

## Autologous hematopoietic stem cell transplantation in classical Hodgkin's lymphoma

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**Background:** Hodgkin's lymphoma has high rates of cure, but in 15% to 20% of general patients and between 35% and 40% of those in advanced stages, the disease will progress or will relapse after initial treatment. For this group, hematopoietic stem cell transplantation is considered one option of salvage therapy.

**Objectives:** To evaluate a group of 106 patients with Hodgkin's lymphoma, who suffered relapse or who were refractory to treatment, submitted to autologous hematopoietic stem cell transplantation in a single transplant center.

**Methods:** A retrospective study was performed with data collected from patient charts. The analysis involved 106 classical Hodgkin's lymphoma patients who were consecutively submitted to high-dose chemotherapy followed by autologous transplants in a single institution from April 1993 to December 2006.

**Results:** The overall survival rates of this population at five and ten years were 86% and 70%, respectively. The disease-free survival was approximately 60% at five years. Four patients died of procedure-related causes but relapse of classical Hodgkin's lymphoma after transplant was the most frequent cause of death. Univariate analysis shows that sensitivity to pre-transplant treatment and hemoglobin < 10 g/dL at diagnosis had an impact on patient survival. Unlike other studies, B-type symptoms did not seem to affect overall survival. Lactic dehydrogenase and serum albumin concentrations analyzed at diagnosis did not influence patient survival either.

**Conclusion:** Autologous hematopoietic stem cell transplantation is an effective treatment strategy for early and late relapse in classical Hodgkin's lymphoma for cases that were responsive to pre-transplant chemotherapy. Refractory to treatment is a sign of worse prognosis. Additionally, a hemoglobin concentration below 10 g/dL at diagnosis of Hodgkin's lymphoma has a negative impact on the survival of patients after transplant. As far as we know this relationship has not been previously reported.

**Keywords:** Hodgkin's lymphoma; Hematopoietic stem cell transplantation; Autologous transplantation; Doxorubicin; Bleomycin; Vinblastine; Dacarbazine; Study retrospective

### Introduction

Classical Hodgkin's lymphoma (cHL) is a disease that has one of the highest cure rates of all human cancers with long survival when patients are submitted to first-line treatment protocols which involve multiple chemotherapeutic agents with or without radiation such as the ABVD protocol. The ABVD protocol consists of four to six 28-day cycles of doxorubicin 25 mg/m<sup>2</sup>, bleomycin 10 mg/m<sup>2</sup>, vinblastine 6 mg/m<sup>2</sup> and dacarbazine 375 mg/m<sup>2</sup> on days one and 15 of each cycle. The four drugs, administered intravenously, have few immediate toxic effects.<sup>(1)</sup> More intense treatment protocols, such as escalated BEACOPP, an association of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone, promote a higher initial remission rate and increased disease-free survival in patients in advanced stages of disease. However the toxic effects and treatment-related mortality are higher.<sup>(2)</sup> Early stages of the disease allow treatment with few cycles of chemotherapy and low dose radiation, thereby minimizing long-term side effects.<sup>(3)</sup> Despite the effectiveness of existing regimens, it has been reported in the literature that about 20% of patients in early disease stage and 35% to 40% of patients with advanced disease will have disease progression or relapse after the initial treatment.<sup>(4)</sup> It is well known that these patients will not have good survival when treated with conventional chemotherapy in particular those considered primary refractory patients and that have early relapse, i.e. within 12 months of initial treatment.<sup>(5)</sup> In order to improve treatment outcomes for this group of patients, autologous hematopoietic stem cell transplantation (HSCT) has been used in refractory and relapsed cHL cases. Today there is

ample documentation of the effectiveness of this approach<sup>(6)</sup> particularly in two randomized studies, the British National Lymphoma Investigation (BNLI)<sup>(7)</sup> and Germany's Lymphoma Study Group (GHSG).<sup>(8)</sup>

Except for response to treatment of the disease prior to HSCT, no other predictive factor was found with an impact on survival in all the publications analyzed.<sup>(9)</sup> With data from a single treatment center in Brazil, the objective of this study was to evaluate patient survival and to identify possible predictors of survival, major treatment-related toxic effects and causes of death.

## Methods

This is a retrospective study with data obtained from patient charts. Analysis involved 106 patients with cHL who were consecutively submitted to high-dose chemotherapy followed by autologous HSCT in a single institution from April 1993 to December 2006. Patients were followed up until December 2007, i.e. twelve months after concluding enrolment in the study; thus the mean follow up time was 47.5 months (12-178 months). For all patients, the bone marrow had no evidence of infiltration by cHL at HSCT as proven by histopathological studies of samples obtained from at least one posterior iliac crest.

After diagnosis patients were submitted to conventional treatment protocols with the MOPP protocol (six 28-day cycles of mechlorethamine 6 mg/m<sup>2</sup>, vincristine 1.4 mg/m<sup>2</sup>, procarbazine 100 mg/m<sup>2</sup> on the first day and prednisone 40 mg/m<sup>2</sup> for five days on days one and eight of each cycle), with ABVD or an association of both being used in 97 patients (91.5%). Involved-field radiotherapy was used as adjuvant treatment for 65% of patients with extensive tumor mass ("bulky").

Complete remission was defined as the absence of tumor for at least four weeks after the completion of chemotherapy pre-HSCT while partial remission was defined as a reduction in over 50% of the volume of the regions affected by the tumor for at least four weeks after chemotherapy without the appearance of new tumor-related lesions.

Patients were stratified as responders to treatment used prior to HSCT when they attained a reduction of more than 50% of the initial tumor in the pre-transplant period (61.9% of cases) and refractory for those who had less than 50% reduction in tumor involvement in the pre-HSCT period (38.1%).

Of the responders, 54 patients were in second complete remission (85%), four in second partial remission, four in third complete remission and one in first partial remission. Pre-HSCT high-dose salvage chemotherapy was performed in 45 patients (42.4%) using regimens based on ifosfamide with etoposide (53.33%), cytarabine with dexamethasone (22.22%) and ifosfamide with gemcitabine (24.44%); 61 patients (57.54%) did not receive salvage chemotherapy. The mobilization of hematopoietic stem cells was attained in 83 patients (78%) with cyclophosphamide 60 mg/kg on two

consecutive days followed by granulocyte colony stimulating factor (G-CSF) at doses of 6 to 17 mcg/kg. For 25 patients (22%), mobilization failed and collection was achieved by multiple bone marrow aspirations. The resulting cells were cryopreserved for use to rescue bone marrow function after conditioning. The conditioning protocols used were BEAM (BCNU 300 mg/m<sup>2</sup> on D-1, cytarabine 400mg/m<sup>2</sup> from D-2 to D-5, etoposide 200 mg/m<sup>2</sup> from D-2 to D-5 and melphalan 140 mg/m<sup>2</sup> on D-6) in 55.38% of patients and CVB (BCNU 300 mg/m<sup>2</sup> on D-7, etoposide 200 mg/m<sup>2</sup> on D-6 to D-3 and cyclophosphamide 60 mg/m<sup>2</sup> on D-2 and D-1) in 27.35% of patients. MVB (a regime that substituted cyclophosphamide for melphalan at a dose of 140 mg/m<sup>2</sup> on D-1) was used for 12.26% of the patients and 4.71% received other conditioning regimens.

The World Health Organization toxicity grading scale, graduated from 0 to 4<sup>(10)</sup> was used to study the toxic effects of HSCT. The first day of two consecutive days with leukocyte counts above 1 x 10<sup>9</sup> cells/L or granulocytes above 0.5 x 10<sup>9</sup> cells/L, or platelets greater than 20 x 10<sup>9</sup> cells/L without transfusion within the previous seven days was considered the time of bone marrow engraftment. Death that occurred before D+100 after infusion of cryopreserved bone marrow cells was considered transplant related. A CD34 cell count by flow cytometry was used to quantify hematopoietic precursor cells harvested and infused in the patient.

This study was approved by the Ethics Committee for the Analysis of Research Projects (CAPPESQ) of the Hospital of the Medicine School, Universidade de São Paulo (number 0332/09 and Resolution 196/96 of the National Health Council). Survival was analyzed using the Kaplan-Meier method<sup>(11)</sup> with multivariate analysis by the Cox model to evaluate prognostic factors for survival. Statistical significance was considered for a p-value < 0.05. Calculations of percentages, means and medians were used when necessary.

## Results

Autologous HSCT for cHL accounted for about 7% of 2067 indications for transplantation performed up to December 2006 at Hospital das Clínicas and about 20% of all autologous transplants in this period. The main characteristics of this transplant population are listed in Table 1. The overall survival rates of this population at five and ten years were 86% and 70%, respectively. The disease-free survival was approximately 60% at five years.

A median of 2.6 x 10<sup>6</sup> CD34<sup>+</sup> cells per kg of body weight was collected utilizing mobilization with a median time to engrafting of 12 days. There was no difference in survival in relation to the conditioning regimens employed (p=0.17). The mobilization of hematopoietic precursor cells in peripheral blood collection was unsuccessful for about a quarter of patients, so for these harvesting was by bone marrow aspiration.<sup>(12)</sup>

Table 1 - Main characteristics of the surveyed population

Characteristic	Result	Nº of patients
Median age - years (range)	28 (6 - 59)	104
Gender (%)		106
Male	51.9%	
Female	48.1%	
Ethnic background (%)		105
White	87.6%	
Black	11.4%	
Disease stage at diagnosis (%)		105
I	1.0%	1
II	50.5%	53
III	19.0%	20
IV	29.5%	31
Hemoglobin concentration at diagnosis (g/dL)	87	
Median (range)	11.9 (7.6 - 16.2)	
B-type symptoms at diagnosis		105
Absent	24.8%	26
Present	75.2%	79
Tumoral size > 10 cm at diagnosis		105
Absent	65.7%	69
Present	34.3%	36
Hemoglobin < 10 g/dL at diagnosis	87	
Absent	74.7%	65
Present	25.3%	22
Time to relapse after initial treatment	63	
Relapse ≤ 1 year	5.7%	6
Relapse > 1 year	56.2%	57
Number of CD34 cells obtained		
Median	2.6 (0.2 - 10.8)	

Univariate analysis (Table 2) shows that sensitivity to pre-HSCT treatment and hemoglobin < 10 g/dL at diagnosis had an impact on patient survival. Unlike other studies, B-type symptoms did not affect overall survival. Lactic dehydrogenase and serum albumin concentrations analyzed at diagnosis did not influence patient survival either.

Four patients had died by D+100 after HSCT (3.74%). The causes were severe systemic infection in three cases and one case of bronchiolitis probably due to the use of a chemotherapeutic agent.

Relapse of cHL after HSCT was the most frequent cause of death. Of the 24 deaths after D+100, cHL as a cause, that is, progression after ASCT, accounted for 13 cases (54%). Septicemia was the cause of death in four patients (6.6%). One patient died of acute myocardial infarction, one from pneumonia, one by bleeding of the colon followed by hypovolemic shock, one by systemic aspergillosis and one had respiratory failure of undefined cause. In two cases the exact cause of death was not identified. Myelodysplastic syndrome (MDS), classified as multilineage dysplasia, diagnosed two years after the HSCT, was considered a late

Table 2 - Factors evaluated and their impact on survival after hematopoietic stem cell transplantation (Univariate Analysis)

Variable	Category	p-value
Gender	Male vs. female	0.2213
Disease stage	I/II vs. III/IV	0.3513
Condition of disease for indication of autologous HSCT	Refractory disease Relapse in ≤1 year Relapse in > 1 year	0.5832
B-type symptoms at diagnosis	Present vs. Absent	0.0554
Tumoral mass >10 cm at diagnosis	Present vs. Absent	0.7208
Pre-transplant anemia (Hb < 10 g/dL)	Present vs. Absent	0.0239*
Response to chemotherapy	Responsive vs. Non-responsive	0.0095*

HSCT = hematopoietic stem cell transplantation; \* data with statistical significance; Hb = hemoglobin

treatment-related complication of one patient who was still alive at the end of the study period.

Fever was the most frequent complication in the first 100 days after HSCT, present in 91.5% of patients. Fever without identified focus (38.7%), proven bacterial infection (27.37%), catheter infection (11.3%), sepsis (6.6%), systemic candidiasis (3.77%), aspergillosis (1.88%) and cytomegalovirus infection (1.88%) were reported.

## Discussion

Patients with cHL refractory to treatment and those that suffer relapse are problematic; on comparing current treatment strategies, autologous HSCT provides the best results for these individuals. In this study, the overall survival at five years was around 80% with evidence of low toxicity and procedure-related mortality. Figure 1 shows the overall survival curve after autologous HSCT of patients diagnosed with cHL.

Today this group of patients can be treated, from a practical standpoint, with conventional chemotherapy followed by high dose chemotherapy and autologous or allogeneic HSCT, as well as with experimental therapies, often involving specific monoclonal antibodies and/or palliative radiotherapy. High-dose chemotherapy gives different results when applied to patients with minimal disease compared to patients with extensive areas of tumor; survival at three years ranges from 70% in the former group compared to only 15% for patients of the latter.<sup>(13)</sup> Primary refractory cases and those with early relapse, i.e. within 12 months of initial treatment, do not respond well to conventional treatment;<sup>(14)</sup> Bonadonna et al. reported less than 15% of these patients had disease-free survival at five years.<sup>(15)</sup>

The use of conventional salvage therapy achieved cure rates of less than 20% in the various series of published cases.<sup>(16)</sup> The results of this study showed that patients with relapsed and refractory cHL benefit from autologous HSCT.

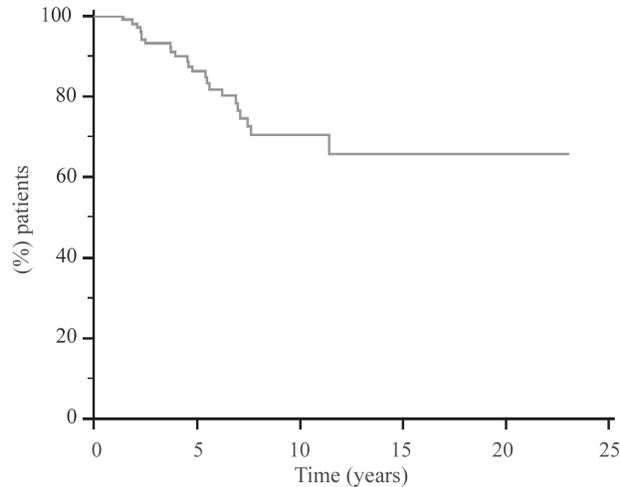


Figure 1– Overall survival of patients with classic Hodgkin's lymphoma after autologous hematopoietic stem cell transplantation (n = 105)

In regard to prognostic factors, serum hemoglobin concentrations below 10 g/dL at diagnosis had a negative impact on survival; this has not been reported in any other publications and should thus be confirmed in future studies (Figure 2). The worse outcomes correlated with the presence of B-type symptoms as reported by other authors was not confirmed in our study. However, response to pre-transplant chemotherapy was the main determinant of improved survival after HSCT, as illustrated in Figure 3.

Refractory cases could benefit from a more intense initial approach, as a more precise diagnosis can be attained today through studies using positron emission tomography.<sup>(17,18)</sup> Sureda et al., on analyzing 494 cHL patients submitted to HSCT by the Spanish Lymphoma Study Group, also noted that chemosensitivity is an important variable that determines response to HSCT. These authors even suggested that refractory patients should be treated more aggressively in the early stages of treatment.<sup>(19)</sup> The group at Seattle's Fred Hutchinson Cancer Research Center, in a study published in 2008 that analyzed 167 patients with refractory cHL submitted to HSCT, failed to define any predictors of survival in this group. They concluded, however, that HSCT can be performed in refractory patients, but only one in three patients will survive more than five years.<sup>(9)</sup>

Due to the high number of CD30 cells expressed in cHL, this is considered a promising disease for targeted monoclonal therapy with the use of anti-CD30 antibodies. Some forms of humanized antibodies have been tested in clinical trials but showed low response rates and caused grade II and III pulmonary and hepatic toxicity and suppression of bone marrow function when used as therapy in isolation,<sup>(20)</sup> thus they give worse outcomes than HSCT.

Radiotherapy may be useful as adjuvant therapy in the treatment of localized relapse, but without a complete cure being expected. Lymphomas are malignant tumors that are highly sensitive to radiotherapy, especially cHL.<sup>(21)</sup> Allogeneic

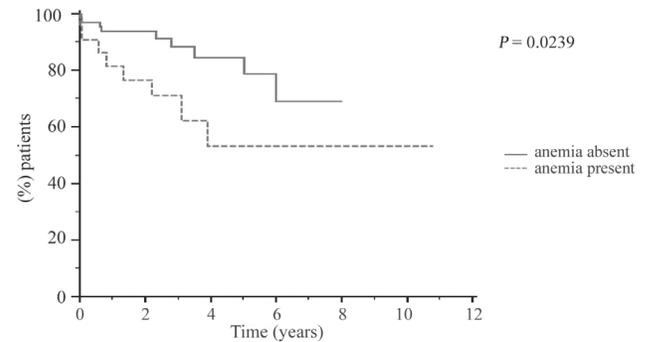


Figure 2 – Hemoglobin less than 10 g/dL at diagnosis and survival after hematopoietic stem cell transplantation (n = 105)

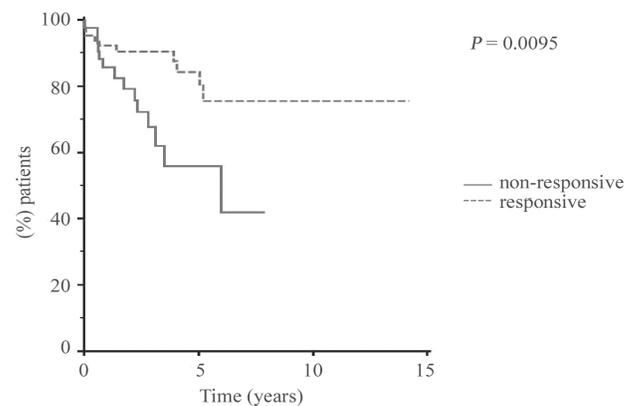


Figure 3 – Survival after hematopoietic stem cell transplantation according to response to pre-transplant chemotherapy (n = 105)

transplants, even with reduced conditioning doses, should be reserved for selected refractory cases and patients that relapse after autologous transplants because the higher mortality rate in cHL patients makes indication a difficult decision.<sup>(22)</sup> Survival does not seem to be higher than in autologous transplants due to the high rate of procedure-related mortality, in spite of the biological graft-versus-lymphoma effect.<sup>(23)</sup>

## Conclusion

We believe that autologous HSCT is an effective treatment strategy for early and late relapse in cHL cases that are responsive to pre-HSCT chemotherapy, giving an overall survival rate of greater than 80% at five years. Patients are tolerant to the BEAM and CVB conditioning regimens and in our series of patients the mortality rate within one hundred days of HSCT was 3.74%. Patients who are refractory to primary treatment do not exhibit the same response as those who responded to pre-HSCT chemotherapy, and thus refractory to treatment is a sign of worse prognosis.

The presence of hemoglobin concentrations below 10 g/dL at diagnosis of cHL is a negative impact factor on the survival of patients after HSCT. We did not find any mention of this relationship in the literature but according to the sample in this study we believe that the hemoglobin level at diagnosis may be a possible predictive factor of poor prognosis, which should be taken into account when indicating HSCT.

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