STIMULUS REPORT

blood advances

Hispanic ethnicity is associated with younger age at presentation but worse survival in acute myeloid leukemia

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Key Points

- SEER data and a Bronx validation cohort demonstrate that Hispanics present with AML at younger age but have shorter survival than whites.
- Increased frequency of high-risk mutations in Hispanics provides a potential biologic explanation for poorer outcomes in Hispanics.

Introduction

Ethnic and racial disparities have been described in the outcome of several cancers and have been attributed to a combination of biologic and nonbiologic factors.[1-4] Such data in adult acute myeloid leukemia (AML) are largely limited to the comparison of black and white patients.[5-7] Hispanics are known to have higher rates of B-cell acute lymphoblastic leukemia and acute promyelocytic leukemia (APL), but there exist no definitive data on epidemiologic or outcome differences in non-APL AML compared with whites.[8-10] We compare the baseline characteristics and treatment outcomes of Hispanic and white AML patients. Such ethnic differences should trigger study of their potentially biologic basis that would contribute to the everlasting struggle to eliminate disease outcome disparities in minorities.

Methods

Cohorts

An adult AML cohort was generated from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registry.[11,12] Only AML cases at ≥18 years of age registered between 2000 and 2010 were examined. APL cases were excluded (ICD-0-3 code 9866/3). We narrowed our search to Hispanics and non-Hispanic whites. We extracted data on demographics, year of diagnosis, duration of follow-up, and vital status.

Cytogenetic information available in the SEER registry was primarily informative for the t(8;21)(q22;q22) RUNX1-RUNX1T1, inv(16)(p13.1q22), and t(16;16)(p13.1;q22)CBFB-MYH11 alterations and did not allow complete cytogenetic risk classification. Two prognostic groups were developed: a favorable group (for the core binding factor leukemias) and a nonfavorable group (for all other cases).

A validation cohort was generated from a minority-rich population of AML patients treated within the Montefiore Medical system in the Bronx, NY, from 1 January 2000 to 31 December 2010, with the use of Clinical Looking Glass, a software tool developed at Montefiore Medical Center. It included all Hispanic and white newly diagnosed AML patients aged ≥18 years. Demographic information was obtained at patient registration. Ethnicity and race were self-reported.

Manual chart review retrieved data on date of diagnosis, cytogenetics, prior chemotherapy/radiation or myeloid neoplasm, treatment (including allogeneic transplantation), response, and date of death or last known encounter. Three cytogenetic risk categories were generated.[13-16] All cases of APL were excluded.

We performed targeted sequencing at 500× coverage (Genoptix, Carlsbad, CA) for genomic profiling of AML cases in Bronx, NY, from 30 November 2013 to 30 October 2016. In conjunction with data from The Cancer Genome Atlas (TCGA) Network,[17] we looked for genomic differences by ethnicity. The study was approved by the Montefiore-Einstein institutional review board in accordance with the Declaration of Helsinki.

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Table 1. Patient and disease characteristics by ethnicity in the SEER and validation cohorts

	SEER cohort			Bronx validation cohort		
	Hispanic (n = 2664)	Non-Hispanic white (n = 20 905)	*P*	Hispanic (n = 73)	Non-Hispanic white (n = 79)	*P*
Median age, y (range)	59 (18-102)	71 (18-111)	<.001	59 (21-88)	71 (22-96)	<.001
Sex, male	1432 (53.8)	11 540 (55.2)	.16	30 (41.1)	35 (44.3)	.69
Cytogenetic risk*	—	—	<.001	—	—	.28
Favorable	104 (3.9)	536 (2.6)	—	5 (6.9)	2 (2.5)	—
Intermediate	—	—	—	28 (38.4)	31 (39.2)	—
Poor	2560 (96.1)	20 369 (97.4)	—	24 (32.9)	20 (25.3)	—
Unknown	—	—	—	16 (21.9)	26 (32.9)	—
s-AML	—	—	—	22 (30.1)	37 (46.8)	.04
Therapy	—	—	—	—	—	.08
None/Bsc	—	—	—	7 (9.6)	9 (11.4)	—
ICT	—	—	—	48 (65.8)	39 (49.4)	—
HMT	—	—	—	0 (0.0)	4 (5.1)	—
Unknown	—	—	—	18 (24.7)	27 (34.2)	—

Data are presented as n (%) of patients unless otherwise indicated.
Bsc, best supportive care; HMT, hypomethylating agent; ICT, intensive chemotherapy, s-AML, antecedent hematological disorder and therapy related AML.
*Two cytogenetic risk categories were generated because of incomplete information on cytogenetics in the SEER cohort: (1) favorable (to include AML with t(8;21), inv(16), and t(16;16)) and (2) all other.

Statistical analysis

Age distribution between Hispanic and white AML patients was compared with the Mann-Whitney *U* test. Comparison of proportions was done with the Pearson's χ^2 test or Fisher's exact test for scarce data.

Differences in survival between Hispanics and whites were assessed with the Kaplan-Meier function and tested with the log-rank test. Multivariable Cox proportional hazard models were constructed to look at the mortality risk associated with ethnicity, adjusted for age, sex, cytogenetic risk (in both cohorts) and initial therapy (in the Bronx cohort). Variables selected on the basis of their clinical significance were forced to the models. The linearity assumption was evaluated with fractional polynomial regression, postestimation partial residual plots, and the dummy variable method. The proportional hazard assumption was tested by analysis of Schoenfeld residuals and assessed graphically with log–log curves. Statistical significance was determined at the 2-tailed α .05 level.

Statistical analyses were performed with STATA software, version 12.0.

Results and discussion

The SEER cohort consisted of 2664 Hispanic and 20 905 white AML patients (Table 1). The median follow-up time was 8 months. Hispanics were diagnosed at a significantly younger age than whites (median age 59 vs 71 years; $P < .001$) and had a slightly higher representation of favorable risk cytogenetics (3.9 vs 2.6%; $P < .001$) (Table 1). Multivariable Cox regression analysis adjusted for age, sex, and cytogenetics showed significantly shorter overall survival (OS) in Hispanics compared with whites (hazard ratio, 1.08; 95% confidence interval, 1.02-1.13; $P < .01$); the median survival 26 months for Hispanics <50 years and 33 months for whites within the same age range.

The Bronx validation cohort included 152 patients (73 Hispanic and 79 non-Hispanic white) (Table 1), with a median follow-up time of 6.8 months. Similar to SEER, Hispanics were younger than whites at diagnosis (median age, 59 vs 71 years; $P < .001$) but had similar cytogenetic risk distribution ($P = .28$). There were no significant differences in rates of intensive chemotherapy (65.8 vs 49.4%; $P = .08$) (Table 1) or complete remission (68.4 vs 75.8%; $P = .49$) between Hispanics and whites. The rates of allogeneic transplantation were similar (Hispanics: 9.6%; whites: 8.9%; $P = .98$). The age-adjusted OS was significantly shorter for Hispanics than for whites (hazard ratio, 1.79, 95% confidence interval, 1.10-2.90; $P = .02$) in a multivariable Cox model that additionally adjusted for sex, cytogenetic risk, and selected therapy.

Mutational analysis in a Bronx subcohort revealed no statistically significant differences in the frequency of ASXL1 (19.6 vs 12.0%; $P = .52$) and TET2 mutations (23.9 vs 20.0%; $P = .71$) in Hispanics and whites, possibly due to small numbers. However, analysis of a combined cohort with additional AML cases genotyped by the TCGA demonstrated significantly higher frequency of ASXL1 ($P < .001$) and TET2 mutations ($P = .03$) in Hispanics than in whites (Table 2).

Differences in treatment intensity are difficult to ascertain outside a randomized clinical trial. In the validation cohort, we found similar rates of intensive chemotherapy, per standard of care protocols, and allogeneic transplantation in both Hispanics and whites. Superior clinical fitness in the younger Hispanic group, donor availability in multimember Hispanic families, and use of haploidentical donors could have counterbalanced minority underrepresentation in donor registries. We had no information on socioeconomic status (SES); however, in the urban population represented by our single-institution cohort, no substantial variations in SES are expected. The concordant results in both cohorts further argue against the confounding effect of treatment or SES. Although a cohort and not a population-based study to allow age-specific AML incidence estimation, the size of the SEER-generated cohort study

Table 2. Frequency of common mutations in Bronx AML cohort and a combined Bronx and TCGA AML cohort

	Bronx cohort			Bronx and TCGA cohorts		
Mutation	**Hispanic (n = 46)**	**Non-Hispanic white (n = 25)**	***P***	**Hispanic (n = 49)**	**Non-Hispanic white (n = 202)**	***P***
TET2	11 (23.9)	5 (20.0)	.71	11 (22.4)	21 (10.4)	.03
DNMT3A	11 (23.9)	6 (24.0)	.99	13 (26.5)	48 (23.8)	.71
ASXL1	9 (19.6)	3 (12.0)	.52	10 (20.4)	7 (3.5)	<.001
TP53	7 (15.2)	2 (8.0)	.48	7 (14.3)	17 (8.4)	.28
NRAS	7 (15.2)	3 (12.0)	.99	7 (14.3)	18 (8.9)	.29
RUNX1	6 (13.0)	2 (8.0)	.70	6 (12.2)	17 (8.4)	.41
IDH1	5 (10.9)	2 (8.0)	.99	5 (10.2)	19 (9.4)	.79
IDH2	7 (15.2)	1 (4.0)	.25	8 (16.3)	17 (8.4)	.11
NPM1	8 (17.4)	4 (16.0)	.99	8 (16.3)	51 (25.2)	.26
CEBPA	1 (2.2)	1 (4.0)	.99	1 (2.0)	13 (0.5)	.32
FLT3_ITD	6 (13.0)	1 (4.0)	.41	7 (14.3)	50 (24.8)	.13

Data are presented as n (%) of patients unless otherwise indicated.

provides large-scale evidence of differences in age of AML presentation and outcomes between Hispanics and whites. These observations were confirmed in our ethnically diverse validation cohort.

In contrast to Swords et al and in concordance with Patel et al, we observed that Hispanics present with AML at a younger age compared with whites.[8,10] In addition, age-adjusted OS was surprisingly worse in Hispanics, a result particularly intriguing when seen in context with the so-called Hispanic epidemiologic paradox.[18] Finally, in our study, we attempted for the first time to compare the genomic profile of myeloid neoplasms between the 2 ethnic groups. Differences in representation of Hispanics and de novo cases in the TCGA and Bronx cohorts could confound the comparison and future studies are required for further verification. However, the combined cohort provided a sizeable pool of genomic data, and the results suggest the presence of mutations of adverse prognostic significance at higher frequency in Hispanic than white AML patients, which may provide a biologic explanation for the inferior outcomes of the former.

The underlying cause of the observed ethnic differences in age of onset and biologic behavior of AML remains elusive. Future investigation into how the complex interaction between environmental exposures and genetic factors impacts AML development may one day help to further elucidate our observations. These data support ethnicity-specific analysis of germline and somatic mutations in future studies.

Authorship

Contribution: K.D., A.S., A.B., A.V., and I.M. conceived the idea and designed this study; K.D., A.S., A.B., D.H., R.S., K.P., J.S.-E., S.G., M.J., A.F.B., N.S.K., O.D., K.G., U.S., I.B., A.V., and I.M. carried out the study; I.M. and K.P. analyzed the data; and K.D., A.S., and A.B. wrote the initial draft of the paper, which was revised and approved by all authors.

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