



High-dose sequential chemotherapy versus a less intensive regimen followed by peripheral blood autologous hematopoietic stem cell transplantation as salvage treatment in relapsed and refractory Hodgkin's disease

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A B S T R A C T

Background and Objective. High-dose sequential chemotherapy (HDS) has been given to patients with Hodgkin's disease (HD) before autologous hematopoietic stem cell transplantation (HSCT), but its effectiveness has not been evaluated in comparison with less-aggressive regimens. In this study we compared HDS with a less-aggressive regimen as preparation to autologous HSCT in patients with HD.

Design and Methods. Retrospective non-randomized comparison between patients receiving HDS (group 1, n=52) or a less-aggressive regimen (group 2, n=60). HDS consisted of the sequential administration of cyclophosphamide (7 g/m²) and G-CSF (300 µg/day) with stem cell collection, methotrexate (8 g/m²) plus vincristine (1.4 mg/m²), and etoposide (2 g/m²). Group 2 patients received of 2 cycles of DHAP, followed by cyclophosphamide (1.5 g/m²) plus G-CSF and stem cell collection.

Results. Group 1 patients were more likely to have stage IV (40% vs. 13%, $p=0.001$) and bulky disease (62% vs. 39%, $p=0.02$) at diagnosis. Disease status after chemotherapy improved in 59% in group 1 and 8% in group 2 ($p<0.001$), mostly in patients with disease progression (DP): 50% in group 1 (4 CR and 12 PR) and none in group 2 ($p<0.001$). Treatment-related toxicity occurred in 5/32 patients with DP in group 1, and 0/28 patients in group 2 ($p=0.01$). Overall survival was 49% in group 1 and 59% in group 2 ($p=0.098$).

Interpretation and Conclusions. HDS seems to be useful in patients with DP, whereas patients with CR do well with less-intensive chemotherapy.

Current treatment regimens for Hodgkin disease (HD) result in complete remission (CR) rates as high as 95%, and cure rates exceeding 80%,^{1,2} depending on the stage of the disease at presentation³ and other prognostic factors.⁴ In Brazil, the majority of patients have advanced disease at diagnosis, with a high incidence of bulky disease, bone marrow involvement and adverse prognostic factors.⁵⁻⁷ Patients with these features have poorer progression-free survival (~50%) with primary chemotherapy.^{4,8} Indeed, in a prospective multicenter study conducted in Brazil, the failure-free survival was 59%, although the overall survival was 81%.⁹ For those patients with refractory or relapsed HD, high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (HSCT) has become the standard therapy.¹⁰⁻¹² Recently, high-dose sequential chemotherapy (HDS) before autologous HSCT has been evaluated. In this approach, an intensified debulking phase consisting of sequential intensive chemotherapy precedes HSCT. Preliminary studies suggested that the use of this strategy may improve the out-

come without increasing significantly the toxicity.¹³⁻¹⁶ However, the lack of comparison between HDS and a more conservative strategy hampers any strong conclusion about the effectiveness of HDS. In this paper, we retrospectively compared the outcome of patients with relapsed or refractory HD who underwent an autologous HSCT in two Brazilian institutions that have different practices before HSCT: one using HDS (UNICAMP) and the other giving a less-intensive chemotherapy regimen (UFRJ).

Materials and Methods

Patients

One hundred and twelve consecutive patients with relapsed or primarily refractory HD after a primary standard chemotherapy received an autologous HSCT in the two institutions between January 1994 and July 2005. All patients were transplantation-eligible, with age <60 years, weight >30 kg and adequate organ function as defined by normal cardiac, renal, pulmonary and hepatic functions, Eastern Cooperative

Table 1. Baseline characteristics of patients.

	HDS (n= 52)	Non-HDS (n= 60)	p
Gender M:F	34:18	33:27	0.26
Age, median (range)	24 (9-71)	26 (11-56)	0.26
Histology			0.76
Nodular sclerosis	33 (64%)	42 (70%)	
Mixed cellularity	13 (25%)	11 (18%)	
Other	6 (11%)	7 (12%)	
Stage I-II	16 (31%)	26 (43%)*	0.002
Stage III	15 (29%)	22 (37%)	0.38
Stage IV	21 (40%)	8 (13%)	0.001
B symptoms	36 (69%)	42 (70%)	0.93
Bulky disease	32 (62%)	22 (39%)	0.02

*4 cases: unknown.

Oncology Group (ECOG) performance status ≤ 2 , negative tests for antibody against human immunodeficiency virus, human T-cell lymphotropic virus, B and C hepatitis virus, and free of active infection. All patients were staged at diagnosis according to the Ann Arbor System, and treated with conventional chemotherapy, including MOPP, C-MOPP, C-MOPP-ABVD and ABVD.

Treatment procedures and definitions

The therapeutic regimen at UNICAMP (group 1) consisted of the sequential administration of cyclophosphamide (7 g/m²) and G-CSF (300 µg/day) followed by stem cell yield, methotrexate (8 g/m²) plus vincristine (1.4 mg/m²), and by etoposide (2 g/m²). After HDS, the patients were conditioned with BEAM (BCNU 300 mg/m², etoposide 800 mg/m², cytarabine 1.6 g/m², melphalan 140 mg/m²), and received an autologous HSCT. The regimen at UFRJ (group 2) consisted of the administration of 2 cycles of DHAP (dexamethasone 40 mg/day on days 1-4, high-dose cytarabine 2 g/m² every 12 hours on day 2, and cisplatinum 100 mg/m² on day 1), followed by a mobilization with cyclophosphamide (1.5 g/m²) plus G-CSF and stem cell collection. The patients were then conditioned with CBV (cyclophosphamide 6 g/m², BCNU 300mg/m², etoposide 1.2 mg/m²), and received an autologous HSCT.

Disease status before HSCT was assessed at 2 time points: before HDS and before cyclophosphamide (first assessment) in group 1 and group 2, respectively, and before HSCT (second assessment) in both groups. Patients were classified as being in complete remission (CR) if there were no clinical manifestations of HD, evaluated by clinical exam and image methods (CT scan, Galium 67 schintigraphy), partial remission (PR) if there was a >50% reduction in tumor mass, and in disease progression (DP) if there was <50% or no response to treatment.

Data collection and statistical analysis

Patients were retrospectively evaluated using the database of each Institution. Analysis was based on data of July 2005. Overall survival (OS) was calculated from the beginning of salvage therapy until the date of death or last follow-up. Disease-free survival (DFS) applies only for patients in CR, and was calculated from the time of CR assessment to the date of relapse, last follow-up or death. Dichotomous variables were compared using Fisher exact test or Chi-square test. Actuarial curves of OS and DFS were estimated according to the Kaplan-Meier method, and compared by the log-rank test. Multivariate predictors of outcome (OS) were assessed by Cox regression analysis. P values were two-sided, and were considered statistically significant with values <0.05. All statistical analysis was performed using SPSS 11.0 (SPSS Inc., 1989-2001).

Results

Patient characteristics

One hundred and twelve patients were evaluated in the study, 67 males and 45 female patients. The median age was 25 years (range, 8 – 31 years). Histological classification according to WHO was: nodular sclerosis (70%), mixed cellularity (22%), lymphocytic depletion (4%) and lymphocyte predominance (4%). Most of patients (59%) had extensive disease (stage III/IV) at diagnosis. B symptoms were present in 78 patients (70%), and bulky disease in 52 (48%). At the time of the first assessment for transplant, 60 patients (54%) had DP after initial treatment, 38 patients (34%) had PR and 14 (12%) were in CR.

Table 1 shows the characteristics of patients in the two groups (52 patients in group 1 and 60 patients in group 2). The groups were comparable regarding gender, age and histologic classification. However, patients from group 1 were more likely to have stage IV (40% vs. 13%, $p=0.001$) and bulky disease (62% vs. 39%, $p=0.02$) at diagnosis.

Disease status in the first assessment (see definition above) showed a higher proportion of patients with DP in group 1 (61% vs. 47%) and of patients in CR in group 2 (18% vs. 6%), although the difference was not statistically significant ($p=0.09$).

Response rates before HSCT

Response rates before HSCT are shown in Table 2. The disease status after chemotherapy (HDS in group 1 and cyclophosphamide in group 2) improved in 24 of the 49 patients (59%) in group 1 compared to 4 of the 49 patients (8%) in group 2 ($p<0.001$). The most striking difference was in patients in DP: 16 of 32 patients

Table 1. Disease status before transplantation.

First assessment*	Second assessment**			
	Complete remission	Partial remission	Disease progression	Death
	Group 1 n=52			
Complete remission n=3	3 (100%)	0	0	0
Partial remission n=17	8 (47%)	8 (47%)	1 (6%)	0
Disease progression n=32	4 (9%)	12 (37%)	9 (28%) ^a	7 (22%) ^b
	Group 2 n=60			
Complete remission n=11	10 (91%)	0	1 (9%)	0
Partial remission n=21	3 (14%)	13 (62%)	4 (19%)	0
Disease progression n=28	0	0	28 (100%) ^a	0 ^b

* First assessment: before HDS in the HDS group and before cyclophosphamide in the non-HDS group; **Second assessment: before transplantation in both groups; ^a p=0.005; ^b p=0.004.

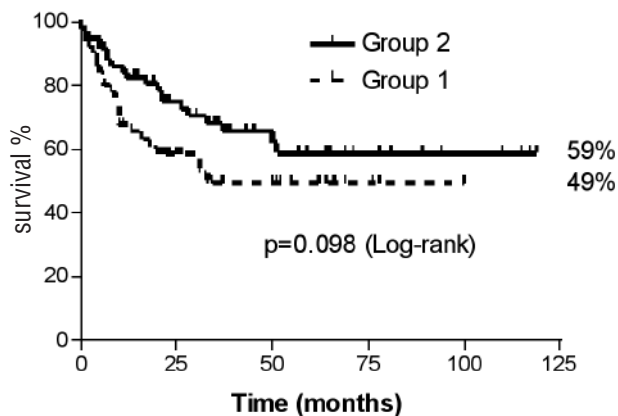


Figure 1. Overall survival of patients with Hodgkin's disease in the two groups.

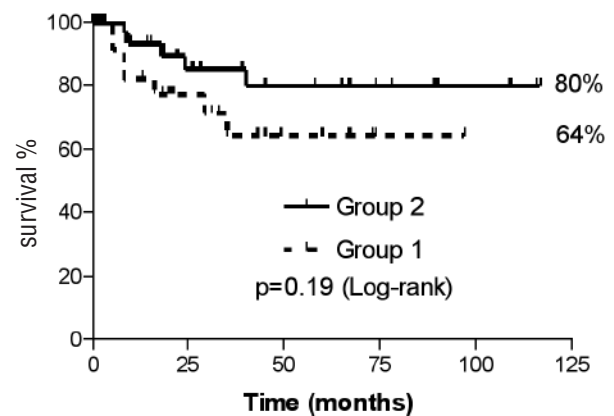


Figure 2. Disease-free survival among patients with Hodgkin's disease who obtained complete remission (26 patients in group 1 and 32 patients in group 2).

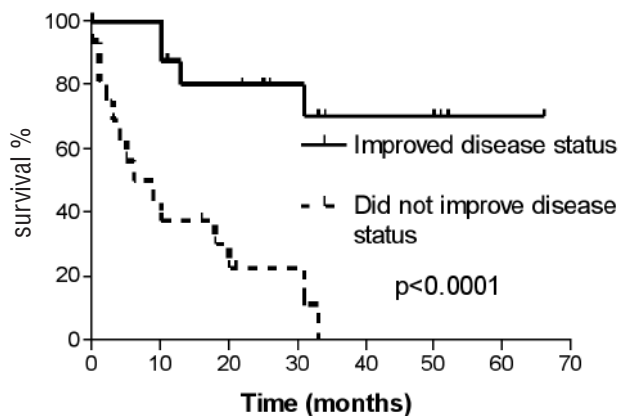


Figure 3. Overall survival of patients in group 1 with disease progression before HDS according to their response to HDS.

(50%) in group 1 improved (4 CR and 12 PR), compared to none of the 28 patients in group 2 ($p < 0.001$). On the other hand, 7 of the 32 patients with DP in group 1 died before HSCT (5 of toxicity related to treatment

and 2 of DP), compared to none of the 28 patients with DP in group 2 ($p = 0.01$). These differences in response after HDS (group 1) and cyclophosphamide (group 2) resulted in a similar proportion of patients in CR or PR by the time of HSCT (29% in group 1 vs. 22% in group 2, $p = 0.38$).

Outcome

The OS of the 112 patients was 54%, and was not different among the 2 groups: 49% in group 1, with a median survival of 33 months vs. 59% in group 2 (median survival not reached), $p = 0.098$ (Figure 1). The actuarial survival from HSCT was 59% in group 1 and 48% in group 2 ($p = 0.06$). DFS for patients who achieved CR (n=57, 51%) was 64% in group 1 and 80% in group 2 ($p = 0.19$) (Figure 2).

We analyzed the outcome of patients with DP in group 1. Patients who improved their disease status after receiving HDS had a significantly better OS than patients who remained in DP (Figure 3).

By univariate analysis, being in complete remission

both in the first ($p=0.057$) and in the second assessment ($p=0.059$), as well as belonging to group 2 ($p=0.098$) were marginally associated with better survival. In multivariate analysis that included stage IV and bulky disease (the two variables that were significantly different in the baseline characteristics of the two groups), disease status before HSCT was the single variable associated with longer survival (Hazard ratio 2.43, 95% confidence interval 1.20–4.93, $p=0.01$), and belonging to group 2 was not significant (Hazard ratio 1.36, 95% confidence interval 0.96–1.94, $p=0.085$).

Causes of death

The regimen of HDS was associated with a death rate of 13% (7 of 52 patients). By contrast, no patient in group 2 died before HSCT ($p=0.004$). Death was associated with infection in 4 cases, toxicity other than infection in 1 and disease progression in 2. All deaths occurred in patients with DP. The death rate at day 40 after HSCT was not 9% in group 1 and 5% in group 2 ($p=0.46$). Similarly, the death rates at the last follow-up were not different (42% in group 1 and 28% in group 2, $p=0.14$), with most patients dying from disease progression.

Discussion

Our study yielded several findings. The use of HDS was associated with a significant improvement in disease status (59% compared to 8% in group 2). On the other hand, this strategy was associated with significant toxicity, with an overall death rate of 13% (compared to zero in patients receiving a less-aggressive regimen), especially in patients with DP (22% death rate). However, patients with DP were those who obtained the best benefit of HDS, since 50% of these patients responded to HDS, and improved their disease status by the time HSCT was performed. This reflected on the OS: patients with DP before HDS who improved their disease status with HDS had a significantly better OS than patients who remained in DP. By contrast, none of DP patients who received a less-intensive chemotherapeutic regimen (group 2) changed their disease status. In this context, it seems that in patients with DP, HDS selects the best and the worst: in those who respond, the OS is increased significantly, and those who do not respond have a high risk to die due to toxicity or disease progression. These findings suggest that HDS is able to overcome primary chemo-resistance in a significant proportion of refractory patients.

High-dose chemotherapy followed by autologous HSCT has become an attractive option for patients

with HD who failure to achieve CR, or relapse after first-line chemotherapy.^{10,11} An important factor that impacts on the outcome after HSCT is a reduction in tumor with conventional salvage therapy prior to HSCT.¹⁷ In this context, sequential HDS has been employed as preparative regimens before HSCT, but the lack of randomized studies hampers any conclusion about its effectiveness in comparison with a less-aggressive regimen. The potential benefit of HDS in reducing tumor burden before HSCT is counter balanced by the potential increase in toxicity, as well as the possibility of second malignancies. In a multicenter phase II study, 102 patients were treated with HDS followed by autologous HSCT. The OS was 78%, and only 2 patients (2%) died due to toxicity of the regimen.¹⁶ In another study, 102 patients were treated with another HDS schedule, followed by HSCT. Six patients developed a second malignancy and 5 patients (5%) died for causes related to the toxicity of HDS.¹⁵ These low rates of treatment-related mortality contrast with the 10% rate (5 of 52 patients) observed in the present study.

Our study has many limitations. The first and most important is its retrospective nature. Furthermore, the two groups had important baseline differences that may impact on the outcome, limiting the comparative analysis. With this regard, we cannot conclude that a more conservative approach is as effective as HDS, but it is reasonable to conclude that it is much less toxic. Regarding HDS, our data suggest that patients with DP may benefit from this strategy. On the other hand, patients in CR do very well with less-intensive chemotherapy, with high OS and DFS. Future studies in our population of patients are needed to better characterize DP patients at risk to die from toxicity, in order to implement preventive measures. Finally, randomized clinical trials are needed to determine the role of HDS in the treatment of HD.

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