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Autologous stem cell transplantation for high-risk Hodgkin's disease: improvement over time and impact of conditioning regimen

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ABSTRACT

Background and Objectives. **High-dose chemo/radiotherapy with autologous stem cell support is increasingly being used in Hodgkin's disease (HD) patients who do not respond to or who relapse after conventional chemotherapy. In this work we analyze the results of 56 consecutive high-risk HD patients autografted in our institution and the role of possible prognostic factors.**

Design and Methods. **There were 34 males and 22 females with a median age of 31 years. At transplantation, 24 patients (43%) were in complete remission and 32 (57%) were autografted while with active disease. Twenty-nine patients were autografted before January 1993. Bone marrow was used as the source of stem cells in 40 patients (71%) and peripheral blood (PB) in 16 (29%). Forty-five patients received chemotherapy-based conditioning regimens (40 CBV and 5 BEAM) while the remaining 11 received cyclophosphamide (Cy) and total body irradiation (TBI).**

Results. **Two bone marrow transplantation (BMT) recipients did not engraft. Hematologic recovery was significantly faster in patients transplanted with PB progenitor cells. Early transplant-related mortality (early TRM) (before day 100 after transplantation) was 9%; it was higher in patients transplanted before January 1993 than in patients transplanted afterwards (14% vs 4%) and in patients receiving TBI (18% vs 7%), although these differences did not reach statistical significance. Overall TRM (before and after day 100) was 14%. TBI-containing regimens significantly increased overall TRM (36% and 9%, $p = 0.03$). Actuarial 3.5-year overall survival (OS), event-free survival (EFS) and progression-free survival (PFS) were 57%, 58% and 65%, respectively. On multivariable analysis, TBI containing regimens and transplantation before 1993 significantly reduced OS and EFS.**

Interpretation and Conclusions. **Our results confirm that high-dose therapy followed by autologous stem cell transplantation is associated with sustained PFS in a remarkable proportion of patients with HD unlikely to be cured with standard chemotherapy. Results improved over time and TBI containing regimens had a negative effect on post-transplant outcome.**

Key words: Hodgkin's disease, autologous stem cell transplantation, conditioning regimens

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Up to 80% of patients with advanced Hodgkin's disease (HD) can be cured by combination chemotherapy (CT).[1] Despite these encouraging overall results, patients refractory to the initial treatment and those relapsing after an initial response frequently cannot be cured by conventional therapy with only 20% becoming long-term disease-free survivors.[2,3] These poor results led us to investigate the efficacy of high-dose therapy followed by autologous stem cell transplantation (ASCT) in this population. ASCT in poor prognosis HD patients has been reported by several authors to give complete response (CR) rates ranging between 50-80% and disease-free survival (DFS) rates between 20% and 60%.[4-8] Nevertheless, in this setting there is only one randomized study, carried out by the *British National Lymphoma Investigation Group*, which has demonstrated a clear advantage in terms of event-free survival (EFS) in favor of high-dose therapy compared to conventional-dose treatment.[9]

Several prognostic factors have been reported to be predictors of a poor outcome following ASCT: presence of B symptoms, extranodal disease at relapse, extensive therapy before transplant, brief first CR duration, bulky tumor at transplant, poor performance status at ASCT, resistance to conventional salvage CT and disease status at transplantation.[4,5,8,10–13] In addition, some studies suggest that the use of TBI worsens the final outcome of these patients.[14-16]

The significance of each of the prognostic factors listed has not been uniformly confirmed in the literature, and for this reason we investigated the variables influencing the results of ASCT in patients with poor prognosis HD treated at our institution over the last 10 years.

Design and Methods

Inclusion criteria

Between March 1987 and December 1997, 56 consecutive patients with HD received an ASCT in our institution. Pathologic diagnosis was reviewed in all referred patients. Patients were accepted for ASCT on the basis of the presence of poor prognostic features with conventional therapy: 1) need for 2 or more CT lines to obtain a 1st CR, 2) achievement of a partial remission (PR) or disease progression after 1st line therapy, 3) 1st CR of short duration (<12 months) and 4) 2nd or subsequent relapses. Four patients with 2 or more adverse prognostic factors according to the Strauss classification[17] were auto-

grafted in 1st CR achieved after first line conventional CT. Patients' characteristics at diagnosis and ASCT are shown in Table 1.

Conditioning regimen for transplantation

Forty-five patients were conditioned with chemotherapy; 40 received the CBV protocol (Cy 1.5-1.8 g/m^2 iv $\times$ 4 days, etoposide 150–400 mg/m^2 twice daily iv $\times$ 3 days and BCNU 300–600 mg/m^2 iv x 1 day) and the other 5 the BEAM regimen (BCNU 300 mg/m^2 iv $\times$ 1 day, etoposide 200 mg/m^2 iv $\times$ 4 days, cytarabine 200 mg/m^2 twice daily iv $\times$ 4 days and melphalan 140 mg/m^2 iv $\times$ 1 day). Eleven patients received Cy (60 mg/kg iv $\times$ 2 days) plus TBI (12 Gy in 4 fractions over 4 days).

Source of stem cells

Stem cells were obtained from BM for 40 patients (71%). A median (range) number of 1.11 $\times$ 10^8/kg (0.36 to 4) MNC and 3.83$\times$10^4/kg (0.4 to 66.7) CFU-GM were infused. Mobilized peripheral blood (PB) was used for the remaining 16 (29%) patients; 8 patients received low-dose Cy (1.5 g/m^2 iv) + G-CSF at 5 µg/kg/day sc[18] as mobilization protocol and the remaining 8 the IAPVP-16 salvage chemotherapy (ifosfamide 5 g/m^2 iv $\times$ 1 day, VP-16 100 mg/m^2 iv $\times$ 3 days, Ara-C 1.2 g/m^2 twice daily $\times$ 2 days and methylprednisolone 80 mg/m^2 iv $\times$ 5 days) plus G-CSF.[19] A median of 2 (1 to 6) aphereses were performed to collect a target number of 2.5$\times$10^6 CD34$^+$ cells/kg. A median (range) number of 4.89$\times$10^8/kg MNC (2.73 to 12.9), 8.40$\times$10^4/kg CFU-GM (2.22 to 59.6) and 4.14$\times$10^6/kg CD34$^+$ cells (2.43 to 17.25) were infused. Sixteen patients (15 recipients of BMT and 1 recipient of PBSCT), were given G-CSF 5 µg/kg/day sc from day +1 to hematologic recovery (neutrophil count > 1.5$\times$10^9/L for 3 consecutive days).

Additional treatment and follow-up after transplantation

Six patients received involved-field RT after ASCT; 3 because of residual disease and 3 because of prior bulky disease. To assess response to ASCT, patients' clinical examination and CT scan were performed 3 months after transplantation. Subsequent controls were every six months for the first 2 years, and yearly afterwards. Patients showing no evidence of disease on CT scans were considered to be in CR, those achieving a greater than 50% reduction in tumor mass were defined as being in PR and those with a less than 50% reduction in tumor mass as non-responders.

Statistics

Clinical characteristics at diagnosis and at ASCT were summarized using descriptive statistics. Treatment related deaths occurring within 100 days after the date of stem cell reinfusion were defined as early transplant-related mortality (TRM); those occurring within 100 days or later as overall TRM. The following clinical and biological characteristics were evaluated in univariate and multivariate analyses: histologic Rye subtype, year of transplant, previous splenectomy, previous RT, response to first line therapy, number of treatment lines, duration of first CR, disease status at transplant, conditioning regimen, source of stem cells, use of G-CSF after ASCT, days to ANC > 0.5$\times$10^9/L, days to platelet count > 25$\times$10^9/L, Ann Arbor stage, B symptoms, extranodal involvement, BM involvement and bulky disease. The last 5 characteristics were evaluated at diagnosis and at ASCT. Comparison of CR and TRM rates between groups was performed by Fisher's exact test and logistic regression analysis. Comparison of continuous variables was performed by Mann-Whitney's U test and linear regression analysis. Overall survival (OS) was calculated from the time of progenitor cell infusion until death or last follow-up. Progression-free survival (PFS) was calculated from the time of progenitor cell infusion until date of relapse or progression; when analyzing this end-point, toxic deaths and second malignancies were censored. EFS was calcu-

Table 1. Patients' characteristics at diagnosis and ASCT.

	No. (%)
Sex	
Males/females	34 (61)/22 (39)
Age [median (range)]	31 (15–65) years
Histology	
Nodular sclerosis	35 (63)
Mixed cellularity	17 (30)
Lymphocyte predominance	4 (7)
Ann Arbor stage at diagnosis	
I–II/III–IV	19 (34)/37 (66)
B symptoms	36 (64)
Bulky disease (> 10 cm)	15 (27)
No. extranodal sites	
0–1/≥ 2	15 (27)/2 (4)
BM involvement	6 (11)
First line therapy	
Chemotherapy	50 (89)
MOPP-like regimens	21 (37)
ABVD	8 (14)
MOPP/ABVD	14 (25)
Hybrid protocol	5 (9)
Others	2 (4)
Radiotherapy	6 (11)
Extended field radiotherapy	23 (41)
Duration of first CR (n = 45)	
≤ 12 months	19 (39)
> 12 months	18 (37)
Unknown	13 (29)
No. lines of previous therapy	
1 – 2/≥ 3	38 (67)/18 (32)
Disease status at ASCT	
Complete remission	24 (43)
1st complete remission	7 (12)
2nd complete remission	11 (20)
3rd complete remission	6 (11)
Active disease	32 (57)
Primary refractory disease	5 (9)
Untreated relapse	4 (7)
Sensitive relapse	17 (30)
Resistant relapse	6 (11)
Ann Arbor stage at ASCT (n = 32)	
I–II/III–IV	13 (41)/19 (59)
B symptoms (n = 32)	5 (16)
Bulky disease (n = 32)	5 (16)
Extranodal involvement (n = 32)	7 (22)
Date of ASCT	
Before January 1993/After January 1993	29 (52)/27 (48)

lated from the time of stem cell infusion until death from any cause, relapse, progression or occurrence of a second neoplasm. Probabilities were estimated by the Kaplan-Meier method (log-rank test). All *p* values reported are two-sided and statistical significance is defined as a *p* value < 0.05.

Results

Antitumor response

Of the 28 patients with active disease at ASCT evaluable for response to transplant, 21 (75%) patients achieved a CR, 6 (21%) a PR and 1 (4%) progressed. Extranodal involvement and B symptoms at diagnosis and disease refractoriness at ASCT significantly reduced CR rates (43% vs 86%, $p = 0.04$, 61% vs 100%, $p = 0.02$ and 50% vs 89%, $p = 0.03$, respectively). On multiple regression analysis the only significant variable was disease sensitivity ($p = 0.04$).

Toxicity

Five patients (9%) died from early TRM: veno-occlusive disease (2 patients), interstitial pneumonitis (IP) (2 patients) and cardiac failure (1 patient). Three patients died more than 100 days after transplantation from causes other than disease progression: 1 patient from a stroke 7 months after ASCT, 1 from secondary graft failure and pulmonary aspergillosis 11 months post-ASCT and 1 from a secondary malignancy (rhabdomyosarcoma) 42 months after ASCT; overall TRM is 14%. Early TRM was not significantly influenced by any of the variables analyzed although there was a trend for a higher early TRM in patients autografted before January 1993 than thereafter (14% vs 4%, $p = 0.1$). Patients conditioned with TBI had a significantly higher overall TRM than patients conditioned with chemotherapy alone (36% vs 9%, $p = 0.03$).

Hematologic recovery

Seven patients did not engraft. Median time to achieve an ANC > 0.5×10^9/L was 16 days (range 10 to 57) and to reach a platelet count > 25×10^9/L was 16 days (range 9 to 76); median (range) duration of hospital admission was 29 days (14-76). In univariate analysis, ASCT after January 1993 and the use of PBSC were associated with fast hematologic recovery, both for ANC (13 days vs 23 days, $p = 0.0001$, and 13 days vs 19.5 days, $p = 0.0001$, respectively) and platelets (13 days vs 27 days, $p = 0.0001$ and 11 days vs 26 days, $p = 0.0001$, respectively). The same variables affected duration of hospitalization, it being advantageous to have been autografted after January 1993 and to have received PBSC (25 days vs 38 days, $p = 0.002$, and 24 days vs 37 days, $p = 0.0001$, respectively). Linear regression analysis showed that the source of stem cells was the only variable influencing hematologic recovery. In ABMT patients, ANC recovery was significantly faster in patients who had received G-CSF (13 vs 34 days, $p = 0.007$).

Survival

Median follow-up after ASCT of the entire group is 18.5 months with a maximum follow-up of 11.3 years. Figure 1 illustrates the Kaplan-Meier survival curves for the whole population. The actuarial 3.5 year OS is 57 % (95% confidence interval [CI] 43% to 71%). EFS at the same time point is 58% (CI 44% to 71%) and PFS is 65% (CI 52% to 79%). Seven patients (15%) relapsed at a median (range) time of 9 (6–24) months after ASCT. There have been 13 deaths (23%) due to progressive disease and one patient is alive with active disease (AD).

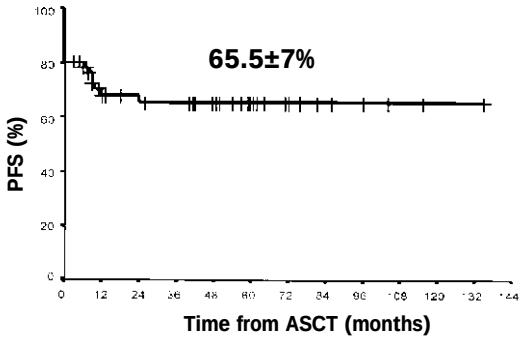

Figure 1. Actuarial PFS of the whole series (n=56).

Disease status before ASCT is considered one of the most important prognostic factors for long term outcome after transplantation. Patients autografted in CR had a significant better outcome in terms of OS (52% vs 20%, $p = 0.03$), EFS (76% vs 45%, $p = 0.01$) and PFS (80% vs 55%, $p = 0.02$) than patients autografted with AD. Overall TRM is also lower in patients autografted in CR than in patients with AD (4.2% vs 12.5%). Outcome has been specially good in high risk patients autografted in 1st CR (OS 100% and PFS 100%) and in those autografted in 2nd CR (OS 78% and PFS 81%). Results have been better in patients transplanted in sensitive disease in relation to those in 3rd CR (OS 60% vs 45% and PFS 66% vs 55%). Patients autografted in primary refractory disease or resistant relapse have an extremely poor prognosis with an OS of 16%, EFS 18% and PFS of 36%.

Univariate and multivariate analyses were performed for the 3 survival end-points (Table 2). On multivariate analysis, year of transplantation (before vs after January 1993) and conditioning regimen (TBI vs non-TBI containing regimens) (Figure 2) were the significant prognostic factors for OS and EFS.

Discussion

Our results show that high-dose chemo/radiotherapy followed by an ASCT can induce long-term disease control in this cohort of patients with refractory or advanced HD; PFS of the whole series is 65% and our survival curves are comparable to those reported by other groups in the literature.[6,8,20-23]

Although the number of patients receiving TBI in this series was small, it is of note that multivariate analysis identified conditioning as a strong prognostic factor for final outcome. TBI regimens significantly worsened OS (66% vs 15%, $p = 0.003$) and EFS (67% vs 16%, $p = 0.004$). Response rates were similar between patients autografted using TBI and patients receiving only chemotherapy containing regimens (62% vs 80%, $p = 0.3$) but overall TRM was significantly higher in patients receiving TBI (36% vs 9%, $p =$

Table 2. Analysis of variables for PFS, EFS and OS.

Variables	*PFS (P)*		*OS (P)*		*EFS (P)*	
Year of transplant						
<1993 (n = 29)	52.5±18%	0.05	45±18%	0.04	45±18%	0.03
*1993 (n = 27)	81.5±14%		74±22%		71±22%	
B symptoms at diagnosis						
No (n = 37)	61±17%	ns	52.5±18%	0.02	53±17%	ns
Yes (n = 5)	40±43%		20±35%		20±35%	
Response to first line therapy						
Sensitive (n = 51)	70±13%	0.007	61±15%	0.006	61.5±14%	0.01
Refractory (n = 5)	20±35%		20±35%		20±35%	
Status at transplant						
CR (n = 24)	80±18%	0.02	52.5±18%	0.03	76±18%	0.01
No CR (n = 32)	55±17%		20±35%		45±17%	
Conditioning regimen						
CT (n = 45)	71±14%	0.04	66.5±15%	0.003	67±14%	0.004
CT + TBI (n = 11)	43.5±30%		15.5±26%		16±27%	
Multivariate analysis						
Conditioning	ns		0.01	RR: 2.7	0.05	RR: 2
Year of transplant	ns		0.02	RR: 2.2	0.03	RR: 2.5

PFS, progression-free survival; OS, overall survival; EFS, event-free survival; CT, chemotherapy; CR, complete remission; ns, not significant; RR, relative risk.

0.03). Some studies have evaluated the influence of TBI on ASCT outcome in HD.[6,8,14-16,20-22,24] The initial reports on TBI associated with Cy and/or etoposide reported a TRM as high as 20%.[14-16] Yahalom *et al.*[23] incorporated hyperfractionated total-lymphoid irradiation into the combination with high-dose etoposide and Cy followed by ABMT in 47 patients with relapsed or chemoresistant HD who had not received prior RT. CR was 74% and actuarial DFS at 6.5 years was 50%. However, a relatively high (17%) TRM rate was observed, mostly due to respiratory failure secondary to diffuse alveolar hemorrhage. More recent reports[6,8] suggest that the combination of TBI and high-dose CT along with patient selection (no prior RT) and supportive care can improve the outcome of this subgroup of patients. Prior mediastinal irradiation has been found to result in a high incidence of interstitial pneumonitis (IP) in patients conditioned with TBI by some authors;[14,16,25] nevertheless, this has not been confirmed by others.[24] In our series we were not able to identify prior mediastinal irradiation as a prognostic factor for ASCT-related IP. The only 2 patients who died of IP were both conditioned with CBV and prior mediastinal RT was not associated with higher early or overall TRM (9.7% vs 8% and 13% vs 16%, respectively). In our experience, TBI-containing regimens were associated with an increased rate of fatal late events, which were responsible for the lower EFS and OS. High-dose CT based regimens or other irradiation approaches might be used as pre-transplant regimens in HD.

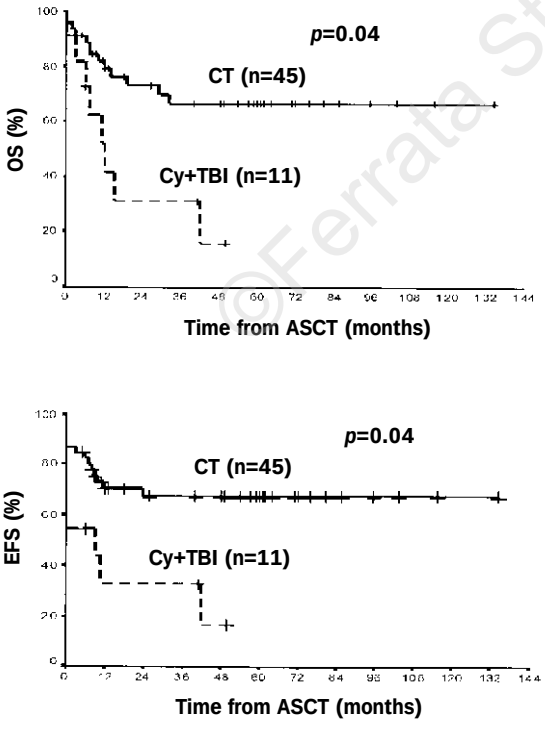

Figure 2. Survival curves stratified by conditioning regimen. CT: chemotherapy.

Improvements in transplant support and a better patient selection could be the reasons for a significantly better OS and EFS for patients autografted after January 1993. Both early and overall TRM were higher in patients autografted before this date. Lancet, too, reported a TRM of 13% in a group of 46 relapsed or refractory HD patients transplanted before 1993 compared to a rate of only 4% in 24 autografted after January 1993.[26] In our series, prior RT was more frequent in patients autografted before 1993 (73% vs 37%, $p = 0.01$) but this factor was inde-

pendent of year of transplant in multivariate analysis. PB was the main source of hematopoietic progenitors after 1993 (59.2% vs 0%, $p = 0.00001$). This is consistent with the fact that during the last 10 years BM has been progressively abandoned by many groups in favor of PBSC. Hematologic recovery of both neutrophils and platelets was significantly faster in patients autografted from PB than for those autografted from BM. G-CSF administration after BM infusion significantly decreased neutrophil recovery without influencing platelet recovery and duration of hospitalization. In fact, neutrophil recovery of patients autografted from BM and receiving G-CSF was similar to that of patients autografted from PB.

Disease status at ASCT is one of the factors which most strongly predicts post-transplant survival.[4,5,8,21,22,27] In our series, outcome has been especially good in patients autografted in 1st CR and 2nd CR. The role of ASCT in poor prognosis HD patients in 1st CR remains unknown. There have been several attempts to identify a subpopulation of bad prognosis HD patients who might benefit from undergoing consolidation high-dose therapy after achieving a 1st CR with standard CT.[17,27] Recently, a prognostic score for advanced HD has defined 7 independent prognostic variables; nevertheless, a distinct group of patients at very high risk could not be identified.[28] Several retrospective analyses[29-32] have shown DFS rates higher than 75%, relapse rates below 20% and a TRM < 5% in poor risk HD patients autografted in 1st CR and a prospective randomized study comparing high dose chemotherapy with conventional treatment in this subpopulation is currently underway within the EBMT.[33] Patients autografted in 3rd CR have a worse outcome than patients transplanted with sensitive disease. These results may be the reflection of accumulated toxicities due to previous CT regimens and of more resistant disease; the number of lines of prior CT has been shown to influence OS and PFS significantly in some series.[6,34] We have not been able to show that the number of previous lines of CT has a prognostic value, probably because of the small numbers of patients included in each group. As shown by other authors,[4-8] refractory patients (PRD or RR) have the worst prognosis. Investigational approaches such as tandem transplants, post-ASCT immunotherapy or allogeneic stem cell transplantation need to be explored in these patients.

In conclusion, our experience confirms that ASCT is associated with improved survival in a substantial proportion of patients with poor prognosis HD. Results improved over time and TBI-containing regimens had a negative effect on post-ASCT outcome. Therefore, high dose chemotherapy protocols should be administered for conditioning and post-transplant RT considered in particular subgroups of patients.

Contributions and Acknowledgments

MS contributed along with AS to the study design, collected and analyzed the data, and prepared the first draft of the manuscript. AS had the initial idea of performing this study. She contributed to the study design, interpretation of the data and writing of the manuscript. AS, RM, AA and SB were responsible for the transplant procedures, recruitment and clinical day-to-day management of the patients. RM, AA and SB also reviewed the final version of the manuscript. JG is the head of the Cryobiology and Cellular Therapy Department of the Cancer Research Institute and was the responsible for all the biological monitoring of hematopoietic progenitors for transplantation. CC collaborated in the data collection and statistical analysis. ADA was the former head of the Unit and JS critically corrected the different versions of the manuscript.

The order of the authors tries to take into account the time, work and scientific contribution given by all the authors, the second author being the idea promoter and the last the senior member of the research group.

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Disclosures

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Potential implications for clinical practice

- Disease status at ASCT remains the most important predictor of ASCT outcome.
- TBI-containing regimens seem to have a negative effect on post- ASCT outcome in HD patients.
- High-dose chemotherapy protocols should be preferred as conditioning regimens for the majority of HD patients.

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