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Risk assessment in diffuse large cell lymphoma at first relapse. A study by the Italian Intergroup for Lymphomas

CESARE GUGLIELMI, MAURIZIO MARTELLI, MASSIMO FEDERICO, PIER LUIGI ZINZANI, UMBERTO VITOLO, GIAMPIERO BELLESI, GINO SANTINI, CORRADO TARELLA, FRANCESCO ZALLIO, PATRIZIA PREGNO, NICOLA DI RENZO, LUIGI RESEGOTTI

On behalf of the Italian Intergroup for Lymphomas with: Gruppo Italiano di Studio sui Linfomi (GISL), Gruppo Roma-Bologna, Gruppo Multiregionale, Non-Hodgkin's Lymphoma Study Group (NHLSG), Cattedra e Divisione di Ematologia, University of Florence, Divisione di Ematologia, University of Turin and Dipartimento di Biotecnologie Cellulari ed Ematologia, University "La Sapienza", Rome, Italy

Background and Objectives. Our aim was to identify risk factors in adults with diffuse large cell lymphoma (DLCL) at first relapse.

Design and Methods. We studied 474 patients observed at 45 centers in Italy. The median time from diagnosis to relapse was 395 days, the median age at relapse was 55 years and the median follow-up from relapse was 3.3 years. Salvage therapy consisted of polychemotherapy in 79% of patients, monochemotherapy and/or radiotherapy and/or surgery alone in 16%, and palliative therapy in 5%. Salvage treatment was intensified with high-dose chemotherapy + stem cell transplant in 20% of patients. Overall survival (OS) and progression-free survival (PFS) were compared by sex, International Prognostic Index at diagnosis, histology, B/T phenotype, initial treatment, salvage therapy, and features at relapse: time from diagnosis, lactate dehydrogenase (LDH), stage, performance status and bone marrow involvement. Cox models, adjusted for salvage therapy, were performed with factors related to overall survival and progression-free survival.

Results. Overall response (complete + partial) was 63%, OS at 3 years 35% and PFS at 3 years 26%. Relapse within 12 months from diagnosis, elevated serum LDH, advanced stage and poor performance status were independent adverse factors for OS and PFS. The cumulative number of adverse factors is proposed as a prognostic index for DLCL at first relapse since it identifies risk groups (p<0.0001) and has been validated (p=0.01). Moreover, it predicts OS and PFS in the selected group of patients with a responsive relapse (p<0.0001).

Correspondence: Dr. Cesare Guglielmi, MD, Dipartimento di Biotecnologie Cellulari ed Ematologia, Università "La Sapienza", via Benevento 6, 00161 Roma, Italy.
Phone: international +39.06.857951.
Fax: international +39.06.44241984.
E-mail: guglielmi@bce.med.uniroma1.it

Interpretation and Conclusions. Delay from initial diagnosis, LDH, stage and performance status at relapse should be balanced in comparative studies of salvage therapy of adults with DLCL. Patients with more than 2 adverse factors account for one third of all cases and deserve more effective salvage treatments.

Key words: lymphoma, relapse, prognosis, adults, transplantation.

A significant proportion of patients with histologically aggressive non-Hodgkin's lymphoma relapse after achieving a complete response (CR) with combination chemotherapy.[1-6] Different salvage chemotherapy regimens induce CR or partial response (PR) in more than 50% of such patients[7-12] and those with sensitive relapses benefit from adjuvant high-dose therapy (HDT) with autologous stem cell transplant (SCT).[13] However, it appears that a worse prognosis is associated with an early relapse or with any of the following features at relapse: poor performance status, large tumor mass, high lactate dehydrogenase (LDH) levels, more than 3 nodal sites or an advanced Ann Arbor stage.[8,14-18] More recently, the age-adjusted International Prognostic Index (IPI)[19] at relapse was associated with both overall survival (OS) and progression-free survival (PFS) and its prognostic value was independent from time to relapse.[20-21] These results must be validated on other series, since they were achieved either in single institutions[8,14,16,18] or in the selected group of adults aged less than 60 years who were enrolled in the PARMA trial.[17,20,21] Moreover, while the majority of

patients included in the PARMA trial had histologic types which for clinical purposes are grouped as diffuse large cell lymphoma (DLCL), a significant number had histologic types (ie. lymphoblastic lymphoma, diffuse small non-cleaved cell lymphoma, follicular large cell lymphoma and diffuse small-cleaved cell lymphoma) with clinical behaviors different from that of DLCL.[22-25]

Therefore, in Italy, we analyzed prognostic factors for OS and PFS after first relapse in 474 patients with DLCL selected from a large cohort of patients enrolled in prospective trials of initial therapy with an anthracycline-containing combination chemotherapy regimen.

Design and Methods

Patients

Between January 1987 and April 1997, 1,775 patients aged 13-81 years (median age 50 years) were initially treated with an anthracycline-including combination chemotherapy regimen for DLCL (patients with lymphoblastic lymphoma or Burkitt's lymphoma or with HIV infection were excluded) at 41 Italian centers participating in clinical trials. Many of the patients have been previously described in reports of initial treatment.[29-37] Overall, 1,247 patients (70%) achieved a CR and, as of June 1998, 494 of them (40%) had relapsed. The first relapse occurred in May 1988, the last in April 1998.

Information on pathologic and clinical features of the disease at time of first diagnosis, date of first relapse and survival status at last follow-up were prospectically registered at each participating center. The information on some selected features of the disease at relapse, modality of salvage therapy and results of such treatments were obtained retrospectively. Questionnaires were sent to participating centers in June 1998 and as of December 1998 they had been collected for a total of 474 patients. Therefore, 96% of relapsed patients could be evaluated. The median follow-up time from first relapse was 38 months.

Statistics

Potential prognostic factors were scored as follows: sex (male vs female), age at relapse (<65 years vs ≥65 years), histologic grade according to the Working Formulation (WF) for clinical usage[21] (intermediate grade vs high grade), histologic type according to the *Revised European American Lymphoma* (REAL) classification[22] (diffuse large B-cell vs peripheral T-cell vs anaplastic large-cell), tumor immunophenotype (B vs T), IPI at diagnosis (<3 vs >3), initial chemotherapy regimen (weekly vs others), time to relapse (<12 months from initial diagnosis vs ≥12 months), Ann Arbor stage at relapse (I-II vs III-IV), LDH levels at relapse (normal vs elevated), World Health Organization (WHO) performance status at relapse (0-1 vs >1), bone marrow involvement at relapse (yes vs no), therapy at relapse (chemotherapy and/or radiotherapy and/or surgery alone vs palliative therapy), intensity of therapy at relapse (polychemotherapy ± radiotherapy vs single drug chemotherapy and/or radiotherapy and/or surgery alone), and polychemotherapy regimen at relapse (salvage regimen vs 1st or 3rd generation regimen). The association between variables was analyzed by the chi-squared test, with the appropriate degrees of freedom. All tests were two-sided, and a p value of less than 0.05 was considered to indicate statistical significance. Actuarial probabilities at 3 years are reported throughout, if not otherwise specified.

OS was calculated from date of relapse to death or to last follow-up and PFS from date of relapse to the first evidence of progressive disease, relapse or to the last follow-up. Actuarial curves were computed according to the Kaplan and Meier method[26] and compared by the two-sided log rank test.[27] Patients for whom all of the variables potentially having prognostic value were assessed constituted the group in which a Cox proportional-hazards model according to a backward selection was constructed to detect independent predictors of OS and PFS.[28] Validation of criteria for the definition of risk after relapse were performed by log-rank on patients, selected from among those excluded from the previous group, for whom, however, all of the variables contributing to the Cox models had been assessed. The prognostic value of independent factors and of therapy at relapse was also evaluated in the whole population and in treatment subgroups.

Results

Salvage therapy and outcome

Three hundred and seventy-three patients (79%) were treated at relapse with combination chemotherapy (associated with radiotherapy in 59 cases): their median age at time of relapse was 58 years (16-85) with 17% of them older than 65 years. Their overall response rate was 66% (157 CR, 91 PR), OS and PFS were 0.35 and 0.25, respectively. Various regimens were employed at relapse: a 1st or 3rd generation regimen in 93 patients, a salvage regimen in 216 patients. Salvage regimens consisted of dexamethasone+cytarabine+cisplatin (DHAP) in 55 patients, ifosphamide+etoposide based regimen in

Table 1. Therapy at relapse and outcome.

	Patients		RR*	OS°	PFS°
Salvage therapy					
Combination chemotherapy±RT	373		66%	35±2	25±2
1st or 3rd generation regimen	*93*		70%	35±5	23±4
Salvage regimen	*216*		68%	36±3	26±3
DHAP		55	66%	30±6	19±5
IFO+ETO based		56	75%	42±7	28±6
Mito±ETO±CYTA		64	63%	28±6	23±5
Other		41	68%	44±8	36±7
Unknown regimen	*64*		56%	32±6	27±6
Monochemotherapy and/or RT and/or surgery alone	78		63%	39±6	26±5
Palliative	23		0%	9±6	4±4#
Total	474		63%	35±2	26±3

*Abbreviations: RR, response rate; OS, overall survival; PFS, progression-free survival; CR complete response; PR, partial response; RT, radiotherapy; DHAP, dexamethasone+cytarabine+cisplatin.[8] IFO, ifosfmide; ETO, etoposide; Mito, mitoxantrone; CYTA, cytarabine; *complete or partial response; °actuarial% at 3 years±standard error; #actuarial% at 2 years±standard error.*

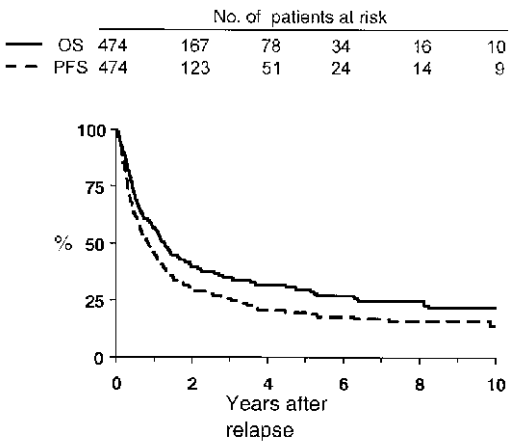

Figure 1. Actuarial overall survival (OS) and progression-free survival (PFS) from first relapse in 474 patients with diffuse large cell lymphoma.

56, mitoxantrone±etoposide±cytarabine based regimen in 64, and other combinations in 41. No significant differences were recorded in the outcome according to the type of combination chemotherapy. Seventy-eight patients (16%) received less intensive treatments (single agent chemotherapy in 34, single agent chemotherapy with radiotherapy in 7, radiotherapy alone in 32 and surgery alone in 5). The median age of these patients at time of relapse was 64 years (20-83) with 60% of them being older than 65 years. Their response-rate was 63% (23 CR, 24 PR), OS and PFS were 0.39 and 0.26, respectively.

Another 23 cases (5%), with a median age of 67 years, received only palliative therapy. None of them responded, OS was 0.09, and PFS at 2 years was 0.04. In 95 patients salvage treatment was intensified by HDT and SCT (91 autologous, 3 allogeneic from an HLA-identical sibling and 1 syngeneic). The median age of these patients at time of relapse was 43 years (range 16-66). Eighty-seven patients were in CR or PR at time of intensification, 4 were stable, 3 had progressive disease and 1 was not evaluated (Table 1).

So far, 162 responders (94 CRs and 68 PRs) have relapsed or progressed at a median time of 9 months (range 2-118 months): 92% within 3 years of relapse. Overall, 309 patients have died and 165 are alive. Among responders, 61 CRs died after relapse, 60 PRs died after disease progression and 17 (9 CRs and 8 PRs) died without disease relapse or progression. OS and PFS in all patients were 0.35 and 0.26, respectively, but the majority are expected to die or to have treatment failure within 2 years of the relapse (Figure 1). OS and PFS in patients intensified with HDT and SCT were 0.52 and 0.41, respectively (not shown).

Prognostic factors for overall survival and progression-free survival

The univariate analysis is summarized in Table 2. The patients' sex and age at relapse did not significantly influence OS and PFS. According to the WF,[21] patients with high-grade histology had a significantly worse OS and PFS than patients with intermediate-grade lymphoma. By contrast, the histologic group of the REAL classification[22] and tumor immunophenotype had no significant prognostic value for OS and PFS. IPI at diagnosis was correlated with OS and PFS: patients scoring ≥3 had a worse outcome after relapse than those scoring <3. Initial chemotherapy regimens, classified as weekly vs others, had no prognostic value after relapse: the 2 groups were comparable both for age at relapse (median age was 55 years in both groups) and overall response to salvage therapy (59% in those receiving a weekly regimen vs 64% in the others, p = n.s.). In our study, the strong predictive value of time to relapse is confirmed: patients who relapse within 12 months from the initial diagnosis have a significantly shorter OS and PFS than those relapsing later. Half of the patients

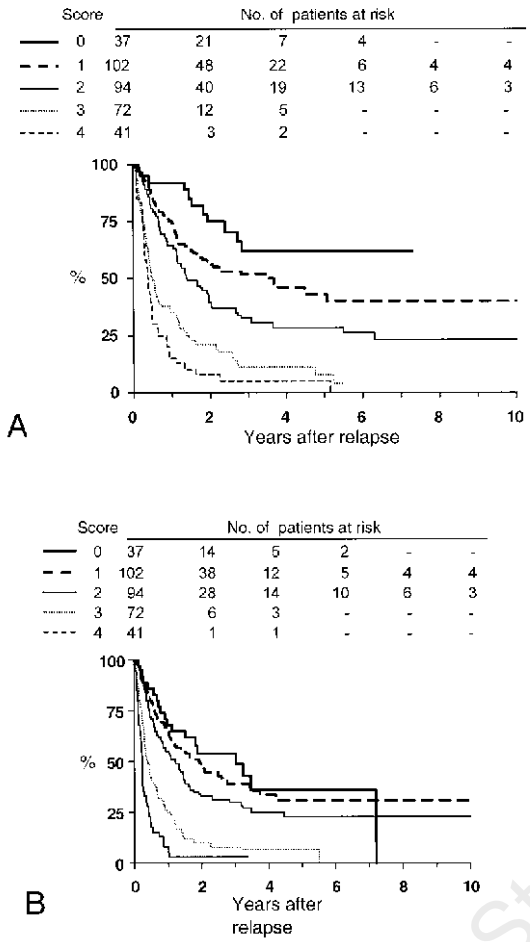

Figure 2. Actuarial curves from first relapse in 346 patients with diffuse large cell lymphoma according to the risk category as predicted by 4 variables at relapse (time from diagnosis, LDH levels, Ann Arbor stage and WHO performance status): score 4 means time from diagnosis <12 months, LDH above upper normal level, stage III-IV and performance status >1; score 3, 2, 1 and 0 mean 3, 2, 1 and 0 of the bad prognostic variables, respectively. A, overall survival; B, progression-free survival.

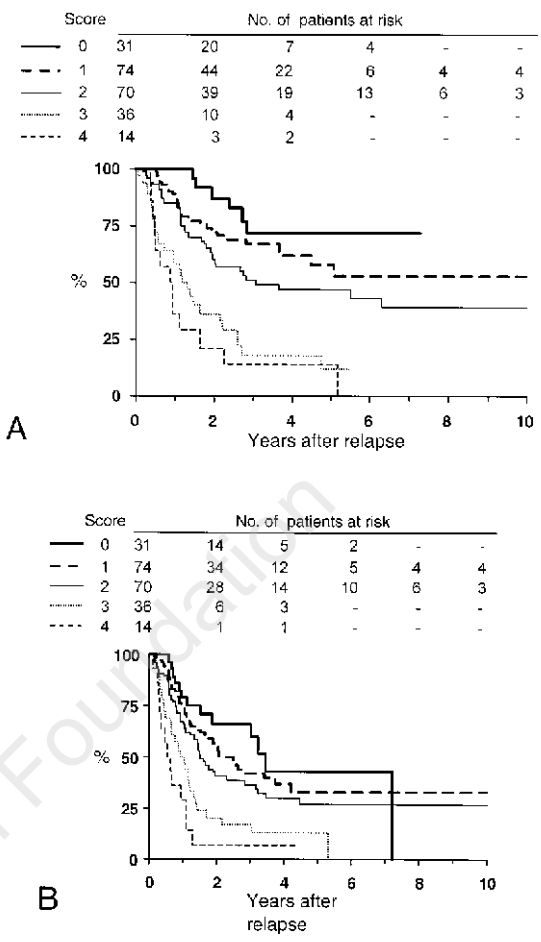

Figure 3. Actuarial curves from first relapse in 252 evaluable patients with a sensitive relapse of diffuse large cell lymphoma according to the risk category as predicted by 4 variables at relapse (time from diagnosis, LDH levels, Ann Arbor stage and WHO performance status): score 4 means time from diagnosis <12 months, LDH above upper normal level, stage III-IV and performance status >1; score 3, 2, 1 and 0 mean 3, 2, 1 and 0 of the bad prognostic variables, respectively. A, overall survival; B, progression-free survival.

with an early relapse died within 7 months and only 22% of them are expected to be alive at 3 years. In contrast, the median OS of patients relapsing later is 2 years with a 46% projection at 3 years. We found that other factors at relapse (ie. Ann Arbor stage, LDH serum levels and performance status) had statistically significant effects on OS and on PFS in the univariate analysis. Bone marrow involvement at relapse was related to shorter OS and PFS than in patients without such a feature, but the difference was not statistically significant. Multivariate analysis of prognostic factors for OS and PFS was performed on 283 of our patients (60%) in whom all of the following variables were assessed: WF histology, IPI score at diagnosis, time to relapse, stage at relapse, LDH at relapse and PS at relapse. Their OS and PFS were comparable to the OS and PFS of the other 191 patients excluded because of missing variables.

Time to relapse, LDH serum levels, performance status and Ann Arbor stage contributed to the Cox models for OS and PFS (Table 3A). Histology and IPI

Table 2. Features of 474 patients and outcome after first relapse.

Features	*No.*	*OS*[1]	*p*	*PFS*[1]	*p*
Sex					
Female	218	34±2.4	>0.10	28±2.5	>0.10
Male	256	35±2.2		24±2.4	
Age (years)[2]					
<65	353	36±2.7	0.22	27±2.5	>0.10
≥65	121	31±4.6		22±4.3	
Histology by WF					
Intermediate-grade	216	39±3.5	0.01	30±3.3	<0.01
High-grade	207				
Histology by REAL					
Diffuse large B-cell	294	33±2.2	>0.10	26±2.6	>0.10
Peripheral T-cell	68	38±5.1		24±2.9	
Anaplastic large cell	31	34±5.3		15±4.0	
Immunophenotype					
B	311	34±3.2	>0.10	26±2.5	>0.10
T	74	38±5.8		24±3.1	
IPI at diagnosis					
<3	294	40±3.0	<0.01	30±2.8	<0.01
=3	130	24±4.0		16±3.5	
Initial chemotherapy regimen					
Weekly	217	31±2.2	>0.10	23±2.3	>0.10
Others	257	38±3.2		28±2.8	
Time to relapse[3]					
=12 months	259	46±3.3	<0.01	32±3.2	<0.01
<12 months	215	27±2.7		18±2.7	
Ann Arbor stage[2]					
I-II	158	51±4.3	<0.01	35±4.2	<0.01
=III-IV	310	27±2.7		21±2.4	
LDH[2]					
Normal	195	48±3.9	<0.01	38±3.7	<0.01
Elevated	161	18±3.2		10±2.6	
WHO performance status[2]					
0-1	263	47±3.3	<0.01	35±3.2	<0.01
>1	194	19±3.0		14±2.6	
Bone marrow involvement[2]					
No	289	42±2.7	>0.10	32±2.5	>0.10
Yes	89	33±4.9		20±2.9	
Total	474	35±2.4		26±2.6	

Abbreviations: OS, overall survival; PFS, progression-free survival; WF, Working Formulation;[22] REAL, revised European American classification of lymphoid malignancies;[23] IPI, International Prognostic Index;[19] LDH, lactate dehydrogenase; WHO, World Health Organization.[1]actuarial % at 3 years±standard error; [2]at time of first relapse; [3]interval from the initial diagnosis to the first relapse.

at diagnosis were not independent prognostic factors in these models. The prognostic value of the 4 independent prognostic factors and of therapy at relapse was also evaluated in the whole population and in treatment subgroups. Giving palliative therapy at relapse was a poor prognostic factor for OS and PFS (Table 3B). In contrast, OS and PFS were not significantly influenced by intensity of therapy at relapse (Table 3C) or by polychemotherapy regimen at relapse (Table 3D). Relative risks associated with each of the four prognostic variables (time to relapse, disease stage, LDH serum levels, and performance status) in models including the kind of therapy at relapse (Table 3B, C, and D) are comparable to those in the model not taking into account therapy at relapse (Table 3A).

Prognostic index for patients at first relapse

After our prognostic analysis, we attempted to generate a new prognostic index for patients with DLCL at first relapse with 4 non-exclusive binary variables: time from diagnosis to relapse (0, ≥12 months; 1, <12 months), LDH at relapse (0, below upper normal level; 1, above upper normal level), Ann Arbor stage at relapse (0, I-II; 1, III-IV) and WHO performance status at relapse (0, 0-1; 1, >1). The 4 independent prognostic factors were all assessed in a total of 346 patients: 283 in the Cox model and 63 previously excluded from the Cox model not having been assessed for WF histology and/or IPI at diagnosis. The sum score predicts OS and PFS both in the former (p<0.0001) and in the latter group (p=0.01), thereby validating this prognostic index. Eleven percent of our 346 evaluable patients scored 0 with this new index, 29% scored 1, 27% scored 2, 21% scored 3 and 12% scored 4. These groups had comparable median age at relapse, ranging from 56 years in those scoring 0 to 50 years in those scoring 4. Moreover the mean score was 1.94 both in the 67 evaluable patients older than 65 years at relapse and in the 279 younger evaluable patients. The new index discriminates distinct prognostic groups: the probability of OS was 0.62, 0.52, 0.38, 0.11, and 0.05 in patients scoring 0, 1, 2, 3 and 4, respectively (p<0.0001)(Figure 2A). The median OS was 4, 6, 21, 42 months and >7 years in patients scoring 4, 3, 2, 1 and 0, respectively. PFS ranged from 0.54 in score 0 patients to 0.03 in score 4 ones (p<0.0001)(Figure 2B). Overall response rate to salvage therapy was strongly correlated to this new prognostic index, ranging from 81% in patients scoring 0 to 29% in those scoring 4 (p<0.0001). We, therefore,

also calculated actuarial curves by this index in 252 patients with a sensitive relapse: OS probability was 0.72, 0.67, 0.52, 0.18, and 0.14 in patients scoring 1, 2, 3 and 4, respectively (p<0.0001, Figure 3A). PFS ranged from 0.66 in score 0 patients to 0.07 in score 4 ones (p=0.0021)(Figure 3B). Intensification with HDT and SCT was performed in 20% of responders scoring 0, 33% scoring 1, 31% scoring 2, 32% scoring 3, and 42% scoring 4 (p = n.s.). The probability of OS ranged from 0.71 in score 0 patients to 0.14 in score 4 patients (p=0.0008) in those with responsive relapses who were given intensified treatment with HDT and SCT (not shown). PFS ranged from 0.58 in score 0 to 0.00 in score 4 (p=0.0065), in the same group of patients (not shown).

Discussion

So far, this is the first retrospective multicenter prognostic study in an unselected group of adults with DLCL at first relapse. With the aim of identifying the more relevant prognostic features in patients with DLCL at first relapse, we wished to minimize any patient selection which may have influenced the results of previous prognostic studies in relapsed aggressive NHL.[8,14-18,20-21] We, therefore, included the great majority of relapses observed in a large cohort of patients who achieved CR in prospective trials of initial treatment with an anthracycline-including regimen at 41 Italian centers.

Most of our patients received an effective salvage therapy. In fact, including all cases, 62% achieved a complete or a partial response and 35% are expected to survive 3 years after their first relapse. These results, obtained without any patient selection, are certainly comparable to those achieved with the more effective salvage chemotherapy regimens, showing that this series is appropriate for an analysis of prognostic factors.[7-12] In our series, which includes mainly relapses observed before 1995, the outcome was not significantly correlated to a specific salvage regimen and only a minority of patients with responsive relapse received intensified treatment by HDT and autologous SCT in agreement with the indications of the PARMA study.[13] Unfortunately, the intention to intensify treatment with transplant after response to salvage therapy was not known in our retrospective study. Therefore, intensification with transplant was not included in our prognostic analysis. Despite the limitations of this analysis, ie. treatment at initial diagnosis and at relapse not being uniform, it confirms the previous information that patients with DLCL at first relapse may have quite different outcomes depending on time from diagnosis to relapse, LDH at relapse, Ann Arbor stage at relapse, and performance status at relapse.[16,17,19] These four

Table 3. Multiple regression analysis of prognostic factors after relapse (Cox model).

A. All patients are analyzed without therapy at relapse being included into the model.

	Overall survival			Progression-free survival		
Factor	RR	CI95	p	RR	CI95	p
Time from diagnosis to relapse[a]	1.6	1.2-2.1	<0.01	1.5	1.1-1.9	<0.01
Ann Arbor stage at relapse[b]	1.5	1.0-2.0	=0.03	1.3	1.0-1.8	=0.04
LDH level at relapse[c]	1.9	1.4-2.5	<0.01	1.7	1.3-2.3	<0.01
WHO performance status at relapse[d]	2.3	1.7-3.2	<0.01	2.0	1.5-2.7	<0.01

B. All patients are analyzed and therapy at relapse is introduced into the model.

	Overall survival			Progression-free survival		
Factor	RR	CI95	p	RR	CI95	p
Time from diagnosis to relapse[1]	1.8	1.4-2.4	<0.01	1.6	1.2-2.0	<0.01
Ann Arbor stage at relapse[2]	1.4	1.1-1.9	=0.02	1.2	0.9-1.5	=0.09
LDH level at relapse[3]	1.7	1.3-2.2	<0.01	1.7	1.3-2.2	<0.01
WHO performance status at relapse[4]	1.9	1.5-2.5	<0.01	1.8	1.4-2.4	<0.01
Therapy at relapse[5]	4.4	2.2-9.1	<0.01	4.4	2.2-8.7	<0.01

C. All patients but those given palliative therapy at relapse are analyzed and intensity of therapy at relapse is introduced into the model.

	Overall survival			Progression-free survival		
Factor	RR	CI950	p	RR	CI950	p
Time from diagnosis to relapse[1]	1.9	1.4-2.4	<0.01	1.6	1.3-2.0	<0.01
Ann Arbor stage at relapse[2]	1.5	1.1-2.0	<0.01	1.2	0.9-1.6	=0.12
LDH level at relapse[3]	1.7	1.3-2.2	<0.01	1.7	1.3-2.2	<0.01
WHO performance status at relapse[4]	1.9	1.5-2.5	<0.01	1.8	1.4-2.4	<0.01
Intensity of therapy at relapse[6]	1.3	0.9-1.8	=0.18	1.1	0.8-1.6	=0.42

D. Patients given polychemotherapy ± radiotherapy at relapse are analyzed and polychemotherapy regimen at relapse is included into the model.

	Overall survival			Progression-free survival		
Factor	RR	CI95	p	RR	CI95	p
Time from diagnosis to relapse[1]	1.7	1.3-2.3	<0.01	1.5	1.2-2.1	<0.01
Ann Arbor stage at relapse[2]	1.7	1.2-2.4	<0.01	1.2	0.9-1.6	=0.21
LDH level at relapse[3]	1.8	1.3-2.4	<0.01	1.7	1.3-2.3	<0.01
WHO performance status at relapse[4]	2.2	1.6-3.0	<0.01	2.2	1.6-2.9	<0.01
Polychemotherapy regimen at relapse[7]	1.1	0.8-1.6	=0.41	1.1	0.8-1.5	=0.42

Abbreviations: RR, risk ratio; CI95, 95% confidence interval; LDH, lactate dehydrogenase; WHO, World Health Organization. [1]coded 0 = ≥12 months; 1= <12 month; [2]coded 0 = I-II; 1= III-IV; [3]coded 0 = normal; 1= increased; [4]coded 0 = 0-1; 1= >1; [5]coded 0 = chemotherapy and/or radiotherapy and/or surgery alone; 1=palliative therapy; [6]coded 0 = polychemotherapy ± radiotherapy; 1 = single drug chemotherapy and/or radiotherapy and/or surgery alone; [7]coded 0 = salvage regimen; 1= 1st or 3rd generation regimen.

factors retain a prognostic value independently of therapy given to patients at first relapse. A risk index, based on the number of adverse factors present at the time of the first relapse, has been developed and validated. It is relevant that this risk index not only correlates with response to salvage therapy, but that it also predicts OS and PFS in the selected group of patients with sensitive relapses. Patients with 3 or 4 risk factors, representing 33% of all cases and 22% of those with a sensitive relapses, have a dismal outcome and therefore may enter prospective trials of new treatment strategies. Our additional observation that with this index we may identify risk groups in sensitive relapses intensified with transplant confirms a suggestion deriving from the prognostic analysis of time to relapse and age-adjusted IPI at relapse in the PARMA study, but this should be validated by larger studies.[21]

Surprisingly, the patient's age at relapse has no prognostic relevance to OS and PFS. This deserves consideration since no age restriction was applied in most trials from which we derived the relapsed cases. We also included relapses observed in 2 treatment trials designed for patients older than 60 years[29-32] and this should compensate some age restriction adopted in a few other trials. We suspect that the relatively low proportion of younger adults who received intensified treatment after response may obscure a prognostic value of age at relapse in our series. It is possible that age at relapse will have prognostic value when most younger responders are given intensified treatment. Elderly patients, ie. those older than 65 years at relapse, represented a significant proportion of our relapsed cases and deserve specifically designed prospective trials of salvage therapies.

Another result of this study is the lack of a negative prognostic value of T-cell immunophenotype as compared to the B-cell variant in a large series of DLCL, confirming a previous observation in patients of the PARMA trial.[17] Moreover, as in the PARMA trial,[17] the distinction of DLCL into intermediate-grade or high-grade according to the WF is not an independent prognostic factor. Finally, the more recently proposed REAL classification has no prognostic relevance in our relapsed patients. Therefore, we believe that other biological aspects of the diseases that we encompassed in the DLCL group, may reveal features with prognostic relevance for patients at first relapse. Mutation of p53,[38] tumor proliferative index,[39-41] over-expression of bcl-2[42-48] and CD44 antigen expression[49] have been associated with clinical outcome in patients with DLCL at diagnosis. Mutation of p53 and low tumor proliferation, but not bcl-2 expression, are associated with clinical drug resistance in relapsed/refractory non-Hodgkin's lymphoma of various histologies.[50] Further studies may define the prognostic value of such biological features of the disease in patients with DLCL at first relapse. Only a minority of our cases were re-biopsied at the time of the first relapse; we, therefore, included in the prognostic study the pathologic features of the disease, ie. histological classification and tumor immunophenotype, as prospectically defined at diagnosis. The emergence of a histologically different and sometimes less aggressive variant of the disease at relapse can be observed in DLCL particularly among late relapses.[16,51-55] This may partially account for the prognostic value of time to relapse and suggests that the prognostic value of histologic shift should also be explored.

In conclusion, patients with DLCL at different risks may be easily identified at the time of the first relapse by an index calculated from time to relapse, LDH levels, stage and performance status. We propose utilizing this index to stratify patients with DLCL at first relapse in prospective comparative trials of salvage therapy. We acknowledge that a more extensive validation of this index may be necessary also in other countries, and particularly on series in which a higher proportion of patients with sensitive relapse are given intensified treatment with HDT and autologous SCT.

Contributions and Acknowledgments

CG, MM, MF, PLZ, UV, GS, CT, and LR contributed equally to this work and were primarily responsible for it, from conception to submitted manuscript: they should be considered as the principal authors. The remaining authors qualified for authorship according to the World Association of Medical Editors (WAME) criteria, and have taken specific responsibility for the following parts of the content: GB, FZ, PP, NDR, collection of clinical data. Order of authorship. The authors are listed according to a criterion of decreasing individual contribution to the work, with the following exceptions: the first eight authors contributed equally to this article, while the last author had a major role as coordinator of the "Intergruppo Italiano Linfomi".

Disclosures

Conflict of interest: none.

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Potential implications for clinical practice

Improvement of therapy relies on comparative studies, and this prognostic index may facilitate comparison of therapies that are applied to patients with diffuse large cell lymphoma at first relapse.[56,57]

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Appendix

List of participating centers in alphabetical order (city, institution, responsible for this study).

1) Avellino, Divisione di Ematologia, Fioravante Ronconi; 2) Bari, Cattedra e Servizio Autonomo di Ematologia, Università degli Studi, Enzo Pavone; 3) Bari, Dipartimento di Scienze Biomediche, Sezione di Medicina Interna e Oncologia Clinica, Università degli Studi, Vito M. Lauta; 4) Bari, Unità Operativa di Medicina, Istituto Oncologico, Giuseppe Colucci; 5) Bologna, Istituto di Ematologia e Oncologia Medica "Lorenzo e Ariosto Seràgnoli", Pierluigi Zinzani, Massimo Magagnoli; 6) Bolzano, Ematologia, Ospedale Generale e Regionale, Paolo Coser; 7) Cagliari, Divisione di Ematologia, Ospedale Oncologico A. Businco, G. Luxi; 8) Cuneo, Divisione di Ematologia, Az. Ospedaliera S. Croce e Carle, A. Gallamini; 9) Firenze, Cattedra e Divisione di Ematologia, Università, Giampiero Bellesi; 10) Genova, Cattedra di Ematologia, Marco Gobbi; 11) Genova, DIMI A.M. Gatti, V. Secondo; 12) Genova, Divisione di Ematologia 1, Ospedale S.Martino, Gino Santini; 13) L'Aquila-Teramo, Clinica Medica, Università, Dennis Quaglino; 14) Melegnano (MI), Divisione di Medicina I e II , Ospedale di Circolo, Gian Piero Benetti; 15) Messina, Istituto di Clinica Oncologica, Università, Vincenzo Pitini; 16) Milano, Servizio di Ematologia, Centro "G. Marcora", IRCCS Ospedale Maggiore, Anna Teresa Maiolo; 17) Modena, Medicina Interna, Oncologia ed Ematologia, Università, Vittorio Silingardi; 18) Napoli, Cattedra di Ematologia, Università Federico II, Amalia De Renzo; 19) Novara, Divisione di Medicina, Ospedale Maggiore, M.C. Bertoncelli; 20) Palermo, Cattedra e Divisione di Ematologia con T.M.O., Università, Guglielmo Mariani; 21) Pavia, Istituto di Ematologia, Policlinico S. Matteo, E. Brusamolino; 22) Pavia, Medicina Interna ed Oncologia Medica, IRCCS Policlinico "S. Matteo", Edoardo Ascari; 23) Perugia, Istituto di Medicina Interna e Scienze Oncologiche, Policlinico Monteluce, Marina Liberati; 24) Pescara, Dipartimento di Ematologia ed Oncologia, USL, Marco Lombardo; 25) Piacenza, Divisione di Medicina I, Sezione di Ematologia, Ospedale Civile, Luigi Cavanna; 26) Pisa, Dipartimento di Oncologia, Divisione di Ematologia, Az. Ospedaliera Pisana, Mario Petrini; 27) Potenza, Divisione di Ematologia, Ospedale S.Carlo, Michele Pizzuti; 28) Reggio Calabria, Divisione di Ematologia, Presidio Ospedali Riuniti "V.G. Melacrino", Maura Brugiatelli; 29) Reggio Emilia, Divisione di Ematologia, Azienda Ospedaliera "S. Maria Nuova", Luigi Gugliotta; 30) Roma, Cattedra di Ematologia, Università Cattolica Sacro Cuore, Sergio Storti; 31) Roma, Dipartimento di Biotecnologie Cellulari ed Ematologia, Università "La Sapienza", Maurizio Martelli; 32) San Giovanni Rotondo (FG), Divisione di Ematologia, IRCCS "Casa Sollievo della Sofferenza", Mario Carotenuto; 33) Siena, Divisione di Ematologia, Monica Bocchia; 34) Torino, Ematologia Ospedaliera San Giovanni Battista, Umberto Vitolo, Patrizia Pregno; 35) Torino, Divisione Universitaria di Ematologia, Ospedale Le Molinette, Corrado Tarella, Francesco Zallio; 36) Torino, Oncologia Medica, Ospedale Mauriziano, D. Rota Scalabrini; 37) Trento, Divisione di Medicina II, Gino Zambaldi; 38) Udine, Clinica Ematologica, Policlinico Universitario, Francesco Zaja; 39) Verona, Cattedra di Ematologia, Policlinico Borgo Roma, G. Todeschini; 40) Vicenza, Divisione di Ematologia, Teodoro Chisesi; 41) Vigevano (PV), Divisione di Medicina Generale, Ospedale Civile, Giuseppe Attardo Parrinello.