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Comparison of Latino and Non-Latino Patients with Ewing Sarcoma

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Abstract

Background—Ewing sarcoma (ES) is a malignancy of bone and soft tissue in children and adults. Previous registry-based studies indicate that Latino patients with ES have inferior outcomes compared to non-Latino patients, though an etiology for this difference could not be identified. To explore possible differences that might underlie this disparity, we conducted a retrospective study to compare clinical characteristics, tumor features, healthcare access, and treatment outcomes between Latino and non-Latino patients with ES.

Methods—Primary data for 218 ES patients treated at two academic medical centers between 1980 and 2010 were collected. Categorical data were compared using Fisher exact tests; Wilcoxon rank-sum tests were used for continuous variables. Survival was estimated using Kaplan-Meier analysis and compared using log-rank testing.

Results—Latino patients were diagnosed at a younger age (p=0.014). All other clinical and histological data were similar between groups, including radiologic and histologic response to neoadjuvant chemotherapy. Latino patients had lower socioeconomic status (p=0.001), were less likely to have insurance (p=0.001), and were more likely to present to the emergency room at onset of symptoms (p= 0.031) rather than to primary care physicians. Five-year event free survival (EFS) and overall survival (OS) were similar between Latino and non-Latino patients (EFS: 60.5% vs. 50.9% p=0.37; OS: 77.6% vs. 68.6% p=0.54).

Conclusion—Latino patients with ES present at a younger age, and have evidence of impaired access to healthcare. Response to initial therapy appears similar between Latino and non-Latino patients.

Keywords

Ewing sarcoma; Latino; Hispanic; ethnicity; cancer disparities

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Introduction

Ewing sarcoma (ES) is the second most common primary malignancy of bone in children and adolescents.[1,2] These tumors are characterized by the presence of EWSR1 translocations and nearly universal membranous CD99 immunohistochemical staining.[3,4] The incidence, presentation, and survival of ES patients vary by race and ethnicity.[5–8] Although White non-Latino populations have a higher incidence of disease, Latino patients with ES have been shown in previous registry-based studies to have a higher proportion of soft tissue tumors and inferior survival outcomes.[5,9,10] At least one study has shown that the adverse prognostic impact of Latino ethnicity in this disease appears to be independent of differences in socioeconomic status (SES).[11]

Latino ethnicity has been shown to be an independent predictor of poor outcome across pediatric cancers.[12] Additionally, Latinos in the United States have lower socioeconomic status (SES) and reduced access to healthcare compared to White non-Latino populations. [10,13–15] Lower SES correlates with delayed identification and treatment of disease, decreased participation in clinical trials, and frequently, more advanced disease at presentation of other cancers.[16–18] In both adult and pediatric cancers, low SES and unequal access to healthcare have also been associated with more advanced disease at diagnosis, [18–20] and worse outcomes.[21–23]

Previous reports of inferior survival and higher rates of soft tissue tumors in Latino patients with ES suggest possible biologic differences between Latino and non-Latino patients with ES. Previous studies have noted biologic differences in ES patients arising from different ancestral groups.[24] It is not known whether tumor biological differences exist between Latino and non-Latino patients with ES. Multiple studies have shown treatment response and survival differences based on biologic features, [25–27] including *EWSR1* translocation type and histopathologic features.[24,25,28–30] However, there is a paucity of data describing the rate of such disease markers in Latino patients.

Prior comparisons of Latino and White non-Latino patients with ES have largely emerged from analysis of cancer registries, and thus are limited by the narrow scope of data collected in such registries. Notably, these previous reports have not had access to tumor biology markers, details of administered therapy, or details of access to healthcare. To explore these variables and their possible impact on the observed differences in outcomes, we conducted a retrospective study comparing patient characteristics, demographics, tumor biologic features, healthcare access, treatment administered, and treatment outcomes between Latino and non-Latino patients with ES treated at two large academic medical centers.

Methods

Patient and Disease Characteristics

The institutional review boards for both the University of California San Francisco (UCSF) and Stanford University approved this study. All ES patients with tumors of bone, soft tissue, or viscera and treated at either institution between 1980 and 2010 were identified by querying pathology records by International Classification of Disease 9 (ICD-9) codes.

Patients seen only for clinical or pathology consultation without subsequent treatment at either institution were excluded. Clinical data were collected and coded by a single reviewer (JS). Ethnicity was classified as either Latino or non-Latino based on ethnicity noted in the patient record, typically based on patient stated ethnicity.

Two pathologists (AH and FH) centrally reviewed all available materials to confirm the diagnosis of ES and biologic characteristics. Cases not available for central pathology review were included in the analytic cohort only if original pathologic diagnosis of ES was found. Tumor histopathology characteristics for patients whose material was unavailable were not analyzed. Pathologists were blinded to patient ethnicity. Specific histopathologic features analyzed were: CD99 expression; extent of post-treatment tumor necrosis (%); and mitotic activity (#/10 hpf). CD99 expression was coded as present or absent and also as diffuse membranous (99% cells positive) vs. patchy membranous (<99% positive) staining. In addition, the presence and type of *EWSR1* translocation were recorded from pathology and clinical records.

Disease characteristics previously identified as prognostic markers were recorded at presentation including:age at diagnosis (<12 years vs 12 years); primary site; tumor origin (soft tissue v bone); longest tumor dimension (>8 cm vs 8 cm); and stage (localized v metastatic).[10,31,32] Additional variables examined at disease presentation include sex and year of diagnosis. Tumor measurements from staging scans obtained prior to therapy and again prior to local control were centrally reviewed when available by a radiologist (HDL) blinded to ethnicity.

Socioeconomic Status and Healthcare Access

SES was quantified as a single variable for each patient using a composite formula that includes maximum education level achieved, median household income, population below 200% poverty-line, median rent, and median home value.[33] Maximum education achieved for the calculation was extracted as primary data from patient records. All other values were extrapolated from the 2000 US census based on patient zip code.[34] SES score was divided into quintiles based on statewide population statistics for analysis.

Measures of healthcare access included insurance coverage before and after diagnosis, California Children's Services (CCS) eligibility, and enrollment into clinical trial. Additionally, length of time between symptom onset and initial evaluation, the type of initial medical center (academic vs community), and the type of physician (primary care, emergency, specialist) to which the patient first presented were also recorded. For the purpose of the study, each of these serves as a measure to identify the ease with which patients could obtain care without excessive cost. However, they are not widely studied measures of healthcare access.

Treatment and Outcomes

Details of treatment were recorded for all patients, including time between initial symptoms and commencement of chemotherapy, enrollment in a clinical trial or treatment as per guidelines of protocol therapy, and early discontinuation of treatment for any reason. Mode of local control (definitive surgery; definitive radiation; or surgery plus radiation) was

recorded for each patient. Response to initial treatment was assessed radiographically by Response Evaluation Criteria for Solid Tumors (RECIST), [35] and histologically by percent necrosis (if resected). Findings were confirmed by central radiology and pathology review based upon available imaging and pathology materials. Finally, records were reviewed until the time of patient death, loss of follow-up or December 31, 2010, with a median follow-up time of 56 months. Patients were not contacted for follow-up for the current study.

Statistical Methods

Clinical, histologic, and tumor characteristics were compared between Latino and non-Latino patients using Fisher exact tests for categorical variables and Wilcoxon rank sum tests for continuous variables (due to non-normal distributions). No correction was made for multiple testing. Event-free survival (EFS) and overall survival (OS) were estimated using Kaplan-Meier survival curves and differences were compared using the log-rank tests. EFS and OS were expressed as Kaplan-Meier estimate with 95% confidence intervals (95%-CI). EFS was calculated as the time in months between the date of diagnosis and the date of first disease progression/relapse or death. Patients without event were censored at date of last follow-up. Death from all causes was used to define OS. OS was similarly calculated as time in months between the date of diagnosis and the date of death, with alive patients censored at time of last follow-up. All statistical analyses were performed using SAS (version 9; SAS Institute, Inc., Cary, NC) and STATA (version 10; StataCorp, College Station, Tex).

Results

Clinical Characteristics

A total of 282 patients with ES diagnosed between 1980 and 2010 were identified. After excluding 64 patients who did not receive treatment at either institution, the current study population included 218 patients. The cohort included 58 patients (26.6%) identified as Latino, while the remaining 160 patients were non-Latino. Clinical characteristics according to ethnicity are shown in Table I. Latino patients were diagnosed at a younger age compared to non-Latino patients (median age 12 vs 15 yrs; p = 0.02; 47% < 12 yrs vs. 28% <12 yrs; p= 0.014). However, the proportion of patients < 18 yrs was not significantly different between Latino and non-Latino patients 72% vs. 65%; p= 0.33). There were no differences in sex, primary tumor site, soft tissue vs bone origin, tumor size, or stage (Table I). Site of metastatic disease was also evaluated and did not differ between groups.

Baseline Pathologic Features

Initial diagnostic pathology materials were available for 142 patients. Pathology materials from definitive surgical local control after neoadjuvant chemotherapy were available for 91 patients. Pathologic features are summarized according to ethnicity in Table II. Latino and non-Latino patients did not differ with respect to *EWSR1* translocation status, extent of CD99 staining, or mitotic activity.

SES, Healthcare Access, and Treatment Differences

Factors related to SES, healthcare access, and differential treatment according to ethnicity are shown in Table III. Latino patients in the cohort were more likely to have lower SES, be uninsured prior to diagnosis (33% vs. 9%; p<0.001), and utilize state California Children's Services funding for healthcare (69% vs. 31%; p<0.001). As expected, significant differences in patient and parental primary language were observed between groups.

Latino patients reported disease symptoms for a shorter period prior to initial presentation to medical care compared to non-Latino patients (3.7 vs. 5.3 months; p= 0.034). This finding may be due to a higher likelihood of Latino patients to present to the emergency department rather than to a primary care physician (52% vs. 30%; p= 0.031). Once patients presented to healthcare providers, Latino patients were more likely to receive biopsy at a university hospital vs. community hospital compared to non-Latino patients (76% vs. 61%; p= 0.047). Both groups received prompt initiation of treatment (0.56 vs. 0.50 months from initial biopsy; p= 0.265) and were equally likely to receive upfront chemotherapy on trial (19% vs. 19%; p= 1.00). Method of local control of the primary tumor also did not differ based upon ethnicity.

Clinical Outcomes

Latino and non-Latino patients were equally likely to have an objective radiographic response to neoadjuvant chemotherapy (52% vs. 49%; p=0.941). There were no differences in proportion of patients with   50% tumor necrosis after neoadjuvant chemotherapy (Table II; 63% vs. 61%; p=1.000). EFS did not differ significantly between Latino and non-Latino patients [5-year EFS 60.5% (95%-CI 42.1–74.6%) vs. 50.9% (95%-CI 41.2–59.8%); p= 0.370]. Likewise, OS did not differ between Latino and non-Latino patients [5-year OS 77.6% (95%-CI 59.4–88.4%) vs. 62.7% (95%-CI 52.3–71.4%); p= 0.541]. This pattern also held when considering only patients with localized disease.

Discussion

This study was motivated by a desire to understand the mechanism underlying previous observations of inferior outcomes for Latino patients with Ewing sarcoma. Prior registry-based studies have suggested that observed poorer outcomes demonstrated in Latino patients with ES may reflect worse disease clinico- or histopathology, [5] pharmacogenomic differences, lower SES, or impaired access to healthcare.[10] We hypothesized that disparate outcomes could be due to differences in tumor biology, host factors including pharmacogenomic differences, or differential access to medical services. These hypotheses could not be tested in the context of the large registry studies that first identified this difference in outcome. Our results, which are largely negative findings, add to our understanding of this disparity by making the first two of these hypotheses less likely. Specifically, in the current study, younger age at diagnosis was the only meaningful clinical or biologic characteristics to vary between Latino and non-Latino patients. Latino patients did not present with more advanced disease compared with non-Latino patients, as evidenced by similar stage and tumor size data between groups. Treatment approaches and measures of initial response to treatment (post-treatment tumor necrosis and radiologic

response) were also similar between the groups in all variables measured. In contrast, Latino ES patients were more likely to have lower SES and markers of impaired access to healthcare.

While our study did not demonstrate a significant difference in outcome based on Latino ethnicity, multiple registry studies have observed such a difference.[5,8,10] The observed differences in the registry studies have been relatively modest and our sample size was too small to detect a difference if present. Moreover, our study included patients treated at two academic medical centers in a region with a relatively large Latino population and therefore our outcomes may not generalize to general practice. While our sample size limits evaluation of differences in outcomes, a major strength of this study is the ability to conduct a detailed analysis of tumor biological factors, treatment factors, and SES measures not amenable to study using data available from large registries. Central blinded review of available pathology materials, pathology reports, and imaging data also strengthen the current study.

The impact of Latino ethnicity has been studied in other childhood cancers. In acute lymphoblastic leukemia, Latino patients present younger, [36] and have a well-described increased incidence of disease, which appears to be widening.[37] Latino patients with very young and very old.[38] No significant differences in high-risk disease prevalence, or EFS have been seen in Latino neuroblastoma patients.[19] Latino ethnicity has been associated with later diagnosis, [18] and decreased enrollment in clinical trials across pediatric cancers. [16,39]

Lower SES and access to healthcare is independently associated with later and worse initial presentation, [16,20] worse prognosis, [36,40] and worse outcomes in ES [10] and other cancers.[41] Disparate access to screening and primary care also decreases trial enrollment and delivery of care.[18] The current study affirmed the expected differences in SES and healthcare access by Latino patients. The most apparent difference in healthcare access was Latino patient's likelihood to present to the ED early after initial symptoms, compared to non-Latino patients who were more likely to first present to their primary care physicians. Presentation to a higher level of acuity leads to early referral to tertiary centers as previously shown.[42] In the current study, Latino patients did not have delays in diagnosis or treatment initiation, or reduced participation in clinical trials. There were too few patients with early discontinuation to detect potential differences between these two groups. Differences in SES and insurance status prior to diagnosis may have been mitigated by the availability of California public state insurance for treatment of all patients once a diagnosis of childhood cancer has been made.

Basic tumor histopathology, including increased mitotic activity, anaplastic appearance, response in ES.[43,44] Recent work has also begun to identify other histological markers that may have prognostic value, [25–27] but to our knowledge, no prior histopathologic comparison between Latino and non-Latino ES patients has been made. We found similar histologic features between Ewing sarcoma tumors from Latino and non-Latino patients, though more detailed molecular studies will be necessary to exclude other biologic differences.

One hypothesis for differential outcomes between Latino and non-Latino patients with ES is pharmacogenomic differences resulting in less sensitivity to standard chemotherapy regimens. Our study includes two pieces of data that argue against this possibility. First, the extent of post-treatment necrosis did not differ between Latino and non-Latino patients. Second, radiographic objective response rates did not differ between groups. Since these two measures of response are relatively crude, formal pharmacogenomic studies may nevertheless be instructive.

Several limitations must be recognized in this study. In order to conduct a comprehensive analysis of clinical, histological, and outcomes for Latino and non-Latino patients with ES, several variables were compared thus leading to the possibility of multiple testing error. Further, our study was powered to compare clinical and biologic characteristics of ES patients, but a sample large enough to conclude on outcome was not collected. Finally, similar to registry studies of this rare disease, our cohort includes patients treated on numerous iterations of standard therapy regimens over several years.

In conclusion, Latino patients with ES have clinical and biologic features that are relatively similar to non-Latino patients, though Latino patients tend to be younger at initial presentation. Treatment approaches and response to treatment appear similar between groups. Latino patients with ES face disparities in access to healthcare. With the growing Latino population in the United States, future studies should analyze clinical and response data for Latino patients to better define potential differences in this population. Moreover, the only genome wide association study evaluating genetic predisposition to ES focused on non-Latino patients.[45] The extent to which those findings might apply to a Latino population is unclear and should motivate further study of this subgroup.

Acknowledgments

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Table 1

Clinical characteristics of Latino and non-Latino patients with Ewing sarcoma

Characteristic	Latino (n = 58)		Non-Latino (n = 160)		p
	No.	%	No.	%	
Sex					0.751
Male	38	66	99	62	
Female	20	34	61	38	
Age					0.014
<12 yrs	27	47	45	28	
>=12 yrs	31	53	115	72	
Primary Site					0.545
Pelvic	8	14	30	19	
Non-Pelvic	50	86	130	81	
Primary Tissue					0.694
Bone	43	78	124	81	
Soft Tissue	12	22	29	19	
Tumor Size					0.705
>8 cm	25	64	66	60	
<=8 cm	14	36	44	40	
Stage					0.861
Localized	35	69	100	70	
Metastatic	16	31	43	30	

Table 2

Tumor pathologic features of Latino and non-Latino patients with Ewing sarcoma

Characteristic	Latino (n = 58)		Non-Latino (n = 160)		
	No.	%	No.	%	p
EWS Translocation					1.000
Present	24	86	57	84	
Absent	4	14	11	16	
CD99 Expression					0.362
Present	50	94	124	98	
Absent	3	6	3	2	
Membranous CD99					0.594
Diffuse (>=99%)	19	70	48	77	
Patchy (<99%)	8	30	14	23	
Mitotic Activity					0.352
0–9/10 hpf	22	63	69	75	
10–19/10 hpf	5	14	10	11	
20+/10 hpf	8	23	13	14	
Post-treatment Necrosis					1.000
>=50%	17	63	39	61	
<50%	10	37	25	39	

Table 3

Measures of SES and healthcare access in Latino and non-Latino patients with Ewing sarcoma

Characteristic	Latino (n = 58)		Non-Latino (n = 160)		p
	No.	%	No.	%	
SES[i]					0.001
Very Low	12	21	12	8	
Low	5	9	20	14	
Average	15	26	19	13	
High	16	28	37	26	
Very High	9	16	56	39	
Income (CCS[II] Eligible)					<0.001
Eligible	33	69	38	31	
Ineligible	15	31	83	69	
Insurance Prior to Dx					<0.001
None	17	33	14	9	
Public	15	29	30	20	
Private	20	38	107	71	
Initial Presentation					0.031
Outpatient	22	48	90	70	
Emergency	24	52	38	30	
Biopsy Setting					0.047
University	42	76	90	61	
Community	13	24	58	39	
Clinical Trial					1.000
On Study	11	19	30	19	
As per	47	81	130	81	
Local Control					0.452
Surgery	26	57	76	57	
Radiation	19	41	47	35	
Both	1	2	10	8	

[i]SES = Socioeconomic status;

*ii*CCS = California Children's Services