 4).

Importantly, a stratified analysis by ethnicity revealed a large association between adherence and relapse for non-Hispanic whites (adherence rate < 95%: HR, 11.6; 95% CI, 1.4 to 96.5; $P = .02$); the association was more modest for Hispanics (HR, 3.3; 95% CI, 1.1 to 9.8; $P = .03$]; Appendix Table A3, online only). This led to an evaluation of interaction between ethnicity and adherence-related relapse risk.

Modifying effect of ethnicity on adherence-related relapse. As seen in Table 4, at adherence rates ≥ 90%, Hispanics were at higher risk of relapse compared with non-Hispanic whites (≥ 95%: HR, 5.3; 95% CI, 0.6 to 49.2; $P = .14$; 94.9% to 90%: HR, 10.5; 95% CI, 1.1 to 102.3; $P = .04$). However, at adherence rates < 90%, the ethnic difference in relapse risk was abrogated (89.9% to 85%: HR, 0.9; 95% CI, 0.1 to 7.8; $P = .94$; < 85%: HR, 0.5; 95% CI, 0.1 to 2.9; $P = .37$).

DISCUSSION

This report is the first to demonstrate conclusively that adherence to oral MP influences risk of relapse in children with ALL. There was a progressive increase in relapse risk with decreasing levels of adherence after adjusting for known clinical prognosticators. Furthermore, we identified an adherence rate of < 95% to be accompanied by a significant increase in relapse risk; patients who consumed < 95% of the prescribed MP were 2.5-fold more likely to suffer a relapse when compared with those who consumed > 95%. Using < 95% to define nonadherence, the cumulative incidence of relapse was 17% at 4 years among nonadherers and only 5% among adherers.

The current study confirmed adolescents to be vulnerable to nonadherence[25-27]; drift in adherence over time was also confirmed.[26] However, to our knowledge, the current study is the first to document a significantly lower adherence rate among Hispanics as compared with non-Hispanic whites. Additionally, patients from single-mother households were at increased risk for nonadherence. Thus, the lower adherence among Hispanics could in part be explained by a household structure in which effective supervision by a single caregiver is not always possible, and adolescents assume increasing responsibility for self-medication.

Hispanics were at a 2.6-fold increased risk of relapse compared with non-Hispanic whites, confirming the previously reported inferior outcome experienced by Hispanics.[3,28,29] The significantly lower level of adherence along with lower socioeconomic status among Hispanics contributed to the ethnic differences in relapse risk. However, ethnic difference in risk of relapse differed by the level of adherence. Thus, at adherence rates exceeding 90%, Hispanics continued to demonstrate a higher risk of relapse, whereas at adherence rates < 90%, the risk of relapse was comparable to that of non-Hispanic whites. These findings suggest that in the presence of adequate systemic exposure to MP, underlying genetic factors possibly influence relapse risk among Hispanics. On the other hand, at lower levels of adherence, relapse risk is comparable for Hispanics and non-Hispanic whites, suggesting that low systemic exposure to MP possibly supersedes the biologic differences. Supporting the genetic basis for the ethnic difference in outcome are publications demonstrating genomic variation that cosegregated with Native American ancestry and was associated with relapse[5] and demonstrating the association between rearrangement of *CRLF2*, mutation of JAK kinases, alteration of *IKZF1*, Hispanic ethnicity, and outcome.[4] However, neither study measured adherence to oral MP as cocontributor to relapse. A comprehensive evaluation of both the genetic and socioeconomic/cultural/behavioral underpinnings of the ethnic differences in survival is clearly needed and is currently under way.

Adherence to oral medications has been conventionally monitored by self-report and pill counts.[30] Self-report is subject to social desirability bias,[31] and pill counts to patient interference.[32] Previous

studies have reported lack of adherence in 10% to 33% of children with ALL.[10-12] These studies were limited by poor quality of adherence measures (mostly self-report), small sample sizes, brief periods of observation, lack of association between adherence and relapse, and absence of a clinical basis for defining nonadherence. The current study used the MEMS device to monitor adherence for 53,394 person-days and used disease outcome to define a clinically relevant level of adherence. The MEMS device utilizes microelectronic technology to record each time the container is opened and provides the most accurate data in adherence research.[33] Erythrocyte TGN levels are reflective of chronic (past 30 days) exposure[10] but do not allow measurement of day-to-day variation in adherence. On the other hand, the MEMS device does not allow monitoring of pill ingestion, once the cap is opened. In the current study, TGN levels correlated with MEMS-based adherence rate, demonstrating that MEMS was an accurate method for assessing adherence.

Although every attempt was made to approach all eligible patients, this was logistically difficult to enforce at the 78 participating institutions. We addressed the issue of participation bias by comparing salient clinical characteristics of the adherence study participants with those of the corresponding therapeutic studies and demonstrated that there were no systematic differences between the two groups (Appendix Table A4, online only).

Hispanics are projected to account for 29% of the US population by 2050. According to the Institute of Medicine, Hispanics are vulnerable to adverse outcomes because of socioeconomic and cultural issues that create barriers to health care access and influence the understanding of prescribed treatment.[34] This study describes for the first time to our knowledge differences in adherence to oral MP by ethnicity and the contribution of adherence to ethnic differences in ALL outcome.

Of all medication-related hospital admissions in the United States, up to 69% result from poor medication adherence, with a resultant cost of $100 billion per year.[35] Our study demonstrates that 44% of children with ALL are consuming < 95% of prescribed MP and are consequently at increased risk of relapse. In fact, we demonstrate that 59% of all relapses were attributable to nonadherence. Outpatient oral MP treatment is inexpensive, whereas salvage treatment for recurrent ALL is expensive and largely unsuccessful. The current study identifies vulnerable populations that could benefit from targeted interventions to improve adherence, with resultant improvement in long-term survival and elimination of disparities in cancer outcomes. The current study also emphasizes the need to examine adherence to oral medications in other clinical situations; similar studies are currently planned for adolescent and young adult patients with ALL.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Conception and design: Smita Bhatia, Mary V. Relling
Financial support: Smita Bhatia
Administrative support: Smita Bhatia, Lindsey Hageman, Nancy M. Kornegay, William L. Carroll, Mary V. Relling
Provision of study materials or patients: Smita Bhatia, William L. Carroll
Collection and assembly of data: Smita Bhatia, Wendy Landier, Lindsey Hageman, Alexandra N. Schaible, Andrea R. Carter, Cara L. Hanby, Nancy M. Kornegay, Leo Mascarenhas, A. Kim Ritchey, Jacqueline N. Casillas, David S. Dickens, William L. Carroll
Data analysis and interpretation: Smita Bhatia, Wendy Landier, Muyun Shangguan, Cara L. Hanby, Wendy Leisenring, Yutaka Yasui, Jane Meza, William L. Carroll, Mary V. Relling, F. Lennie Wong
Manuscript writing: All authors
Final approval of manuscript: All authors

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