High-dose therapy with autologous transplantation for Hodgkin's disease: the Bologna experience

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Background and Objectives. In this work we examine the characteristics and outcome of patients with Hodgkin's disease (HD) treated with high-dose therapy (HDT) and autologous transplantation at our Institute between 1982 to 2000.

Design and Methods. A retrospective analysis was performed examining patients' characteristics, prior chemotherapy regimens, pre-transplant disease status, HDT regimen, source of stem cells, time for hematopoietic recovery, complications of transplantation, response rates, overall survival (OS) and relapse-free survival (RFS).

Results. Ninety-seven patients with HD were treated and had estimated 10-year OS and RFS rates of 32% and 60%, respectively. Disease status (sensitive vs. refractory) before HDT was the most powerful predictive parameter for OS and RFS in both univariate and multivariate analyses. The rate of transplant-related mortality in the whole cohort was only 1% whereas the rate of second malignancies was 3%.

Interpretation and Conclusions. Our results confirm that HDT with autologous transplantation is associated with a durable RFS in a remarkable proportion of HD patients and that the procedure has a very low global early and late toxicity.

Key words: chemotherapy, ABMT, Hodgkin's disease, relapse-free survival.

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In advanced Hodgkin's disease (HD), current conventional chemotherapy regimens with/without radiation therapy can provide overall complete remission (CR) rates of over 80%.[1,2] However, this approach has two limits. On the one hand, overtreatment of favorable cases needs to be avoided (because of unacceptable side-effects). On the other, alternative approaches are necessary for markedly unfavorable subgroups that are associated with very high rates of failure and/or relapse. In fact, 30% to 50% of such patients undergo disease progression during initial therapy or relapse after having obtained a CR.[3-5] Those patients who are primarily refractory to chemotherapy or who relapse after more than one chemotherapy regimen have a poor prognosis, and only about 20% of them have a long-term relapse-free survival (RFS).[6,7] High-dose therapy (HDT) with autologous transplantation can provide sustained remissions in patients with advanced refractory or recurrent HD, as reported in retrospective series.[8-22] Among the few prospective studies that have evaluated the role of HDT in this setting,[23-26] both randomized trials did not demonstrate a clear advantage in terms of RFS over conventional-dose treatment.[25,26] Response to first-line conventional chemotherapy has been shown to constitute a good predictor of outcome, and early restaging may help to identify poor responders to such treatment.[27,28] The patients most likely to benefit from HDT are those who have received limited prior chemotherapy, lack constitutional symptoms and have disease that is chemotherapy-sensitive, non-bulky and does not involve extranodal sites.[29-32]

Herein, we report on our experience with a large series of patients with HD who received autologous transplantation in our institution between 1982 and 2000.

Design and Methods

Patients

We performed a retrospective analysis of 97 consecutive HD patients who were submitted to HDT with autologous transplantation at the Seràgnoli Institute of Hematology and Medical Oncology between 1982 and 2000. Patients' records were independently reviewed and the diagnosis confirmed by two investigators (MT and AG). Radiological investigations performed pre- and post-transplant were centrally reviewed (by MZ). All patients had biopsy-proven HD, and all specimens underwent central pathology review

(by SP). All patients were transplanted using Institutional review board-approved protocols and gave written informed consent. Patients had received either ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine), MOPP (mustine hydrochloride, vincristine, procarbazine and prednisolone) or both, with/without radiation therapy as first-line treatment. CEP (CCNU, etoposide and prednimustine) and IEV (ifosfamide, epirubicin and etoposide) were used as second- and third-line regimens. Staging and restaging investigations (according to the Ann Arbor staging system) included chest X-ray and computed tomography scans and bone marrow biopsy (which was repeated if previously positive); gallium scans were performed when clinically indicated. Bulky disease was defined as the presence of a lesion with a maximum dimension exceeding 10 cm.

Conditioning regimen for transplantation

All patients were conditioned with chemotherapy: 89 received BEAM (carmustine 300 mg/m^2, day -7; etoposide 200 mg/m^2 and cytarabine 200 mg/m^2 given twice a day, day -6 to day -3; melphalan 140 mg/m^2, day -2), and 8 received CVB (cyclophosphamide 1500 mg/m^2, day -6 to -3; etoposide 250 mg/m^2, day -6 to -4; carmustine 300 mg/m^2, day -6).

Source of stem cells

Stem cell were obtained from bone marrow for 69 patients (71%). A median number of 2.23×10^8/kg (0.70-16.8) nucleated cells were infused. Mobilized peripheral blood was used for the remaining 28 (29%) patients; all these patients received IEV salvage chemotherapy (ifosfamide 2,500 mg/m^2/day, days 1 to 3; epirubicin 100 mg/m^2 on day 1; etoposide 150 mg/m^2, days 1 to 3) plus granulocyte colony-stimulating factor (G-CSF),[33] and achieved the defined minimum transplant dose of 2×10^6 CD34$^+$ cells/kg with one (20 cases) or two (8 cases) aphereses. Eighty-three (86%) patients were given G-CSF 5 μg/kg/day s.c. from day +1 post-transplant until engraftment.

Response criteria and statistical analysis

CR and partial response (PR) were defined according to international criteria.[34] Patients were classified as having resistant disease if their HD progressed through their initial combination chemotherapy treatment (refractory) or if their relapsed disease showed less than a PR to conventional salvage therapy immediately before transplant (resistant relapse). Overall survival (OS), relapse-free survival (RFS), and progression-free survival (PFS) curves were calculated according to the method of Kaplan and Meier.[35] OS was measured from the time of stem-cell infusion until death or last follow-up; RFS was calculated from the time of infusion until date of relapse; PFS was calculated from the time of infusion until date of progression (for this end-point, toxic deaths and second malignancies were censored).

Comparison of the survival curves in univariate analysis was performed using the log-rank test.[36] Comparison of continuous variables was performed by Mann-Whitney's U test and linear regression analysis. Multivariate analysis was performed using a forward stepwise Cox proportional hazards model. The prognostic factors analyzed for both RFS and OS were sex, histology, conditioning regimen, disease status at transplant (sensitive vs. refractory), stem cell source, age, stage (limited vs. advanced), B symptoms, mediastinal involvement, bone marrow involvement, bulky disease, and extranodal involvement (the last six characteristics were evaluated both at diagnosis and transplant). All p values reported are two-sided and statistical significance was defined as a p value less than 0.05. The statistical analyses were computed with SPSS statistical software (SPSS, Inc, Chicago, IL, USA).

Results

The patients' characteristics at diagnosis and before HDT are detailed in Tables 1 and 2, respectively. The majority of patients had advanced disease at presentation, with more 80% having either stage III or IV disease. The median time from diagnosis to transplantation was 2.5 years (range 0.6-6.7 years) and patients had received a median of two prior chemotherapy regimens. At the time of HDT, 18 (19%) patients had primary refractory disease while 10 (10%) patients were in second CR. The median time to absolute neutrophil count (ANC) recovery to $\geq 0.5\times 10^9$/L was 13 days (range 9-17 days) in the peripheral blood subset and 18 days (range 9-30 days) in the bone marrow subset. The median time to recovery of platelets to $\geq 20\times 10^9$/L was 16 days (range 11-37 days) in the peripheral blood subset and 21 days (range 15-67 days) in the bone marrow subset.

Response to HDT

A total of 71 (73%) patients responded to HDT, with 65 (67%) CR and 6 (6%) PR. Table 3 summarizes the clinical response to HDT according to the pre-transplant status. As shown in Figures 1 and 2, the probabilities of RFS and OS after a median follow-up of 45 months (range 2-205 months) from HDT were 60% and 32% at 10 years, respectively. Beyond the 6-year mark, no event has been observed. Figures 3 and 4 show OS and PFS curves according to chemosensitivity prior to transplant (sensitive versus resistant patients). At 10 years the OS was 58% for the sensitive subset and 28% for the resistant subset ($p = 0.0000$); the PFS was 75% for the sensitive subset and 50% for the resistant

Table 1. Characteristics of the patients at diagnosis.

Characteristics	*No.*
Sex (M/F)	56/41 (58/42%)
Age (Years)	
Median	29
Range	11-59
Ann Arbor stage	
II	29 (30%)
III	40 (41%)
IV	28 (29%)
Mediastinal Involvement	74 (76%)
Histology	
NS	84 (87%)
MC	7 (7%)
LP	2 (2%)
LD	4 (4%)
Bone marrow involvement	20 (21%)
B symptoms	56 (58%)
Bulky disease	22 (23%)
Extranodal involvement ≥ 2	26 (27%)
Splenectomy	21 (22%)
Front line chemotherapy	
MOPP	11 (11%)
ABVD	39 (40%)
MOPP+ABVD	47 (48%)
Radiation therapy	52 (54%)
Time to first progression	
≤ 12 months	30 (31%)
> 12 months	67 (69%)

NS: nodular sclerosis; MC: mixed cellularity; LP: lymphocyte predominant disease; LD: lymphocyte depleted disease.

Table 2. Characteristics of the patients before HDT.

Characteristics	*No.*
Ann Arbor stage	
II	17 (18%)
III	52 (54%)
IV	28 (29%)
Mediastinal involvement	50 (52%)
Bone marrow involvement	10 (10%)
B symptoms	50 (52%)
Bulky disease	20 (21%)
Extranodal involvement ≥ 2	23 (24%)
Conditioning regimen	
BEAM	89 (92%)
CVB	8 (8%)
Stem cell source	
Bone marrow	69 (71%)
Peripheral blood	28 (29%)
Disease status	
II CR	10 (10%)
PR	10 (10%)
Refractory	18 (19%)
Responding relapse	26 (27%)
Resistant relapse	19 (20%)
Untested relapse	14 (14%)
Number of therapies	
1	3 (3%)
2	64 (66%)
3	25 (26%)
4	5 (50%)

subset (p=0.05). Of the 65 patients who obtained CR, 44 (68%) are still in CR, while the remaining 21 patients relapsed within 5 years of receiving HDT (Figure 5).

Events

The rate of transplant-related mortality (within 90 days of transplant) was 1%, as this event occurred in 1/97 patients. At the time of writing, 44/97 (45%) patients are in continuous CR (11 in first CR and 33 in second or further CR), 16 are alive with lymphoma and 37 have died. Concerning the causes of death, 33 patients died of progressive disease, one patient of infection (at day +78), and 3 patients died from other hematologic malignancies: one case of high-grade non-Hodgkin's lymphoma 22 months post-HDT and 2 cases of acute myeloid leukemia (AML) at 32 and 45 months. The 6-year incidence of second malignancies is thus 3% (3/97). The two patients who devel-

Table 3. Clinical response to HDT according to the pre-transplant status.

Status pre-HDT	*No. Patients*	*CR (%)*
II CR	10	10(100)
PR	10	9 (90)
Refractory	18	8 (45)
Responding relapse	26	19 (73)
Resistant relapse	19	8 (42)
Untested relapse	14	11 (79)

Table 4. Actual status of all patients according to the pre-HDT status.

Status Pre-HDT	*Actual status*			
	CCR (%)	*AWL*	*LRD*	*DOC*
Second CR	5/10 (50)	1	3	1
PR	5/10 (50)	2	2	1
Refractory	4/18 (22)	4	10	–
Responding relapse	18/26 (69)	3	5	–
Resistant relapse	3/19 (16)	5	10	1
Untested relapse	9/14 (64)	1	3	1

CCR: continuous CR; AWL: alive with lymphoma; LRD: lymphoma-related death; DOC: death from other causes.

oped AML had been globally treated with MOPP (× 4 or 10 courses) plus ABVD (× 4 courses) and with HDT (BEAM as conditioning regimen). The current status of the entire population with respect to pre-HDT status is summarized in Table 4.

Statistical analysis

On univariate analysis, four factors were found to influence OS and RFS: sex (female advantage) (p= 0.02 and p= 0.04, respectively); B symptoms (p= 0.04 and p= 0.05); mediastinal involvement (p= 0.02 and p= 0.04); pre-HDT status (p= 0.0006 and p= 0.003). At multivariate analysis only the pre-HDT status (sensitive vs. refractory) remained significant for OS (p= 0.0007) and RFS (p= 0.004).

Discussion

HDT with autologous transplantation for HD is a continually evolving field. Since its introduction 20 years ago, HDT has become the treatment of choice for the many patients who either fail to respond to induction therapy or who subsequently relapse. In

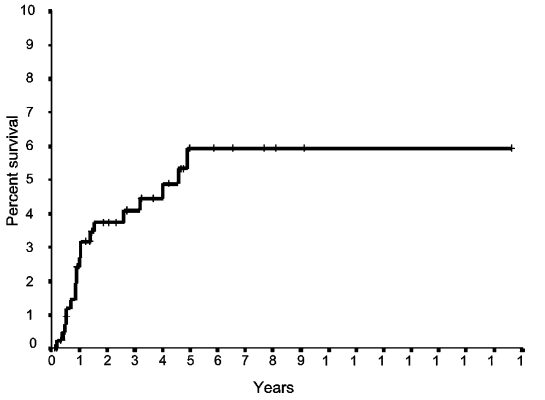

Figure 1. RFS curve of 65 patients who obtained CR with HDT and autologous transplantation.

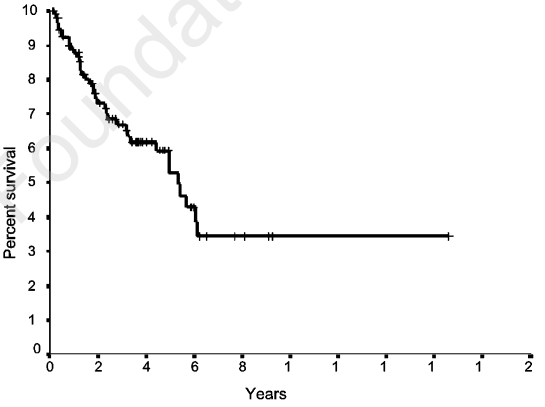

Figure 2. OS curve of all patients.

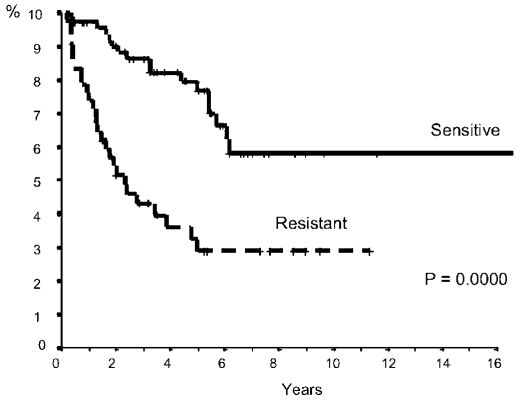

Figure 3. OS curves comparing the subset of sensitive patients versus the subset of resistant patients.

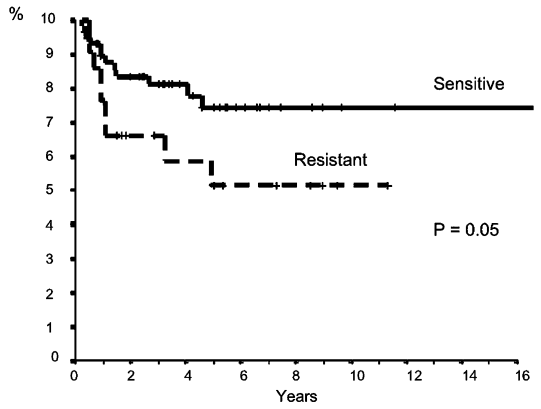

Figure 4. PFS curves comparing the subset of sensitive patients versus the subset of resistant patients.

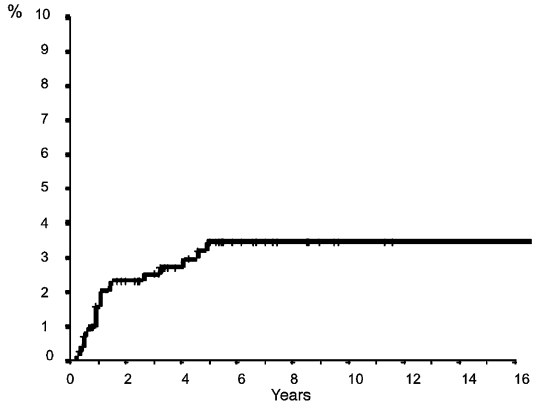

Figure 5. Relapse curve following HDT with autologous transplantation.

particular, conventional chemotherapy remains the treatment of choice for patients who relapse after radiation therapy for early stage HD.[5,37,38] Increasing adoption of HDT with transplantation has also been encouraged worldwide by the reductions in treatment-related mortality achieved over recent years. Although only two randomized controlled trials[25,26] and two historical cohort studies[14,39] are available to support the use of HDT with transplantation in HD patients, the reproducibility of results from many single-center and registry studies, and their superiority over historical control data regarding conventional chemotherapy, highlight the efficacy of this approach. Many studies confirm 5-year RFS rates of 40%-60% following HDT, along with OS rates of 30%-40%.[8-22,40]

Our results highlight how HDT with transplantation can induce long-term disease control in a cohort of patients with refractory/relapsed HD. Subsets of patients treated while in PR or with untested or responding relapses showed CR rates greater than 70%. On the other hand, the resistant relapse subgroup had a CR rate of only 42%. Globally, 65% of patients obtained CR, and with a median follow-up of 4 years 45% of all patients and 68% of those who had CR are in CCR with 10-year RFS and OS curves of 60% and 32%, respectively. The treatment-related mortality rate in this series was 1%, a very low rate considering the range reported by other centers. The 6-year cumulative incidence of second malignancies was 3%, and the actuarial incidence is similar to that found in other reports.[41,42] Despite the low number of patients, the only prognostic factor influencing both RFS and OS that remained significant at both univariate and multivariate analysis was pre-HDT status. These findings underline the positive influence of chemosensitive disease on the outcome of autologous transplantation.

We have probably cured almost half the HD patients we submitted to HDT and transplantation, with very low risks of treatment-related mortality or second malignancies. It should be noted that 80% of our patients were refractory or had relapsed: such patients have little or no chance of cure with conventional chemotherapy.[22,33]

The therapeutic alternatives for patients who relapse after HDT with transplantation are limited. This is a setting in which new drugs (such as gemcitabine)[43,44] or therapeutic approaches (such as monoclonal antibodies), may be tested as alternatives to the difficult and unsatisfactory option of allogeneic bone marrow transplantation or the less toxic approach of non-myeloablative allogeneic transplantation.

An important role for extrapolating the identikit of relapsed/refractory patients who can benefit from autologous transplant is played by the *International Prognostic Factors Project* score.[45] Bierman *et al.* recently demonstrated that the score is useful also in this subset of patients.[46] For upcoming prospective trials it will be essential to include all the score factors in the patients' records.

In conclusion, autologous transplantation appears to increase the RFS of HD in patients who fail to enter CR after induction therapy. When a patient relapses after a CR, HDT with transplantation is probably the best option, especially if the remission lasted for less than 1 year and in patients with late relapses.[26] Open questions regarding the role of HDT in patients with multiple relapses or in high-risk newly diagnosed patients would ideally be answered by randomized control trials. It is important, however, to be aware of the changes that are occurring in the therapy of newly diagnosed and relapsed/refractory HD patients (stan-

dard and escalated BEACOPP, Stanford V),[47,48] and of the impact that these changes may or may not have on the possibilities and the role of autologous transplantation.

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Pre-publication Report & Outcomes of Peer Review

Contributions

PLZ, PR, GB, RML, FG were the principal investigators involved in the conception of the study, its design, and PLZ wrote the paper. SP was involved in the histology review. MZ was involved in the radiological review. AG, MT, SB, VS and LA collected the study data. MRM and SR were involved in stem cell selection. VG and RC were involved in stem cell mobilization. AdV; statistical analysis; MB, ST; critically revised the paper and gave the final approval for its publication. Primary responsibility for the paper: PLZ; primary responsibility for the Tables: PLZ; primary responsibility for the Figures: AdV. We are grateful to Robin M.T. Cooke for scientific editing.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Richard J. Jones, who acted as an Associate Editor. The final decision to accept this paper for publication was taken jointly by Professor Jones and the Editors. Manuscript received October 24, 2002; accepted March 24, 2003.

In the following paragraphs, the Associate Editor summarizes the peer-review process and its outcomes.

What is already known on this topic

High-dose cytotoxic therapy followed by blood or marrow transplantation has become the treatment of choice for refractory of relapsed Hodgkin's disease. Both retrospective and prospective randomized trials have shown it to provide a better long-term disease-free survival for these patients than conventional dose salvage therapy.

What this study adds

This study confirms the safety (transplant-related mortality of 1%) and effectiveness of transplantation in relapsed/refractory Hodgkin's disease in a series with one of the longest follow-ups on record.

Caveats

The role of allogeneic transplantation in a disease affecting young patients still needs to be defined. There are data suggesting that the allogeneic transplantation may significantly decrease relapse and prevent secondary leukemia compared to autologous transplantation; thus, some patients with matched sibling donors may benefit from consideration of this approach.