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ARTÍCULO ORIGINAL

Clinical characteristics and outcomes of patients with Hodgkin lymphoma at first relapse in the real setting before the use of novel agents: importance of autologous stem cell transplantation

Características clínicas y desenlaces de los pacientes con linfoma de Hodgkin en la primera recaída en el entorno de la vida real antes del uso de nuevos agentes: importancia del trasplante autólogo de células madre

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Resumen

Objetivo: El estándar de cuidado del linfoma de Hodgkin (LH) en estado recaído/refractario es la terapia de rescate, incluida la quimioterapia de altas dosis, seguida de trasplante autólogo de células madre. Hasta la fecha, se ha demostrado que este enfoque de tratamiento mejora la supervivencia sin enfermedad, la supervivencia libre de progresión y evita el fracaso del tratamiento en ensayos clínicos controlados. Este estudio tiene como objetivo determinar los resultados prácticos en Colombia, en los pacientes con LH que utilizan esta estrategia en la primera recaída antes del uso ampliado de conjugados de anticuerpo y fármaco o inhibidores de puntos de control.

Métodos: Se presenta una serie de casos retrospectiva de pacientes con diagnóstico de LH R/R atendidos en el Instituto Nacional de Cancerología (INC) de Colombia entre 2013 y 2017.

Resultados: En una base de datos de 171 pacientes se encontraron 31 con LH R/R que cumplían los criterios de inclusión. Los regímenes más utilizados fueron los basados en platino, seguidos de los basados en gemcitabina. La enfermedad sensible a la quimioterapia se demostró en 16 (51,6%) pacientes; la mayoría logró una respuesta completa. En toda la cohorte, la supervivencia general y la supervivencia libre de progresión fueron más bajas que las informadas en otras series. Los pacientes que finalmente se sometieron a trasplante autólogo de células madre tuvieron mejores desenlaces en comparación con quienes no lo tuvieron.

Conclusión: Esta serie de casos retrospectiva mostró que las respuestas y las sobrevidas son más bajas que las descritas en la literatura. El trasplante autólogo de células madre es esencial para lograr una cura potencial en pacientes LH R/R con enfermedad sensible a la quimioterapia. Los sistemas de salud deben garantizarles el acceso al trasplante a todos los pacientes candidatos a esta terapia.

Palabras clave: enfermedad de Hodgkin, quimioterapia combinada, trasplante de células madre.

Abstract

Objective: The standard of care in first relapsed/refractory Hodgkin lymphoma (R/R HL) is salvage therapy, including high-dose chemotherapy (HDT), followed by autologous stem cell transplantation (ASCT). To date, this treatment approach has been shown to improve event-free survival (EFS), progression-free survival (PFS), and freedom from treatment failure (FFTF) in controlled clinical trials. This study aims to determine the outcomes of patients with HL using this strategy at first relapse but in real-world practice in Colombia before the widespread use of novel agents such as antibody-drug conjugates (ADCs) and checkpoint inhibitors (ICIs).

Methods: We present a retrospective case series of patients diagnosed with R/R HL treated at the Instituto Nacional de Cancerología (INC) (Bogotá, Colombia) between 2013 and 2017.

Results: We found 31 patients with R/R HL fulfilling the inclusion criteria from a 171 patients database. The most widely used regimens were platinum-based, followed by gemcitabine-based regimens. Chemotherapy-sensitive disease was demonstrated in 16 (51.6%) patients, where the majority achieved complete response (CR). In the entire cohort, overall survival (OS) and PFS were lower than the rates reported in other series. Patients who ultimately did undergo ASCT had the best PFS and OS compared to those who did not.

Conclusion: Our retrospective case series showed that responses and survivals are lower than those reported in the literature. ASCT is essential for achieving a potential cure in R/R HL patients with chemotherapy-sensitive disease. Health systems must guarantee access to transplantation for all patients who are candidates for this therapy.

Keywords: Hodgkin disease; drug therapy, combination; stem cell transplantation

Introduction

Hodgkin lymphoma (HL) is the most common type of lymphoproliferative disorder in the young adult population with 83,087 new cases reported worldwide and 23,376 deaths in 2020 (0.4% of all new tumors and 0.3% of all cancer deaths), according to data from the Global Cancer Observatory GLOBOCAN (1). In a report by the *Instituto Nacional de Cancerología* (INC) (Bogotá, Colombia) and the Ministry of Health of Colombia, the age-adjusted incidence of Hodgkin lymphoma is 1.0 cases per 100,000 persons/year in men and 0.5 in women, with a mortality rate of 0.4 cases per 100,000 inhabitants/year (2).

It is considered a potentially curable disease, with a 5-year survival probability of more than 80% with standard first-line treatment (3,4). However, the risk of relapse is 30 to 40% for patients with advanced or high-risk diseases, and about 10 to 15% do not achieve a complete response (CR) with the conventional ABVD (Adriamycin, bleomycin, vinblastine, and dacarbazine) chemotherapy regimen (4,5). The standard of care for relapsed/refractory Hodgkin lymphoma (R/R HL) in the first relapse is salvage therapy, including high-dose chemotherapy (HDT) followed by autologous stem cell transplantation (ASCT). To date, this treatment approach has been shown to improve event-free survival (EFS), progression-free survival (PFS), and freedom from treatment failure (FFTF) in controlled clinical trials. Unfortunately, the overall survival (OS) has not improved thus far (6,7).

The ASCT is currently recommended only for patients with chemotherapy-sensitive disease. Different protocols are used in current clinical practice to achieve a second remission, including novel therapies such as antibody-drug conjugates (ADCs) and checkpoint inhibitors (ICIs), but there are no prospective studies that allow a head-to-head comparison (7,8). To our knowledge, there are no studies in Colombian and Latin American populations looking at this very specific scenario (9).

In this study, we present the outcomes and clinical characteristics of patients diagnosed with R/R HL treated between 2013 and 2017 at the INC (Bogotá, Colombia) before the broad use of brentuximab vedotin (BV), pembrolizumab, and nivolumab.

Methods

This retrospective case series used as its source of information the electronic medical records of patients treated at the hematology-oncology unit of the INC between 2013 and 2017, with a diagnosis of R/R HL. Only patients with institutional histological confirmation of R/R HL, measurable disease, and institutional salvage therapy were included. The information obtained from the medical history was recorded by the analysis unit of the Research Electronic Data Capture (REDCap) system. It included sociodemographic and clinical variables of the patients, therapeutic approaches, clinical results, and calculation of OS and PFS rates.

This research was approved by the Research and Ethics Committee of the INC and controlled and followed up by the monitoring group of research projects. A descriptive analysis of the clinical variables was performed. OS and PFS were graphically described, with time functions for the clinical event estimated with the Kaplan-Meier method. Survival time estimate was defined as the time from the date of diagnosis to the last control performed on the patient's death. OS was established as the time in months from the date of diagnosis to the date of death from any cause. PFS was determined as the time in months from the date of application of the first cycle of salvage chemotherapy to the date of administration of a subsequent line of treatment or the last valuation. All statistical analyses were performed in R-Project® version 3.6.1.

Inclusion criteria

- Patients over 18 years of age at the time of R/R HL disease.
- Relapse to first-line ABVD treatment.
- Confirmed histopathological diagnosis of HL by institutional hematology-pathology department.
- Patients with first salvage regimen at the INC.
- Measurable disease.
- Follow-up information available in the medical records (SAP System).

Exclusion criteria

- Patients with any other concurrent neoplasm.
- Any treatment before the salvage regimen at the INC.
- Not being eligible for ASCT.
- Patients who have had treatment with BV, pembrolizumab, or nivolumab.

Results

Between January 2013 and December 2017, 171 patients diagnosed with HL were treated at the INC; 31 of them met the inclusion criteria for this study.

The median age at diagnosis was 44 years (range: 20-69), and 58.1% were women. The most frequent histological type was classical HL nodular sclerosis variant in 74.2% (n=23). All patients included in this study had an advanced stage at diagnosis (IIB, III, and IV); 22.6% of the cases had bulky disease, and 41.9% had extra-nodal involvement. The conventional ABVD chemotherapy protocol was the first-line treatment administered to all patients. Of the 31 patients with R/R HL, 67.7% (n=21) presented with primary refractory disease to ABVD. Only 19.4% (n=6) of the patients received associated consolidative radiotherapy (table 1).

Table 1. Clinical characteristics of 31 patients with R/R HL (N=31)

Characteristic	No. (%)
Age (years)	
Median (range)	44 (20-69)
Gender	
Female	18 (58.1)
Male	13 (41.9)
Disease characteristics **Histological variant**	
Nodular sclerosis	23 (74.2)
Lymphocyte depletion	1 (3.2)
Mixed cellularity	3 (9.7)
Lymphocyte rich Unclassified	1 (3.2) 3 (9.7)
Stage	
Advanced HL	31 (100.0)
Extra-nodal involvement	
Yes	13 (41.9)
No	18 (58.1)
Bulky disease	
Yes	7 (22.6)
No	24 (77.4)
First-line treatment	
ABVD Consolidative radiotherapy	31 (100.0) 6 (19.4)
Response to first-line treatment	
CR	9 (29.0)
Complete ≤1 year	1 (3.2)
Complete >1 year	8 (25.8)
Primary refractory disease	21 (67.7)
Missing data	1 (3.2)
Time between diagnosis and first salvage treatment (months)	
Median (range)	18.6 (2.5-144.3)

R/R HL: relapsed/refractory Hodgkin lymphoma; HL: Hodgkin lymphoma; ABVD: Adriamycin, bleomycin, vinblastine, and dacarbazine; CR: complete response.

Regarding the salvage chemotherapy treatment, platinum-based protocols were the most used regimen in 25 (80.7%) cases, 4 (12.9%) patients received a gemcitabine-based regimen, one patient had retreatment with ABVD because of late relapse, and one patient underwent only radiotherapy due to localized disease (table 2).

Table 2. Salvage chemotherapy protocol

Chemotherapy-based protocol	No. of patients n (%)	Scheme	n (%)
Platinum-based	25 (80.7)	DHAP ESHAP ICE ASHAP	19 (61.3) 3 (9.7) 1 (3.2) 2 (6.5)
Gemcitabine-based	4 (12.9)	IGEV	4 (12.9)
Other	2 (6.4)	ABVD retreatment Radiotherapy only	1 (3.2) 1 (3.2)

DHAP: dexamethasone, high-dose cytarabine (ARA-C), and cisplatin; ESHAP: etoposide, Solumedrol, high-dose cytarabine (ARA-C), and cisplatin; ICE: ifosfamide, carboplatin and etoposide; ASHAP: Adriamycin, Solumedrol, high-dose cytarabine (ARA-C), and cisplatin; IGEV: ifosfamide, gemcitabine, and vinorelbine; ABVD: Adriamycin, bleomycin, vinblastine, and dacarbazine.

In the entire cohort (N=31), chemotherapy-sensitive disease was demonstrated in 16 (51.6%) patients (14 with platinum-based and 2 with gemcitabine-based regimen); most of the 29 patients who received platinum- or gemcitabine-based therapy achieved CR (34.5%) as per Lugano classification by PET-CT or contrast enhanced CT scan. Table 3 shows the response achieved with every regimen received. Only 8 out of 16 patients with chemotherapy-sensitive disease underwent ASCT.

Table 3. Best response achieved by regimen

Chemotherapy-based protocol	No. of	CR (%)	PR (%)	ORR (%) $CI_{95\%}$
Platinum-based	25	10 (40.0)	4 (16.0)	56 (53.0-59.0)
Gemcit-abine-based	4	0	2 (50.0)	50 (48.2-51.8)

CR: complete response; PR: partial response; ORR: overall response rate; CI: confidence interval

The OS and PFS at five years for the entire cohort was 62.4% ($CI_{95\%}$ 44.6-87.5) and 26.0% ($CI_{95\%}$ 12.7-53.3), respectively (figure 1A-B).

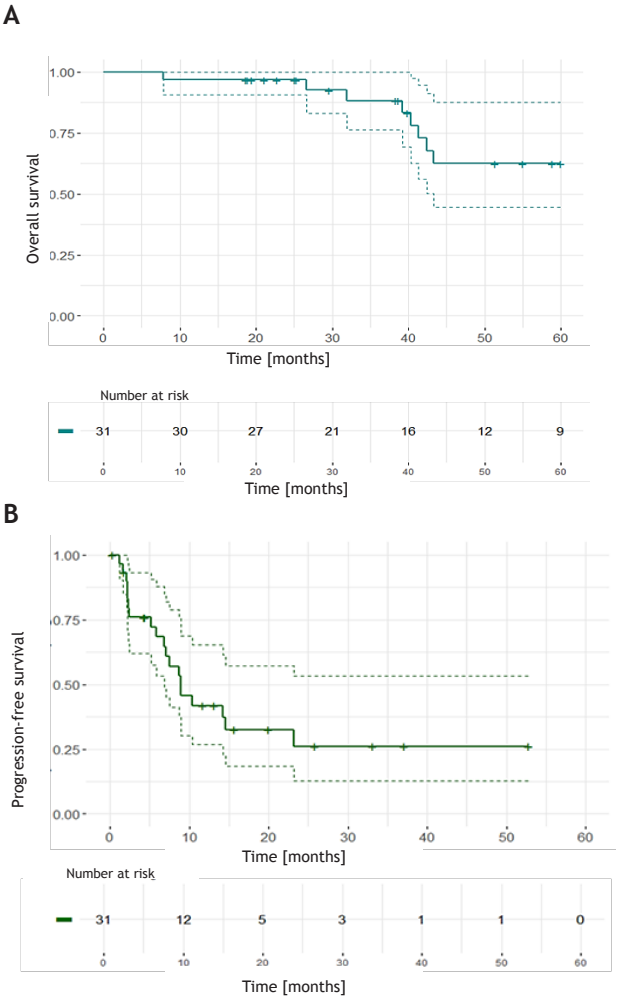

Figure 1. A. Overall survival at five years for the entire cohort. **B.** Progression-free survival

We analyzed the transplanted vs. non-transplanted population in patients with chemotherapy-sensitive disease to evaluate differences in survival (figure 2). It is essential to clarify that the reasons why patients did not undergo ASCT were access barriers (n=6) and other causes not clearly established due to lack of information (n=2); 6 and 2 transplanted patients achieved CR and PR, respectively.

The median PFS in the transplanted group was not achieved, compared to only 7.6 months in the non-transplant group (p=0.0072) (figure 2). The median OS in the non-transplanted group was 62.7 months vs. not reached in the transplanted group (p=0.23) (data not shown).

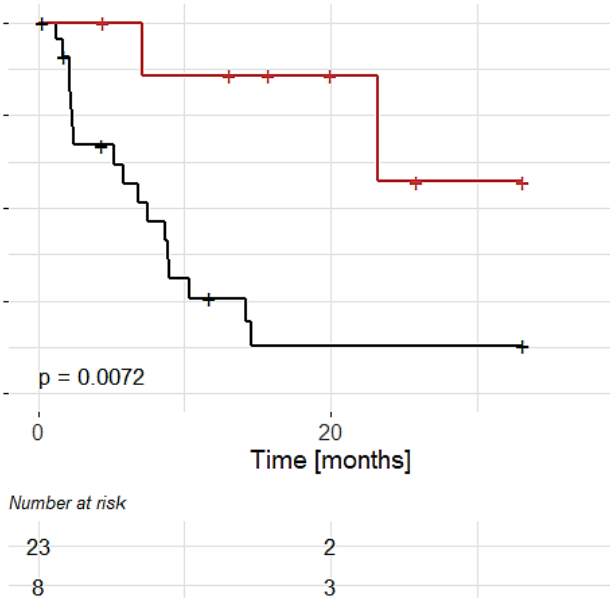

Figure 2. Progression-free survival stratified by ASCT

Discussion

Currently, HL is considered a potentially curable neoplasm; however, the population of patients who relapse or are refractory to first-line treatment constitutes a challenging clinical scenario. At present, there are no direct comparisons between different combinations of salvage chemotherapy to evaluate outcomes. For this reason, there is no consensus on the standard salvage regimen that allows for the best possible response and survival over others (7,8). Thus, it is crucial to recognize that consolidation with ASCT is the most reasonable approach after achieving chemosensitivity. Recently, ASCT as salvage therapy for HL has been shown to improve EFS, PFS, and FFTF, but not OS (6,7).

The present study reports the clinical characteristics and treatment outcomes of 31 patients with R/R HL. A fundamental aspect of this cohort is that all patients were diagnosed in an advanced stage, a condition widely known as an unfavorable risk factor (4,5).

Remarkably, all patients identified in this study received first-line therapy with the ABVD protocol, and the majority had a primary refractory disease at the time of the salvage regimen (67.7%). This finding has already been reported by Jaime-Pérez *et al.* (9) in the Latin American population. A possible hypothesis for this finding is decreased dose density from the first-line regimen with ABVD. (Records from the hematology department show that only nearly 30% of patients receive an adequate dose density and that delays may be as long as two weeks in some case; data not shown). This observation highlights the difficulty of access to timely treatment, possibly derived from access problems that are frequent in current oncology practice in Latin America (10).

The overall response rate (ORR) of patients with chemotherapy-sensitive disease (n=16) to salvage treatment with platinum- or gemcitabine-based protocols (n=29) was 55%, which is lower than the rate reported in large international series, even before the widespread use of BV and ICIs like nivolumab or pembrolizumab. Santoro *et al.* (11) reported an ORR of more than 80% with IGEV regimen, which was similar to other schemes considered in the same paper (8,11). The published reports usually include a heterogeneous population of patients with refractory primary disease and recurrence, and, in many cases, it is not possible to demonstrate significant differences in response to salvage therapy due to a lack of statistical power. There are currently no head-to-head studies comparing salvage regimens prior to ASCT (8,11).

The most important finding of this study was that the patients who could not undergo transplantation due to any situation had an unfavorable prognosis in terms of PFS with statistically significant differences (p=0.0072) and a trend towards worse OS.

We recognize the critical limitations of our study, which are its retrospective nature and the small patient number; in addition, there was no complete information on the International Prognostic Score and disease characteristics at the time of relapse.

A great deal of knowledge about cancer immunotherapy has been generated in the last decade with the advent of monoclonal antibody conjugates such as BV and ICIs, a discovery worthy of the Nobel Prize in Medicine in 2018 (12,13). The anti-PD1 agents nivolumab and pembrolizumab have shown encouraging results in phase 1 and 2 studies with a population of refractory patients, relapses after autologous transplantation, and most patients previously treated with brentuximab. The most recent treatment option proposed by Herrera *et al.* (14) in a phase 1/2 study is the combination of BV and nivolumab as initial salvage therapy in 62 patients with relapsed or refractory classical HL, reporting CR in 61% with an ORR of 82%. In the updated data at a median follow-up of 34.3 months

(15), the estimated PFS rate at 3 years was 77% ($CI_{95\%}$ 65-86%) and 91% ($CI_{95\%}$ 79-96%) for patients undergoing ASCT directly. Overall survival at 3 years was 93% ($CI_{95\%}$ 85-97%) with no new safety concerns

These new agents have generated a hopeful panorama in the treatment of these patients, and it is the reason why we are currently using them as a standard of care in some specific scenarios.

Conclusion

Platinum-based regimens were the most widely used protocols in R/R HL in our study, followed by gemcitabine-based regimens. Chemotherapy-sensitive disease was demonstrated in only 51.6% of the patients, which is clearly lower than what has been reported in international series. The OS and PFS of the entire cohort were lower than the reported rates in other series. Patients who ultimately did undergo ASCT had the best PFS and trend towards better OS compared to those who did not receive high-dose therapy and ASCT.

Primary refractory disease to conventional therapy generates very unfavorable outcomes in terms of survival even when refractoriness is the result of low chemotherapy dose density.

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