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ORIGINAL ARTICLE

Retrospective Cohort Study

Long-term results of the treatment of Hodgkin's lymphoma in a resource-constrained setting: Real-world data from a single center

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Abstract

BACKGROUND

The outcomes of Hodgkin´s lymphoma (HL) in Mexico have not been widely reported. Simplified and affordable treatments have been adopted in middle-income countries.

AIM

The aim was to evaluate long-used therapies for HL in Mexico in a long-term basis.

METHODS

In a 34-year time period, 88 patients with HL were treated at a single institution in Mexico. Patients were treated with adriamycin bleomycin vinblastine and dacarbazine (ABVD) or mechlorethamine, vincristine, procarbazine, and prednisone (MOPP). Relapsed or refractory patients were given ifosfamide, carboplatin, and etoposide (ICE) followed by autologous or allogeneic stem cell transplants.

RESULTS

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Thirty-seven women and 51 men were included; the median age was 29 years. Patients were followed for a mean of 128 mo. The 310-mo overall survival (OS) was 83% for patients treated with MOPP and 88% for those treated with ABVD. The OS of patients who received autologous stem cell transplantation was 76% (330 mo) *vs* 93% (402 mo) in those who did not.

CONCLUSION
HL may be less aggressive in Mexican population than in Caucasians. Combined chemotherapy renders acceptable results, regardless of clinical stage.

Key Words: Hodgkin; Lymphoma; Treatment; ABVD chemotherapy

Core Tip: In a retrospective, observational long-term study, our group found that the treatment of Hodgkin lymphoma in a resource-constrained background may still rely on the use of the traditional adriamycin bleomycin vinblastine and dacarbazine treatment regimen in order to achieve acceptable outcomes. The observations were consistent across different stages of disease and may serve to propose new studies focusing on the comparison of newly approved therapies in contexts where there are some healthcare limitations.

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INTRODUCTION

Hodgkin´s lymphoma (HL) is the model of curative care, with radiation therapy, combination chemotherapy, staging approaches, peripheral blood-stem cell transplantation, and immunotherapy[1]. Following the initial demonstration that radiotherapy could eradicate limited-stage disease, multiagent chemotherapy regimens proved to be curative in a large proportion of patients with advanced disease [1]. In the 40 years since De Vita and colleagues developed the mechlorethamine, vincristine, procarbazine, prednisone (MOPP) chemotherapy regimen, much has been learned about risk stratification to minimize treatment-related toxicity[2]. Doxorubicin (*i.e.* adriamycin), bleomycin, vinblastine, and dacarbazine (ABVD), the most commonly used regimen for both early and advanced stage HL, was developed in the mid-70s[2] and continues to be a standard of care in HL[3]. In recent years, there have been advances, with the introduction of novel therapies and changes in the management algorithms[1]. However, the performance of newer therapies remains unclear in real-world conditions, especially for overall survival (OS) and quality of life of persons with malignant diseases[4]. We analyze here the results of the treatment of a group of 88 patients with HD over a 34-year period at a single institution, treated with combined chemotherapy in a resource-constrained setting of a single institution.

MATERIALS AND METHODS

Patients

All consecutive patients seeking medical care for HL at our institution after 1986 and followed for at least 3 mo were entered into the study. A diagnosis of HL was based on the histological study of a pathology specimen, mainly a lymph node; the same pathologist analyzed all the specimens and defined the histological subtype[5]. The

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clinical stage was defined according to the Ann Arbor classification[5]. Bone marrow biopsies were done only in patients with clinical stages III or IV[6]. Computed tomography (CT) scans were done in all cases prior to starting treatment. Fluorodeoxyglucose positron emission tomography (FDG-PET) scans have been performed since 2002. The study was approved by the institutional review board, and all participants signed an informed consent.

Treatment

Between 1986 and 1997, patients were treated with MOPP, *i.e.* nitrogen mustard (6 mg/m^2 on days 1 and 8 of the cycle), vincristine (1.4 mg/m^2 on days 1 and 8), procarbazine (100 mg/m^2 on days 1 through 14) and prednisone (40 mg/m^2 during cycles 1 and 4 for 14 d)[7]. After 1997, patients were treated with ABVD, *i.e.* doxorubicin (25 mg/m^2), vinblastine (6 mg/m^2), dacarbazine (375 mg/m^2) and bleomycin (10000 units/m^2) on days 1 and 15 of every 4 wk[8] as frontline therapy. Per local protocol, stages I and II, were treated with four cycles of chemotherapy and the response was assessed by a CT scan. If disease activity persisted at that time, four additional cycles were given, whereas two additional cycles were given if the CT scan was negative. For stages III and IV, the CT scans were performed after six cycles, and two or four more cycles were delivered depending on the results, as described above. Bleomycin was administered only in the first three courses and the doxorubicin dose was adjusted to avoid delivering more than 450 mg/m^2. FDG-PET scans have been performed at the end of treatment since 2002. Scans were not performed between cycles. Only patients with disease activity at the end of treatment received radiotherapy. Patients showing activity after treatment were considered as refractory and treated with four courses of ifosfamide, carboplatin and etoposide (ICE)[9]. Autologous or allogeneic peripheral blood hematopoietic stem cell transplant (HSCT) were given to refractory patients after achieving complete remission. High-dose melphalan (200 mg/m^2) was used in autologous transplants; cyclophosphamide, fludarabine, and busulfan were used in allogeneic transplants, which were all from HLA-identical siblings[10]. After the completion of treatment, patients were follow-up every 2 mo for 1 year and every 4 mo from then on. No FDG-PET scans were done during follow-up, unless clinically indicated.

Statistical analysis

The primary outcome measure was OS, defined as the time elapsed between the diagnosis of HL and death from any cause, with censoring of patients who were alive on the last follow-up date. Differences were assessed with Fisher's exact test. OS was estimated by the Kaplan-Meier method, and differences between groups were compared with the log-rank test[11]. Two-sided P values < 0.05 were considered statistically significant. The statistical analysis was carried preformed with Prism 8 (GraphPad Inc. San Diego, CA, United States).

RESULTS

Patient characteristics

Of the 91 patients with HL identified between 1986 and 2020, 88 were followed for 3 mo or more and were included in the analysis. There were 37 women and 51 men. The median age was 29 years (range: 5-73 years). There were 62 patients with nodular sclerosing HL (70%), 19 with mixed cellularity HL, two with lymphocyte depleted HL, and one with lymphocyte predominant HL. In four cases, the histologic variant could not be defined. According to the Ann Arbor classification[5], five patients were stage I, 48 were stage II, 19 were stage III, and 16 were stage IV. Ten patients presented with a mediastinal mass larger than 10 cm in the chest X-ray film. Three cases presented with relapsed disease (Table 1).

Treatment patterns

As frontline therapy, all patients were offered chemotherapy (ChT). Twelve received MOPP and 70 received ABVD; three were treated with initial radiotherapy (RT): two refused ChT, and one was referred after receiving RT. Relapsed or refractory patients were treated with ICE and a subsequent autologous or allogeneic HSCT.

Responses

Patients were followed for a median of 114 mo (range: 4-402). Forty-four are alive, ten

Table 1 Salient features of 88 patients with Hodgkin´s lymphoma

Sex	Women	37 (42)
	Men	51 (57.9)
Age, yr	Median 29 (range: 5-73)	
Type	Nodular sclerosing	62 (70)
	Mixed cellularity	19 (21.5)
	Lymphocyte depleted	2 (2.2)
	Lymphocyte predominant	1 (1.1)
Stage	Stage I	5 (5.6)
	Stage II	48 (54.5)
	Stage III	19 (1.5)
	Stage IV	16 (18.1)

Data are *n* (%)

have died, and 34 were lost to follow-up. Median OS for all patients has not been reached, and is more than 402 mo. OS was 88% 310 mo and 77% 402 mo (Figure 1). Median OS has not been reached and is 94 mo for stage I, 109 mo for stage II, 90 mo for stage III, and 98 for stage IV (P = 0.2). The 310-mo OS was 83% for patients treated with MOPP and 88% for those treated with ABVD [hazard ratio (HR): 0.76, 95% confidence interval (CI): 0.2-2.8, P = 0.6; Figure 2]. Sixteen patients (18%) were refractory to treatment and nine (10%) relapsed. They were treated with ICE followed by HSCT, autologous in 15 patients and allogeneic in ten patients. Patients who underwent autologous HSCT had a median survival of 329 mo and an OS of 92%. Those given allogeneic HSCT had a median survival of 59 mo and an OS of 46% (HR: 0.2, 95%CI: 0.04–1.3, P = 0.057). The OS of patients given and HSCT was 73% at 266 mo and was 93% at 404 mo in those not given HSCT (HR: 4.09, 95%CI: 1.0–16.6, P = 0.01) (Figure 2B). The OS was similar (Figure 2). The causes of death were breast carcinoma in two cases, liver carcinoma in one, and uncontrolled lymphoma activity in the remaining patients.

Long-term toxicity

Twelve patients developed peripheral neuropathy. There were no reported cases of pulmonary, fertility, or cardiovascular toxicity. Five patients developed a secondary neoplasia 18-150 mo after completing treatment; four had received chemotherapy (three ABVD and one MOPP); one had received radiotherapy alone. The salient features of the patients are shown in Table 2.

DISCUSSION

The outcomes of HL in Mexico have not been fully analyzed or reported. We have previously shown that some malignancies in Mexico have different behaviors in the population of Mexican mestizos compared with other populations. For example, multiple myeloma in Mexico is less frequent[12,13] and less aggressive than in Caucasians or African-Americans[12], and chronic lymphocytic leukemia is also less frequent and less aggressive in Mexican mestizos than in other populations[14-16], but promyelocytic leukemia is substantially more frequent in Mexico than in Caucasian populations[14,17]. In the case of HL in Mexico, there is not enough information about its prevalence and clinical behavior. Preliminary data indicate that the prevalence of HL in Mexico is similar to that reported in other populations[17,18]. The data presented here suggest that the clinical picture of the disease may be less aggressive in Mexico, as without employing novel and sophisticated drugs, the OS of this group of patients was 88% at 310 mo, including all stages of the disease, relapsed, and refractory patients (Figure 1). There were no significant differences between patients treated with MOPP or ABVD. The OS of relapsed or refractory patients who were given an HSCT was significantly lower than those who did not require it (Figure 3).

Table 2 Salient features of patients who developed a secondary malignancy after the treatment of lymphoma

	Neoplasm	Age	Sex	Type	Stage	Treatment	HSCT	Time[1], mo
1	Tongue epidermoid carcinoma	32	M	Nodular sclerosing	I	Radiotherapy	No	58
2	Liver adenocarcinoma	22	F	Nodularsclerosing	III	MOPP	No	97
3	Breast cancer	38	F	Mixed cellularity	III	ABVD	No	150
4	NK/T-cell lymphoma	15	M	Nodular sclerosing	IV	ABVD	Autologous	18
5	Breast cancer	23	F	Nodular sclerosing	III	AVBD	Autologous	59

[1]Time in months elapsed between the diagnosis of Hodgkin's lymphoma and the diagnosis of the secondary neoplasia.
HSCT: Hematopoietic stem cell transplant; M: Male; F: Female.

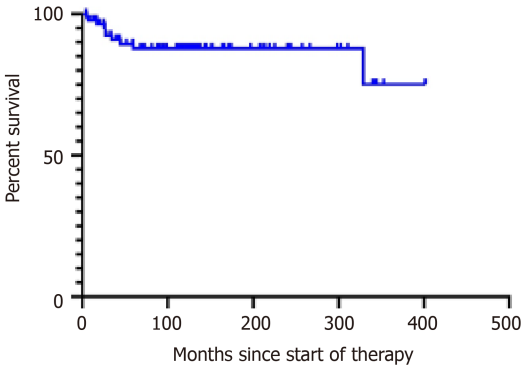

Figure 1 Overall survival of 88 patients with Hodgkin's lymphoma.

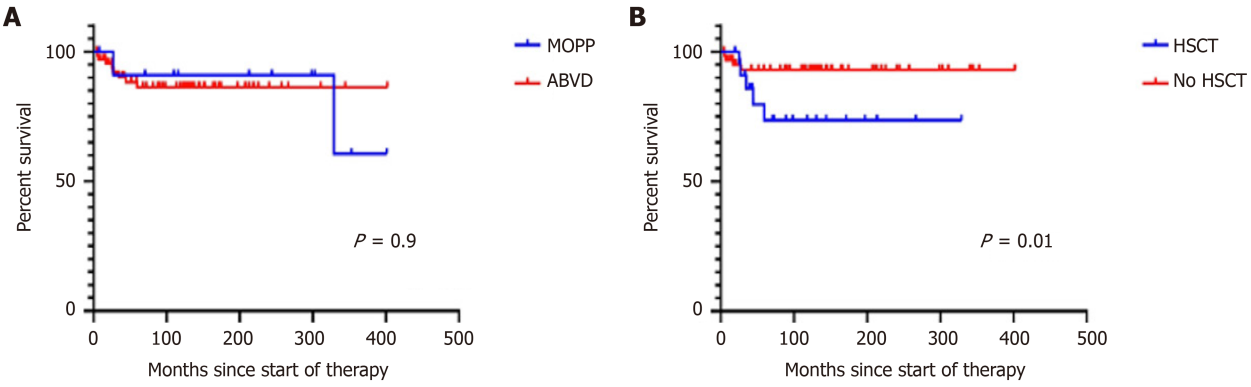

Figure 2 Overall survival of 88 patients with Hodgkin's lymphoma treated with either MOPP or ABVD (A) and treated either with or without hematopoietic stem cell transplants (B). ABVD: adriamycin bleomycin vinblastine and dacarbazine; HSCT: Hematopoietic stem cell transplant; MOPP: mechlorethamine, Oncovin, procarbazine, and prednisone.

Radiation therapy is included in treatment strategies. We have previously suggested that in Mexico, and probably in other underprivileged circumstances where RT facilities are suboptimal, patients with early stages of HL should be treated with ChT alone. The message being "conventional ChT is better than a poor RT"[19,21-24]. The results that we present here support the previous observations. Additionally, patients with relapsed/refractory disease were successfully rescued with ICE followed by HSCT. Figure 3 shows the OS of the patients classified by the prognostic score described by Hayden *et al*[24].

The main observations of treatment which we present here are (1) ABVD was offered to all patients regardless of their clinical stage. (2) Four cycles were administered to patients with stages I and II and six cycles to those with stages III and IV. (3) Two additional cycles were given to all patients after a negative CT scan after receiving 4-6 cycles. (4) No interim FDG-PET scans were done, reserving them for the

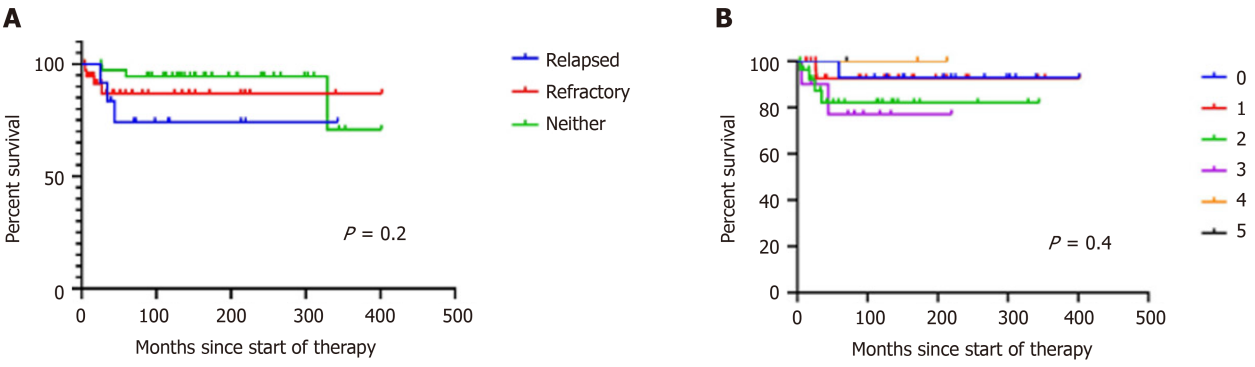

Figure 3 Overall survival of 88 patients with Hodgkin's lymphoma with or without relapsed or refractory disease (A), and overall survival of the patients with Hodgkin's lymphoma classified as described by Diefenbach *et al* (B).

end of treatment. And (5) Relapsed or refractory patients were given ICE followed by an HSCT. The limitations of this study include a relatively small and heterogeneous sample, the potential of referral bias, a high proportion of patients lost to follow-up, and socioeconomic factors.

This simplified approach to the treatment of patients with HL demonstrates adequate results with an OS of 88% at 26 years regardless of the clinical stage or relapsed/refractory disease. Additional data are needed to confirm the observations, which may be useful in circumstances of a restrained economy. The use of novel and expensive drugs such as pembrolizumab, nivolumab, panabinostat, idelalisib, mocetinostat, brentuximab vedotin and others[4,24] should be reserved for multi-relapsed cases and does not appear to be essential as frontline therapy.

CONCLUSION

HL may be less aggressive in the Mexican than in Caucasian populations. Combined chemotherapy without radiotherapy achieves acceptable results. In our context with healthcare limited-resources, chemotherapy alone with ABVD continues to be the treatment of choice in patients with HL.

ARTICLE HIGHLIGHTS

Research background

Hodgkin´s lymphoma (HL) can be treated with different alternatives, the performance of newer and older chemotherapy schemes are unknown in some circumstances.

Research motivation

The motivation was to describe the performance of treatment of HL in a middle-income country.

Research objectives

The objective was to determine performance of classic therapies for HL.

Research methods

This was a comparative study of therapies for HL in a single center over a long-term period.

Research results

HL may be less aggressive in the Mexican population. In addition, the classical ABVD regimen achieved long-term survival in a significant proportion of patients.

Research conclusions

Combined chemotherapy has acceptable efficacy in patients with HL. Our results suggest that classical treatment schemes continue to be an effective alternative. More

studies should be conducted.

Research perspectives

Classic therapies for HL may still be preferable over novel therapies in middle-income countries. The use of ABVD combined with other immunomodulatory agents could be a potential solution for patients not experiencing favorable outcomes.

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