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BEAM-Modified Conditioning Therapy with Cisplatin+Dexamethasone Instead of Carmustine Prior to Autologous Hematopoietic Stem Cell Transplantation (HSCT) in Patients with Hodgkin and Non-Hodgkin Lymphoma

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Background: High-dose chemotherapy followed by autologous hematopoietic stem cell transplant has proven useful in relapsed or refractory cases of Hodgkin and non-Hodgkin lymphoma. BEAM (carmustine, etoposide, cytarabine, melphalan) is frequently used as a conditioning regimen; however, the high cost and limited availability of BCNU hinders its use in Mexico.

Material/Methods: Between January 2013 and February 2019, refractory or relapsing HL and NHL patients were treated with an autologous HSCT conditioned with cisplatin+dexamethasone as substitution for BCNU in BEAM.

Results: Four HL patients and 6 NHL patients were included; 60% were male, the average age was 34.5±15.2 years, the median follow-up was 19.1 months, and 70% had a complete response after transplant. OS at 12 months was 63% for NHL and 100% for HL. Time to hematological recovery was 17.6±2.8 days; all patients developed grade III/IV neutropenia and thrombocytopenia, and 8 patients had transplant-related infections.

Conclusions: This retrospective study based on real-world data introduces the option of substituting carmustine with cisplatin+dexamethasone, with a similar response, expected lower cost, and better accessibility in developing nations.

MeSH Keywords: **Bone Marrow Transplantation • Hodgkin Disease • Lymphoma, Non-Hodgkin • Transplantation Conditioning**

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Background

Intensive chemotherapy as a conditioning regimen prior to autologous hematopoietic stem cell transplantation (HSCT) is a therapeutic option for a subset of patients with Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), especially those with aggressive or refractory disease [1–4]. One of the most commonly used conditioning therapies uses carmustine (BCNU), etoposide, cytarabine, and melphalan (BEAM) [5–8]. However, due to frequent BCNU shortages and its high cost, it has been replaced with other chemotherapeutic agents such as bendamustine, lomustine, and busulfan [9–12].

Similar to BCNU, alkylating agents like cisplatin and carboplatin have been used in conjunction with doxorubicin, etoposide, or dexamethasone as conditioning regimens prior to autologous HSCT for both hematological and non-hematological malignancies [13–16]. Dexamethasone, on the other hand, is used both for its anti-emetic and tumor-suppressive properties [17,18].

To the best of our knowledge, there have been no reports of cisplatin as a substitute for BCNU in BEAM. This could be a feasible option in developing nations with difficult access to carmustine. We report the results of a pilot study of our single-center experience with CEAM-Dex as a conditioning therapy for HL and NHL patients.

Material and Methods

We performed a retrospective record-based study describing our single-center experience with relapsed or refractory HL or NHL patients who underwent autologous HSCT conditioned with CEAM-Dex, from January 2013 to September 2018. The patients included were conditioned using cisplatin 100 mg/m^2 on day –6; etoposide 200 mg/m^2, dexamethasone 40 mg/m^2, and cytarabine 200 mg/m^2 on days –5 to –2; and melphalan 140 mg/m^2 on day –1, all administered intravenously. Unmodified hematopoietic progenitor cells were obtained from filgrastim or filgrastim+prelixafor-mobilized peripheral blood and infused on day 0.

Data collected included disease features at diagnosis and prior to transplant, and transplantation-related factors, including outcome variables. All patients received standard supportive care, including granulocyte colony-stimulating factors and antimicrobial prophylaxis.

Kaplan-Meier method was used to estimate overall survival (OS) and progression-free survival (PFS). We recorded time to neutrophil and platelet recovery, defined as the first of 3 consecutive days with an absolute neutrophil count ≥0.5×10^9/L and a platelet count exceeding ≥20×10^9/L without transfusion support for 7 consecutive days [19,20].

Table 1. Patient demographic data at mobilization.

Characteristic	Value
Age in years, mean (range)	34.5 (19–64)
Gender, (%)	
Female	40
Male	60
Diagnosis, (%)	
HL	40
NHL	60
Stage at diagnosis, (%)	
I/II	30
III/IV	70
Stage at transplant, (%)	
0*	40
I/II	50
III/IV	10
Mobilization agent, (%)	
Filgrastim	70
Plerixafor+Filgrastim	30
Pre-transplant KPS, (%)	
80	20
90	30
100	50

CR – complete response; HL – Hodgkin lymphoma; KPS – Karnofsky performance status; NHL – non-Hodgkin lymphoma; RT – radiotherapy. * Denotes complete remission.

Results

Patient characteristics

A total of 10 patients with either relapsed or refractory lymphoma were included. Patient demographics are summarized in Table 1. Briefly, of the patients included, 40% had Hodgkin lymphoma and 60% non-Hodgkin lymphoma. Of the patients with HL, 75% had nodular sclerosis and 25% had mixed cellularity histology. Most cases (75%) had advanced disease at diagnosis and were classified as high-grade, and all were treated with 2 or more chemotherapy regimens, achieving partial response prior to transplant. NHL patients had anaplastic large-cell lymphoma histology in one-third of the cases, one-third had DLBCL, and one-third had extra-nodal NK/T cell lymphoma, nasal type. The majority of patients (66%) had

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Table 2. Major outcomes of CEAM-Dex conditioned auto-HSCT patients.

Outcomes	Value
Time to neutrophil recovery in days, mean (range)	
Overall	12.44 (10–14)
NHL	11.6 (10–12)
HL	13.5 (12–14)
Time to platelet recovery in days, mean (range)	
Overall	10.33 (5–18)
NHL	10.8 (8–18)
HL	9.75 (5–14)
Time to hematological recovery in days, mean (range)	
Overall	17.56 (12–21)
NHL	16.60 (12–20)
HL	18.75 (17–21)
Anemia, n (%)	
GI/II	7 (70)
GIII/IV	3 (30)
Azoemia, n (%)	
GI/II	1 (10)
Mucositis, n (%)	
GI/II	8 (80)
GIII/IV	2 (20)
Infections, n (%)	
None	2 (20)
Pneumonia	4 (40)
Diarrhea	4 (40)
Other infections	4 (40)
Transplant outcome, n (%)	
CR	7 (70)
Failure	3 (30)

CR – complete remission; HL – Hodgkin lymphoma; NHL – non-Hodgkin lymphoma.

advanced-stage disease and a high IPI score at diagnosis. NHL patients were treated with an average of 2.7 lines; half were on complete response and half were on partial response prior to transplantation.

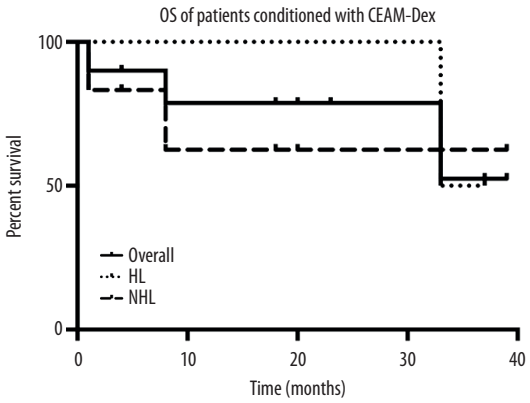

Figure 1. Kaplan-Meier analysis of HL and NHL patients conditioned with CEAM-Dex.

Transplant, toxicity, and hematopoietic recovery

All patients were conditioned with CEAM-Dex prior to the auto-HSCT. Time from diagnosis to transplant was 37.5±22.06 months overall; 53±24.12 for HL patients and 27.17±14.37 for NHL. HSCs were collected from peripheral blood mobilized with either filgrastim (70%) or filgrastim+plerixafor (30%), with an average CD34+ cell infusion of $2.88\pm1.18\times10^6$/kg. Transplant-related toxicities were grade I (GI) anemia in 1 patient, GII in 6 patients, GIII in 1 patient, and GIV in 2 patients. All patients presented with GIV neutropenia and thrombocytopenia, 20% had severe mucositis (GIII/IV), and only 1 patient had reversible azotemia. Eight patients had infections related to the transplant; of these, 4 had pneumonia, 4 had diarrhea, 2 had catheter-related infections, and 1 had acute brucellosis. Neutrophil recovery presented at a mean of 12.4 (10–14) days, while platelet recovery presented at a mean of 10.3 (5–18) days. Hematological recovery was achieved at a mean of 17.5 (range 12–21 days) days in 90% of patients. The mean hospital stay was 25.6 days (range 22–29), summarized in Table 2.

Relapse and survival

The median follow-up time was 19.1 (range 1–39) months. HL patients had a complete response after transplant, with an OS at 12 and 36 months of 100% and 50%, respectively. In patients with NHL, OS was 68.5% at 12 and 36 months. Only 1 patient with anaplastic T NHL relapsed at 6 months. Three deaths were reported in the NHL branch, all attributable to infections, at 1, 8, and 33 months (Figure 1).

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Discussion

Combined conditioning chemotherapy plus autologous HSCT is the treatment of choice for eligible relapsed or refractory lymphoid malignancies; however, no definitive evidence supports the use of one conditioning regimen over others, varying mainly based on local institutional practice. BEAM has been the most commonly administered regimen for both NHL and HL; nonetheless, the high cost and difficult access of BCNU limits its use in our practice [1,2,9].

In our series of relapsed or refractory HL and NHL patients conditioned with CEAM-Dex, we achieved an OS of 78.7% at 12 months and 52.5% at 36 months. Accounting for the inclusion of low-risk DLBCL patients in other studies, this is similar to that reported with BEAM chemotherapy, with an OS at 36 months ranging from 56% to 75% [6,11,21].

As commonly reported in the literature, sever mucositis was a common toxicity, second only in frequency to bone marrow suppression. However, we did not observe non-infectious pulmonary toxicity, commonly attributable to carmustine [1,11,21]. Infectious complications were slightly lower than Puig et al. reported (80% *vs.* 89%).

Time to engraftment, as measured by time to neutrophil and platelet recovery, was 12.4±1.33 days and 10.3±3.7 days, respectively, which is comparable to reports by Puig et al., Sakellari et al., and Caballero et al.

Conclusions

Although our present study has limitations due to its retrospective nature, our results show that cisplatin plus dexamethasone as a substitute for BCNU in BEAM chemotherapy has a response rate, overall survival, and toxicity profile similar to those reported in the literature, thus providing an alternative for developing countries with difficult access to carmustine.

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