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A retrospective analysis of 144 patients with aggressive non-Hodgkin's lymphoma: impact of autologous stem cell transplantation in first remission on outcome

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ABSTRACT

***Background and Objectives*. To analyze the impact of a sequential program including autologous stem cell transplantation in first remission on the outcome of patients with aggressive non-Hodgkin's lymphoma.**

***Design and Methods.* Patients aged less than 60 years old, with an aggressive non-Hodgkin's lymphoma and at least a partial response after first line therapy (chemotherapy ± radiotherapy) were included in the study.**

***Results.* One hundred and forty-four patients were registered: of them 126 reached at least a partial response after first line therapy and 71 (56.5%) were then submitted to autologous stem cell transplantation. The overall survival (OS) and progression-free survival (PFS) of the whole population were respectively 70% and 63% at a median follow-up from diagnosis of 51 months (7-115). The PFS of the transplanted group was 93% at a median follow-up from diagnosis of 54 months (20-155); the PFS of the non-transplanted patients was 43.5% at a median follow-up from diagnosis of 30 months (8-109) (p <0.0001).**

***Interpretation and Conclusions.* The two groups (transplanted vs not transplanted patients in remission after induction therapy) were homogeneous concerning the major risk factors (stage III-IV – p = 0.26; performance status – p = 0.25; B-symptoms – p = 0.3; LDH level – p = 0.4; extranodal disease – p = 0.4; bulky disease – p = 0.7): so we compared them in order to discover clinical features at diagnosis which adversely affected PFS. In a multivariate analysis, factors which adversely affected PFS were: LDH level – p = 0.03; number of extranodal sites – p = 0.04; not performing the transplant – p = 0.02. When patients were stratified by number of extranodal sites and by LDH level, only the transplant being performed retained its positive influence – p = 0.04.**

Key words: non-Hodgkin's lymphoma, autologous stem cell transplantation, first remission

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A long-term progression-free survival (PFS) of no more than 50%, despite a high sensitivity to chemotherapy, represents the rationale for high-dose therapy in intermediate and high-grade non-Hodgkin's lymphoma (NHL).[1-3]

There is evidence, from the literature, that two important determinants for the prognosis of aggressive NHL are dose intensity and attainment of a complete response after conventional chemotherapy.[3-4] It is reasonable to believe that the clinical benefit may be increased if autologous stem cell transplantation (ASCT) is performed early in the course of the disease, i.e. before the development of drug resistance and toxicity.[2,5] Infact it is well known that only a small proportion of relapsed or refractory patients can be cured using high-dose chemotherapy later in the course of the disease.[6-8]

Despite these considerations, and after more than twenty years of clinical trials, ASCT in first remission is still considered experimental and a source of controversial discussions.

Single center studies on high-dose chemotherapy in first complete remission in patients considered to be at risk of relapse, reported favorable results with a relapse-free survival higher than 80%.[9-11] In contrast, a randomized French study of a large cohort of patients showed no advantages for the intensification arm including ASCT.[12] It should be underlined that in a subsequent retrospective analysis according to the International Prognostic Index (I.P.I.),[13] a better outcome emerges for patients with high-intermediate and high-risk disease submitted to the intensification arm.

In 1990 we designed a study, closed in December 1998, with the aim of submitting all patients with aggressive NHL to transplant, immediately after the attainment of a remission (complete or partial) by first-line conventional therapy.

This analysis, based on intention-to-treat, refers to 144 consecutive patients diagnosed and registered for the study. The feasibility of the program, selection of transplanted patients and the impact of the protocol on the survival of the whole population were the main points of investigation of this study.

Design and Methods

Eligibility criteria

Study eligibility requirements were newly diagnosed patients aged less than 60 years old, with a documented diagnosis of aggressive NHL.

Patients were excluded if, at diagnosis, they had: involvement of the central nervous system, positive serology to HIV, a concomitant or previous cancer, congestive heart failure, recent myocardial infarction or conduction abnormalities, liver or kidney failure.

Definition of aggressive disease

Patients were considered as having an aggressive lymphoma and included in the study if they had a documented diagnosis of intermediate or high – grade NHL according to the updated Kiel classification[14,15] and the presence of at least one of these adverse factors: 1) bulky disease defined as a mass ≥10 cm in diameter; bulky mediastinum was defined as a MT ratio ≥ 0.33 (MT= ratio between the maximum mediastinal diameter and the maximum thoracic diameter at the level T5-T6, as detected by standard posteroanterior chest radiographs); 2) B-symptoms; 3) stage III or IV disease.

Staging procedures

Diagnosis was made on pathologic specimens, based on morphologic and immunophenotypic criteria according to the updated Kiel classification. All the diagnoses were also reviewed according to the more recent revised *European-American classification of lymphoid neoplasms* (REAL).[16]

A detailed history was taken from all patients, and all underwent physical examination, routine blood analysis with measurement of lactate dehydrogenase (LDH) levels and serology for HBV, HCV and HIV infections.

Staging procedures included chest radiographs, computed tomography (CT) of the chest and abdomen and bone marrow aspirate and biopsy. Other examinations were performed as clinically indicated. The number of extranodal sites and the diameter of the largest tumor mass were also determined. Staging was defined according to the Ann Arbor criteria. Performance status was assessed according to the *Eastern Cooperative Oncology Group* (ECOG) scale.[17]

For the evaluation of residual mass after therapy, all patients with bulky disease were staged by magnetic resonance imaging (MRI) and ^{67}gallium-scintigraphy (^{67}Ga-S).[18]

Treatment

As first therapeutic intervention, surgery was performed when needed for diagnostic and/or de-bulking purposes.

The induction treatment included: chemotherapy with the third-generation regimen F-MACHOP[19-21] for a total of 6 cycles given every 21 days; chemotherapy according to the ALL0288 protocol[22] (a sequential acute lymphoblastic leukemia-type protocol) for all the lymphoblastic lymphoma patients.

Each course of the F-MACHOP regimen includes: vincristine (0.5 mg/m^2, i.v. bolus, hours 0 and 12), cyclophosphamide (800 mg/m^2, i.v. bolus, hour 36), 5-fluorouracil (15 mg/kg, i.v. 6-hour infusion, hour 36), cytosine-arabinoside (1,000 mg/m^2, i.v. 6-hour infusion, hour 42), doxorubicin (60 mg/m^2, i.v. bolus, hour 48), methotrexate (500 mg/m^2, i.v. 6-hour infusion, hour 60), prednisone (60 mg/m^2, p.o. daily, from day 1 to 14) and folinic acid rescue (20 mg/m^2, i.v. bolus, hours 84, 96, 108 and 120).

Radiotherapy was given (after chemotherapy) if residual mediastinal disease was present.

Inclusion criteria

After completing first-line therapy (chemotherapy ± radiotherapy), all the patients were considered for ASCT as part of the first line-treatment if they fulfilled these inclusion criteria: 1) complete or at least partial response to first-line treatment; 2) good performance status (0-1 according to the ECOG scale); 3) normal renal, hepatic, and cardiac function; 4) informed consent obtained.

Marrow harvest and cryopreservation

The source of hematopoietic progenitors was bone marrow (BM) or peripheral blood (PB). A single BM harvest or three PB aphereses were performed to collect the necessary number of stem cells. Harvested BM and PB were processed on a Fenwall CS 3000 separator (Baxter Health Care Products, Deerfield, IL, USA) and the mononuclear cells were cryopreserved in 20% DMSO with 50% autologous plasma and kept at –196°C.

Conditioning regimen and supportive care

The conditioning regimen used for all patients was BAVC,[23] which consists of carmustine 200 mg/m^2 on day –4, cytosine arabinoside 150 mg/m^2 twice daily, etoposide 150 mg/m^2 twice daily, and cyclophosphamide 45 mg/kg once daily, all from day –5 to day –2.

Patients were treated in private rooms with reverse isolation and a diet low in bacterial and fungal content. Antimicrobical, antifungal, and antiviral prophylaxis consisted in oral co-trimoxazole or ciprofloxacin, itraconazole, nystatin or amphotericin suspension and acyclovir, respectively. Parenteral antibiotics were started if fever ≥ 38°C occurred during neutropenia and maintained until the patient was apyretic for at least 3 consecutive days or for at least 5 days.

Platelet transfusions were administered as required to maintain a platelet count of greater than 20x10^9/L, and transfusions of packed red blood cells to maintain a hemoglobin concentration of greater than 10 g/dL.

After the reinfusion, granulocyte colony-stimulating factor (G-CSF; filgrastim) was administered to all patients from day +4 until the neutrophil count exceeded 1.0×10^9/L for 3 consecutive days, as described elsewhere.[24,25]

Parenteral nutrition was used as clinically indicated.

Response assessment

Patients were routinely restaged after chemotherapy, after radiotherapy, 3 months after ASCT, than at 6 monthly intervals for 2 years and yearly thereafter. Complete remission (CR) was defined as no evidence of disease for at least 4 weeks. With the advent of modern radiographic techniques residual abnormal-

ities of various size are frequently detectable after treatment, making an accurate assessment of CR very difficult. When a remarkable (greater than 80%) reduction but not a complete disappearance of the original bulky mass was observed (a lesion ≥ 2 cm in diameter as detectable by CT), the patient was retrospectively considered to have been in CR only if repeated CT scans did show modifications of the radiographic picture for the next 2 years, and MRI and 67Ga-S were recorded as negative.[18,23]

Partial remission (PR) was defined as a reduction in tumor mass of at least 50%, and resistance (R), as a reduction in tumor mass of less than 50%.

Progressive disease was diagnosed when new lesions or ≥ 50% increase in the size of previously involved sites appeared in spite of disease control elsewhere. Responding relapse was defined using the criteria proposed by Philip *et al.*[26] This status was allocated to those patients who relapsed after a CR and received salvage chemotherapy, achieving at least a 50% reduction in tumor mass. Resistant relapse was defined as a reduction in tumor mass of less than 50% after chemotherapy.

Statistical methods

Study design. This was a retrospective non-randomized study. The primary objective was to detect the impact on the survival of a sequential program including ASCT in patients in remission after first-line therapy.

Statistical analysis. All analyses were performed on an intention-to-treat basis. The stopping date was set as June 1999.

Comparisons between patient groups were based on the χ^2 test for categorical data and Wilcoxon's rank-sum test for continuous data.[27] Overall survival (OS) was calculated from the date of diagnosis to the data of last follow-up evaluation or death. Progression-free survival (PFS) was measured from the date of diagnosis to the first negative event (progression, relapse or death).

Disease-free survival (DFS) was evaluated only in patients who achieved a CR; the duration was calculated from the time of CR assessment to the date of relapse or to the date of death or last follow-up evaluation with the patients free of the disease.

Survival, PFS and DFS curves were computed according to the Kaplan and Meier method and compared by the two-sided log-rank test.[28]

Features independently associated with PFS were identified in multivariate analyses by a Cox proportional hazards regression model.[29]

Test statistics for comparison of major end-points were regarded as significant if the two-sided *p* value was less than 0.05.

Subgroup analysis. A predictive model for aggressive lymphomas has been proposed by the *International Non-Hodgkin's Lymphoma Prognostic Factors Project.*[30] When adjusted for patients younger than 60 years, this model is based on three factors (Ann Arbor stage, LDH level and performance status) and categorizes patients into four groups on the basis of the presence or the absence of these risk factors.

For the purpose of this analysis, all the cases of our study were retrospectively reviewed according to the age-adjusted I.P.I. The CR rate, OS and DFS observed after sequential treatment (chemotherapy ± radiotherapy + ASCT), as opposed to those expected after chemotherapy according to the age-adjusted I.P.I., were compared for each risk group using the χ^2 square Yates – corrected test. All *p* values are two-tailed.

Differences were considered significant if the two-sided *p* value was less than 0.05.

Results

From January 1990 to December 1998, 144 consecutive patients aged less than 60 years old, with an aggressive NHL (according to the mentioned criteria) were registered at the Division of Hematology, Udine for a sequential program including ASCT as part of first-line treatment.

Table 1 shows the distribution of these patients according to histology subtypes. The histology pattern of the nineteen follicular lymphomas was grade II or III and that of six MALT lymphomas showed a prevalence of large cells.

General patient characteristics and clinical features at presentation are listed in Table 2. Eighty percent of the patients were ambulatory (PS 0-1); 71.5% presented with advanced stage disease (III and IV stage); 44.5% with B-symptoms and 43.0% with elevated LDH. Bulky disease was detected in 55.0% of the patients with mediastinal involvement accounting for the majority (35.5%). The distribution according to the age-adjusted I.P.I. shows a prevalence for the low (L + L-I) risk groups (94 patients – 65.0% of the entire population), both in the transplanted and not transplanted arm (50, 70.5% vs 40, 73.5%; $p = 0.8$).

Fifty-six percent of the patients had at least 2 risk factors according to the definition used in our protocol.

Induction treatment

Eighty-nine out of 144 patients (62.0%) achieved a complete remission after induction treatment (chemotherapy ± radiotherapy), 37 (25.5%) a par-

Table 1. Histologic diagnosis of the 144 patients.

Updated KIEL classification	*R.E.A.L. classification*	*TOT.*	
T-cell lymphoblastic L.	T lymphoblastic leukemia/lymphoma	13	
T large cell anaplastic (Ki-1 pos.) L.	Anaplastic large cell L., T and null-cell types	18	
Pleiomorphic T-cell L.	Peripheral T cell L., unspecified	18	
Centroblastic/centrocytic diffuse L.	Follicle center L., follicular	19	
MALT L.	Marginal zone L.	6	
Centroblastic L.		43	}
B immunoblastic L.	Diffuse large B cell L.	4	} 65
B large cell anaplastic (Ki-1 pos.) L.		18	}
Centrocytic L.	Mantle cell L.	5	

L.= lymphoma.

Table 2. Characteristics of the patients at diagnosis.

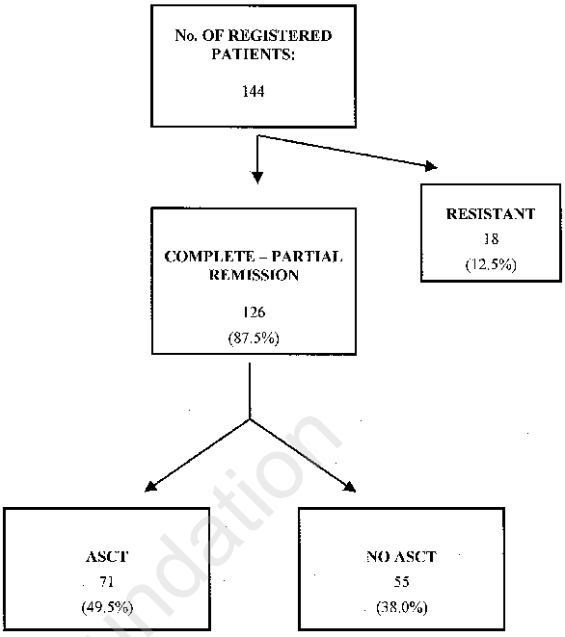
	No.	%	No.	%	No.	%	
No. pts.	144*		71°		55#		p^
Age years median (range)	42 (15-60)		39 (15-57)		48 (19-60)		.04
Age years:							
- 15 – 30	31	21.5	25	35.0	5	9.0	.0003
- 31 – 40	29	20.0	13	18.5	14	26.0	
- 41 – 50	40	27.5	22	31.0	12	22.0	
- 51 – 60	44	31.0	11	15.5	23	43.0	
Gender							
- male	85	59.0	42	59.0	30	55.5	.75
- female	59	41.0	29	41.0	24	44.5	
Stage							
- I + II	41	28.5	25	35.0	13	23.5	.26
- III	20	14.0	8	11.0	11	20.0	
- IV	83	57.5	38	54.0	31	56.5	
Performance Status							
- 0 – 1	116	80.5	55	77.5	49	89.0	.25
- 2 – 4	28	19.5	16	22.5	6	11.0	
B symptoms	64	44.5	39	55.0	13	23.5	<.0001
Serum LDH level							
> normal	62	43.0	26	36.5	20	36.5	.97
Adenopathy							
peripheral	79	55.0	36	50.5	38	70.5	
mediastinal	51	35.5	36	50.5	9	16.5	
retroperitoneal	18	12.5	11	15.5	8	15.0	
abdominal	28	19.5	13	18.5	16	29.5	
hilar	11	7.5	6	8.5	3	5.5	
Extranodal disease							
(total pts.)	90	62.5	43	60.5	32	58.0	.78
bone marrow	37	25.5	10	14.0	18	33.5	
lung	16	11.0	11	15.5	2	3.5	
GI tract	14	9.5	9	12.5	4	7.5	
spleen	13	9.0	4	5.5	6	11.0	
liver	12	8.5	4	5.5	5	9.0	
pleura	10	7.0	6	8.5	1	2.0	
skin	4	2.5	2	3.0	4	7.5	
bone	6	4.0	4	5.5	2	3.5	
soft tissue	4	2.5	2	3.0	2	3.5	
pericardium	5	3.5	5	7.0	-	-	
thyroid - parathyroid	3	2.0	2	3.0	-	-	
Bulky disease (no. pts)	79	55.0	47	66.0	20	36.5	.001
mediastinal	37	25.5	27	38.0	5	9.0	
abdominal	15	10.5	8	12.0	7	13.0	
peripheral	16	11.0	5	7.0	8	15.0	
retroperitoneal	8	5.5	6	8.5	-	-	
spleen	3	2.0	1	1.5	2	3.5	
liver	2	1.5	1	1.5	1	1.5	
lung	1	0.5	1	1.5	-	-	
breast	1	0.5	1	1.5	-	-	
No. extranodal sites							
0	54	37.5	28	39.5	23	42.0	.35
1	53	37.0	31	43.5	18	32.5	
≥2	37	25.5	12	17.0	14	25.5	
A.A.I.P.I.							
L	21	14.5	14	20.0	7	13.0	.53
LI	73	50.5	36	50.5	33	60.0	
HI	30	21.0	11	15.5	10	18.0	
H	20	13.5	10	14.0	5	9.0	
Protocol risk factors							
1	62	43.0	23	32.5	36	65.5	<.0001
2	59	41.0	33	46.5	17	31.0	
3	23	16.0	15	21.0	2	3.5	

**Entire population; °transplanted patients in remission after induction therapy; #non-transplanted patients in remission after induction therapy; ^p value: transplanted vs non-transplanted patients.*

tial remission, while eighteen patients (12.5%) were considered resistant to first-line therapy (Table 3).

Among 126 patients (87.5%) who achieved a complete or partial remission, 55 (38.5%) were not subsequently submitted to ASCT (Table 3). Reasons for exclusion were: protocol violation, 15 patients

Table 3. Algorithm of the study.



(27.0%); refusal, 12 patients (22.0%); early relapse progression, 10 patients (18.0%); concomitant disease, 6 patients (11.0%); harvest failure, 6 patients (11.0%); poor performance status after induction therapy, 3 patients (5.5%); age, 3 patients (5.5%).

Main pre-treatment characteristics, with potential prognostic significance, of the two groups (transplanted vs non-transplanted patients in PR-CR after induction treatment) are listed in Table 2. While non-transplanted patients were, as expected, older than transplanted ones (p=0.04), bulky disease (p=0.001) and B-symptoms (p<0.0001) recur more frequently in the transplanted group. On the other hand, the two groups were well balanced for all the other risk factors (stage, p= 0.26; LDH level, p= 0.97; extranodal disease – p= 0.35; performance status – p= 0.25) and in particular they were comparable according to the age-adjusted IPI (p=0.52).

Transplant-related data

Table 4 shows the main transplant-related data. At a median time of 3.5 months (0.5-12) from the end of chemotherapy, patients underwent bone marrow (38 patients) or peripheral blood harvest (33 patients), with no patients having bone marrow involved by the disease at that time. Autotransplant was performed a median of 3 (0.5-10) months after harvest, with 56.5% of them being reinfused within 12 months from diagnosis. A median of 0.4 (0.2-1.5) $\times 10^8$/kg bone marrow b.w. and a median of 2.0 (1.1 -3.5) $\times 10^6$/kg peripheral blood CD34 positive cells b.w. were reinfused. Engraftment was observed in all. A febrile episode was documented in the period of post-transplant aplasia in 26 and in 18 patients in the

Table 4. Transplant related data.

	BM	PB
No. of patients	48	33
Months from:		
end of therapy to harvest	3.5 (0.5-12)	
harvest to ASCT	3.0 (0.5-10)	
diagnosis to ASCT	13 (7-29)	
ASCT to 30.6.'99	39 (6-106)	
BM MNC×10^8/kg b.w. reinfused	0.4 (0.2-1.5)	
PB CD34×10^6/kg b.w. reinfused	2.0 (1.1.-3.5)	
Days to		
PMN >0.5×10^9/L	13 (10-22)	10 (8-12)
PMN >1.0×10^9/L	14 (10-23)	11 (8-12)
PLT >20×10^9/L	16 (10-30)	10 (3-14)
PLT >50×10^9/L	20 (10-43)	13 (10-23)
No. blood units transfused	6 (0-14)	4 (0-6)
No. PLT aphereses transfused	5 (1-12)	3 (2-7)
No. G-CSF post ASCT*	11 (4-18)	7 (4-11)
No. of febrile patients	26	18
No. Gram ± septicemia	9/2	7/0
No. fever of unknown origin	15	11
No. febrile days/patient	5 (3-10)	5 (3-9)
Days on antibiotics	8 (5-21)	8 (5-14)
Days of hospitalization°	19 (12-32)	16 (10-25)

*PMN = neutrophils; PLT = platelets; *300 µg/administration/daily starting from day +4; °from reinfusion.*

bone marrow and in the peripheral blood group, respectively. Median hospitalization time was 19 (12-32) days and 16 (10-25) days respectively (bone marrow vs peripheral blood).

Outcome, overall and progression-free survival

Entire population. The OS of the 144 patients included in the study is 69% (95% CI 60-86%) at a median time from diagnosis of 51 months (7-115). If we consider only the 126 patients in remission after induction therapy, the OS is 80% (95% CI 70-93%) with a median follow-up from diagnosis of 56 months (8-115). The PFS of the 144 registered patients is 63% (95% CI 60-70%) at a median follow-up from diagnosis of 46 months (7-115) (Figure 1). Considering only the 126 responding patients the PFS is 71% (95% CI 70-79%) at a median time from diagnosis of 50 months (8-115) (Figure 2).

Transplanted patients. At the time of transplant, 48 patients (67.5%) were in CR, while 23 (32.5%) were considered partial responders to first-line treatment.

After ASCT 20 patients, transplanted in PR, entered CR, with a conversion from partial to complete response of about 90%.

The OS of the transplanted group is 97% (95% CI – 96.0-100%) at a median follow-up from diagnosis of 54 months (20-155).

Non-transplanted patients. Among the 55 patients who achieved a complete (41 patients, 74.5%) or partial response (14-25.5%) to induction treatment, 17 (31%) subsequently relapsed while all the partial responders progressed. At the time of the analysis, 25 (45.5%) patients were in continuous CR. In 9 patients we were able to harvest a sufficient number of nucleated cells, and subsequently to submit them to salvage ASCT. Two (22.0%) of them achieved and maintained a second CR. Another 5 patients, from among those relapsed or progressed, obtained a second CR after conventional salvage chemotherapy. The OS of the non-transplanted group is 59.0% (95% CI, 50.0-89.0%) at a median time of 49 months (11-109) from diagnosis.

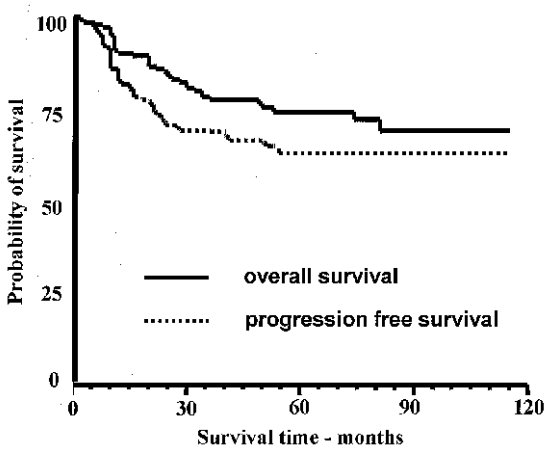


Figure 1. Overall survival and progression free survival: entire population.

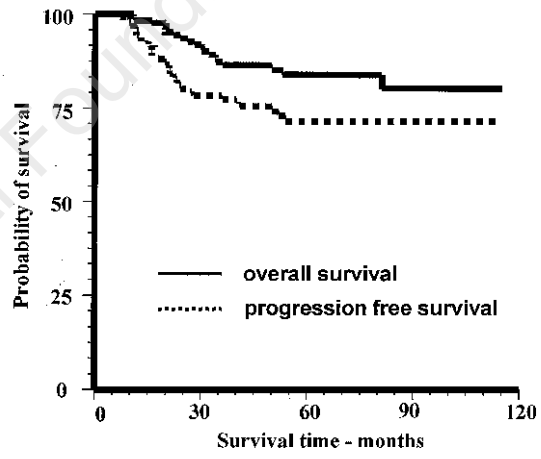


Figure 2. Overall survival and progression free survival of the 126 patients in remission after induction therapy.

The PFS of the two groups (transplanted vs non-transplanted) is respectively 93.0% (95% CI, 92.0-98.5%) and 43.5% (95% CI, 40-70%) at a median time of 54 months (20-115) and 30 months (8-109) from diagnosis ($p \leq 0.0001$) (Figure 3).

Multivariate analysis

Considering that the two groups (transplanted and not transplanted patients in remission after induc-

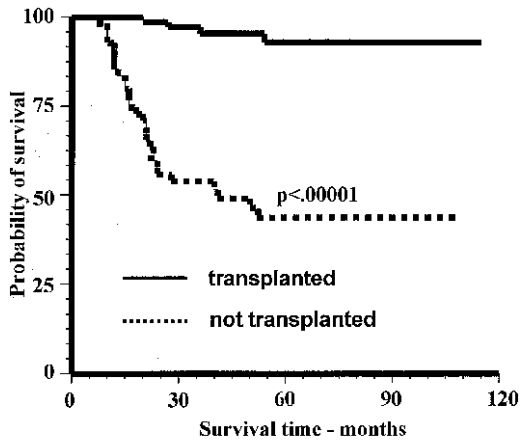


Figure 3. Progression-free survival: transplanted vs. not transplanted patients in remission after induction therapy.

tion therapy) were balanced for most of the risk factors (as described above) we compared them in order to discover the features present at diagnosis which adversely influenced the outcome. The variables testing in multivariate analysis were: age, sex, performance status, stage, B-symptoms, LDH level, number of extranodal sites, bulky disease, protocol risk factors and I.P.I. score. Taking into account that first remission patients submitted to transplant could have already been cured, (as they did not relapse in the meantime), we performed a time-dependent multivariate analysis.

Factors adversely affecting progression-free survival in this kind of analysis were:

- LDH level (p=0.03); number of extranodal sites (p=0.04); not performing the transplant (p=0.02);
- when we stratified patients by number of extranodal sites or by LDH level (data not shown), only the transplant being performed retained its positive influence on PFS (p = 0.04).

Age-adjusted International Prognostic Index

Response to induction therapy. Response to induction therapy according to the age-adjusted I.P.I. is listed in Table 5. The CR rate of the whole population is 63.2% but is higher if only the low-risk patients (71%) are considered. Given that the rate of partial responders does not differ substantially among the 4 risks group, resistant patients are almost all included in the high-risk group (as expected).

Patients with 0 or 1 risk factor and patients with 2 or 3 risk factors could be combined (because of the small number in each group) respectively into two groups (low and high risk). Comparing low *vs* high-risk patients, there is a statistically significant difference in the rate of resistant patients (higher, 28% in high risk group; p<.0001). On the other hand no differences emerge, among the 4 groups, in the rate of responding patients who underwent transplantation.

Response to sequential treatment. In terms of CR rate, the sequential treatment is better than chemotherapy (i.e. the actually observed CR is higher than that expected after chemotherapy) in both risk groups (low risk, p =0.02; high risk, p =0.001).

The 2-year OS advantage was 10% (p=0.02), 17% (p=0.03), 31% (p=0.11) and 63% (p=0.001) in the 4 risk groups whereas the 2-year DFS advantage was 12% (p=0.16), 26% (p=0.001), 38% (p=0.03) and 49% (p=0.02). Even more striking are the 5-year projected advantages both in terms of OS (17%, p=0.09; 31%, p=0.02; 44%, p=0.03; 68%, p=0.0007), and DFS (14%, p=0.13; 34%, p= 0.0001; 47%, p=0.01; 42%, p=0.002).

Major toxic events

Five major toxic events were recorded. A 31-year old female patient with anaplastic large cell lymphoma (ALCL) died of pulmonary vein thrombosis during conditioning. She was in PR due to a residual mediastinal mass, which was shown by autopsy to compress the pulmonary vein. In a second patient, a 45-year old male with ALCL, previously submitted to chemotherapy and radiotherapy to a residual mediastinal mass, symptomatic heart failure developed soon after transplantion. He is currently in CR and in

Table 5. Response to induction therapy according to the age-adjusted IPI.

Risk group	No. Pts	CR		PR		RES.		ASCT	
		N	%	N	%	N	%	N	%
Low	22	16	73.0	6	27.0	-	-	14	20.0
Low-intermediate	71	50	71.0	16	22.0	4	5.0	36	50.5
High-intermediate	30	14	45.0	8	28.0	9	31.0	11	15.5
High	21	11	52.0	5	24.0	5	24.0	10	14.0
TOTAL	144	91	63.2	35	24.3	18	12.5	71	49.3

Risk group	No. pts	CR/PR		RES		CR/PR vs RES
		N	%	N	%	*p*
Low	93	88	94.4	5	4.2	
High	51	38	74.0	13	28.0	0.0001

a stable cardiac condition (on chronic medication). A third patient, a 40-year old male with ALCL, developed immune thrombocytopenic purpura while in CR 32 months after transplantation. The fourth patient, a 54-year old female with a lymphoblastic lymphoma previously treated according to the ALL protocol, PB harvest after G-CSF priming and reinfusion with 5.3×10^8/kg MNC/kg b.w., developed a secondary acute myeloid leukemia while in CR 6 months after ASCT. She was treated, obtaining a CR, but subsequently died of relapse. The last patient, a 53-year old male with a lymphoblastic lymphoma, in CR after induction therapy, developed autoimmune hemolytic anemia. He is alive on medication.

Discussion

High-dose therapy with autologous stem cell transplantation for aggressive non-Hodgkin's lymphoma is recommended in different settings: for patients with a chemosensitive relapse; for high-intermediate and high-risk patients as consolidation of a complete remission; for partial responders after front-line therapy.[6]

Whereas there is consistent proof of the efficacy of ASCT in a sensitive relapse as shown by randomized studies,[26] the role of transplantation in partial or complete responders is still uncertain.[2,31] In particular the hypothesis that, in this setting, ASCT should be restricted to higher risk groups is based on a retrospective analysis[13,32] and must be confirmed in prospective, randomized studies.

Several investigators have reported the use of high-dose therapy with ASCT as part of primary treatment in patients with intermediate-high grade NHL, but only few randomized studies are focused on ASCT performed in complete or partial responders after induction therapy.

A French study considered the value of high-dose therapy and ASCT for newly diagnosed patients with aggressive NHL and no marrow involvement. Sixty hundred and fourteen patients (67%) out of 916 obtained a CR and 541 were subsequently randomized to sequential chemotherapy or ASCT. No differences in 5-year OS were observed between the two arms (67% vs 69%). In the higher-risk population (236, 47%) the 5-year OS and DFS rates were superior in the ASCT arm (125, 53%): OS 65% vs 52% (p=0.06); DFS 59% vs 39% (p=0.01). Twelve per cent of the patients were lost after achieving a CR and before the randomization, while about 26% were lost after randomization and before ASCT. Transplantation was compared with conventional chemotherapy: both arms did well with an OS of about 70%; no mention was made about the outcome of partial responders.[13] In 1998 Santini *et al*. randomized 124 patients between VACOP-B for12 weeks ± DHAP as salvage regimen and VACOP-B for 12 weeks + ASCT. The 6-year OS and DFS were comparable in both arms, but it should be kept in mind that at the time of randomization the response to induction therapy was not known, so ASCT was performed both in partial responders and in resistant patients. In a retrospective analysis, a statistically significant improvement in terms of DFS was observed for intermediate-high and high-risk patients. It must be underlined that about 70% of the patients in PR obtained a CR after ASCT, the feasibility of the procedure was the major problem in ASCT arm, and 29% of the enrolled patients did not undergo ASCT because of death, progression or refusal.[32]

In 1994 Gianni *et al.* randomized patients with newly diagnosed aggressive B-cell NHL (marrow negative) to 12 cycles of MACOP vs high-dose sequential therapy and ASCT. The 7-year event-free survival rate demonstrated a statistically significant advantage for the transplanted group while OS did not. This series has not been subsequently updated.[11]

Finally Verdonk *et al.* in 1995 showed that early application of high dose marrow-ablative chemoradiotherapy did not improve outcome in a cohort of 69 patients who were partial responders to first-line therapy. Eight out of 34 patients assigned to ASCT did not proceed to it; among the others, ASCT produced a conversion from partial to complete response of about 88%.[33]

A comparison between these studies and our experience seems difficult but some points emerge and should be highlighted: 1) studies dealing with the use of high-dose therapy in first remission are substantially of two types: ASCT is performed either upfront in a sequential setting, or after an abbreviated or full course of conventional chemotherapy. In the former context, results of transplant in remission are weighted by the intention-to-treat view of the analysis; in the second context patients are selected by response; 2) for many reasons the feasibility of the procedure is only about 60-70%; 3) ASCT converts partial to complete response in more than 70% of the cases; 4) the outcome of patients who obtain CR with ASCT is as good as that of patients transplanted in CR.

Meeting highlights, educational sessions and workshop discussions point out that conventional chemotherapy cures the majority of intermediate and high-grade NHL and, apart from a subset of high-risk patients, the strategy of transplanting all patients responding to induction therapy does not seem correct from an ethical point of view. Despite this, it seems reasonable to explore at diagnosis all the chances in order to obtain the best response.

The aim of our study was to define the impact of a sequential program including ASCT performed in first remission on the outcome of a group of patients with aggressive NHL.

The response rate to the induction therapy in our group was 87.5% (CR 62%), which could be considered a good result. No deaths during front-line therapy occurred and only 18 patients were considered resistant. Of the 126 patients who obtained a response (complete or partial) after first-line therapy, 71 (56%) were subsequently submitted to transplant according to the aim of our protocol. Reasons for exclusion were predominantly non-medical; infact protocol violation (that means patients considered eligible to receive the entire program but who did not complete it for reasons other than clinical ones) and patient refusal accounted for 49% of unperformed transplants (27 patients), while relapse or progression was the reason for not performing the transplant in only 10 (18%) patients.

Comparing the two groups (transplanted vs non-

transplanted patients) two statistically significant differences emerge: the median age (younger patients in the transplanted group - 39 vs 48 years) and the distribution according to the protocol risk factors (in favor of the non-transplanted patients). These two differences could explain, in part, the violations of the protocol. It should be underlined that the distribution according to the age-adjusted I.P.I. was similar in the two groups, with the majority of the patients included in the L-I risk category in both arms.

Analyzing the distribution of histologic subtypes between transplanted vs not transplanted patients (as detailed in Table 1), few differences emerge. While around 2/3 (61.5%) of the patients with lymphoblastic lymphoma and almost all (89.0%) with anaplastic large cell lymphoma completed the program, less than 1/3 (27.5%) of those with T-peripheral and follicular lymphoma (31.5%) were submitted to ASCT. It is not easy to explain this, but the majority of the resistant/relapsed patient were in the T-peripheral group, while nearly all the protocol violations were registered in the follicular lymphoma group.

In the ASCT group no patients relapsed after achieving a CR while the relapse rate in the other group was 31%. Using a multivariate analysis to test negative factors that could predict a poor outcome in the cohort of responding patients, the only factor that correlated positively with PFS was performing the transplant and this correlation was not time related. This conclusion (which seems obvious as no events happen in the ASCT arm) reinforced the idea that ASCT in a series of patients managed with the intention to transplant is a prognostic factor independent of the time necessary to reach the procedure which represents a system of selecting patients with a good prognosis (stable response, no early progression, successful harvest and so on).

In our cohort of patients the I.P.I. score also predicts response to first-line therapy, but the outcome of responding patients, as we have already published,[34] depends on the transplant being performed. This means that ASCT confers an advantage in all the risks groups, and so it should be performed independently of the risk group.

In our hands, the feasibility of such a program, including ASCT in first remission, is only about 50%: the major contribution to this low rate was non-medical reasons. Despite the good results in the transplant arm, the impact on the survival of the whole population is not so relevant.

In our experience, transplantation was performed only occasionally in other stages of disease (resistant or relapsing disease). It seems that multicenter studies overestimate this chance.

In conclusion, and with the limitations of a small single center series, the review of our experience strongly emphasizes the concept that a second chance in the treatment of high-grade lymphoma is often theoretical and that an intensive program should be applied at diagnosis (total therapy: chemotherapy ± radiotherapy + ASCT).

The other message that should be considered is that in a time-dependent multivariate analysis, performing the transplant seems to be the only statistically significant prognostic factor for PFS: that means that we should try to perform the transplant as soon as possible in order to avoid early relapse/progression.

Considering that the I.P.I. could identify resistant patients (as mentioned above), a big effort should be made to discover different, more intensive induction therapies in order to rescue these patients for ASCT in remission. Our data, as those already published, show that at least a partial response to induction therapy could be enough to predict a good outcome after ASCT.

The results in terms of prolonged survival and the toxicity of the protocol in the transplanted arm represent good reasons to force patients in this direction and so to reduce the reasons for exclusion (in particular protocol violation and patient refusal).

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RF and AS were the main investigators and designed the study, reviewed clinical data and performed the literature revision; they wrote the article and were responsible for the data interpretation. CRE carried on the statistical analysis. FZ was responsible for the lymphoma protocol and for the inclusion of the patients. RS, AG, MC and FP and MFC were responsible for the clinical management and direct clinical data acquisition. DD was responsible for the harvest and laboratory analysis procedures. MB was the main co-ordinator of the group and reviewed the article to obtain the final form. Name appearance was decided according to previous criteria.

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Potential implications for clinical practice

- ASCT gives an advantage in term of CR rate and PFS not related to the I.P.I. score (all the risk groups do better after transplant).
- ASCT improves the quality of the response in about 90% of the patients and maintains it overtime.
- A big effort should be made to discover different induction therapies in order to rescue resistant patients for ASCT at least in partial remission

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