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

Introduction

The therapeutic of malignant lymphomas has undergone several advances through the last decades. Despite these advances, the management of relapsed and resistant patients with malignant lymphomas using conventional chemotherapy is disappointing. While patients with Hodgkin's lymphoma (HL) have a favorable outcome when treated with regimens such as ABVD, MOPP-ABV and BEACOPP, with complete remission (CR) rates as high as 95%, and cure rates of 60-85%.[1,2] Some patients with advanced disease and poor prognostic factors have a poor outcome, with disease free survival (DFS) of about 10%.[3-5]

As for the non-Hodgkin lymphomas (NHL), the management of relapsed and resistant patients using conventional chemotherapy, such as CHOP, is disappointing, with overall survival (OS) rates lesser than 10%.[6-8] Even with the introduction of monoclonal antibodies, specifically the anti-CD20 monoclonal antibody, rituximab, which has improved treatment of B-cell NHL, benefits are not clearly seen when it is used as salvage therapy.[9]

Within this context, high dose sequential therapy (HDS) followed by autologous hematopoietic stem cells transplantation (ASCT), remains as a valid treatment for patients with resistant and relapsed malignant lymphomas, playing an important role as an effective and feasible salvage therapy.[10-27] High-dose sequential chemotherapy (HDS) is a chemotherapeutic program with an intensified debulking phase consisting of the sequential administration of high-dose cyclophosphamide followed by high-dose etoposide, peripheral blood progenitor cells (PBPC) yield, HDT and ASCT.[28]

Nevertheless, there are few studies using this strategy in Brazil, and few groups evaluated the use of this therapy with follow-up periods longer than 5 years. Our aim was, therefore, to evaluate the effectiveness and toxicity of HDS used as a salvage therapy for malignant lymphomas, focusing on overall survival (OS), disease-free survival (DFS) and progression-free survival (PFS).

Methods

Seventy-seven patients diagnosed with relapsed or refractory HL and one hundred and six

patients diagnosed with high grade NHL were treated with HDS from May 1st, 1998 until November 30th, 2006 in three different institutions: Hemocentro – University of Campinas – Unicamp, Vera Cruz Hospital and Boldrini Children's Cancer Center. Data was obtained from the patients' medical records. Eligibility criteria included failure to achieve complete remission (CR) after first-line treatment (non-responsive, NR), relapsed disease, even when in CR before mobilization, and absence of psychiatric conditions. All patients or their legal representatives provided a written, informed consent form before receiving this regimen. Treatment procedures were approved by the committee on ethics in research from each participating institution, according to the principles of the Helsinki Declaration. HDS consisted of the sequential administration of high-dose cyclophosphamide (HDCY - 4 or 7 g/m^2 dose, decided upon clinical features of the patient during treatment, mainly age and cardiac function) and G-CSF (300 μg/day), followed by 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). Aphaeresis was performed after HDCY, aiming to collect ≥5×10^6 CD34$^+$ cells/kg. Patients with an insufficient number of CD34$^+$ underwent another collection after HDVP-16. After HDS, patients were conditioned with different regimens, including, BEAM (BCNU 300 mg/m^2; etoposide 800 mg/m^2; cytarabine 800 mg/m^2 and melphalan 180 mg/m^2), or CBV (cyclophosphamide 6 mg/m^2, BCNU 300 mg/m^2 and etoposide 600 mg/m^2) or Mito/Melph (mitoxantrone 60 mg/m^2 and melphalan 180 mg/m^2). Disease status was assessed with peripheral blood counts, hemossedimentation rate, muco-proteins, protein electrophoresis, and abdominal ultrasound or computerized tomography, depending on the sites of disease. These assessments were preferably done before HDCY, before ASCT, after ASCT and throughout the long-term follow-up (every three months in the first year, every six months in the second year and annually thereafter). CR was defined as the absence of clinical, laboratory or imaging findings (CT scan and Gallium 67 scintigraphy), confirming absence of neoplasia persisting for over 3 months. Partial remission (PR) was defined as a tumor mass reduction >50% after treatment. Non responsive (NR) disease was a tumor mass reduction <50%, and disease progression (DP) was defined as an increase in tumor mass after treatment or a new tumor mass or CNS infiltration during treatment. Relapsed disease (RD) was defined as the appearance of clinical, laboratory or imaging findings confirming the presence of new malignancy after CR had been achieved. PET/CT was not available for response assessment.

Data collection and statistical analysis

Patients were retrospectively analyzed using databases from each institution. Analysis was based on data of February 2009. OS was calculated from HDCY date until the date of death or last follow-up. DFS included only patients who achieved CR, being calculated from the date of CR assessment until the date of relapse, last follow-up or death. PFS included all patients and was calculated from HDCY date until the date of progression, relapse, last follow-up or date of death, no matter the cause. Dichotomous variables were compared using Fisher's test or Chi-square test, 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 forward stepwise Wald test. Two sided P values were considered statistically significant with values <0.05. Statistical analysis was performed using SPSS 15.0.

Results

Hodgkin's lymphoma

Seventy-seven patients with a median age of 23 (7-68) years at diagnosis were enrolled in this study, being 46 (59.7%) males and 31 (40.3%) females. Histopathological diagnosis according to WHO criteria[29] was: nodular sclerosis 50 patients (64.9%), mixed cellularity 19 (24.7%), lymphocyte depleted 5 (6.5%), lymphocyte predominant 1 (1.3%) and 2 (2.6%) patients unknown. At diagnosis, 50 patients (65%) presented with extensive disease (stage III or IV, according to the Ann Arbor System,[30] 55 (71.4%) had B symptoms, 10 (14.1%) had bone marrow involvement and 29 (39.7%) had bulky disease (≥10 cm). Table 1 shows the characteristics of these patients. Before HDCY, patients were treated with a median of two therapeutic lines, including conventional chemotherapy and radiotherapy. Three patients were in CR after treatment with conventional therapy for relapsed disease and 42 (54.5%) were in DP before mobilizing with HDCY.

Cyclophosphamide was administered after a median time of 1.5 years after diagnosis. Thirty patients (39%) received a dose of 4 g/m^2, due to advanced age (>65 years) or borderline cardiac function, and 47 patients (61%) received 7 g/m^2. The median day of leukapheresis after HDCY was +13 (range 8-27), with a median of 3 sessions (1-8) and a median number of harvested CD34$^+$ cells of 5.98×10^6($0.23\text{-}45.01\times10^6$) cells/kg.

After HDCY, twenty-four patients (31.2%)

Table 1. Patients' characteristics.

Features	*HL (n= 77)*		*NHL (n= 106)*	
Age at diagnosis: median/years (range)	23.1 (7.8-68.3)		45 (8-65)	
Age at HDCY: median/years (range)	25.8 (8.8-71.5)		47 (8-66)	
Gender				
Male	46	59.7%	66	62.3%
Female	31	40.3%	40	37.7%
Stage				
I+II	27	35.0%	18	17.0%
III	20	26.0%	15	14.1%
IV	30	39.0%	73	68.9%
B symptoms	55	71.4%	67	63.2%
Bone marrow involvement	10	14.1%	34	32.4%
Bulky disease	29	39.7%	65	61.9%
LDH - median (range)	387 (102-1257)		503 (113-4590)	
Therapeutic prior to CY/median (range)	2 (1-4)		2 (1-4)	
Cyclophosphamide dose				
4 g/m^2	30	39.0%	42	39.6%
7 g/m^2	47	61.0%	64	60.4%
Disease status before CY				
Complete remission	03	3.9%	06	5.7%
Partial remission	17	22.1%	38	35.8%
Disease progression	42	54.5%	46	43.4%
Relapsed	15	19.5%	16	15.1%
Overall survival - median months (range)	18 (0.1-128)		30 (0.2-124)	

were not able to perform ASCT. Twenty-one patients (27.3%) died after HDCY [7 (9.1%), from toxicity, 9 (11.7%) from DP, 4 (6.5%) from sepsis in DP and another 1 (1.3%) did not collect enough cells, developed myelodisplastic syndrome (MDS) and died from sepsis while in CR)], 1 did not raise enough stem cells to perform ASCT, 1 lost follow-up and 1 still awaits ASCT.

We obtained data on toxicity of 71 patients. Sixty-six patients (93%) had WHO grade IV toxicity for white blood cell counts, 37 (52.1%) had grade IV toxicity for hemoglobin, and 56 (78.9%) had grade IV toxicity for platelets. Forty patients (56.3%) experienced some kind of gastrointestinal toxicity. Nine patients (12.5%) presented cardiac toxicity. Seven patients (9.7%) developed acute renal failure not related to sepsis. Finally, 19 patients (26.7%) had fever of unknown origin.

Autografting was performed in 53 patients (68.8%), after a median of 118 days after HDCY (62-407). The median time for granulocyte (>0.5×10^9/L) and platelet (>20×10^9/L) engraftment was 11 days (9-27) and 17 days (6-88), respectively. Autograftment related mortality was 5.7% (3 out of 53): 2 from pulmonary hemorrhage and 1 from engraftment syndrome. OS for transplanted patients was 46% in 5 years. Twenty-nine patients died after ASCT: three from ASCT toxicity, 14 from DP, eight from sepsis while in DP, one from sepsis in CR, two developed acute myeloid leukemia (AML) and MDS, one patient was submitted to a reduced intensity conditioning allogeneic transplantation, and died due to extensive chronic GVHD in CR. Another patient developed MDS and is alive, adding up to 4 patients (5.2%) who developed AML/MDS. A total of 27 patients are alive, for a median of 66 months after HDCY (3-128). Eighteen patients (66.7%) are in CR, for a median of 70 months after HDCY (17-128). OS was 27% for all patients, with a median time of 18 months (0.1-128); DFS was 57%, with a median duration of 45 months (1.5-125); PFS was 25%, with a median duration of 13 months (0.1-128), as can be seen on Figure 1. We analyzed the survival of patients initially in DP (57-74%) according to their disease status before

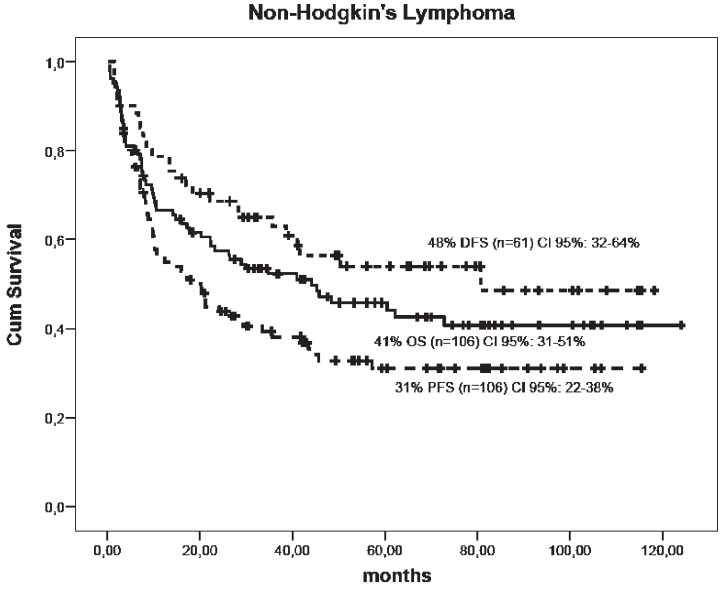

Figure 1. Kaplan-Meier survival analysis for non-Hodgkin lymphomas and Hodgkin's lymphoma.

HDCY. Patients who achieved CR after HDCY (24/57-42%) had a significantly better OS and PFS (36% and 33% respectively) than patients who remained in DP (10% and 17% respectively). We also analyzed survival data based on age, stage, histopathological findings at diagnosis and dose of cyclophosphamide. We did not observe any prognostic value in these variables. From the variables included in univariate analysis DP before HDCY (Hazard ratio 2.34, 95% CI 1.13-4.84, $p<0.02$) and after (HR 3.46, 95% CI 1.7-6.6, $p<0.0001$) was associated with worse OS, as was high LDH serum level (HR 2.37, 95% CI 1.22-4.60, $p<0.01$); as a continuous or as a categorical variable. As for the multivariate analysis two variables remained significant: LDH (as categorical variable - HR 2.41 95% CI 1.04-5.59, $p=0.04$) and DP after HDCY (HR 3.97 95% CI 1.73-9.10, $p=0.001$). These findings are summarized on Table 2.

In summary, 50/77 (65%) patients died; 23/50 (46%) from DP, 13/50 (26%) from sepsis, 7/50 (14%) had HDS-related deaths, 3/50 (6%) had ASCT-related deaths, 3/50 (6%) had AML/MDS and 1/50 (2%) had extensive chronic GVHD.

Table 2. Multivariate analysis for overall survival.

	NHL		
	Hazard ratio	*p-value*	*95% CI*
Variables			
B symptoms	2.26	0.01	1.2-4.2
LDH (abnormal)	1.93	0.02	1.1-3.3
DP after HDS	3.0	<0.0001	1.6-5.5
	HL		
DP after HDS	3.97	0.001	1.7-9.1
LDH (abnormal)	2.41	0.04	1.0-5.6

Non-Hodgkin Lymphoma

One hundred and six patients with a median age of 45 (8-65) years were enrolled in this study, being 66 (62.3%) male and 40 (37.7%) female. Histopathological classification according to WHO criteria[29] was: DLBCL 83 (78.3%) patients, T and Anaplastic 13 (12.3%) patients and Mantle cell 10 (9.4%) patients. At diagnosis, 88 (83%) patients presented with extensive disease (stage III or IV, according to the Ann Arbor Staging System[30]), 67 (63.2%) with B symptoms, 34 (32.4%) with bone marrow involvement, 65 (61.9%) had bulky disease and 45 (42.5%) had high-intermediate or high risk IPI31 (Table 1).

Before HDCY, patients were treated with a median of one therapeutic line, including conventional chemotherapy and radiotherapy. Six (5.7%) patients were in CR after their 1st relapse after treatment with conventional chemotherapy and 38 (35.8%) were in PR. More than half were in DP or refractory relapsed disease

Cyclophosphamide was administered after a median time of 10 months after diagnosis. Forty-two patients (39.6%) received a dose of 4 g/m^2 dose, due to advanced age (>65 years) or borderline cardiac function, and 64 patients (60.4%) received 7 g/m^2. The median leukapheresis day after the HDCY was +13 (range 3-83), with a median of 2 sessions (1-7) and a median number of harvested cells of CD34$^+$ of 6.74×10^6 ($1.29\text{-}44.01\times10^6$) cells/kg. One patient was not able to mobilize a sufficient number of PBPCs in order to autograft, having need for a surgical collection of progenitor cells directly from the bone marrow.

Twenty-six patients (24.5%) were not submitted to ASCT. Eighteen patients (16.9%) died [7 (6.6%) from HDS-related toxicity, 5 (4.7%) from DP, 5 (4.7%) from sepsis, while in DP and 1 (0.9%) from an unknown cause – death occurred at another facility, from whom information was not available], 3 (2.8%) did not consent ASCT, 1 (0.9%) was diagnosed with esophageal varices and became ineligi-

ble for the procedure, 3 (2.8%) still awaits ASCT and 1 (0.9%) for an unknown reason.

We were able to recover toxicity data from 102 (96.2%) patients. All patients presented some kind of hematologic toxicity. Ninety-four (88.6%) had WHO grade IV toxicity for WBC, 11 (10.4%) grade IV toxicity for hemoglobin and 66 (62.3%) grade IV toxicity for platelets. Forty-seven (44.3%) patients experienced some kind of gastrointestinal toxicity. Ten patients (9.4%) presented cardiac toxicity: 6 patients had asymptomatic reduction of the ejection fraction, 2 experienced clinical heart failure, 1 endured a severe pleural effusion that required immediate surgical drainage and 1 died in severe congestive heart failure. Four (3.8%) patients presented acute renal failure that was not due to sepsis. Finally, 27 (25.5%) patients presented fever of unknown origin.

ASCT was performed in 80 (75.5%) patients after a median of 123 (45-1710) days from HDCY. The median time for granulocyte engraftment (neutrophil count $>0.5\times10^9$/L) was 11 (6-29) days and 16 (5-70) days for platelet engraftment (platelet count $>20\times10^9$/L. Eleven patients (13.7%) died after ASCT: 1 from pulmonary hemorrhage, 6 from sepsis, 2 from interstitial pneumonia, 1 from herpetic encephalitis and 1 from cardiac toxicity. Twenty-six (24.5%) patients did not autograft, for the reasons mentioned above. Only six patients who were not submitted to ASCT are alive: 1 is in DP, 2 in CR and 2 in PR.

Eighty patients were submitted to autografting, after which 38/80 (47.5%) were in CR and 12/80 (15%) died, all from toxicity. Their overall survival was 45% in 8 years. Along the follow-up, another 35 patients died [4 CR, 1 PR, 2 RD and 28 PD], 11 of which (31.4%) had not performed ASCT

Until the closing date of this analysis, we have 49/106 (46%) alive patients, with a median observation time of 68 months. Whereas the OS was 41% for all patients; with a median time of 30 (0.2-124) months and PFS was 31%, with a median time of 16 (0.2-124) months (Figure 1) OS by B symptoms patients was 27% *vs.* 60% (p=0.003) and PFS was 24% *vs.* 40% (p=0.02).

We analyzed the survival of patients initially in DP or NR (62) according to their disease status after HDCY. Patients who achieved CR after HDCY (38) had a significantly better OS and PFS (44% and 27% respectively) than patients who remained in DP (24 patients with 0% and 0% respectively)

Survival was not affected by cyclophosphamide dose, with an OS for the 4 g/m^2 group of about 52% compared with an OS of 36% for the 7 g/m^2 group (p=NS). This was also noted for PFS and DFS, 42% and 64%, respectively for the 4 g/m^2 compared with 23% and 40%, respectively for the 7 g/m^2. We also analyzed the outcome of patients based on age, stage, histopathological findings at diagnosis and IPI and did not notice prognostic value in any of these variables.

From the variables included in univariate analysis, DP before (Hazard ratio: 2.56, CI 95%: 1.42-4.62 p<0.001) and after (Hazard ratio: 5.52, CI 95%: 3.01-10.1, $p\leq0.001$) HDCY were associated with worse OS.

On multivariate analysis, four variables related to disease at the time of diagnosis maintained their prognostic value for overall survival, they were: presence of B symptoms, LDH, and DP or relapse before HDCY. Two of these variables were also important on EFS: B symptoms and DP or relapse before HDCY (Table 2).

Overall, mortality was 57/106 (53.7%); their cause was 23/57 (40.4%) DP, 7/57 (12.3%) related to HDCY, 11/57 (19.3%) related to ASCT, 13/57 (22.7%) infections and 1/57 (1.8%) GVHD. In addition, 1/106 (1.8%) patient developed MDS and is alive.

Discussion

The aim of this study was to assess the use of HDS as salvage treatment for malignant lymphomas in a Brazilian cohort with long-term follow up. The intention of analyzing 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 series from the Northern hemisphere.[32-34] 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.

As a result of the greater prevalence of worse prognostic factors in our population, we observed different OS and PFS rates (29% and 26% for HL and 37% and 28% for NHL, respectively) compared to other studies, that reported OS and PFS ranging from 40-45% for HL[35-39] and 40-50% for NHL.[40-43]

We observed that patients previously in DP, who responded to HDCY and achieved a CR, had a better overall survival (for both NHL and HL), indicating a debulking effect of HDCY and its ability to overcome primary chemoresistance in a significant proportion of refractory patients. This benefit was not observed in patients not responding to HDCY, with a greater mortality among patients performing ASCT not in CR, as already observed by others.[28,35,44] These findings highlight the importance of HDS in assessing chemossensitivity for malignant lymphomas

These benefits, on the other hand, were associated with significant toxicity, and were not improved with the augmentation of HDCY dose, as patients receiving 7 g/m^2 did not perform better than patients receiving 4 g/m^2, for both HL and NHL.

Nevertheless, our study has some limitations typical of retrospective studies. However, we can conclude that despite the significant number of toxicity-related deaths, our data 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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