ORIGINAL ARTICLE

Autologous stem-cell transplantation in Hodgkin's lymphoma: analysis of a therapeutic option

Transplante autólogo de células-tronco em linfoma de Hodgkin: análise de uma opção terapêutica

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ABSTRACT

Objective: To report the clinical progress of patients with Hodgkin's lymphoma treated with autologous transplantation after failure or relapse of first-line treatment with chemotherapy and/or radiation therapy. **Methods:** The results of a retrospective analysis of 31 patients submitted to autologous transplantation as second-line treatment, between April 2000 and December 2008, were analyzed. Fourteen men and seventeen women, with a median age of 27 years, were submitted to autologous transplantation for relapsed (n = 21) or refractory (n = 10) Hodgkin's lymphoma. **Results:** Mortality related to treatment in the first 100 days after transplant was 3.2%. With a mean follow-up period of 18 months (range: 1 to 88 months), the probability of global survival and progression-free survival in 18 months was 84 and 80%, respectively. The probability of global survival and progression-free survival at 18 months for patients with chemosensitive relapses (n = 21) was 95 and 90%, respectively, *versus* 60 and 45% for patients with relapses resistant to chemotherapy (n = 10) (p = 0.001 for global survival; p = 0.003 for progression-free survival). In the multivariate analysis, absence of disease or pre-transplant disease < 5 cm were favorable factors for global survival (p= 0.02; RR: 0.072; 95%CI: 0.01-0.85) and progression-free survival (p= 0.01; RR: 0.040; 95%CI: 0.007-0.78). **Conclusion:** Autologous transplantation of stem-cells is a therapeutic option for Hodgkin's lymphoma patients after the first relapse. Promising results were observed in patients with a low tumor burden at transplant.

Keywords: Hematopoietic stem-cell transplantation/drug therapy; Hodgkin's disease; Recurrence

RESUMO

Objetivo: Relatar a evolução dos pacientes com linfoma de Hodgkin tratados com transplante autólogo após falha ou recidiva do tratamento de primeira escolha com quimioterapia e/ou radioterapia. **Métodos:** Foram analisados os resultados de uma análise retrospectiva em 31 pacientes submetidos a transplante autólogo como terapia de segunda escolha, entre Abril de 2000 e Dezembro de 2008. Quatorze homens e dezessete mulheres, com idade mediana de 27 anos, foram submetidos a transplante autólogo por linfoma de Hodgkin após recidiva (n = 21) ou por refratariedade (n = 10). **Resultados:** A mortalidade relacionada ao tratamento nos primeiros 100 dias pós-transplante foi de 3,2%. Com um acompanhamento médio de 18 meses (variação: 1 a 88), a probabilidade de sobrevida global e sobrevida livre de progressão em 18 meses foi de 84 e 80%, respectivamente. A probabilidade de sobrevida global e sobrevida livre de progressão aos 18 meses para pacientes com recidivas quimiossensíveis (n = 21) foi de 95 e 90%, respectivamente, *versus* 60 e 45% para os pacientes com recidiva resistente à quimioterapia (n = 10) (p = 0,001 para sobrevida global; p = 0,003 para sobrevida livre de progressão). Na análise multivariada, a ausência de doença ou doença pré-transplante < 5 cm foi um fator favorável para a sobrevida global (p= 0,02; RR: 0,072; IC95%: 0,01-0,85) e sobrevida livre de progressão (p= 0,01; RR: 0,040; IC95%: 0,007-0,78). **Conclusão:** O transplante autólogo de células-tronco constitui uma opção terapêutica para pacientes com linfoma de Hodgkin após uma primeira recaída. Resultados promissores foram observados em pacientes com baixa carga tumoral ao transplante.

Descritores: Transplante de células-tronco hematopoiéticas/quimioterapia; Doença de Hodgkin; Recidiva

INTRODUCTION

Hodgkin's lymphoma (HL) is considered a curable disease in approximately 75% of the cases. However, 10 to 15% of patients with localized and 25 to 30% with disseminated classical HL fail to respond or relapse after

Study carried out at Hospital Araújo Jorge – HAJ, Goiânia (GO), Brazil.

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primary conventional treatment with chemotherapy alone or combined with radiation therapy[1,2].

Patients with HL who experience disease progression after doxorubicin-based chemotherapy (primary refractory HL) and those whose disease relapses after a complete response have a second chance of cure with autologous stem-cell transplantation (ASCT). High-dose therapy followed by ASCT has been frequently used to treat this group of patients, with a 5-year survival free of progression or relapse of 40 to 60%[3-6].

ASCT is now considered the standard of care for most patients with refractory and relapsed HL. Two randomized trials testing multi-agent chemotherapy compared to intensification with high-dose carmustine, etoposide, cytarabine and melphalan (BEAM) showed major event-free survival for patients receiving the intensive chemotherapy supported by ASCT (53 *versus* 10%)[7,8].

OBJECTIVE

In order to determine prognostic factors for a successful outcome, data were collected and analyzed on the first patients who underwent ASCT for HL at Hospital Araújo Jorge (HAJ), in Goiânia (GO), Brazil.

METHODS

Patient characteristics

This was a retrospective cohort analysis. From November 2000 to December 2008, a total of 31 consecutive patients underwent ASCT for HL at HAJ. Patients were staged according to the Ann Arbor system.

MOPP/ABV hybrid chemotherapy (mechlorethamine, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, and vinblastine) was the first-line treatment until 2002. After this year, patients were treated with ABVD chemotherapy (adriamycin, bleomycin, vinblastine, dacarbazine). Data related to radiation therapy included field (mantle, para-aortic, spleen) and local irradiation. The radiation dose was based on the occurrence of bulky disease and the Ann Arbor staging, with total doses between 20 and 36 Gy.

All patients were submitted to a response evaluation (both clinical and radiological) in the middle and at the end of planned initial treatment. At relapse, treatment varied depending on prior chemotherapy used. Patients received well-described regimens of treatment before the ASCT: ICE (ifosfamide, carboplatin and etoposide); DHAP (ARA-c, cisplatin and dexamethasone); and GDP (gemcitabine, dexamethasone and cisplatin).

Status at the time of ASCT was categorized as follows: in chemosensitive complete remission, there were patients with no clinical or radiological evidence of disease; in chemosensitive partial remission, there were patients with > 50% reduction in size of the tumor on a computed tomography scan. Patients who did not fit any of these criteria were classified as having resistant disease.

Mobilization

On the 5º day after the start of the 3º cycle of salvage chemotherapy, patients were stimulated with granulocyte colony stimulating factor (G-CSF) to collect peripheral blood (PB) progenitor cells by aphaeresis. Patients who did not achieve the minimum target of 2 x 10^6 CD34 cells/kg were eligible to undergo cyclophosphamide 4g/m^2 and G-CSF 10 μg/kg, at the 5º day of the start of mobilization. If patients failed again, bone marrow (BM) was harvested as long as it was of adequate cellularity and free of disease, with a minimum target of 2 x 10^8/kg of total nucleated cells.

Before high-dose chemotherapy and transplantation, all patients were required to have adequate hematological, renal, hepatic, pulmonary, and cardiac functions.

High-dose chemotherapy

From November 2000 to July 2002, three patients received TBI-based preparative regimen. The regimen included cyclophosphamide 60 mg/kg on days - 5, - 4 (total dose: 120mg/kg), and fractionated TBI 1200 cGy at 200 cGy per fraction, with lung blocks from day -3 to -1. After July 2002, all patients received the conditioning regimen of BEAM chemotherapy (carmustine 300 mg/m^2 IV on day -6; etoposide 200 mg/m^2 IV daily, for 4 days, on days -5, -4, -3, and -2; Ara-C 200 mg/m^2 IV, q 12 h (twice a day) daily for four days, on days - 5, -4, -3, and -2; and melphalan 140mg/m^2 IV on day -1. Stem-cell reinfusion was performed on day 0 and G-CSF 300 mg SC, twice a day, was started from day 1 until engraftment in both conditioning regimens.

Statistical analysis

Overall survival (OS) was measured from the date of ASCT to the date of death from any cause. Progression-free survival (PFS) was measured from the date of ASCT to time of progression or death from any cause or last follow-up. Non-relapse mortality was defined as death from any cause other than HL. Survival analysis was carried out according to the Kaplan-Meier method. Multivariate analysis was done using a forward stepwise Cox proportional hazards model. Statistical analyses were computed by means of the Statistical Package for the Social Science (SPSS).

Prognostic factors analyzed for both PFS and OS were number of treatment lines before ASCT (≤2 *versus* > 2), serum albumin level (< 4 g/dL *versus* ≥ 4 g/dL), source of stem-cells (marrow *versus* PB stem-cells), disease *status* at ASCT (chemosensitive – CR + PR *versus* resistant), and bulky disease ≥ 5 cm (yes *versus* absent/< 5cm). In order to better predict the outcome in this group of patients, the International Prognostic Index (Hasenclever index)[9] was included in the analysis at the time of ASCT. This index incorporates seven prognostic factors: serum albumin level < 4 g/dL, hemoglobin < 10.5 g/dL, male sex, age ≥ 45 years, stage IV, leukocytosis (≥ 15 × 10^9/L), and lymphocytopenia (< 0.6 × 10^9/L, < 8% of white cells, or both). Patients were divided into groups of those with zero to two or with three or more factors.

All patients and/or their parents provided written informed consent for salvage chemotherapy, related procedures, and ASCT. The ASCT protocol was approved by the Institutional Review Board of HAJ.

RESULTS

Patient and disease characteristics of the 31 patients at the time of initial diagnosis of HL and at progression are summarized on table 1. The median age at initial diagnosis was 27 years (range: 8 to 51 years), and 54.8% of the patients were male. Nodular sclerosis HL was the most common histology (65%). Commonly used first-line chemotherapy regimens included adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) in 27 patients (87%). Seven patients had been submitted to prior radiation therapy, three with mantle field, one with extended field radiation (mantle and para-aortic fields together), and three patients with localized irradiation.

Stem-cell sources included BM in 14 patients (45.1%) and PB in 17 patients (54.9%). The median nucleated cell number and CD34+ infused was 3.9 x 10^8/kg (range: 1.8 to 8.7) and 5.4 x 10^6/kg (range: 2.8 to 17), respectively. All patients achieved complete hematopoietic recovery. The median number of days to reach sustained engraftment was 12 days (range: 7 to 20).

After first-line chemotherapy, patients with relapse or progression were heavily pretreated, with a median of three (two to seven) treatment lines. A total of 26 patients were alive at median follow-up of 18 months (Figure 1A). The median OS for the whole group was 18 months (95%CI: 1-88 months). Eighteen-month OS was 84% ± 7.8 (95%CI) and 18 months PFS was 80% ± 8 (95%CI) for the whole group.

The 18-month OS for patients who were chemosensitive at the time of ASCT was 95%, compared to 60% chemoresistant (Figure 2A). The 18-month PFS for patients who were chemosensitive at the time of ASCT was 90%, compared to 45% for those with resistant disease at the time of ASCT (p= 0.003). The 18-month OS for patients who received PB as source of stem-cells was 95%, compared to 68% for those who received BM (p= 0.09). The 18-month PFS for patients who received PB was 100% *versus* 52% with BM (p= 0.03).

Death attributable to toxicity-related mortality (TRM) included one death prior to day +100 with hepatic veno-occlusive disease. One patient died from a second malignancy (lung adenocarcinoma), 45 months after ASCT, in complete remission of HL.

The 18-month OS for patients with a Hasenclever index of 0 to 2 was 86.3 *versus* 55.5% for those with three or more prognostic factors (p= 0.09). The 18-month PFS for patients with a Hasenclever index of 0 to 2 was 81.8%, compared to 55% for those with

Table 1. Patient characteristics

Number of patients	31
Primary histology	
Nodular sclerosis	20 (65%)
Mixed cellularity	9 (29%)
Lymphocyte depleted	1 (3%)
Lymphocyte predominant	1 (3%)
Front-line chemotherapy	
ABVD	27 (87%)
MOPP/ABV	4 (13%)
Prior radiotherapy	7 (22%)
At progression	
Median age (rage)	27 (8-15)
Gender	
Male	17 (54.8%)
Female	14 (45.2%)
Stage	
I	1 (3%)
II	9 (29%)
III	16 (51.6%)
IV	5 (16.4%)
B symptoms	24 (77%)
Sensitivity to conventional salvage chemotherapy	
Chemosensitive-CR	7 (22.5%)
Chemosensitive-PR	14 (45.3%)
Resistant	10 (32.2%)
High-dose chemotherapy	
BEAM	28 (90.3%)
Others	3 (9.7%)
Cell source	
Bone marrow	14 (45.1%)
Peripheral blood	17 (54.9%)
Median cells infused (range)	
TNC/kg x 10^8	3.9 (1.8-8.7)
CD34/kg x 10^6	5.4 (2.8-17)

ABVD: adriamycin, bleomycin, vinblastine and dacarbazine; MOPP/ABV: mechlorethamine, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, and vinblastine; CR: complete remission; PR: parcial remission; BEAM: carmustine, etoposide, cytarabine, and melphalan ; TNC: total nucleated cell

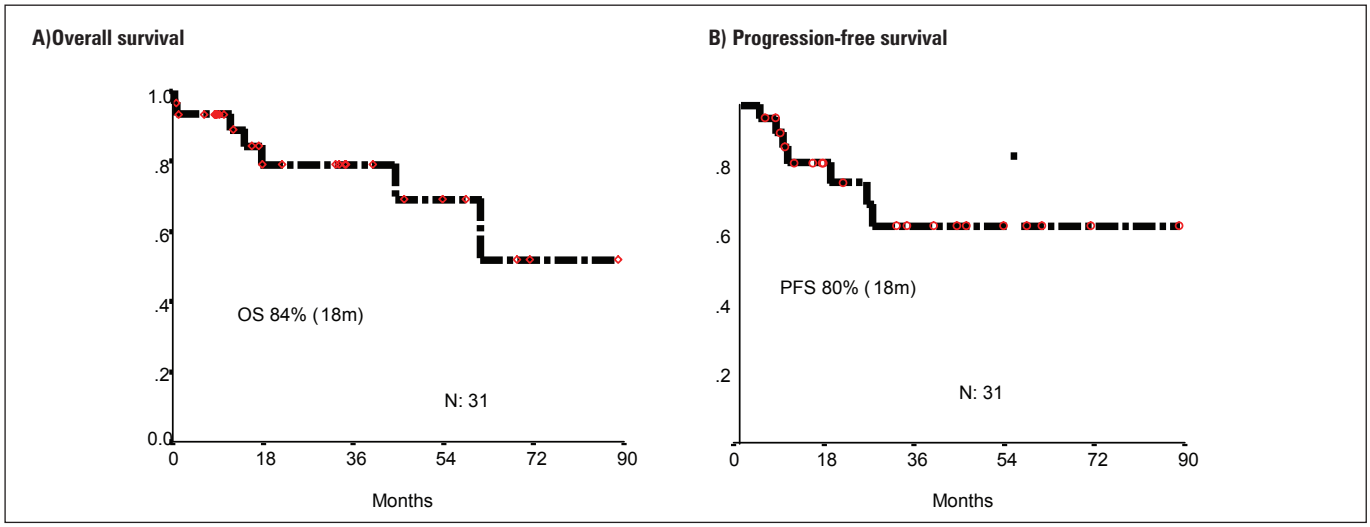

Figure 1. (A and B) Overall and progression-free survival

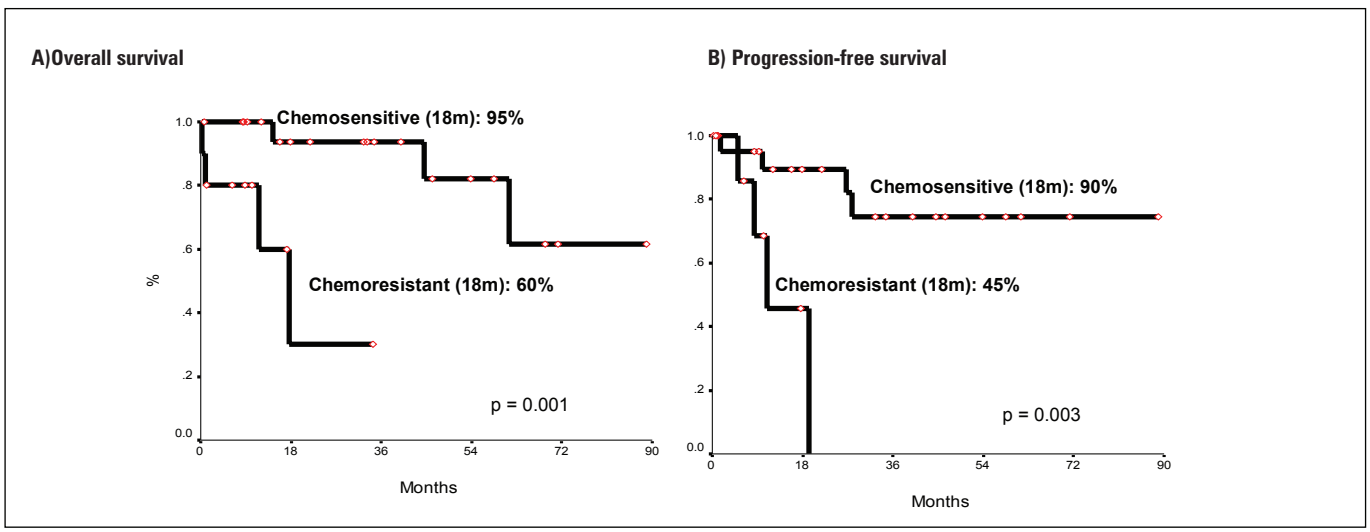

Figure 2. (A and B) The effect of chemosensitive disease at time of autologous stem cell transplant on overall and progression-free survival

three or more prognostic factors (p =0.08). Variables significantly affecting OS and PFS in univariate and multivariate analyses are listed in table 2. In the multivariate analysis, the only factors independently predictive of favorable OS (p= 0.02; RR: 0.072; range: 0.01- 0.85) and PFS (p= 0.01; RR: 0.040; range: 0.007-0.78) were absent disease or bulky disease < 5 cm.

DISCUSSION

This report comprises an 18-month follow-up of a single institution cohort of patients with primary refractory or relapsed HL who underwent ASCT. The results showed that high-dose chemotherapy or chemotherapy/radiation therapy, followed by ASCT, can induce disease control and improve the prognosis of patients with advanced refractory or relapsed HL. The patient population of this study was heterogeneous and heavily pretreated, with a median of three chemotherapy regimens before transplantation. Despite this, 84% of the patients were alive and 80% disease-free at a median follow-up of 18 months. The results of this present study also showed that it is possible to treat patients with multiple recurrences and attain disease control.

Prior series identified numerous prognostic factors with predictive value in this setting[10-15]. At the time of ASCT, disease bulk, performance *status*, BM involvement, presence of B symptoms, albumin, elevated serum lactate dehydrogenase levels, extranodal disease, and relapse within a previously irradiated field have all been shown to have predictive value for PFS, event-free survival, and/or OS. We confirmed in this small group that a low tumor burden (bulky disease < 5 cm) at transplantation is a favorable independent prognostic factor for OS and PFS. Other factors, such

Table 2. Analysis of variables predicting significantly overall survival and progression-free survival

End point	Factor	Univariate	Multivariate		
		p value	RR	CI	p value
OS					
	At least 2 prior CT regimens	0.12	-	-	-
	Albumin < 4g/dL *versus* ≥ 4 g/dL	0.04	-	-	0.14
	PBSC *versus* BM	0.09	-	-	0.20
	Bulky diseases e absent or < 5 cm at SCT	< 0.001	0.072	0.01-0.85	0.02
	Chemosensitive *versus* chemoresistant	0.001	-	-	0.55
	Hasenclever index 0-2 *versus* ≥ 3 factors	0.09	-	-	0.12
PFS					
	At least 2 prior CT regimens	0.07	-	-	0.46
	Albumin < 4g/dL *versus* ≥ 4 g/dL	0.01	-	-	0.08
	PBSC *versus* BM	0.03	-	-	0.35
	Bulky diseases e absent or < 5 cm at SCT	< 0.001	0.040	0.007-0.78	0.01
	Chemosensitive *versus chemoresistant*	0.003	-	-	0.52
	Hasenclever index 0-2 *versus* ≥ 3 factors	0.08	-	-	0.14

RR: relative risk; CI: confidence interval; OS: overall survival; CT: chemotherapy; PBSC: peripheral blood stem cell; BM: bone marrow; SCT: stem cell transplantation; PFS: progression-free survival

as albumin ≥ 4.0 g/dL and chemosensitivity, were observed in the univariate analysis, but not confirmed in the multivariate analysis.

The Hasenclever index has been successfully tested in the context of HL diagnosis[9]. Recently, Sirogi et al.[16] showed that a Hasenclever index < 3 influences outcome favorably, and that attaining complete remission at ASCT leads to a better outcome. In this group of patients, OS and PFS were higher in the group of patients with less than three factors, although this was not statistically significant. Small numbers of patients and a short follow-up can explain this result.

Patients with resistant HL did not attain prolonged PFS, therefore new effective approaches are critically needed in this population, as the vast majority will still relapse and die of their disease. Recent data suggest that gemcitabine-based regimens can induce remissions in patients that have not responded to more traditional salvage therapies[17,18]. Such secondary pre-transplant responses could both improve outcomes via tumor debulking and better identify disease that might respond to high-dose therapies. Individuals with resistant disease could be considered for investigational strategies using novel agents such as anti-CD30 monoclonal antibodies or transplants via reduced intensity allografting or tandem ASCT[19-21].

ASCT constitutes a therapeutic option for HL patients after a first relapse. Promising results are observed in patients with a low tumor burden (bulky disease < 5 cm) at transplantation. Overall, patients with chemoresistant advanced HL need a more aggressive therapeutic approach, and ASCT in its current form is an inadequate treatment option for these patients. Innovative approaches should be pursued for patients with risk factors for relapse.

CONCLUSION

Autologous transplantation of stem-cells is a therapeutic option for Hodgkin's lymphoma patients after the first relapse. Promising results were observed in patients with a low tumor burden at transplant. Innovative approaches should be sought for patients with risk factors for relapses.

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