Brazilian experience using high dose sequential chemotherapy followed by autologous hematopoietic stem cell transplantation for malignant lymphomas

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Objective: *To evaluate the use of high-dose sequential chemotherapy in a Brazilian population.*

Methods: *High-dose cyclophosphamide followed by autologous hematopoietic stem cell transplantation is an effective and feasible therapy for refractory/relapsed lymphomas; this regimen has never before been evaluated in a Brazilian population. All patients (106 with high-grade non-Hodgkin lymphoma and 77 with Hodgkin's lymphoma) submitted to this treatment between 1998 and 2006 were analyzed. Chemotherapy consisted of the sequential administration of high-dose cyclophosphamide (4 or 7 g/m^2) and granulocyte-colony stimulating factor (300 µg/day), followed by peripheral blood progenitor cell harvesting, administration of etoposide (2g/m^2) and methotrexate (8 g/m^2 only for Hodgkin's lymphoma) and autologous hematopoietic stem cell transplantation.*

Results: *At diagnosis, non-Hodgkin lymphoma patients had a median age of 45 (range: 8-65) years old, 78% had diffuse large B-cell lymphoma and 83% had stage III/IV disease. The Hodgkin's lymphoma patients had a median age of 23 (range: 7-68) years old, 64.9% had the nodular sclerosis subtype and 65% had stage III/IV disease. Nine Hodgkin's lymphoma patients (13%) and 10 (9%) non-Hodgkin lymphoma patients had some kind of cardiac toxicity. The overall survival, disease-free survival and progression-free survival in Hodgkin's lymphoma were 29%, 59% and 26%, respectively. In non-Hodgkin lymphoma, these values were 40%, 49% and 31%, respectively. High-dose cyclophosphamide-related mortality was 10% for Hodgkin's lymphoma and 5% for non-Hodgkin lymphoma patients. High-dose cyclophosphamide dosing had no impact on toxicity or survival for both groups.*

Conclusions: *Despite a greater prevalence of poor prognostic factors, our results are comparable to the literature. The incidence of secondary neoplasias is noteworthy. Our study suggests that this approach is efficient and feasible, regardless of toxicity-related mortality.*

Keywords*: Transplantation, autologous; Hodgkin disease/drug therapy; Lymphoma; Lymphoma, non-Hodgkin; Antineoplastic Combined Chemotherapy Protocols/administration & dosage; Cyclophosphamide/administration & dosage; Hematopoietic stem cell transplantation*

Introduction

There have been many advances in the treatment of malignant lymphomas over the last few decades. Even so, management of relapsed and resistant disease using conventional chemotherapy is disappointing.

The use of state-of-the-art regimens, such as doxorubicin [Adriamycin], bleomycin, vinblastine, dacarbazine (ABVD) and bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone (BEACOPP), has improved the outcome in Hodgkin's lymphoma (HL) and patients with good prognostic factors achieve complete remission (CR) rates as high as 95%.[1,2] However, patients with advanced disease and poor prognostic factors do not perform so well and present with either chemo-resistant or relapsing disease. [3]

As for non-Hodgkin lymphomas (NHL), today, with Rituximab containing cyclophosphamide, vincristine, doxorubicin, prednisolone (CHOP)-like regimens as standard treatment, survival has improved significantly.[4,5] However, management of relapsed and resistant disease with conventional salvage regimens is disappointing, with overall survival (OS) rates lower than 10%.[1,6] The Parma Trial[7] showed the benefit of using high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (HSCT) as salvage therapy giving response rates close to 90%. Nevertheless, more than 50% of these patients relapsed and most died from progressive disease.[1]

In such a scenario, a dose intensified regimen, such as high-dose sequential chemotherapy (HDS) followed by HSCT, represents an effective and feasible salvage therapy for resistant and relapsed malignant lymphomas.[8,9]

Despite proof of its efficacy for both HL[10,11] and NHL,[12] there are few studies using this strategy in Brazil and few groups worldwide evaluated the use of this therapy with follow-up periods longer than 5 years. The use of this strategy for HL has already been reported in patients from this institution.[13] The objective of the current study was to compare the experience of this strategy between 2 groups of malignant lymphomas (HL and NHL). The aim was, therefore, to evaluate the effectiveness and toxicity of HDS used as a salvage therapy comparing these two groups of malignant lymphomas, focusing on overall survival (OS), disease-free survival (DFS) and progression-free survival (PFS).

Methods

A retrospective analysis was performed of all refractory HL patients (77) and high grade NHL patients (106) who were submitted to HDS from May 1st 1998 to November 30th 2006 in two institutions: Hemocentro, University of Campinas (UNICAMP) and Vera Cruz Hospital. Patients were eligible for treatment if they had failed to achieve CR after first-line treatment (non-responsive – NR) or presented with relapsed disease, even if CR had been achieved before mobilization. Patients were excluded if they have been diagnosed with any psychiatric condition. All patients or their legal representatives provided written informed consent before receiving this regimen. Treatment procedures were approved by the institutional review boards of both participating institutions.

Treatment procedures and definitions

HDS consisted of the sequential administration of high doses of cyclophosphamide (4 or 7 g/m^2 depending upon the patients' clinical features during treatment, in particular age and heart function) and granulocyte colony stimulating factor (G-CSF) 300 µg/day from day +1 after high-dose cyclophosphamide (HDCY), followed by peripheral blood progenitor cell (PBPC) harvesting, when the white blood cell count (WBC) had increased to > 1.0 x 10^9/L with the aim of collecting > 5 x 10^6 CD34$^+$ cells/kg body weight.

Patients with an insufficient number of CD34$^+$ cells underwent another collection after the administration of etoposide. In some cases where peripheral cells could not be harvestedfrom peripheral blood, harvesting was made directly from the bone marrow. After PBPC harvesting, methotrexate (8 g/m^2) plus vincristine (1.4 mg/m^2) – only in patients with HL – and etoposide (2 g/m^2) were administered. Different regimens HDS were then administered including carmustine, etoposide, cytarabine and melphalan (BEAM), cyclophosphamide, carmustine, and etoposide (CBV) and mitoxantrone and melphalan (Mito/Melph). Subsequently, autologous HSCT was performed.

Disease status was assessed by abdominal ultrasound and computed tomography (CT), depending on the sites of disease. Positron Emission Tomography/CT was not available for response assessment. These assessments, when possible, were performed before HDCY, before and after autologous HSCT and throughout the long-term follow-up (every 3 months in the first year, every 6 months in the second year and annually thereafter). CR was defined as the absence of clinical, laboratory and imaging findings confirming absence of disease persisting for at least 3 months. Partial remission (PR) was defined as a tumor mass reduction > 50% after treatment. Non-responsive (NR) disease was defined when a reduction in tumor mass of < 50% was observed and disease progression was defined as an increase in tumor mass after treatment, or a new tumor mass or central nervous system infiltration during treatment. Relapsed disease (RD) was defined as the re-appearance of disease identified by clinical, laboratory or imaging findings after CR had been achieved.

Data collection and statistical analysis

Analysis was based on data as of May 2010. Dichotomous variables were compared using the Fisher's exact or Chi-square tests, as appropriate, whereas continuous variables were compared using the Mann-Whitney test. Actuarial curves of OS, DFS and PFS were analyzed using the Kaplan-Meier method, and compared by the log-rank test. Multivariate predictors of outcome (OS, DFS and PFS) were assessed by Cox regression analysis, using the forward stepwise Wald test. Statistical analysis was performed using the Statistical Package for the Social Sciences version 15.0 (SPSS Inc, USA).

Results

Patients' characteristics

Seventy-seven HL patients and 106 NHL patients were enrolled in the study. HL histological types, according to World Health Organization (WHO) criteria[14] were: nodular sclerosis in 51 patients (66.2%); mixed cellularity in 20 (26%); lymphocyte depleted in five (6.5%) and lymphocyte predominant in one (1.3%). The NHL histopathological classifications according to WHO criteria[14] were: diffuse large B-cell lymphoma (DLBCL) in 83 patients (78.3%), T and anaplastic lymphoma in 13 patients (12.3%) and mantle cell lymphoma in 10 patients (9.4%). Table 1 shows the characteristics of these patients.

Before HDCY, 41 HL patients (53.2%) and 25 NHL patients (24%) received radiation therapy, either as a consolidation therapy, as a treatment for relapsed disease, or as treatment for oncologic emergencies. One HL and six NHL patients were in CR after conventional treatment for their first relapse before being referred to the institution.

Table 1 - Patients' characteristics

Characteristic	HL (n= 77)	NHL (n= 106)
Median age at diagnosis, years (range)	23 (7-68)	45 (8-65)
Median age at HDCY, years (range)	25 (8-71)	47 (8-66)
Gender, n (%)		
Male	46 (59.7)	66 (62.3)
Female	31 (40.3)	40 (37.7)
Stage, n (%)[a,b]		
I+II	27 (35.0)	18 (17.0)
III	20 (26.0)	15 (14.1)
IV	30 (39.0)	73 (68.9)
B symptoms, n (%)[a,c]	55 (71.4)	67 (63.2)
Bone marrow involvement, n (%)[a]	10 (14.1)	34 (32.4)
Bulky disease, n (%)[a]	29 (39.7)	65 (61.9)
LDH, U/L Median (range)[a]	387 (102-1257)	503 (113-4590)
Median therapeutic lines before CY n (range)	2 (1-4)	2 (1-4)
CY dose, n (%)		
4 g/m^2	30 (39)	42 (39.6)
7 g/m^2	47 (61)	64 (60.4)
Disease status before CY, n (%)		
Complete remission	1 (1.3)	6 (5.7)
Partial remission	17 (22.1)	38 (35.8)
Disease progression	41 (53.2)	46 (43.4)
Relapsed	18 (23.4)	16 (15.1)

HL: Hodgkin's Lymphoma; NHL: Non-Hodgkin's Lymphoma; [a]At diagnosis; [b] Staging according to the Ann Arbor staging system; [c]B symptoms as defined by the Ann Arbor staging system (fever, sudoresis, pruritus, loss of weight); CY= cyclophosphamide; HDCY= high-dose cyclophosphamide; LDH= lactate dehydrogenase

Mobilization, peripheral blood progenitor cell harvesting and toxicity

Cyclophosphamide was administered after a median of 1.5 years from diagnosis for HL patients and after 10 months for NHL patients. Thirty HL patients (39%) and 64 NHL patients (60.4%) received a dose of 4 g/m^2 due to advanced age (> 65 years) or borderline heart function. There were no differences in gender, histopathological subtype, LDH values, bone marrow involvement, bulky disease, stage, or number of previous chemotherapy lines between the two 4 and 7 g/m^2 groups for both HL and NHL.

The median time between the completion of HDCY and leukapheresis was 13 days for both HL (range: 8-27) and NHL (range: 3-83) groups, with a median of three sessions (range: 1-8) for HL and two sessions (range: 1-7) for NHL and a median number of harvested CD34$^+$ cells of 5.98 x 10^6 (range: 0.23-45.01 x 10^6) cells/kg body weight for HL and 6.74 x 10^6 (range: 1.29-44.01 x 10^6) cells/kg body weight for NHL patients.

Twenty-two HL patients (27.3%) died after HDCY, but only eight (10.4%) died from treatment-related toxicity (two from sepsis, one from liver failure, one from tumor lysis syndrome, two from refractory congestive heart failure and two due to high-dose methotrexate-toxicity). Ten died from DP and three died from sepsis while in DP. Finally, one patient did no collect enough cells, evolved with myelodysplastic syndrome (MDS) and died from sepsis while in CR. In addition to these 22 patients, two more were not submitted to HSCT: one lost follow-up and one was awaiting HSCT at closure of this analysis.

Nineteen NHL patients (18%) died after HDCY. Six patients (5.7%) died from HDCY-related toxicity (one with tumor lysis syndrome, four from sepsis and one from invasive pulmonary aspergillosis), nine from DP, three from sepsis while in DP and one from sepsis not related to therapy in PR. In addition, seven other patients did not undergo autologous HSCT: five did not consent, one was diagnosed with esophageal varices and became ineligible for the procedure, and one lost follow-up giving a total of 26 patients (24.5%) who were not submitted to autologous HSCT.

Data on toxicity were recorded for 71 HL patients and 102 NHL patients. Sixty-six HL patients (93%) and 94 (88.6%) NHL patients had WHO grade IV toxicity for white blood cell counts (neutropenia). Forty HL patients (56%) and 47 NHL patients (44%) experienced some kind of gastrointestinal toxicity. Additionally, nine HL patients (13%) presented cardiac toxicity of some type with two dying due to myocarditis. Similarly, ten NHL patients (9.4%) had some kind of cardiac toxicity with one dying from severe congestive heart failure.

Seven HL patients (9.7%) and four NHL patients (3.8%) developed acute renal failure not related to sepsis.

Hematopoietic stem cell transplantation results

Autologous HSCT was performed in 53 HL patients (68.8%) and 80 NHL patients (75.5%), with median times of four months (range: 2-13) and two months (range: 1-15) after HDCY, respectively. Two patients, one with HL and another with NHL, who achieved CR after HDCY, decided to undergo HSCT only 56 and 57 months after HDCY, respectively. BEAM was the most frequently used conditioning regime, administered to 43 HL patients (81%) and 70 NHL patients (87%). The median times for granulocyte (> 0.5 x 10^9/L) and platelet (> 20 x 10^9/L) engraftment were 11 (range: 9-27) and 17 days (range: 6-88) for HL patients and 11 (range: 6-29) and 16 (range: 5-70) days for NHL patients, respectively. Mortality related to autografts occurred in six HL patients (11%): three due to pulmonary hemorrhage, one due to tumor lysis syndrome and two due to fungemia. As for NHL patients, HSCT-related mortality occurred in ten (12%) patients: one from acute heart failure, one from fusariosis,

one from herpetic encephalitis, one from typhlitis, one from cytomegalovirus pneumonitis, one from pulmonary hemorrhage and four from sepsis. Two patients died from engraftment syndrome, one in the HL group and one in the NHL group. OS for transplanted patients was 46% for patients with HL and 49% for patients with NHL.

Long-term Outcome

Distributions of status in different treatment stages can be seen in Table 2. A total of 27 patients with HL and 48 with NHL are alive in a median of 66 (range: 3-128) and 68 (range: 1-115) months after HDCY, respectively.

OS, DFS and PFS data for both HL and NHL are shown in Figure 1. Median durations of OS, DFS, and PFS for HL were 18 (range: 1-128), 45 (range: 2-125) and 13 (range: 1-128) months, respectively and for NHL patients they were 29 (range: 1-125), 36 (range: 2-118.2) and 17 months (range: 1-115), respectively.

The survival of patients initially in DP (57/77– 74% for HL patients and 62/106 – 58%) were analyzed according to their disease status before HDCY. Patients who achieved CR after HDCY (24/57 – 42% for HL patients and 38/62 – 61% for NHL patients) had significantly better OS and PFS (36% and 33% respectively, for HL and 44 and 22%, respectively, for NHL) than patients who remained in DP (10% [p-value = 0.002] and 17% [p-value = 0.001] respectively, for HL patients and 0% [p-value < 0.001] and 0% [p-value = 0.003], respectively, for NHL patients – Figure 2). The survival of patients according to HDCY dose was also analyzed but there was no statistical significant difference between the 4 g/m^2 and 7 g/m^2 groups.

For NHL patients, those who presented without B symptoms had better OS and PFS (60% and 39%, respectively) than patients with B symptoms (26% and 26%, respectively; p-value = 0.002 and p-value = 0.042, respectively). Survival data based on age, stage, histopathological and laboratory findings at diagnosis were also analyzed; there was no association between survival and any of these variables.

Of the variables included in the univariate analysis of HL patients, DP before (hazard ratio [HR]: 2.34; 95% confidence interval [95% CI]: 1.13-4.84; p-value < 0.02) and

Table 2 - Disease status at the date of first assessment after HDCY and after ASCT according to disease status before HDCY

	HL	NHL	HL	NHL	HL	NHL	HL	NHL
Status	Before HDCY	n (%)	After HDCY	n (%)	After aHSCT	n (%)	Current Status	n (%)
CR	3 (3.9)	6 (5.6)	16 (20.8)	43 (40.6)	26 (31.2)	39 (48.8)	18 (23.3)	35 (36.1)
PR	17 (22.1)	38 (35.8)	22 (28.6)	33 (31.1)	4 (5.2)	8 (10)	3 (3.9)	5 (5.2)
Relapsed	15 (19.5)	46 (43.4)	0 (0)	0 (0)	2 (2.6)	12 (15)	6 (7.8)	9 (9.3)
DP	42 (54.5)	16 (15.2)	27 (35)	11 (10.4)	13 (16.9)	10 (12.4)		
Deaths	0	0	12 (15.6)	19 (17.9)	8 (10.4)	11 (13.8)	50 (65)	48 (49.5)
Total	77	106	77	106	53	80	77	106

HL: Hodgkin's lymphoma; NHL: Non-Hodgkin's lymphoma; HDCY: High-dose cyclophosphamide; aHSCT: Autologous stem cell transplantation; CR: complete remission; PR: partial remission; DP: disease progression

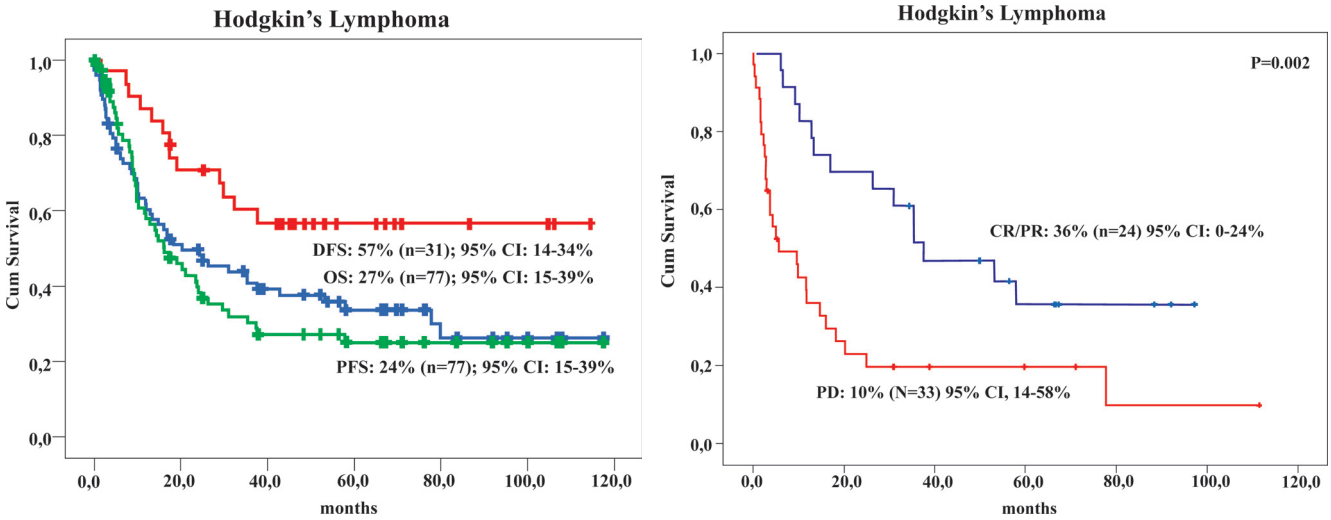

Figure 1 – Overall (OS), disease-free (DFS) and progression-free survival (DFS) for all 77 Hodgkin's lymphoma and 106 non-Hodgkin lymphoma patients by the Kaplan-Meier method

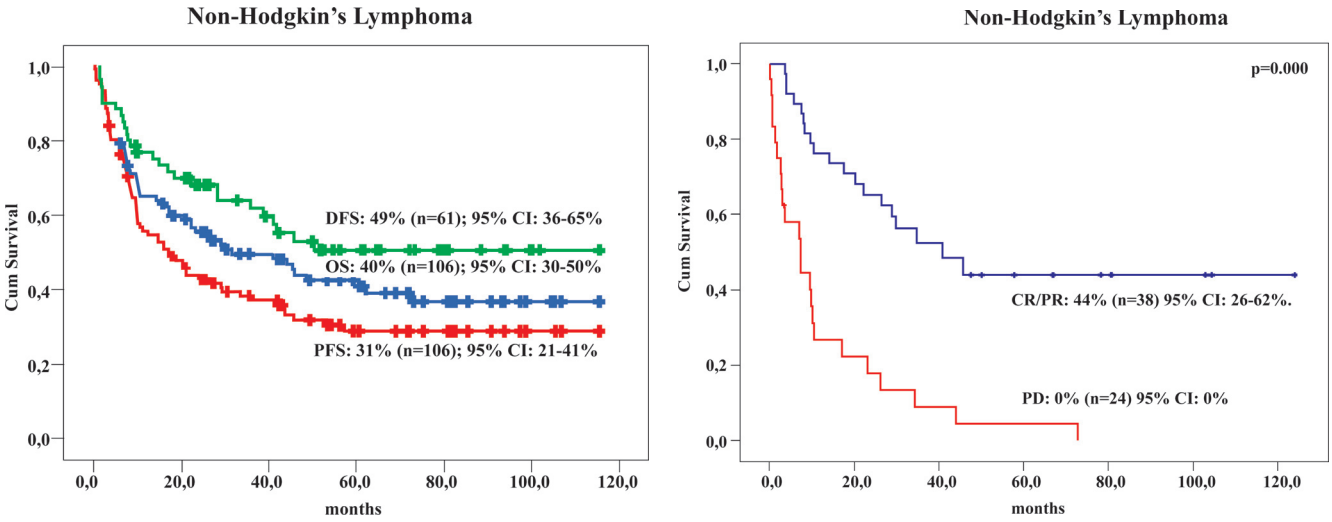

Figure 2 – Overall survival according to disease status after high-dose cyclophosphamide [complete remission (CR) and partial remission (PR) vs. disease progression (DP)] in patients initially in DP by the Kaplan Meier method with Log Rank test

Table 3 - Univariate and multivariate analysis for overall survival from HDCY

Endpoint/Variable	p-value	Hazard ratio (95% CI)
Hodgkin's lymphoma		
Univariate analysis		
LDH (normal vs. altered)	0.01	2.4 (1.2-4.6) 1.002-1.006
PD before HDCY	0.02	2.3 (1.1-4.8)
PD after HDCY	0.0001	3.5 (1.7-6.6)
Multivariate analysis		
LDH (normal vs. altered)	0.04	2.4 (1.0-5.6)
DP after HDCY	0.001	4 (1.7-9.1)
Non-Hodgkin lymphoma		
Univariate analysis		1.521-5.144
DP before HDCY	0.001	2.7 (1.5-4.8)
DP after HDCY	0.001	5.9 (3.2-10.7)
B symptoms presence	0.01	2.3 (1.23-4.4)
Multivariate analysis		
B symptoms presence	0.003	2.6 (1.4-4.8)
B symptoms presence	0.003	2.6 (1.4-4.8)

95% CI: 95% confidence interval; Univariate and multivariate analysis using Cox regression models; LDH: Lactate dehydrogenase; DP: Disease progression; HDCY: High-dose cyclophosphamide

after HDCY (HR: 3.46; 95% CI: 1.7-6.6; p-value < 0.0001) were associated with poorer OS, as was high serum LDH level (HR: 2.37; 95% CI: 1.22-4.60; p-value < 0.01) both as continuous or categorical variables. In the univariate analysis of NHL patients, only DP before (HR: 2.66; 95% CI: 1.48-4.78; p-value < 0.001) and after HDCY (HR: 5.91; 95% CI: 3.25-10.73; p-value < 0.001) were associated with poorer OS. By multivariate analysis, two variables remained significant for HL patients: serum LDH (as a categorical variable - HR: 2.41; 95% CI: 1.04-5.59; p-value = 0.04) and DP after HDCY (HR: 3.97; 95% CI: 1.73-9.10; p-value = 0.001). As for NHL patients, two variables related to disease at the time of diagnosis maintained their prognostic value for overall survival by multivariate analysis. These findings are summarized in Table 3.

Discussion

This study offers the first analysis of a large Brazilian cohort submitted to HDS chemotherapy for high-risk lymphoma. The analysis of a Brazilian cohort has several implications because the frequency of some important poor prognostic factors, such as B symptoms and bulky disease, are higher in our patients compared to cohorts from the Northern Hemisphere.[15-17] In an Italian study[18] evaluating HDS in 102 patients with refractory or recurrent HL, 42% had B symptoms and 29% had bulky disease. In another study[19] evaluating the use of HDT and autologous HSCT in 494 Spanish patients with refractory or recurrent HL, 40.5% had B symptoms and 33% had bulky disease. These numbers contrast with the 71% of patients with B symptoms and the 40% of patients with bulky disease seen in our patients with HL. The same is true with NHL patients. The higher prevalence of such variables in our population indicates that they are probably expected to have poorer results when compared to other populations in developed countries, despite differences in the therapeutic strategies employed.

Another possible factor contributing to a worse outcome in our patients is a higher prevalence of Epstein-Barr virus (EBV)-associated HL, although we did not investigate this information. Despite the controversy surrounding the possible influence of EBV in the outcome of HL, some studies suggest that the OS is worse in adult patients with EBV-associated HL.[20] While the prevalence of

EBV in developed countries is around 30%,[20] one study performed at the institution of the current study showed a prevalence of 64%.[16] The aforementioned differences may be due to low socioeconomic status[16] as this is a governmental institution which provides care to low income patients, and not due to ethnical differences between our population and those from developed countries.[16]

The higher prevalence of poor prognostic factors in this population reflects in poorer OS and PFS of HL patients (27 and 25%) compared to other studies in which the OS and PFS ranged from 50 to 65%.[18,21] However, this was not observed for NHL patients, with an OS of 41% and a PFS of 31%, similar to those reported in other studies (40 to 45%).[12,21,22] Although a higher prevalence of high-risk patients may explain the worse OS observed in the HL patients of this study, it should also have negatively impacted survival of NHL patients. This finding in a population of similar sociodemographic conditions with advanced disease treated under the same protocol and within the same institution highlights the different biology of both diseases and points to a need of different salvage strategies for each.

These data show the necessity of a review of HDCY use in HL, which is usually a more benign disease, as patients may benefit from less intensive regimens; a recent study comparing HDCY with BEAM as salvage therapies, showed no benefit of the dose intensified therapy (HDCY) on PFS and OS.[23]

A lack of benefit of using a higher dose regimen for both HL and NHL was not expected. The use of a regimen at two different doses (4 g/m^2 and 7 g/m^2) was based on findings of the Italian group.[22] This was developed based on the Norton-Simon hypothesis,[24] which states that an ideal treatment should seek the highest possible dosing, over the minimum period of time, with an acceptable toxicity. By showing no extra benefit of the higher dose regimen, either in OS or in response rates, our study suggests that its benefit was exceeded by its toxicity, resulting in the similar survival rate to the lower dose regimen.

Even though the 7g/m^2 regimen did not improve survival, the role of a high-dose debulking regimen is highlighted by the observation that patients previously in DP, who responded to HDCY and achieved a CR, had a better overall survival. This not only shows the ability of HDCY to overcome primary chemoresistance in a significant proportion of refractory patients, but also its importance in assessing chemosensitivity of lymphoma, since there was no benefit in submitting patients to autologous HSCT when they did not respond to HDCY, with no additional benefit of autologous HSCT in patients in DP.

Nevertheless, this high-dose debulking regimen imposed a high toxicity burden (cardiological, renal and gastrointestinal), with HDCY-related mortality of 5.7% for NHL and 10.4% for HL, which is slightly worse than the 5% rate observed elsewhere,[22] but still acceptable. Moreover, a mortality rate of 10% for autologous transplantation is noteworthy, further corroborating the toxicity burden associated with this therapy.

Another point that should be noted is the incidence of secondary hematological malignancy, especially in HL patients. Death due to secondary cancers represents the most common cause of mortality among long-term survivors of HL.[25] The incidence of secondary hematological malignancies in our study was 5.2%. This rate appears to be similar to rates observed in other studies,[26,27] and although credited to the cytotoxic effects of alkylating agents, the role of cytogenetic instability related to the disease and autologous HSCT has yet to be determined, especially when we consider the significantly lower incidence of this complication in patients with NHL in our study (0.9%), treated under the same regimen.

Conclusions

This study has some limitations typical of retrospective studies. However, it can be concluded that despite the significant number of toxicity-related deaths, the data of this study suggest that this regimen is feasible, mainly for chemosensitive patients. The development of secondary neoplasia is a special concern in this setting, particularly for HL patients.

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