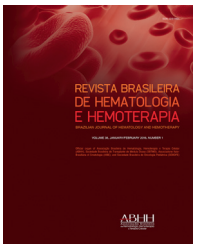
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Original article

High frequency of primary refractory disease and low progression-free survival rate of Hodgkin's lymphoma: a decade of experience in a Latin American center

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ABSTRACT

Background: Reports dealing with clinical outcomes of classical Hodgkin's lymphoma in low- to middle-income countries are scarce and response to therapy is poorly documented. This report describes the characteristics and clinical outcomes of patients with classical Hodgkin's lymphoma from a single institution in Latin America.

Method: A retrospective study was conducted over ten years of patients with classical Hodgkin's lymphoma treated at a referral center. Progression-free and overall survival rates were estimated by Kaplan–Meier analysis. The univariate Cox regression model was used to estimate associations between important variables and clinical outcomes.

Main results: One hundred and twenty-eight patients were analyzed. The mean age was 28.5 years. The five-year progression-free and overall survival were 37.3% and 78.9%, respectively. Of the whole group, 55 (43%) were primary refractory cases. Only 39/83 (47%) patients with advanced disease vs. 34/45 (75.6%) in early stages (p-value = 0.002) achieved complete remission. Those with advanced disease had a five-year overall survival of 68.7% vs. 91.8% for early disease (p-value = 0.132). Thirty-one patients relapsed (24.2%) and 20 (64.5%) received a transplant. The hazard ratio for progression with bone marrow infiltration was 2.628 (p-value = 0.037). For death, an International Prognostic Score $\geq$4 had a hazard ratio of 3.355 (p-value = 0.050) in univariate analysis. Two-thirds of classical Hodgkin's lymphoma patients diagnosed at advanced stages had a low progression-free survival but an overall survival similar to high-income countries.

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Conclusion: Patients belonging to the general population diagnosed with classical Hodgkin's lymphoma in Northeastern Mexico had a significantly low progression-free survival rate and presented with advanced disease, underscoring the need for earlier diagnosis and improved contemporary therapeutic strategies in these mainly young productive-age Hodgkin's lymphoma patients.

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Introduction

Hodgkin's lymphoma (HL) is one of the most common malignancies in the young population; it has a bimodal distribution, first between 15 and 34 years of age and then after 55 years.[1] This hematologic neoplasm affects approximately 9050 new patients in the United States each year and 5000 in Latin America,[2] thus a low incidence but with high mortality is observed in Mexico.[3] Furthermore, a lower overall survival (OS) has been observed in Hispanics living in the United States, with the diagnosis established at more advanced stages and with a greater male prevalence.[4,5]

Contrary to non-Hodgkin lymphoma, the incidence of HL has remained constant over time.[1] Two distinct disease entities compose HL, classical (cHL) and the rare nodular lymphocyte predominant HL, which comprises only 5% of all cases.[6] Although HL is highly responsive to chemotherapy, approximately one third of patients with an advanced stage will have primary resistant disease[7] or will relapse after conventional treatment.[8] Standard treatment in these cases is based on autologous hematopoietic stem cell transplantation (HSCT) or high doses of chemotherapy, with the PFS reaching 30–50% in patients with relapsed disease and 20–40% in patients with refractory HL.[9–11]

There is scarce information on the characteristics of HL patients in populations where most individuals are diagnosed in advanced stages. This study reports a comprehensive descriptive analysis of incidence patterns, clinical evolution, and treatment outcomes of low-income uninsured patients with HL attending a public referral center for the general population in Northeastern Mexico over a ten-year period.

Methods

This observational, longitudinal and retrospective study included patients with a diagnosis of HL treated at the Hematology Department of the Dr. José E. González University Hospital of the School of Medicine, Universidad Autónoma de Nuevo León in Monterrey, Mexico between January 2005 and September 2015. Clinical and electronic records as well as histopathology records were reviewed and frequencies for each subtype of lymphoma were determined. The study protocol was approved by the Research Ethics Committee of the institution.

Clinical data including age, gender, Ann Arbor stage, presence or absence of B-symptoms, initial complete blood count (CBC), International Prognostic Score (IPS), bulky disease, treatment regimen and survival data were accrued and analyzed. Advanced disease was defined as bulky disease or an Ann Arbor stage III–IV. Two groups were defined according to the IPS: low risk (score: 0–3) and high risk (score: 4–7). To define HL subtypes, cases were reviewed by a hematopathologist with the immunohistochemical profile of HL being investigated in 83% of the studied patients including the following biomarkers: CD30, CD15, CD20, CD3, CD45, ALK-1, and PAX-5.[12] Due to financial restrictions at this public institution caring for patients without health insurance coverage, the Epstein–Barr virus (EBV) status was not documented in the biopsies. A computed tomography (CT) scan was performed in all patients for stratification and was reviewed by radiologists with expertise in staging lymphomas. Only selected patients were submitted to a bone marrow (BM) biopsy – patients with an Ann Arbor stage ≥III or with B-symptoms had an indication for this procedure. In this respect, it has previously been shown that only about 2% of patients in this population with HL have a positive BM biopsy.[13]

Treatment

Patients received a chemotherapy regimen chosen by the treating physician according to standard protocols including ABVD (adriamycin, bleomycin, vincristine and dacarbazine) or COPP/ABV (cyclophosphamide, vincristine, prednisone, procarbazine, doxorubicin, bleomycin and vinblastine).[14] All drugs were from original manufacturers with no generic brands administered. Some patients with bulky disease received complementary radiotherapy (RT), using intensity-modulated radiotherapy (IMRT) at doses of 30–36 Gy depending on the tumor size. The protocol consists of the delivery of 1.5–2 Gy per day until completion.[15] However, not all of these patients were treated at the study center and radiotherapy is not a regular part of the standard protocol; this is intended to limit radio-toxicity in patients customarily presenting with advanced disease. Autologous HSCT, based on a reduced intensity conditioning regimen,[16] was carried out in patients with a poor prognosis, including those who relapsed in <12 months, those who relapsed at previously irradiated sites, had disease regression <50% after 4–6 cycles of chemotherapy, or disease progression during induction or within 90 days after the end of first-line treatment.

Follow-up

Positron emission tomography (PET) studies were not available during the study period and thus classification of HL

response was according to the criteria specified in the Lugano Classification,[17] based on size reduction of the affected lymph nodes measured by CT scan in all patients.

Definition of response

CR was defined as disappearance of all clinical and radiological symptoms, no further therapeutic intervention is necessary. Partial remission (PR) was defined as at least a 50% decrease in the sum of the product of the diameters of up to six of the largest dominant nodes or nodal masses. Stable disease was considered when a patient failed to meet the criteria for CR or PR, but did not fulfill those for progressive disease (PD). Relapsed disease or PD was defined as the occurrence of new lesions or an increase of ≥50% from nadir of previously involved sites.[17]

Statistical analysis

All statistical testing was performed using SPSS version 22.0. Descriptive analysis including median and ranges was applied to continuous variables. The Kaplan–Meier method was used to obtain the OS from the date of diagnosis until the date of death or last update of clinical status. PFS was defined from the date of diagnosis to the date of the first event (progression/relapse or death for any reason) or the last follow-up.[17] The Cox proportional hazard regression model was used to examine the association between the different variables and their effect on OS and PFS in HL.

Results

Baseline characteristics

Data for 128 patients with a diagnosis of HL were collected. Clinical characteristics are shown in Table 1. B-symptoms were reported by 45 (35.1%) patients at the time of initial clinical history. Complete blood count (CBC) at diagnosis showed a median hemoglobin (Hb) level of 11.4 g/dL (range: 5.9–17 g/dL), a white blood cell count of 8.29×10^9/L (range: 1.11–25.57 $\times 10^9$/L) and a platelet count of 308×10^9/L (range: 41.0–629.0 $\times 10^9$/L). Bone marrow biopsy was performed in 46 (35.9%) patients in advanced stages with a positive result being found in 14 (30.4%).

Table 1 – Epidemiological and clinical characteristics of 128 patients diagnosed with Hodgkin's lymphoma in the Hospital Universitario Dr. José E. González, Universidad Autónoma de Nuevo León, Monterrey, Mexico.

Characteristic	
Age (years) – median (range)	28.5 (5–81)
Sex – n (%)	
Male	69 (53.9%)
Female	59 (46.1%)
Bulky disease – n (%)	
Present	27 (21.1%)
Absent	101 (78.9%)
Subtype – n (%)	
Nodular sclerosis	75 (58.6)
Mixed cellularity	23 (18.0)
Lymphocyte-rich	5 (3.9)
Lymphocyte depleted	3 (2.3)
Unclassified	22 (17.2)
Clinical stage – n (%)	
I	16 (11.7)
II	38 (29.7)
III	35 (27.3)
IV	40 (31.3)
IPS score – n (%)	
0–3	98 (76.6)
4–7	30 (23.4)
Disease status – n (%)	
Early disease	45 (35.2)
Advanced disease	83 (64.8)

IPS: International Prognostic Score.

Clinical outcome in classical Hodgkin's lymphoma

One hundred and twenty-eight patients were analyzed, 112 (87.5%) received ABVD (median: 6 cycles; range: 1–8 cycles) and 16 (12.5%) received the COPP/ABV regimen (median: 6 cycles; range: 2–8 cycles). CR was achieved in 73/128 (57%) patients; 30/73 (41%) relapsed at a median of 23.7 months. From the group of 30 relapsed patients, 26 (86.7%) are alive after five years of follow-up and four deaths have been documented. Of the whole group, 55 (43%) were primary refractory cases; from this subgroup 20 (36.4%) had partial remission, 29 (52.7%) stable disease after first frontline chemotherapy, and six (10.9%) presented disease progression during administration of the primary therapy protocol. Eleven deaths (7.75%) were documented after receiving at least one cycle of chemotherapy with sepsis being the most common cause. Twenty-two (17.2%) patients who completed therapy as scheduled had a reduction in dose due to toxicity. Twenty-eight (21.87%) patients did not complete planned treatment with the most common cause being disease progression in 19, whereas nine patients abandoned treatment. Six patients that abandoned treatment went on to continue chemotherapy in other institutions; three patients were too sick to receive full doses and cycles of therapy. There were no instances of missing drugs.

Median follow-ups for PFS and OS were 15.88 (range 1.2–87.8) and 24.26 (range 1.43–176) months, respectively. PFS at five years for the whole group of 128 patients was 37.3 ± 6.9%. Median PFS at five years was 46.09 months [95% confidence interval (CI): 34.06–58.12]. After five years of follow-up, the OS was 78.9 ± 6.8% and the median OS was not reached. Patients who achieved CR with first line treatment had a five-year OS of 88.1 ± 6.3% vs. 59 ± 15.7%, in those who did not (p-value = 0.012).

Of 11 patients who died, two did so from sepsis and neutropenia related to drug toxicity and in seven, death was due to disease progression; two patients died at other institutions and the cause was not reported.

When comparing chemotherapy regimens, the five-year PFS for patients treated with ABVD was 37.5 ± 7.9% vs. 33.5 ± 13.9% for those who received a different scheme (p-value = 0.224). Five-year OS for patients primarily treated with ABVD was 81.5 ± 7.7% vs. 63.1 ± 15.8% for those receiving

COPP/ABV (p-value = 0.057). Median time to receive six cycles of therapy was six months (range: 6–9 months).

Of the patients with advanced disease, a CR was reached in 39/83 (47%) vs. 34/45 (75.6%) in those in early HL stages (p-value = 0.002). Five-year PFS for patients presenting with advanced disease was 38.3 ± 8.9% vs. 39.1 ± 11.5% in individuals with early disease (p-value = 0.893). Median PFS for advanced and early disease was 42.7 months (95% CI 27.51–57.90) and 49.5 months (95% CI 39.28–59.81), respectively. Overall survival at five years was 69.7 ± 10.6% in patients with advanced disease compared to 91.8 ± 5.6% in those with early disease (p-value = 0.132; data not shown). Median OS was not reached in either group.

Fifteen pediatric HL patients (11.7%) ≤16 years and 113 (88.3%) >16 years were treated. PFS at five years was higher in those >16 years of age, but it was not statistically significant (20.9 ± 12.9% vs. 36.0 ± 8.4%, respectively), median of PFS was 34.72 months (95% CI 16.59–52.86) vs. 48 months (95% CI 37.41–58.59; p = 0.240), respectively. Pediatric patients had a non-significantly higher five-year OS than older patients (80.0 ± 12.6% vs. 76.2 ± 9.3%; p-value = 0.871). After analyzing survival according to the IPS, patients with a score ≥4 had a five-year PFS of 33.7 ± 14.9% vs. 34.9 ± 8.4% in those with an IPS <4 (p-value = 0.786). The five-year OS between these groups was 66.1 ± 13.8% vs. 84.1 ± 7.1%, respectively (p-value = 0.036).

Thirty-two patients (25%) underwent autologous HSCT, achieving a five-year PFS of 32.6% (95% CI: 32.40–32.80) after HSCT at a median of 20 months and the five-year OS was 73.1%; the median OS was not reached. Of the 32 autografted patients, six (18.8%) deaths were documented and 15 (46.9%) suffered disease progression or relapsed after HSCT.

Outcome after relapse

Of 30 relapsed patients, 20 (66.7%) underwent autologous HSCT and 11 (55%) suffered a second relapse. Five-year PFS and OS for these 20 HSCT patients were 31.4 ± 9.1% and 81.4 ± 9.7%, respectively; median PFS was 12 months and the median OS was not reached. Three deaths were documented in this group due to disease progression. Of the remaining 10 relapsed patients who were not transplanted, two went to another institution after relapse and eight were lost to follow-up after a median 6.4 months.

Predictive factors of relapse, progression and death

In univariate analysis for PFS, BM infiltration and incomplete treatment were significant for disease progression (Table 2). For OS, an IPS ≥4 and incomplete treatment were significant predictors of death (Table 2).

Table 2 – Hazard ratios for relapse, progression or death according to univariate Cox proportional regression analysis for 128 patients with classical Hodgkin's lymphoma and associations with clinical, laboratory and histopathological characteristics.

Factor	n	Progression free survival		Overall survival	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Bulky disease					
Present	27	0.965 (0.458–2.030)	0.925	0.812 (0.161–4.095)	0.801
Absent	71				
IPS					
≥4	30	0.912 (0.439–1.895)	0.805	3.355 (1.000–11.256)	0.050
<4	98				
Bone marrow infiltration					
Positive	14	2.628 (1.058–6.525)	0.037	4.511 (0.408–49.863)	0.219
Negative	32				
B-symptoms					
Yes	41	0.672 (0.358–1.263)	0.217	0.384 (0.083–1.789)	0.222
No	87				
Incomplete treatment					
Yes	28	2.793 (1.364–5.719)	0.005	8.246 (2.483–27.377)	0.001
No	100				

HR: hazard ratio; CI: confidence interval; IPS: International Prognostic Score.

Discussion

Although recent research has provided meaningful insights into the biological and molecular characteristics of HL, it remains an intriguing disease, with many factors implicated in its pathogenesis but with none definitely established.[18] Previous epidemiologic studies have contributed in elucidating specific features and current status of HL in the Americas.[3] Subtype distribution in this group was similar to that in the United States and Canada.[19] Interestingly, the HL cohort in this study was a decade younger than that reported in developed countries[1,2] as observed in a previous all-age inclusive study focused on Hispanics.[20]

In low- to middle-income countries, more than 60% of cHL patients are diagnosed in advanced clinical stages at presentation.[21] Progress in survival is evident in those with early stages, whereas in advanced disease an unsubstantial improvement has been reported in the last 30 years.[22] This study found an OS close to that reported by centers in developed countries, yet a low PFS, highlighting the lower cure rate for advanced disease.[23] A higher PFS was found in central Mexico than that identified in this study; however, OS was similar,[21] showing regional differences in the clinical course of HL.

In previous studies from high-income countries including the United States and Europe, CR and OS rates of up to 80% were reported in patients with advanced clinical stages at diagnosis.[23–25] However, low CR and OS rates were found for the population with advanced disease in the current study; only 47% achieved CR after primary treatment, their five-year PFS was 38.3% with an OS of 68.7%. The high rate of primary refractory disease and low PFS in this group can to be explained in part by the large proportion of advanced

stage cases related to late diagnosis, biologic heterogeneity in lymphoma behavior, as well as epigenetic modifiers of response to cHL. Additional factors that can contribute to further explain these suboptimal results include dose reductions due to high toxicity in 22% of patients, treatment abandonment was important at 7%, and sociocultural as well as financial limitations of this population. Furthermore, lack of fluorodeoxyglucose (FDG)-PET studies could have led to lower intensity treatment, although there are heterogeneous results regarding the impact of interim FDG-PET; its use however is a valuable method for risk stratification.[17] Developing countries are just starting to use this resource due to its high cost, limiting comparison of treatment response rates for HL between developing and industrialized regions.

Over a third of the patients in this study had primary refractory disease, more than two times the 15% reported in most studies[1,8]; this finding helps to explain the low PFS observed. For this group, high-dose chemotherapy followed by autologous HSCT has become the treatment of choice.[26,27] This leads to a significant increase in PFS, but has no effect on OS. Of 30 relapsed patients in this study, 20 underwent an autologous HSCT after achieving a second remission induced by chemotherapy and 85% of them are alive at five years. Thus, the OS after transplantation is comparable to other studies reporting rates ranging from 66% to 77%.[28]

The prognosis of relapsed patients is also influenced by the presence of negative prognostic risk factors such as early relapse three to 12 months after treatment, stage III or IV disease, and anemia at the time of relapse. A retrospective analysis of the German Hodgkin Study Group showed that patients presenting all three risk factors had a lower four-year freedom from second treatment failure of 17% and a low OS of 27% compared to patients without risk factors (48% and 83%, respectively).[29] Although most of the patients in this cohort were diagnosed at an advanced stage, the median of relapse was 22.8 months and this was associated with high survival rates after relapse.

Limitations in this report include its retrospective design, reduced sample size, lack of PET scan staging, and the number of patients lost to follow-up. However, this report provides an overview of the contemporary landscape of clinical and histopathology characteristics of a well-defined HL low-income group over ten years in a single institution of Latin America.

In conclusion, it is necessary to analyze cHL epidemiological data in developing countries and assess efficacy of current diagnostic methods and modalities of treatment, with the main goal of improving the low PFS documented in this population.

Conflicts of interest

The authors declare no conflicts of interest.

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