

High-dose therapy and autologous stem cell transplantation for high-risk Hodgkin's lymphoma: a single center experience

Autologous stem cell transplantation (ASCT) is largely employed in primary resistant or recurrent Hodgkin's lymphoma (HL), while its role early in the course of the disease is still controversial. Our purpose was to analyze the results of 44 high-risk HL patients autografted at our Institution and the role of possible prognostic risk factors for their outcome.

The role of high-dose therapy with ASCT has been widely investigated in patients with refractory or relapsed HL;¹⁻² it has been shown to produce higher complete remission (CR) rates than conventional chemotherapy (CHT). In contrast, the role of ASCT in first remission is still a subject of controversy;³⁻⁴ in this setting, only patients considered at diagnosis as likely to have a poor outcome after conventional CHT should be candidates for ASCT.

Although prognostic factors in advanced HL have been extensively studied in an effort to identify, at diagnosis, patients with poor outcome, so far the optimal risk factors for the selection of these candidates remain to be defined.

Between May 1992 to January 2001, we submitted 44 HL patients considered to have high-risk disease to ASCT. The patients were assigned to this risk stratification if they presented at least one of the following at diagnosis: 1) bulky disease (mass \geq 10 cm in diameter); 2) B-symptoms; 3) stage IV disease. The primary objective of our retrospective study was to detect the impact on the survival of a program including ASCT at the end of induction treatment in high-risk HL patients. The general characteristics of the patients and their clinical features at presentation are listed in Table 1. Before transplant, patients were treated with the MOPP (6 patients -13.5%) or the ABVD regimen (38 patients-86.5%). The source of hematopoietic progenitors cells was: steady state bone marrow, 11 patients; peripheral blood, 24 patients; or bone marrow, 9 patients, after *in vivo* priming with G-CSF.⁵ The conditioning regimen used was BEAM. Engraftment was observed in all (Table 1). No transplant-related mortality was recorded. As of April 2001, all the patients transplanted in first complete remission (CR) - 10 (22.5%) are alive in continuous CR; sixteen out of the 18 (41.0%) patients submitted to transplant in partial remission (PR) achieved and maintained a CR after ASCT, with a conversion from partial to complete response of 89%.

The other 16 (36.5%) patients had active disease at the time of transplantation: 6 had resistant disease and 10 had disease progression (4 proceeded to transplant without any other therapy while 6 received 2 cycles of salvage chemotherapy). Of them, 6 (37.5%) are alive in continuous CR at a median follow-up from transplant of 75 months (range: 63 - 90); 3 (18.5%) are alive with disease and all the other 7 patients (44.0%) died of their disease.

The overall survival and progression-free survival (PFS) of the whole population are, respectively, 77.0% and 66.5% at a median follow-up from transplant of 32 and 24 months (range 2-105), respectively. PFS according to status at transplant is reported in Figure 1.

The prognostic factors analyzed for PFS, in univariate and multivariate analyses (performed using a stepwise Cox proportional hazards model) were: age, sex (<45 vs \geq 45 years), histology, B-symptoms, stage, bulky disease, status at transplant, Hasencalver⁶ and Proctor index.⁷ Of these, sex ($p=0.03$), bulky disease ($p=0.05$), distribution according to the Proctor index ($p=0.05$) and status at transplant ($p=0.02$) resulted as being adverse features in univariate analysis; in multivariate

Table 1. Patients' characteristics and transplant-related data.

Characteristics	No.	%
Total no. patients	44	
Male	27	61.5
Female	17	38.5
Age ys. Median (range)	31 (13-61)	
Histology		
Nodular sclerosis	29	66.0
Mixed cellularity	11	25.0
Lymphocyte depletion	2	4.5
Lymphocyte predominance	2	4.5
Performance status		
0-1	43	97.5
Ann Arbor stage:		
II	10	22.5
III	14	32.0
IV	20	45.5
B-symptoms	35	79.5
Serum LDH level > normal	10	52.0
ESR > normal	23	52.0
Extranodal disease (total no. of pts):	24	54.5
Bulky disease (total no. of pts):		
Mediastinal	17	38.5
Peripheral	5	11.5
Abdominal	3	6.5
No. extranodal sites:		
1	15	34.0
\geq 2	9	20.5
Transplant-related data		
Days to PMN > $0.5 \times 10^9/L$	12 (8-24)	
Days to PLT > $20 \times 10^9/L^*$	14 (9-32)	
No. of febrile patients	15	
No. Gram +ve/-ve septicemia	6/0	
No. FUO ^o	8	
No. of febrile days/patient	4 (2-7)	
Days on antibiotics	8 (5-10)	
Days of hospitalization ^f	20 (11-32)	

LDH: lactate dehydrogenase; ESR: erythrocyte sedimentation rate; PMN: polymorphonuclear cells; *PLT = platelets; ^oFUO = fever of unknown origin; ^ffrom reinfusion.

analysis only status at transplant retained its positive influence ($p=0.002$). This finding was consistent with previous reports,⁸ with status at transplant being the only factor influencing the survival, the best response being observed in patients transplanted during CR. Moreover, the conversion from partial to CR of 89% observed in our series, with a PFS of 77.5% for patients transplanted in PR (Figure 1), suggests that it would be reasonable to identify at diagnosis patients likely to have a poor out-

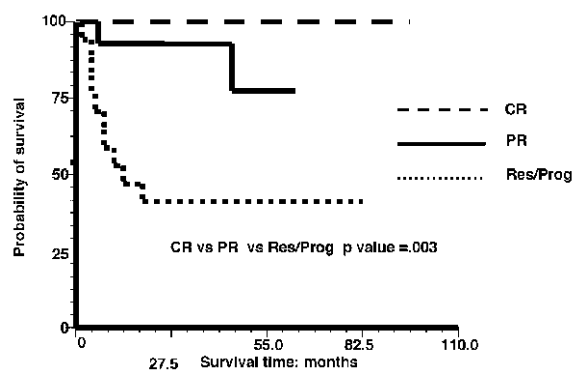


Figure 1. Progression-free survival according to status at transplant. PFR: CR patients: 100% median follow-up from transplant 32 months (2-105); PR patients: 77.5% median follow-up from transplant 24 months (3-69); Res/prog patients: median follow-up from transplant 15 months (2-90).

come with standard therapy, and try to rescue them with more intensive induction treatment and ASCT in at least partial response.

Finally, when analyzing ASCT as part of the initial treatment, another point should be considered: the late complications. In several series secondary tumors emerged as a serious problem after ASCT,⁹ but the role of high-dose therapy versus conventional treatment in the development of secondary malignancies is still controversial.¹⁰ Up to now, with a follow-up from transplant of 31 months (range: 2-79), no major complications, including secondary malignancies, have been observed in our series. It must be underlined that no data are currently available to predict the long-term effects on lung and endocrine function in our group of patients. In summary, our study highlights the possibility of achieving long-term PFS with ASCT in HL patients, even in those autografted with active disease. The low transplant-related mortality and promising PFS should encourage the inclusion of patients with high-risk disease in prospective randomized studies to compare this approach with conventional chemotherapy. These studies should offer more definite conclusions on the real impact of early intensive treatment in high-risk HL.

Alessandra Sperotto, Francesco Zaja, Daniela Damiani, Francesca Patriarca, Antonella Geromin, Renato Fanin

Chair and Division of Hematology, Bone Marrow Transplant Unit, Department of Medical and Morphological Research, University Hospital, Udine, Italy

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Correspondence: Alessandra Sperotto, MD, Division of Haematology, University Hospital P.le S. Maria della Misericordia, 33100 Udine, Italy.

Phone: international +39.0432.559662. **Fax:** international +39.0432.55966. **E-mail:** ematologia@drmm.uniud.it

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