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Efficacy of two different ProMACE-CytaBOM derived regimens in advanced aggressive non-Hodgkin's lymphoma. Final report of a multicenter trial conducted by GISL

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Abstract

Background and Objective. **To compare the efficacy of ProME(Epidoxorubicin)CE-CytaBOM (PE-C) and ProMI(Idarubicin)CE-CytaBOM (PI-C) in the treatment of adult patients with aggressive non Hodgkin's lymphoma in a multicenter randomized controlled trial performed by 18 centers of the Italian Lymphoma Study Group (GISL).**

Design and Methods. **One hundred and twenty-eight and 122 patients were randomly assigned to receive either 6 courses of PE-C or PI-C, respectively. Some patients achieving complete remission with induction therapy participated in another randomized study comparing no further therapy versus maintenance therapy consisting of four blocks of two drugs.**

Results. **The rate of CRs was 62% and 64% for patients treated with PE-C and PI-C, respectively (p=0.51). The 5-year relapse-free survival was 60% for PE-C and 53% for PI-C (p=0.29). The estimated relapse-free disease survival rates at 4 years were 75% for patients in the consolidation group and 57% for those in the observation group (p=0.11). Patients alive in first complete remission 4 years after study entry were estimated to be 39% in the PE-C arm and 38% in the PI-C arm (p=0.90). The 3-year and 5-year estimated survival rates were 61% and 55% for the PE-C group and 56% and 47% for the PI-C group (p=0.26). Fatal toxicities occurred in 7 patients (2.9%) with active disease and in 4 patients (1.7%) in complete remission. Stage (p=0.04), bulky disease (p=0.02), serum LDH (p=0.0006), serum albumin (p=0.0051), hemoglobin (p=0.0011), performance status (p=0.0001), International prognostic index (p<0.0001) and the index proposed by the French group G.E.L.A. (p<0.0001) were of prognostic value. In a multivariate analysis (Cox regression model) alternatively IPI alone or G.E.L.A. index plus performance status emerged as independent prognostic factors.**

Interpretation and Conclusions. **The present study indicates that epirubicin and idarubicin in a combined chemotherapy regimen, have similar activities. The toxic profile also indicates the safety of both anthracyclines at the dosages employed, suggesting their possible dose escalation in a combined chemotherapy setting. PE-C and PI-C were both effective and feasible regimens in an outpatient setting, with acceptable cardiovascular toxicity. The trend toward a better outcome in patients undergoing consolidation therapy after the achievement of a complete remission, warrants further investigation.**

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Key words: non-Hodgkin's lymphoma, combined chemotherapy, ProMACE-CytaBOM, dose intensity, toxicity

Twenty years on from the introduction of the cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen, the optimal therapy of aggressive non-Hodgkin's lymphomas (NHL) is still a matter of debate.[1,2] Although no doubt exists that different doxorubicin-based regimens are effective therapies for patients with aggressive NHL,[3-8] the magnitude of the benefit of the so called second and third generation regimens over CHOP seems questionable.[9-14] In fact, although some prospective randomized trials have shown no advantage of second or third generation regimens over CHOP,[9-12] other groups have found a significant benefit with dose intensification, including the EORTC study comparing CHVmP vs CHVmP plus vincristine and bleomycin[13] and the Italian NCI study performed by Gianni *et al.*, comparing MACOP-B to more intensive therapy.[14]

In the mid '80s several pilot studies produced very promising results, suggesting that the majority of patients with advanced, diffuse, aggressive NHL could be cured. The combination of methotrexate, bleo-

mycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone (m-BACOD);[3] methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin (MACOP-B);[4] cyclophosphamide, doxorubicin, etoposide, prednisone, bleomycin, cytarabine, and methotrexate (ProMACE-CytaBOM);[5] doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisolone, and intrathecal methotrexate (ACVB)[6] all determined CR rates of over 80%, allowing the notion that significant progress in the cure of NHL had been achieved. However, these very promising results were not confirmed by large phase III randomized studies,[9-12,16,17] confirming that multicenter trials yield less favorable results in the attempt to reproduce the best results published in the literature. When ProMACE-CytaBOM was used in a multicenter trial by SWOG, the CR rate decreased to 65%.[18] In the period 1988-1990 our cooperative group undertook a randomized study comparing MACOP-B and ProMACE-CytaBOM in patients with intermediate and high grade NHL. The final results of this experience showed that no more than 63% of patients achieved a CR, with MACOP-B and ProMACE-CytaBOM being similarly effective.[15]

In 1991, in an effort to improve the results of treatment of aggressive NHL, we designed the prospective study LA02, based on induction therapy with ProMACE-CytaBOM. The aims of the study were: 1) the comparison of two different anthracyclines substituting adriamycin in ProMACE-CytaBOM; 2) to assess the usefulness of a short maintenance treatment for patients achieving complete remission; 3) to evaluate the efficacy of early salvage therapy for patients not responding after three courses of ProMACE-CytaBOM.

Following two preliminary reports containing the results of a formal interim analysis,[19,20] we now report the final results of this trial, closed in June 1993, when the planned 250 patients had been accrued.

Materials and Methods

Between April 1991 and June 1993, 250 patients with NHL were registered for the study and randomized to receive combination chemotherapy with either ProME(Epidoxorubicin)CE-CytaBOM (PE-C) or ProMI(Idarubicin)CE-Cytabom (PI-C). Criteria for inclusion in the study were histologic diagnosis of intermediate-grade (IG) or high-grade (HG) NHL other than lymphoblastic lymphoma (i.e. categories D-H and K of Working Formulation); no prior treatment; clinical stage II, III, and IV, or clinical stage I with bulky disease; age over 12 years. Patients over 70 years of age were also included on the basis of good performance status and in the absence of underlying coronary artery or pulmonary disease.

All patients were clinically staged according to the Ann Arbor system. Patients with acquired immune deficiency syndrome (AIDS), AIDS-related complex (ARC), or positive serology for HIV were not eligible for this study and were assigned to a different treatment program.

Treatment protocol

Patients were randomly assigned to receive either 6 courses of PE-C or PI-C and were stratified on the basis of stage (II-III or IV) and participating center. The two ProMACE-CytaBOM derived regimens were given according to the schedule proposed by Fisher *et al*.[5] Briefly, chemotherapy was administered as follows: cyclophosphamide 650 mg/m^2 intravenously (IV), etoposide 120 mg/m^2 IV, epidoxorubicin 30 mg/m^2 IV (or idarubicin 6 mg/m^2 IV) all on day 1, prednisone 60 mg/m^2 orally on days 1-14, and cytarabine 300 mg/m^2 IV, bleomycin 5 mg/m^2 IV, vincristine 1.4 mg/m^2 IV (cap = 2 mg), methotrexate 120 mg/m^2 IV on day 8 with leucovorin 10 mg/m^2 orally for 5 doses beginning 24 hours after methotrexate administration. Epidoxorubicin was chosen on the basis of its lower cardiac toxicity but same tumor effectiveness.[21] Idarubicin was chosen because it has shown promising results in most lymphoproliferative disorders, including acute leukemias and relapsed or refractory malignant lymphomas.[22]

Cycles were repeated every three weeks. After three cycles of therapy, patients achieving complete or partial remission continued to receive 3 additional courses, whereas non responding patients were shifted to different salvage treatments. At the end of the 6 planned courses of therapy, patients could receive additional radiotherapy on residual masses or on sites of previously bulky disease. Finally, patients achieving complete remission with induction therapy were invited to participate in a randomized study comparing no further therapy versus a consolidation regimen consisting of four blocks of two drugs, according to the following schedule: thioguanine 300 mg/m^2 on days 1-4 and cyclophosphamide 600 mg/m^2 on day 5; hydroxyurea 2400 mg/m^2 on days 1-4 and epidoxorubicin 50 mg/m^2 on day 5; methotrexate 10 mg/m^2 on days 1-4 and carmustine 60 mg/m^2 on day 5; cytarabine 150 mg/m^2 on days 1-4 and vincristine 1.5 mg/m^2 on day 5. Each block was administered every two weeks; after the fourth block the sequence was repeated once, starting from block 1. Dosage modifications were made according to WBC and platelet counts on the day of scheduled treatment.

All patients received prophylactic cotrimoxazole and ketoconazole or fluconazole daily throughout the treatment program. Antiemetic prophylaxis consisted primarily in almost all cases of 50 mg promethazine, i.m., 45 minutes before chemotherapy, and 0.5 mg/kg metoclopramide or levosulpiride i.v. immediately before chemotherapy.

Assessment of response

Response to treatment was assessed one month after the end of induction therapy by performing all examinations necessary to check abnormal findings present at the time of entry to the study. Complete remission (CR) was defined as the disappearance of all clinical evidence of disease and the normalization of

all laboratory values and radiographs that had been considered abnormal before starting treatment. Patients with stable residual masses lasting 6 months were retrospectively classified as CR. Moreover, patients who achieved a CR during therapy, but who relapsed within 30 days of therapy having been completed, were classified as non responders. Partial remission (PR) was defined as a greater than 50% reduction in the largest dimension of each anatomic site of measurable disease for at least one month. No remission (NR) was defined as a less than 50% regression or stable or progressive disease. All early deaths due to disease progression or treatment-related toxicity were considered as treatment failure, and included in the group of NRs. Toxicity was assessed according to the WHO criteria.

Statistical analysis

All data were analyzed with the Statistical Package for the Social Sciences (SPSS).[23] Differences in CR rates, number and severity of therapy related side effects, and causes of death between the two groups were analyzed by Fisher's exact test for contingency tables. Grades were grouped when there were too few patients with higher grades. Survival, disease free survival (DFS), and time to treatment failure (TTF) curves were estimated by the Kaplan-Meier method. The log-rank test was used to assess the significance of differences in survival, DFS, or TTF for each prognostic factor. Survival was calculated from the beginning of treatment until death from any cause. DFS was calculated from the end of induction therapy to the first evidence of disease relapse. TTF was measured from the beginning of therapy to the time of disease progression, relapse, or death. Response rates, TTF, survival, and toxicity were analyzed among the patients who were eligible and could be evaluated. Differences in survival according to treatment group were studied between randomized patients in an intention-to-treat analysis. Cox proportional hazards regression modeling was used in multivariate analysis to determine whether the identified risk factors independently influenced survival rates. The relevance of the international NHL prognostic factors project index[24] (IPI), and of the prognostic index proposed by the French Group G.E.L.A.[25] was also evaluated. The clinical usefulness of the prognostic index proposed at the M.D. Anderson Cancer Center[26] was not tested because the value of β_2-microglobulin was lacking for the majority of cases. For the assessment of the IPI we had to convert the value of performance status in our patients from the Karnofsky to the ECOG scale. We considered the presence of a Karnofsky performance status of 0 to 70 to be an adverse prognostic factor. A p value of 0.05 (two-sided) was considered the limit of significance for all the analyses.

Dose intensity

The dose intensity (DI) analysis was performed according to the method proposed by Hryniuk.[27] For patients completing the planned 6 courses of chemotherapy the DI of each drug was considered the amount of each drug, normalized to the body surface area, administered during the first 119 days, 119 days being the time necessary to deliver 6 courses of therapy one every 3 weeks. The time necessary to complete the sixth course was considered to be 14 days. For patients who received less than 6 courses of chemotherapy because of early death or disease progression, DI was expressed as the ratio of the dose actually delivered to the dose prescribed in the regimen over the same time frame.

Results

One patient out of the 250 enrolled was subsequently considered ineligible when the histology was reviewed. The remaining 249 patients, 128 in the PE-C arm and 121 in the PI-C arm, were included in the analysis. Table 1 summarizes the characteristics of these patients, divided according to the two treatment arms. No statistical differences between study arms were observed as regards the baseline characteristics.

Response

Eight patients were withdrawn from the study before the first assessment of response, planned after three courses. Reasons for early withdrawn were: refusal to receive planned therapy (n = 3); major toxicity after the first course (n = 4, one fatal); death due to cerebral hemorrhage after the first course (n = 1). The remaining 241 patients (125 in the PE-C and 116 in the PI-C arm) were assessable for response (Table 2).

After three courses of therapy, 46 patients (37%) treated with PE-C and 46 (39%) treated with PI-C achieved a CR, with no significant difference between the two treatment arms (p=0.27). Moreover, 60 patients (48%) treated with PE-C and 58 (50%) treated with PI-C achieved a PR. The objective response (CR+PR) rate for the whole group was 87%. Thirty-one patients were classified has having stable or progressive disease. Sixteen deaths were recorded among these non responding patients (13 for disease progression, 2 due to toxicity and 1 from sudden death) within the 3 months following study entry. Fourteen patients with stable or progressive disease left the study and were subsequently shifted to salvage therapy; only one patient achieved a CR with second line therapy. Finally, regardless of an unsatisfactory initial response, one patient continued with initial therapy on judgment of the physician, obtaining a minimal response at the end of 6 courses. This patient subsequently obtained a CR, lasting 3 years, with high-dose therapy followed by stem cell support.

After six cycles, 71 patients (57%) treated with PE-C and 73 (63%) treated with PI-C achieved a CR, and again the differences between the two treatment arms were not significant (P=0.36). Eight patients in PR after chemotherapy achieved a CR with additional IF-RT. In conclusion 152 patients (63%) achieved a CR with induction therapy. The rate of CRs was 62%

Characteristic	ProMECE-CytaBOM (N = 128)	ProMICE-CytaBOM (N =121)	P value
	no. of patients (%)		
Age			0.81
≤ 60 years	77 (60)	74 (61)	
> 60 years	51 (40)	46 (39)	
Sex			0.26
Female	46 (36)	52 (43)	
Male	82 (64)	69 (57)	
Ann Arbor stage			0.71
I (bulky) - II	40 (32)	43 (35)	
III	30 (23)	24 (20)	
IV	58 (45)	54 (45)	
Tumor histology			0.57
Intermediate grade	93 (73)	84 (70)	
High grade	35 (27)	37 (30)	
Extranodal involvement			0.60
Absent	34 (27)	34 (28)	
Present	94 (73)	87 (72)	
Bone marrow involvement			0.90
Absent	33 (26)	32 (26)	
Present	95 (74)	89 (74)	
Bulky disease			0.47
Absent	90 (70)	80 (66)	
Present	38 (30)	41 (34)	
Systemic symptoms			0.26
Absent	87 (68)	74 (61)	
Present	41 (32)	47 (39)	
Performance status (Karnofsky)			0.50
0 - 70	41 (32)	34 (28)	
80 - 100	87 (68)	87 (72)	
Serum LDH level (223 cases)			0.20
Normal	77 (70)	70 (62)	
Above upper normal limit	33 (30)	43 (38)	
Unknown	18 (-)	8 (-)	
Serum albumin level			0.07
> 3.0 g/dl	90 (70)	97 (80)	
≤ 3.0 g/dl	38 (30)	24 (20)	
Hemoglobin			0.21
≥ 12 g/10^{9}L (10 for w)	86 (67)	90 (74)	
< 12 g/10^{9}L (10 for w)	42 (33)	31 (26)	
International Prognostic Index			0.66
Low risk	35 (33)	41 (37)	
Low intermediate risk	40 (37)	33 (29)	
High intermediate risk	22 (20)	22 (19)	
High risk	11 (10)	17 (15)	
Unknown	20 (-)	8 (-)	
G.E.L.A. Index			0.14
Low risk	18 (16)	18 (16)	
Intermediate risk	62 (54)	48 (42)	
High risk	34 (30)	47 (42)	
Unknown	14 (-)	8 (-)	

Table 1. Characteristics of Patients according to treatment arm.

Table 2. Response rates according to treatment arm.

	Response								
	CR		PR		NR		NA		
Time of Evaluation	No.	%	No.	%	No.	%	No.	%	p°
After 3 courses									0.27
PE-C	46	37	60	48	19	15	3	2	
PI-C	46	39	58	50	12	11	5	4	
All	92	38	118	49	31	13	8	3	
After 6 courses									
PE-C	71	57	30	24	24	19			0.36
PI-C	73	63	19	16	24	20			
All	144	60	49	20	48	19			
Overall response (6 courses + RT)									0.51
PE-C	77	62	24	19	24	19			
PI-C	75	64	18	15	23	19			
All	152	63	42	17	47	19			

Abbreviations: CR: complete remission; PR: partial remission; NR: no response; NA: not assessable.
°: c2 (2 df) test, excluding NA patients.

and 64% for patients treated with PE-C and PI-C respectively, with no significant differences between the two groups (P=0.51). Sixty-one relapses (40%) occurred among 152 patients achieving CR. The rate of relapses was similar in the two groups, 29/77 (38%) in the PE-C arm and 31/75 (43%) in the PI-C arm (P=0.33). The 5-year relapse-free survival was 60% in PE-C group and 53% in PI-C group (Figure 1). The differences in relapse-free survival were not significant (P=0.29). A second complete remission was obtained with salvage therapy in 17 patients (28%).

Failures

At the time of the present analysis we recorded 160 treatment failures, including resistance to initial therapy, relapses, or death from any cause. We observed 82/125 failures (66%) in the group treated with PE-C and 78/116 failures (67%) among those treated with PI-C (p=0.78). The percentages of patients alive in first complete remission 4 years after study entry were estimated to be 39% in the PE-C arm and 38% in the PI-C arm (Figure 2); the difference between the groups was not significant (p=0.90). When the 10 patients who failed to achieve a CR with initial therapy but obtained a CR with second line therapy, and 17 patients who relapsed and achieved a second CR were also considered, the percentage of patients alive without disease at four years was estimated to be 53% and 49% in the PE and PI groups respectively. The differences between the two groups were not significant (p=0.46).

Consolidation

Forty-two patients achieving CR with induction therapy were randomly assigned to consolidation therapy or observation only. The remaining 110 patients in CR were not randomized for different reasons, including refusal from the patient or lack of compliance from the physician. Twenty-one patients, 10 in the PE-C and 11 in the PI-C arm, were randomized to consolidation therapy and 21 to observation only. After a median follow-up of 35 months, 4 relapses (19%) were observed among treated patients and 9 relapses (43%) among patients in the observation arm, suggesting a better, although not statistically significant (p=0.10) outcome for patients undergoing a maintenance program. Interestingly, the rate of relapse of patients in the observation arm was similar to the rate of relapse (48 patients, 44%) observed in the group of 110 patients who were not enrolled in this part of the trial. The estimated relapse-free disease survival rates at 4 years were 75% for patients randomized to maintenance, 57% for patients randomized to observation and 53% for those not randomized (p=0.15 considering all 3 groups, 0.11 considering only the study arms) (Figure 3).

Survival

After a median follow-up of 34 months (53 months for patients alive), 118 patients (47%) had died, 7 had been lost from follow-up (3%) and 124 were alive; there were 56 deaths (44%) among 129 patients assigned to the PE-C arm and 60 (49%) among the 121 patients assigned to the PI-C arm. The causes of death are summarized in Table 3. No significant difference in death-rate was found between the two treatment arms (p=0.28). One patient in each group died in a car accident, while in CR. These two patients were censored at the time of death. As expected, the majority of deaths (n = 103)

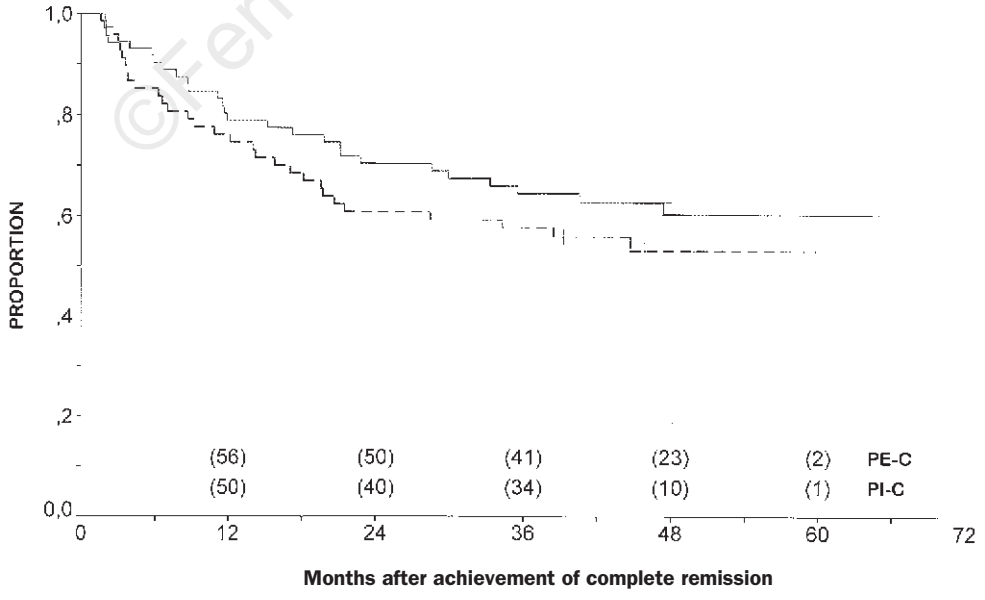

Figure 1: Relapse-free survival according to treatment group for the 152 patients who achieved complete remission with induction therapy. (—) PE-C, 77 cases; (- - - -) PI-C, 75 cases (Log rank test = 1.12, p = 0.29).

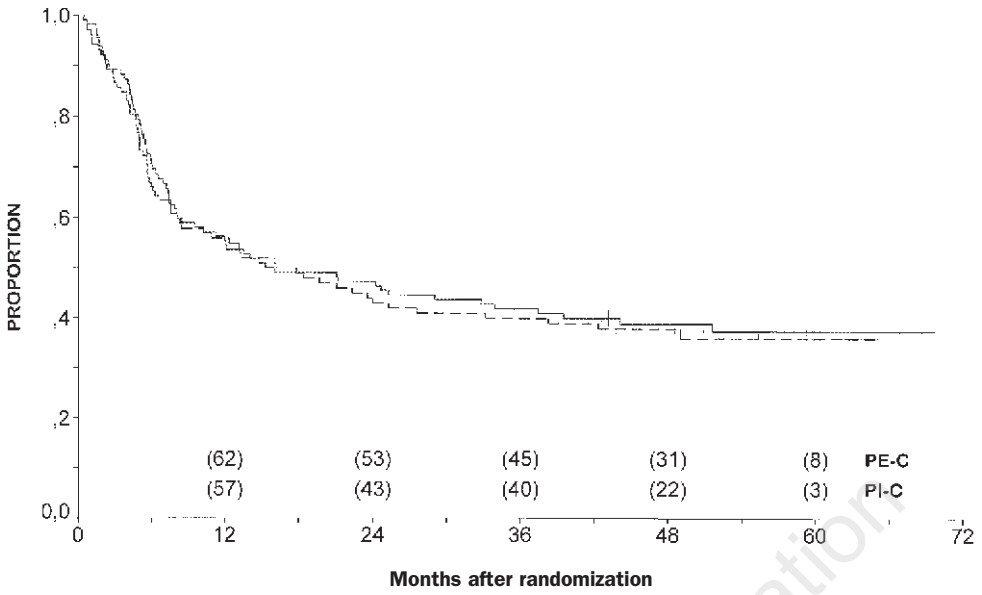

Figure 2. Failure-free survival according to treatment group. (—) PE-C: 125 patients at risk, 82 failures; (- - - -) PI-C:, 116 patients at risk, 78 failures. (Log rank test = 0.02, p=0.90).

occurred in patients with active disease. However 13 deaths occurred in patients in complete remission after a median time of 18 months from study entry. Two cases of acute hepatitis and one of CMV infection occurred in patients who had successfully completed the planned induction therapy. Finally, one patient in CR after induction therapy underwent autologous bone marrow transplantation (ABMT) and died of ABMT-related toxicity. Fifty-one percent of the 249 patients were estimated to be alive at 5 years. The 3-year and 5-year estimated survival rates were respectively 61% and 55% for the PE-C group and 56% and 47% for the PI-C group (Figure 4). The difference was not significant (p=0.26).

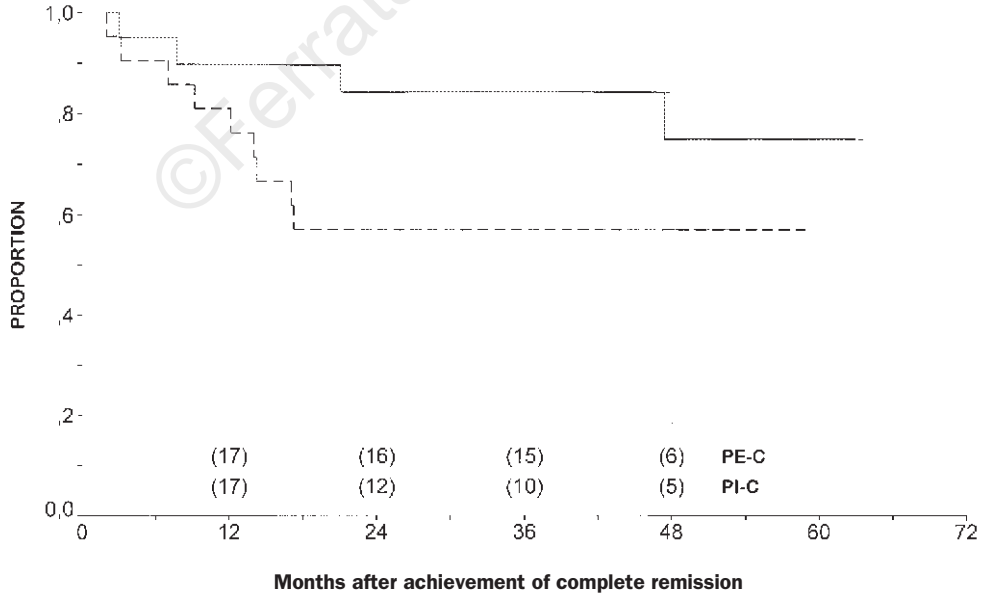

Figure 3. Relapse-free survival of patients who achieved complete remission and were randomized to maintenance therapy or to observation. (—) Maintenance arm: 21 patients at risk, 4 relapses; (- - - -) observation arm: 21 patients at risk, 9 failures. (Log rank test = 2.51, P=0.11).

Table 3. Causes of death, according to treatment group°.

Cause	ProMECE-CytaBOM	ProMICE-CytaBOM
	no. of deaths	
Active disease		
Disease progression	42	48
Neutropenia and/or sepsis	6	2
Acute myocardial infarction	1	1
Cerebrovascular accident	0	2
Hemorrhagic shock	0	1
	49	*54*
Complete remission		
Neutropenia and/or sepsis	2	3
Acute hepatitis	1	1
CMV infection	1	0
ABMT-related toxicity	1	0
Second neoplasm	2	1
Unknown	0	1
	7	*6*
Total	56	60

°Excluding one patient per arm who died due to a car accident.

Cardiovascular toxicity

The hematologic and non hematologic toxicity was acceptable in both arms as previously reported.[20]

The incidence, distribution and severity of cardiovascular toxicity was similar in the two groups (Table 4). Five patients treated with PE-C and 7 treated with PI-C experienced a cardiovascular adverse event. All 4 patients who died of cardiovascular toxicity had active disease at the time of death. The remaining 8 patients experiencing cardiac abnormalities recovered completely with appropriate treatment.

Analysis of prognostic factors

Advanced stage (p=0.04), presence of bulky disease (p=0.02), serum LDH above the upper normal limit (p=0.0006), low serum albumin (p=0.0051) low hemoglobin (p=0.0011) and low performance status (p=0.0001) were associated with a poorer prognosis in a univariate analysis of survival (Table 5). Moreover, the international prognostic index (IPI) and the prognostic index adopted by the French group G.E.L.A. both provided highly significant prognostic value. Using IPI the 5-year survival rate was 61% in the group at low risk, 56% in the group at intermediate-low risk, 41% in the group at high-intermediate risk, and 22% in the group at high risk ($p < 0.0001$). Using the G.E.L.A. index, the 5-year survival was 75% in the group at low risk, 55% in the group at intermediate risk and 36% in the group at high risk ($p < 0.0001$). Dose intensity was not found to be a prognostic factor for patients accrued in the present trial. However, only a minority of patients received less than the planned dose. Several cut-off levels of DI (0.70, 0.75, 0.80, 0.90) were explored, but no differences emerged as regards to overall survival, DFS or TTF (data not shown).

In a multivariate analysis of those prognostic factors of statistical significance in univariate analysis of survival performed using the Cox regression model, no independent factors emerged, probably because most of the variables reflect similar biological phenomena. However excluding from the model those variables already considered by IPI (i.e. stage, LDH,

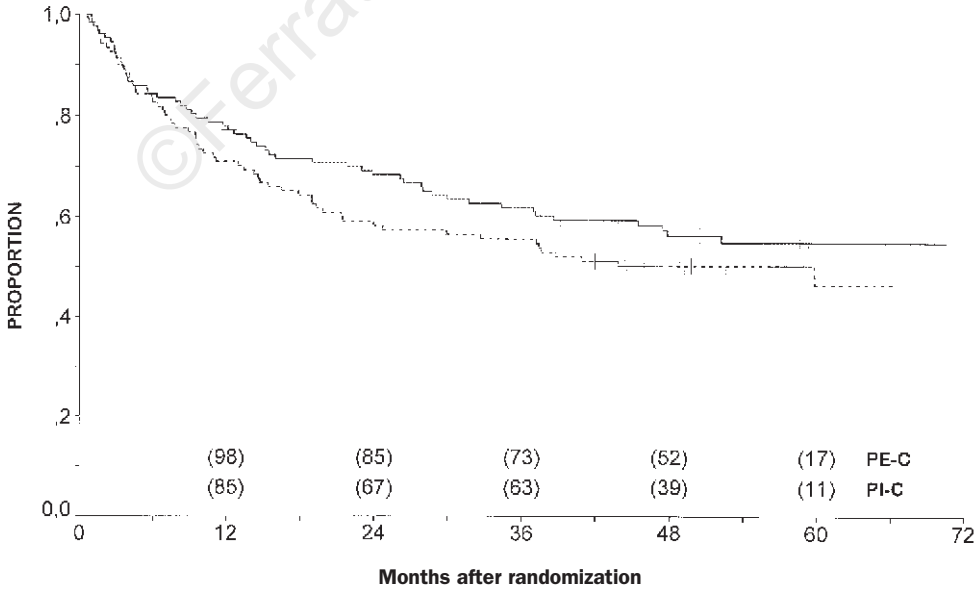

Figure 4. Overall survival by treatment group, according to intent-to-treat analysis. (—) PE-C: 128 patients at risk, 56 deaths; (- - - -) PI-C:, 121 patients at risk, 60 deaths. (Log rank test = 1.29, p = 0.28).

Table 5. Five-year survival rates according to patient characteristics.

	No. of Patients	% Surviving	P value
Therapy			0.26
PE-C	128	56	
PI-C	121	47	
Age			0.33
≤ 60 years	148	52	
> 60 years	95	49	
Sex			0.81
Female	98	49	
Male	150	52	
Ann Arbor stage			**0.04**
I (bulky) - II	82	62	
III-IV	166	46	
Tumor histology			0.37
Intermediate grade	176	52	
High grade	72	47	
Bone marrow involvement			0.06
Absent	183	53	
Present	65	44	
Bulky disease			**0.02**
Absent	169	55	
Present	79	42	
Systemic symptoms			0.20
Absent	100	54	
Present	88	46	
Performance status (Karnofsky)			**0.0001**
0 - 70	74	35	
80 - 100	174	58	
Serum LDH level			**0.0006**
Normal	147	57	
Above upper normal limit	76	39	
Serum albumin level			**0.0051**
> 3.0 g/dl	187	56	
≤ 3.0 g/dl	61	36	
Hemoglobin			**0.0011**
≥ 12 g/10^9L	176	57	
< 12 g/10^9L	62	35	
International Prognostic Index			**<0.0001**
Low risk	76	61	
Low intermediate risk	73	56	
High intermediate risk	44	41	
High risk	28	22	
G.E.L.A. Index			**<0.0001**
Low risk	36	75	
Intermediate risk	110	55	
High risk	81	36	

Table 4. Incidence of cardiovascular toxicity in 249 patients treated with PE-C or PI-C.

	ProMECE-CytaBOM	ProMICE-CytaBOM
Early death		
Acute myocardial infarction	1	1
Cerebrovascular accident	0	2
Other toxicity		
WHO grade 1 or 2	3	3
WHO grade 3	1	1
Total	**5 (4%)**	**7 (6%)**

Table 6. Relationship between the International Prognostic Index and G.E.L.A. Index in the group of 221 patients assessable for both indices.

	G.E.L.A. Index			Total
IPI	Low	Intermediate	High	
Low	**33**	40	3	76
Low-intermediate	**2**	**42**	29	73
Intermediate-high		19	**25**	44
High		4	**24**	28
Total	35	105	81	221

Table 7. Comparative studies with regards to the percentage of patients considered elegible after enrolment.

Study Group	Regimen	No. enrolled	No. eligible	Rate of eligible (%)
Fisher et al.[9]	CHOP m-BACOD ProMACE-CytaBOM MACOP-B	1138	899	79
Gordon et al.[10]	CHOP m-BACOD	392	325	83
Cooper et al.[11]	CHOP MACOP-B	304	236	78
Montserrat et al.[12]	CHOP ProMACE-CytaBOM	175	148	85
Meerwaldt et al.[13]	CHVmP CHVmP/OB	430	346	80
Bezwoda et al.[34]	CHOP CNOP	325	263	81
Meyer et al.[40]	BACOP ESCALATED BACOP	298	236	79
Present study	ProMACE-CytaBOM ProMICE-CytaBOM	250	249	99

and PS) the latter resulted of independent value, but no additional factor was able to improve the prognostic power of the model. In contrast a multivariate analysis considering hemoglobin, serum albumin, PS and G.E.L.A. index revealed an independent prognostic value of G.E.L.A. and PS.

As expected, a highly significant correlation was found between the IPI and G.E.L.A. index ($p < 0.0001$) although complete agreement in the assessment of the risk was observed in only 57% of cases, as shown in Table 6. In the group of patients aged 60 or less, and more likely to be suitable for more aggressive treatments, including high-dose therapy followed by stem cell support, 28 were at intermediate-high or high risk according to IPI, and 56 resulted at high risk according to the G.E.L.A. index. Twenty-five patients were at high risk according to both prognostic models, 3 according to the IPI but not to the G.E.L.A. index, and 31 according to the G.E.L.A. index but not to the IPI.

Dose intensity

Data for calculation of dose intensity were available in 217 patients (115 treated with PE and 102 treated with PI). Patients received 81% of the planned dose of vincristine, and 93%, 94%, 94%, 96%, 97%, 97%, and 100% of the planned doses of idarubicin, methotrexate, epidoxorubicin, cytarabine, cyclophosphamide, etoposide, and bleomycin, respectively. The average DI of vincristine was low because almost all patients had body surface areas >1.43 m^2 and were thus able to receive the upper limit of 2 mg. However, in most cases some delay in the delivery of therapy occurred. The mean duration of the six cycles was 23, 24, 27, 25, 25, and 22 days, respectively. The higher mean duration of the third course was in part dependent on the necessity of performing the re-staging procedures planned after three courses of chemotherapy. Considering both the dose of drugs delivered and the time necessary for completing the planned therapy, the actual DI was equal to 92% in the whole group. The actual DI was 92% in the group treated with PE-C and 91% in the group treated with PI-C ($p=0.67$). Several cut-off levels of DI (0.70, 0.75, 0.80, 0.90) were explored, but no differences emerged as regards to overall survival, DFS or TTF.

Discussion

The principal end-point of the LA02 protocol was the demonstration that PI-C had equivalent efficacy to PE-C with an improved toxicity profile, and the trial showed that there were no differences in the rate of complete remission, failure-free survival, relapse-free survival and overall survival between the two study groups, well balanced with respect to prognostic factors. In agreement with other reports, the present study also indicates that epirubicin and idarubicin in a combination chemotherapy regimen have similar activities. In a randomized trial comparing VACOP-B versus VICOP-B, Bertini *et al.* found that both regimens had the same efficacy in the treatment of patients with diffuse large cell lymphoma.[30]

Similarly, Zinzani *et al.* tested the efficacy of idarubicin instead of doxorubicin in the CHOP regimen, and found that the idarubicin arm had an equivalent therapeutic efficacy in comparison to the standard doxorubicin containing CHOP.[31] Cardiovascular toxicity was also comparable, although in this case the lack of difference is possibly due to the limited number of cardiovascular events recorded in both study arms. However, this toxic profile indicates the safety of both anthracyclines at the dosages employed, suggesting their possible dose-escalation in a combination chemotherapy setting.

Several Institutions or Cooperative groups have adopted ProMACE-CytaBOM as first line therapy of patients with aggressive NHL.[5,9,15,18,32,35] In a randomized trial conducted at NCI comparing ProMACE-CytaBOM with ProMACE-MOPP in more than 200 patients, Longo *et al.* reported that ProMACE-CytaBOM was highly effective, with a complete response rate of 86%, and an estimated overall survival rate at 6 years of 69%.[28] However this was a trial conducted in a single institute and, like most trials of this type, some selection bias could have favored these excellent results. Although we were not able to replicate the very promising results obtained at NCI, our results are consistent with those obtained by other multicenter trials. In the large SWOG-ECOG trial comparing CHOP with m-BACOD, MACOP-B and ProMACE-CytaBOM the complete remission rate achieved with ProMACE-CytaBOM was 56%.[9] In the SWOG study reported by Miller *et al.*, a CR was

obtained in 65% of 78 previously untreated patients.[18] Other investigators reported CR rates ranging from 62 to 70%.[12,29,32] In our opinion the complete remission rate of 62% and 64% achieved with PE-C and PI-C are of value, mostly considering that LA02 is a multicenter randomized study performed in 18 institutions and that response rate was calculated on nearly all randomized patients. After study entry no patient was excluded from the analysis for lack of complete agreement with inclusion criteria (i.e. low performance status, concomitant diseases, advanced age and so on). Thus in the present study 96% of patients were included in the calculation of response and 99% in the analysis of survival, while in other trials the percentage of cases excluded from the analysis after study entry is relevant, sometimes exceeding 20% of enrolled patients.[9-13,33,34,40] A comparison between our trial and these other studies is summarized in Table 7. Our evaluation policy, which includes as many patients as possible after study entry, is meant to offer a more realistic measure of the efficacy of regimens under study. The effect on the response rate of the exclusion of a significant number of enrolled patients was clearly highlighted by Bezwoda *et al.* in a study comparing CHOP with CNOP chemotherapy in patients with intermediate and high-grade NHL: in that study the CR rate was 5% higher if the analysis was performed on eligible instead of on all randomized patients.[34]

Since 1987 our group has treated more than 800 adult patients with NHL with ProMACE-CytaBOM-derived schedules. Following a pilot study performed in 1987 on 35 patients with aggressive NHL, between 1988 and 1991 we completed a randomized trial comparing ProMECE-CytaBOM with MACOP-B. In that trial 106 patients were treated with PE-C, and 62% achieved a CR.[15] In addition to the 250 patients enrolled in the present trial, we have used PE-C in 35 patients aged less than 55 years and affected by advanced follicular NHL[35] obtaining CR in 55% and a 5-year disease free survival of 60%; in patients with anaplastic large cell lymphoma[36] we recorded a complete remission rate of 62% in the PE-C group with an estimated survival rate at 4 years of 54%. Moreover, we currently treat patients with localized aggressive NHL with 4 courses of PE-C followed by IF-RT. Finally, our on-going LA03 trial comparing a fixed versus a flexible schedule of PE-C or PI-C has already enrolled more than 330 patients. One of the most convincing reasons for continuing to treat patients with ProMACE-CytaBOM despite the fact that the National High Priority Lymphoma Study comparing CHOP with m-BACOD, ProMACE-CytaBOM, and MACOP-B concluded that "*CHOP remains the best available treatment for patients with advanced-stage intermediate-grade or high-grade NHL*",[9] is that when physicians become familiar with intensive regimens, protocols like ProMACE-CytaBOM should yield better results than CHOP, as suggested by Longo and Duffey.[37]

An additional goal of our trial was the demonstration that a short maintenance treatment for patients achieving complete remission could ameliorate the RFD survival. In the group of 42 patients who were randomized, the 4-year RFS rate was 75% in the maintenance and 57% in the observation arm, suggesting a better outcome for patients continuing with a maintenance program, although the difference was not statistically significant (p=0.11). Unfortunately since only a minority (28%) of patients in complete remission after induction therapy was enrolled in this part of the study, a definite answer on the role of a maintenance therapy deserves further investigations.

With this trial we also wanted to verify whether early salvage therapy could be of benefit to patients not responding after 3 courses of PE-C or PI-C. From the present experience we noted that the majority of initially non responding cases died before receiving salvage treatment and that the response to an early second-line therapy was very poor. In fact, only one of 14 patients shifted to salvage therapy achieved a CR with a salvage regimen. These results indirectly indicate the great importance of prognostic stratification at the onset of disease, with immediate therapy intensification in high risk cases rather than an early change of treatment to rescue cases with poor response after the first courses.

In an attempt to improve the rate of cure of aggressive NHL many investigators have explored the usefulness of a policy of DI intensification. Dose intensity is considered a major determinant of outcome, and correlations between DI and survival have been reported in retrospective analyses.[38-41] Although it would seem obvious that DI is an important determinant of treatment outcome, the results of the very few prospective trials are controversial. Based on available data, it remains unclear what impact DI has on treatment outcome. The *Clinical Trials Group of the National Cancer Institute of Canada* recently reported the results of a randomized trial comparing standard BACOP with BACOP that included escalated doses of doxorubicin. The complete remissions were 59% and 61% respectively, with no significant differences between the two groups.[40] In a phase I trial of dose escalation with growth factor support performed by ECOG, the CR rate in the group of patients treated with a dose equal to 200% of standard ProMACE-CytaBOM was 66%,[42] not dissimilar to the success rate expected using standard doses. However, very promising results were achieved by Shipp *et al.* using high-dose CHOP,[43] by Tanosaki *et al.* using bi-weekly CHOP,[44] and by Bergmann *et al.* using VACPE, an intensified chemotherapy regimen consisting of vincristine, doxorubicin, cyclophosphamide, prednisone and etoposide.[45]

Dose intensity was not found to have a prognostic impact on patients included in the present trial. This apparent lack of relevance of DI probably depends on the fact that the actual DI was 92%, indicating good dose delivery. Moreover, only a few patients com-

pleted the planned therapy at DI lower than 80%.

In our study factors of prognostic value were stage of disease, bulky disease, serum LDH, serum albumin, hemoglobin, performance status, IPI, and the prognostic index adopted by the French group G.E.L.A. In a multivariate analysis performed using the Cox regression model IPI alone or PS and G.E.L.A. index had independent prognostic values. As expected, a highly significant correlation was found between IPI and G.E.L.A. index although complete agreement in the assessment of the risk was observed only in 57% of cases. In the group of patients aged 60 or less, and probably suitable for more aggressive treatments, 25 patients were at high risk according to both prognostic models, 3 according to IPI but not to the G.E.L.A. index, and 31 according to G.E.L.A. alone. This comparison was performed in view of the adoption of a prognostic index for selecting patients who would be more likely to benefit from high-dose therapy followed by stem cell support.[14,46]

In conclusion, our study has demonstrated that standard dose regimens such as PE-C and PI-C are effective therapies for patients with aggressive NHL at low or intermediate risk.

Different approaches, including high-dose therapy should be offered to patients at high risk, although it should be taken into account that the definitions of this risk category are widely heterogeneous and are influenced by the adopted index. For example, the use of the prognostic index proposed by G.E.L.A. results in a 40% higher proportion of patients being defined at high-risk than as by IPI.

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MF, LB, MB, PG were responsible for the conception of the study and its design; MF was also responsible for interpretation of data and writing of the paper; VC was responsible for randomization, data handling and for drafting the paper with MF; PG collaborated in reviewing the manuscript; DV, DD, ML, PA, NDR were responsible for patient care and reviewed the manuscript; VS gave the final approvation.

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