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The length of treatment of aggressive non-Hodgkin's lymphomas established according to the international prognostic index score: long-term results of the GISL LA03 study

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Abstract: *Objectives*: To compare two different schedules of two different anthracycline-containing regimens, where length of treatment is modulated according to the international prognostic index (IPI) in patients with aggressive non-Hodgkin's Lymphoma (NHL). *Methods*: In 1993 the Gruppo Italiano per lo Studio dei Linfomi (GISL) started a randomized 2×2 factorial phase III clinical trial for patients with newly diagnosed aggressive NHL comparing ProME(Epidoxorubicin)CE-CytaBOM (PE-C) to ProMI(Idarubicin)CE-CytaBOM (PI-C) and a fixed to a flexible treatment schedule where anthracycline dose was to be modulated according to observed hematological toxicity. Patients with low or low-intermediate IPI (IPI 0-2) and those with intermediate-high or high IPI (IPI 3-5) should receive six or eight courses, respectively. Involved-field radiotherapy was allowed for patients with initial bulky disease or with residual masses. *Results*: Three hundred and fifty-six patients were registered into the study and randomized. Patients were well balanced among the four study arms in terms of clinical characteristics and prognostic factors. Three hundred and forty-five patients were available for evaluation of study endpoints. At the end of induction therapy complete remission rate was 61%, 5-year failure-free survival (FFS) rate was 40% and 5-year overall survival (OS) rate was 59%; no differences were observed according to treatment arms. Patients in the flexible arm received higher dose intensity of anthracycline ($P < 0.001$) with no apparent increase in toxicity. However, the flexible schedule was not superior to the fixed one. Patients with IPI 3–5 showed lower response rates (45% vs. 67%: $P < 0.0001$) and lower 5-year FFS (29% vs. 45%: $P < 0.0001$) compared to those with IPI 0–2. *Conclusions*: six courses of fixed or flexible PE-C or PI-C can determine a promising success rate in patients with advanced aggressive NHL with IPI 0–2, whereas the same regimens are less effective in patients with IPI 3–5, even if two additional courses are delivered. For the latter group of patients innovative approaches are warranted.

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Key words: aggressive NHL; epidoxorubicin; idarubicin; IPI; ProMACE-CytaBOM

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The non-Hodgkin's lymphomas (NHLs) are a heterogeneous group of diseases that differ in biology, clinical course, and sensitivity to currently available treatment strategies. In recent years there have been significant advances in understanding the biology and treatment of NHLs. The prognosis of

aggressive NHL has improved in recent years with combination chemotherapy, with the cure rate rising from approximately 30% in the early 1970s to over 50% today (1).

However, 30 yr since the introduction of the cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen (2), the optimal therapy for aggressive NHL is still a matter of debate. In the mid 1980s, several pilot studies produced very promising results suggesting that the majority of patients with advanced, diffuse, aggressive NHL could be cured. Combinations of methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone (m-BACOD); methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin (MACOP-B); cyclophosphamide, doxorubicin, etoposide, prednisone, bleomycin, cytarabine, and methotrexate (Pro-MACE-CytaBOM); and doxorubicin, ciclophosphamide, vindesine, bleomycin, prednisolone, and intrathecal methotrexate (ACVB) all achieved complete remission (CR) rates of 70–85%, encouraging the notion that very rapid progress in the treatment of NHL had been achieved (3–6). However, these promising results were not confirmed by large phase III randomized studies (7–10), although some trials, including the study performed by Gianni *et al*. comparing MACOP-B to more intensive therapy, have shown significant benefit with dose intensification (11). Only with the recent advent of the anti-CD20 monoclonal antibody Rituximab and its use in combination with CHOP chemotherapy has the survival of patients with aggressive B NHL been improved and R-CHOP is now considered the new standard treatment (12).

A role in predicting the course of the disease has been demonstrated for several clinical and biological factors, and different prognostic indexes have been proposed. Among those specifically devised for patients with aggressive NHL, the international prognostic index (IPI) identifies four risk groups (13). Since its publication, IPI has been used and validated in large series of patients with aggressive NHL and in other histotypes, but so far only a few studies have used the model to prospectively define treatment plans.

Since 1987, the Gruppo Italiano per lo Studio dei Linfomi (GISL) selected ProMECE-CytaBOM (P-C) as standard regimen for patients with aggressive NHL and to date more than 1000 patients have been treated with this regimen. Following the conclusion of the LA01 (14) and LA02 (15) trials, in 1993 the GISL started a randomized 2×2 factorial study comparing two different schedules of two different anthracycline-containing P-C regimens. The main objective of the study was to verify if increasing anthracycline doses according to hematological toxicity would have determined a higher response rate and better survival.

When the study was designed in 1993, the Fisher study had not been published yet (7) and P-C was considered among the best most promising third-generation regimens. In the following years, moreover, additional confirmations of the efficacy of P-C derived regimens were published (16–19).

In the present study, length of treatment was modulated according to the IPI at diagnosis. We present the final and mature results of the LA03 study, closed on June 1997 when 356 patients had been accrued.

Methods

Patient eligibility criteria

Criteria for inclusion in the study were histological diagnosis of intermediate-grade or high-grade NHL other than lymphoblastic lymphoma (i.e., categories D-H and K of the Working Formulation); no prior treatment; Ann Arbor clinical stage II, III, or IV, or clinical stage I with bulky disease (bulky defined as mediastinal mass greater than 1/3 of the maximal diameter of the chest measured at level of D_5-D_6, or any mass outside the thorax with at least one diameter ≥10 cm.); age over 16 yr. Patients over 70 yr of age were included in the absence of underlying coronary artery or pulmonary disease and if their clinical condition did not present major contraindications to chemotherapy. Patients with impaired renal and hepatic function, inadequate bone marrow function, uncontrolled serious medical conditions, and known positivity for HIV were excluded from the study.

The protocol was approved by the Ethical Committee of the coordinating center. It was the responsibility of the Investigator to ensure that each patient gave her or his informed consent in writing prior to participating in this study.

Treatment plan

Patients were randomly assigned to receive fixed ProME(Epidoxorubicin)CE-CytaBOM (fixed PE-C), fixed ProMI(Idarubicin)CE-CytaBOM (fixed PI-C), flexible ProME(Epidoxorubicin)CE-CytaBOM (flexible PE-C), or flexible ProMI(Idarubicin)CE-CytaBOM (flexible PI-C), in a 1 : 1 : 1 : 1 ratio.

Epidoxorubicin was chosen on the basis of its lower cardiac toxicity and equal tumor effectiveness compared to Doxorubicin (20). Idarubicin was chosen because it has shown promising activity in relapsed or refractory NHL (21) and in previously untreated patients with aggressive NHL (15).

The four ProMACE-CytaBOM-derived regimens were given according to the schedule proposed by Longo *et al*. [5]. In the two fixed-treatment arms, chemotherapy was administered as follows: cyclophosphamide 650 mg/sm intravenously (IV), etoposide 120 mg/sm IV, and epidoxorubicin 40 mg/sm IV (or idarubicin 8 mg/sm IV), all on day 1; prednisone 60 mg/sm orally on days 1–14; and cytarabine 300 mg/sm IV, bleomycin 5 mg/sm IV, vincristine 1.4 mg/sm IV (cap = 2 mg), and methotrexate 120 mg/sm IV on day 8, with leucovorin 10 mg/sm orally for five doses beginning 24 h after methotrexate administration. In all four-treatment arms cycles were repeated every 3 wk. All patients received prophylactic cotrimoxazole and ketoconazole or fluconazole daily throughout the treatment program. Granulocyte colony-stimulating factor was allowed for the treatment of neutropenic fever; no prophylactic usage was recommended.

In the flexible arms after the first course of therapy and for each new cycle, the dose of epidoxorubicin (EPI) or idarubicin (IDA) planned for the next course was modified according to the WBC and platelet counts at nadir. This was done on the basis of the following criteria: dose was increased by 20% if WBCs were >4000 and platelets >150 000 at nadir; in case of WHO grade 1 toxicity, the dose was increased by 10%; in case of grade 2 toxicity, the dose was unchanged; in case of grade 3 or 4 toxicity, the dose was decreased by 10%.

For all the other drugs, doses were calculated according to Table 1. Blood counts were obtained weekly; the lowest test result was considered for calculating dose modifications for the next cycle.

After four cycles of therapy, responding patients with IPI 0–2 and those with IPI 3–5 were treated with two or four additional courses of P-C, respectively. In the flexible arms, the doses of EPI and IDA were prescribed at the same dose delivered in the fourth course. Not-responding patients were shifted to various salvage treatments. At the end of planned chemotherapy, patients could receive additional radiotherapy (RT) on residual masses or on sites of previously bulky disease.

Table 1. Dose modifications

Leukocyte count at nadir (10^9/L)		Platelet count at nadir (10^9/L)	Epidoxorubicin	Idarubicin
≥4.0	And	>150	+20%	+20%
3.9–3.0	And	>150	+10%	+10%
2.9–1.0	And	>50	0%	0%
<1.0	Or	<50	−10%	−10%

Leukocyte count on day of therapy (10^9/L)	%*	Drug
≥4.0	100	All‡
3.9–3.0	100	PDN, MTX, ARA-C, VCR, BLM
	75	CTX, EPI/IDA†, VP-16
2.9–2.0	100	PDN, MTX, VCR, BLM
	75	VP-16, ARA-C
	50	CTX, EPI/IDA†
<2.0	100	PDN, BLM
	50	VCR, MTX, ARA-C, VP-16
	0	CTX, EPI/IDA†
Platelet count on day of therapy (10^9/L)	**%***	**Drug**
>100	100	All‡
99–50	100	PDN, VCR, BLM
	50	MTX, VP-16, ARA-C
	25	CTX, EPI/IDA†
<50	100	PDN, VCR, BLM
	50	MTX, ARA-C
	0	CTX, EPI/IDA†, VP-16

*Percent of theoretical dose to be administered. In the presence of specifical clinical condition contraindicating the administration of chemotherapy, the start of a new cycle was to be delayed of 1 wk.
†Only for fixed arm.
‡Except EPI/IDA for whom the dose was defined according to blood count at nadir.
ARA-C, cytarabine; BLM, bleomycin; CTX, cyclophospamide; EPI, epidoxorubicin; IDA, idarubicin; MTX, methotrexate; PDN, prednisone; VCR, vincristine; VP-16, etoposide.

Assessment of response and survival

Response to treatment was assessed after the fourth chemotherapy cycle and 1 month after the end of the therapeutic program by means of CT scan and by re-performing all examinations that showed abnormal findings at time of study entry. All sites of disease were evaluated by measuring tumor sites' maximum transverse diameters. 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 were retrospectively classified as CR. Moreover, patients who achieved CR during therapy but relapsed within 30 d after therapy had been completed were classified as no remission (NR). 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 1 month. 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.

Overall Survival (OS) was calculated from the beginning of treatment until death from any cause. Relapse-free survival (RFS) was calculated from the end of induction therapy to the first evidence of disease relapse (only for patients achieving CR). Failure-free survival (FFS) was calculated for all patients from the start of therapy to the time of

treatment failure, disease progression, relapse, or death from any cause.

Toxicity

Toxicity was assessed according to the WHO criteria. All toxicities were graded on a 0–4 scales.

Dose intensity

Dose intensity (DI) was calculated for the first four courses of therapy according to the method proposed by Hryniuk and Bush (22). The DI of each drug administered in the first four cycles was considered the amount of each drug, normalized to the body surface area, that was administered during the first 77 d (77 d being the time necessary to deliver four courses of therapy every 3 wk, with the time necessary for completing the fourth course considered equal to 14 rather than 21 d). For patients who received less than four courses of chemotherapy because of early death, disease progression, or early withdrawal, DI was expressed as ratio of the dose actually delivered to the dose prescribed in the regimen over the same time frame.

Statistical methods

In the present study, 5-year FFS was the primary endpoint. Additional endpoints were response rate, 5-year RFS, 5-year OS, and treatment-related toxicity.

Sample size was calculated assuming a 5-year FFS rate of 40% for patients treated with fixed arms and 60% for patients treated with flexible arms. In order for a one-sided test with a power of 80% and a significance level of 0.05 to be applied, each treatment arm required 149 patients. With an estimated patient dropout rate of 10%, a final accrual of 330 patients was planned.

All randomizations were centralized at the GISL trial office. Patients were stratified on the basis of stages (II–III vs. IV) and participating center.

All data were analyzed with the Statistical Package for the Social Sciences Version 11.0 (SPSS). Differences in CR rates, number and severity of therapy-related side effects, and causes of death between groups were analyzed by the Fisher's exact test for contingency tables. OS, RFS, and FFS curves were estimated by the Kaplan–Meier method. The log-rank test was used to assess the significance of differences in OS, RFS, or FFS. Response rates, survival, and toxicities were analyzed for 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. A P value of 0.05 (two-sided) was considered the limit of significance for all analyses.

Results

Patients characteristics

Between July 1993 and June 1997, 356 patients were registered into the study by 22 centers. Ninety-six were allocated to fixed PE-C, 84 to fixed PI-C, 87 to flexible PE-C, and 89 to flexible PI-C. After randomization, four patients were excluded for revised histology and seven for major protocol violations (Fig. 1).

The remaining 345 patients (97% of those randomized) were eligible for the study. Two hundred and forty-nine had IPI 0-2 (low risk) and 96 had IPI 3-5 (high risk) according to a two-groups simplified IPI model. Patients' groups were well balanced in terms of clinical features and prognostic factors; baseline characteristics of all valuable randomized patients are summarized in Table 2.

Treatment response

Five patients could not be assessed for response because they withdrew early. After the first four courses of treatment, 151 patients out of 340 achieved CR (44%: 95% CI, 39–50%) and 128 achieved PR (38%: 95% CI, 33–43%), with no evidence of a significant difference between treatment arms (flexible P-C vs. fixed P-C: $P = 0.894$; EPI vs. IDA: $P = 0.144$). However, the objective response rate was 86% and 72% for patients with IPI 0–2 and IPI 3–5, respectively, and this difference was statistically significant ($P < 0.0001$).

At the end of induction chemotherapy (six or eight cycles of P-C for patients at low or high risk, respectively), 208 patients (61%: 95% CI, 56–66%) achieved CR, and 59 (17%: 95% CI, 13–21%) achieved PR. Again, the differences between patients treated with fixed or flexible P-C ($P = 0.871$) and with EPI or IDA containing P-C ($P = 0.159$) were not significant. In contrast, CR rates at the end of chemotherapy were 67% and 45% for patients with low and high risk, respectively, and this difference was statistically significant ($P < 0.0001$).

Eighty-five patients (65 in CR and 20 in PR) received consolidation RT. Ten patients initially in PR achieved CR with RT. One patient progressed during radiation treatment. After chemotherapy

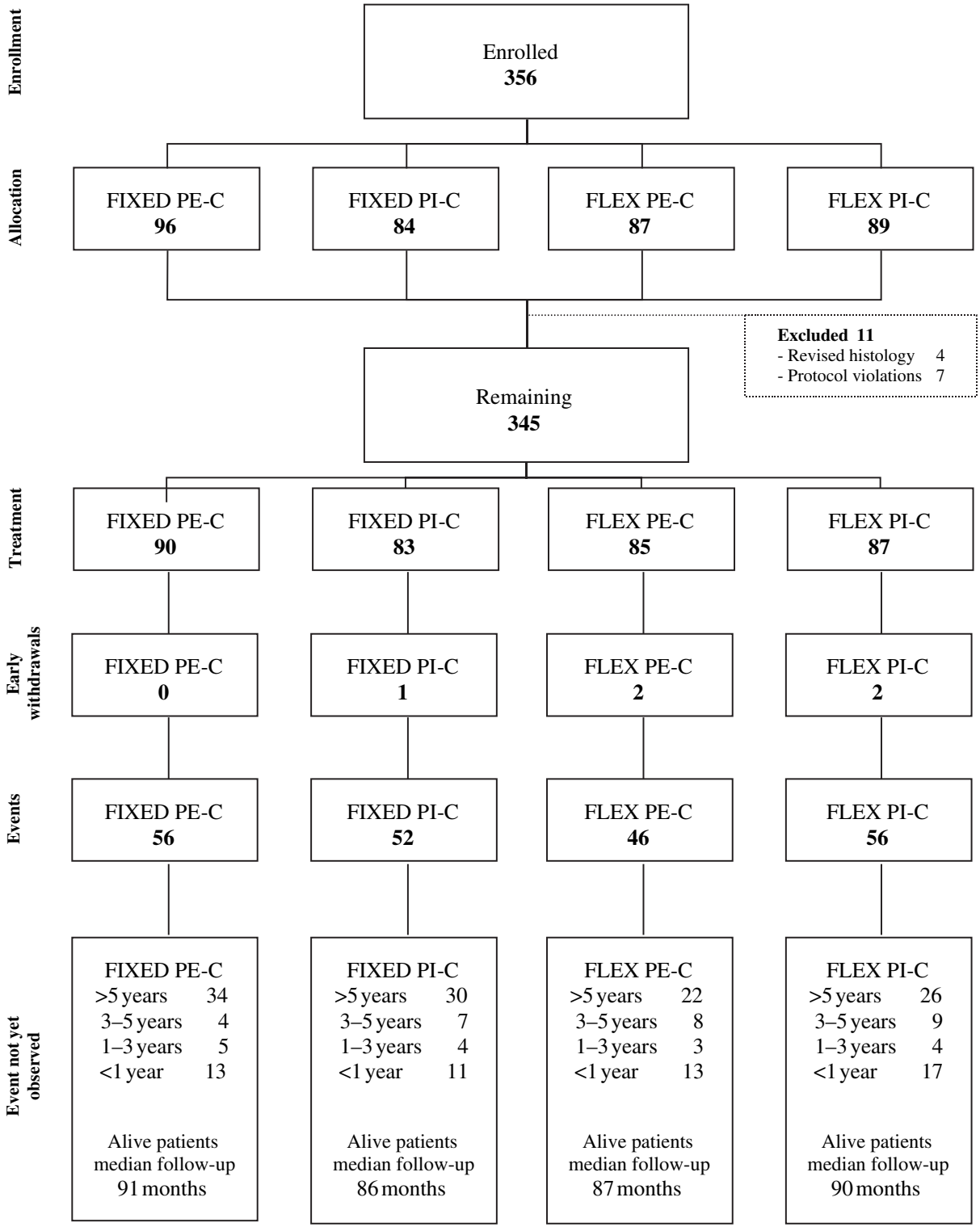

Fig. 1. PE-C,ProME(Epidoxorubicin)CE-CytaBOM; PI-C,ProMI(Idarubicin)CE-CytaBOM.

plus RT, 217 patients (64%: 95% CI, 59–69%) achieved CR (Table 3 and 4). Moreover, 11 patients achieved CR with different consolidation or salvage therapies, being in PR (seven cases) or less than PR (four cases) after P-C.

Survival

Median follow-up for the whole series was 57 months (range 1–121 months) and 89 months for alive patients (range 3–121 months). Seventy-

Table 2. Patients' characteristics and DI according to treatment arm

Characteristics	No. of patients (%)				*P* value
	Fixed PE-C ($n = 90$)	Fixed PI-C ($n = 83$)	Flexible PE-C ($n = 85$)	Flexible PI-C ($n = 87$)	
Age					
Median (year)	54	55	53	53	NS
Range (year)	17–74	22–70	17–72	26–70	
Gender					
Male	51 (57)	55 (66)	49 (58)	51 (59)	NS
Ann Arbor stage					
I (bulky)–II	29 (32)	30 (36)	27 (32)	27 (31)	NS
III–IV	61 (68)	53 (64)	58 (68)	60 (69)	
Histology (working formulation)					
E	4 (5)	8 (10)	2 (2)	9 (11)	NS
F	22 (24)	17 (21)	15 (18)	22 (25)	
G	39 (43)	45 (54)	51 (60)	41 (47)	
H	20 (23)	10 (12)	13 (16)	12 (14)	
Other	5 (5)	3 (3)	4 (4)	3 (3)	
Bone marrow involvement					
Absent	69 (77)	67 (81)	64 (75)	59 (68)	NS
Present	21 (23)	16 (19)	21 (25)	28 (32)	
Bulky disease					
Absent	60 (67)	63 (76)	64 (75)	69 (79)	NS
Present	30 (33)	20 (24)	21 (25)	18 (21)	
Systemic symptoms					
Absent	70 (78)	60 (72)	63 (74)	60 (69)	NS
Present	20 (22)	23 (28)	22 (26)	27 (31)	
ECOG performance status					
0–1	89 (99)	78 (94)	78 (92)	80 (92)	NS
2–4	1 (1)	5 (6)	7 (8)	7 (8)	
Serum LDH level					
Normal	54 (60)	51 (61)	48 (57)	49 (56)	NS
Above upper normal limit	36 (40)	32 (39)	37 (43)	38 (44)	
IPI					
0–1	41 (46)	41 (49)	35 (41)	33 (38)	NS
2	21 (23)	24 (29)	24 (28)	30 (35)	
3	22 (24)	12 (15)	16 (19)	17 (20)	
4–5	6 (7)	6 (7)	10 (12)	7 (7)	
Dose intensity					
Median overall	0.88	0.84	0.89	0.89	NS
Median anthracycline	0.93	0.89	1.08	1.08	<0.001*

*A statistically significant difference was observed comparing median overall anthracycline DI between flexible and fixed arm and comparing drug specific median dose intensity (epirubicin vs. idarubicin) between the two arms.
PE-C, ProME(Epidoxorubicin)CE-CytaBOM; PI-C, ProMI(Idarubicin)CE-CytaBOM.

seven relapses (34%: 95% CI, 28–40%) were observed among 229 patients in CR. One hundred and fifty-one patients died during follow-up, disease progression beingthe most frequent cause of death (73%); seven (5%) patients died of infections, five (3%) as a result of treatment and four (2%) from other cancer. Thirteen patients died from other causes (predominantly cardiovascular and respiratory) and 12 from unknown causes (Table 5). No differences according to treatment arm was observed.

FFS rate at 5 yr was 42% (95% CI, 34–50%) for flexible P-C and 39% (95% CI, 32–47%) for fixed P-C ($P = 0.704$), and was 37% (95% CI, 30–45%) and 44% (95% CI, 36–52%) for the IDA- and EPI-containing P-C, respectively ($P = 0.144$). Patients with IPI 0–2 had a better 5-year FFS compared to those with IPI 3-5 (45% vs. 29%; $P < 0.0001$) (Fig. 2).

RFS rate at 5 yr was 65% (95% CI, 59–79%), being 66% (95% CI, 56–75%) for flexible P-C ($P = 0.614$) and 64% (95% CI, 55–74%) for fixed P-C and 63% (95% CI, 54–73%) and 68% (95% CI, 57–75%) for EPI- and IDA-containing P-C regimens, respectively ($P = 0.497$). Patients with IPI 0–2 and IPI 3–5 had a 5-year RFS of 64% (95% CI, 58–73%) and 66% (95% CI, 51–79%), respectively ($P = 0.977$) (Fig. 3).

Five-year OS rate was 59% (95% CI, 53–64%) for the whole series. Patients in the flexible and fixed P-C had 5-year OS rates of 59% (95% CI, 51–66%) and 58% (95% CI, 47–64%), respectively ($P = 0.852$). Over the same interval the survival rates were 60% (95% CI, 52–67%) and 57% (95% CI, 47–63%) for EPI- and IDA-containing regimens ($P = 0.362$). Differences in OS were observed between patients with IPI 0–2 (66%: 95% CI, 60–72%) and those with

Table 3. Response rates and DI by treatment arm

Response (340 pts)	No. of patients (%) Fixed PE-C ($n = 90$)	Fixed PI-C ($n = 83$)	Flexible PE-C ($n = 85$)	Flexible PI-C ($n = 87$)	*P* value
Response after four courses					
CR	40 (45)	39 (47)	40 (48)	32 (38)	0.575
PR	37 (41)	27 (33)	31 (37)	33 (39)	
NR	13 (14)	16 (20)	12 (15)	20 (23)	
Overall median DI	0.87	0.85	0.93	0.90	0.740
Anthracycline DI	0.97	0.93	1.09	1.07	<0.001
Response after 6–8 courses					
CR	61 (68)	47 (57)	54 (65)	46 (54)	0.669
PR	13 (14)	17 (21)	14 (17)	15 (18)	
NR	16 (18)	18 (22)	15 (18)	24 (28)	
Overall median DI	0.88	0.84	0.89	0.89	0.700
Anthracycline DI	0.93	0.89	1.08	1.08	<0.001
Final response, after chemotherapy ± radiotherapy					
CR	62 (69)	50 (61)	57 (69)	48 (57)	0.561
PR	12 (13)	14 (17)	10 (12)	13 (15)	
NR	16 (18)	18 (22)	16 (19)	24 (28)	

CR, Complete response; DI, Dose intensity; NR, No remission; PE-C, ProME(Epidoxorubicin)CE-CytaBOM; PI-C, ProMI(Idarubicin)CE-CytaBOM; PR, Partial response.

Table 4. Patients' outcome according to IPI

	No. of patients (%) IPI 0–2	IPI 3–5	*P* value
Response after four courses			
CR	125 (51)	26 (27)	<0.001
PR	85 (35)	43 (45)	
NR	35 (14)	26 (28)	
Final response, after chemotherapy ± radiotherapy			
CR	172 (70)	45 (47)	<0.001
PR	33 (14)	16 (17)	
NR	40 (16)	34 (36)	
Survival			
5-year FFS	45	29	<0.001
5-year OS	66	39	<0.001
5-year RFS	64	66	NS

CR, Complete response; FFS, Failure free survival; NR, No remission; NS, Not significant; OS, Overall survival; PR, Partial response; RFS, Relapse free survival.

Table 5. Causes of death

Cause of death	Number	Percentage
Disease related	110	73
Infections	7	5
Treatment related	5	3
Other cancer	4	2
Other causes	13	9
Not specified	12	8

IPI 3–5 (39%: 95% CI, 29–49%) ($P < 0.0001$) (Fig. 4).

Dose intensity and toxicity

In the whole series, the median DI for the first four courses of therapy was 88%. As summarized in Table 2, the DI of all drugs but anthracyclines was similar in all four arms. The DIs of EPI and IDA were significantly higher in the flexible arms ($P = 0.001$ and $P < 0.001$, respectively).

During the first four courses, 11% of patients had an anthracycline dose reduction of no more than 10%; for 11% of patients, the anthracycline dose was not changed or increased less than 10%. Twenty-two percent of patients received a dose increase of 10–20% of the starting dose, in 56% of patients the dose was increased more than 20%, and in 21% of patients the dose was increased more than 40%. Both EPI and IDA had similar dose modifications (data not shown). Interestingly, no difference in terms of OS was observed comparing the type of regimen (fixed vs. flexible) for patients with low or high risk (IPI 0–2 vs. 3–5) (Fig. 5). Moreover, in a subset analysis for patients actually treated with higher doses of anthracycline, no difference was observed in terms of response and survival (data not shown).

Overall, toxicity was evaluable in 322 patients. Grade III or IV infections were reported in 11 (7%) and 7 (4%) patients treated with fixed or flexible P-C, respectively; this difference was not statistically significant ($P = 0.48$). Sixty-six percent of patients had at least a 1-week delay for incomplete WBC count recovery; however, grade III or IV hematological toxicity was observed in only 32%. No difference among the four treatment arms and between patients treated with fixed or flexible P-C was observed (Table 6). In particular, the increase in DI did not result in increased acute toxicity. Finally, no cases of acute cardiac toxicity were reported.

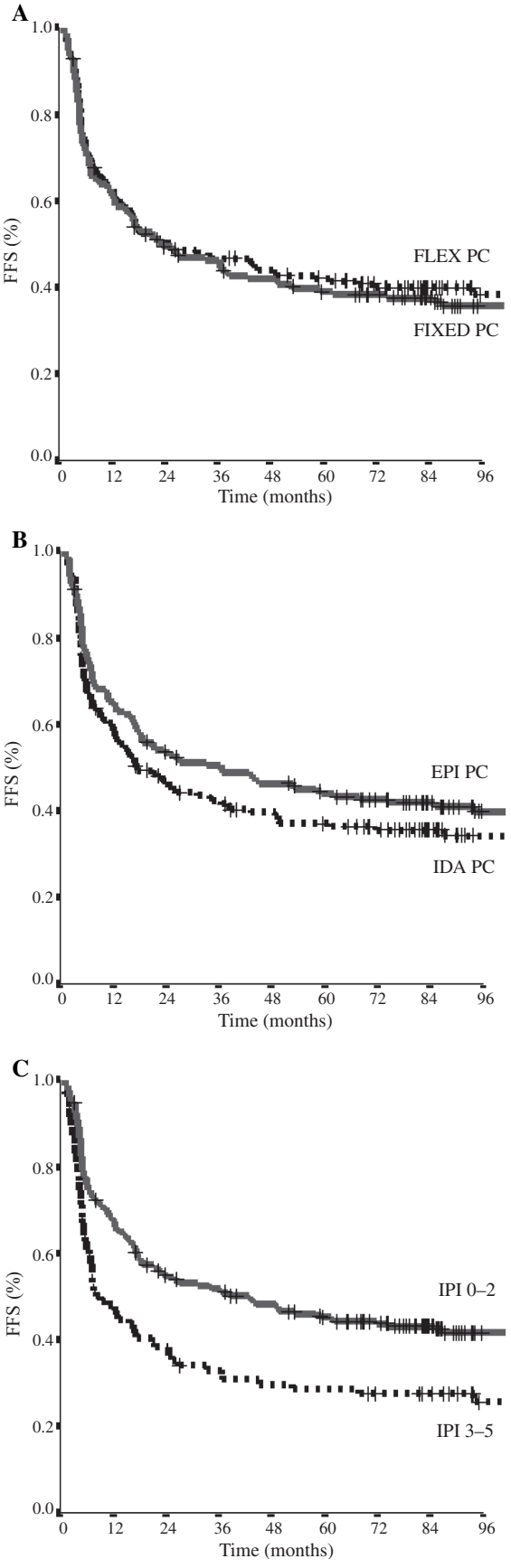

Fig. 2. (A) Failure-free survival (FFS) according to regimen ($P = 0.704$). PC, ProMACE-CytaBOM. (B) Failure free survival (FFS) according to anthracycline type ($P = 0.144$). PC, ProMACE-CytaBOM; EPI, Epidoxorubicin; IDA, Idarubicin. (C) Failure free survival (FFS) according to simplified IPI ($P < 0.0001$).

Discussion

The mature results of the LA03 study demonstrate that six courses of P-C based chemotherapy offer a promising success rate in patients with advanced aggressive NHL with IPI 0–2, whereas are less effective in patients with IPI 3–5, even if two additional courses are delivered. We confirm that IPI is a powerful tool with which to identify patients at high risk of treatment failure, but that these patients' increased risk of failure or of death cannot be overcome simply by extending the length of therapy. The main goal for patients with aggressive NHL should be the achievement of response during the first cycles of treatment. The achievement of early CR has been shown to be predictive of a more favourable outcome in both low and high risk groups, but the number of patients achieving CR with the first four cycles of P-C was significantly lower for patients with IPI 3–5. Thus, patients at high risk should be offered different therapeutic approaches up front.

Also, although our study did not directly compare P-C with CHOP, the results obtained with this third-generation regimen seem comparable to those of the standard CHOP chemotherapy and do not differ markedly from those of other third-generation regimen (Table 7) (7, 11, 14, 15, 23–26).

The 2×2 factorial design of our study allowed us to answer two questions: first, to compare the efficacy of IDA vs. EPI in a P-C regimen; second, to test the feasibility and efficacy of a flexible schedule for the administration of anthracycline tailored to observed hematological toxicity.

The results of our trial demonstrated that PI-C is similar to PE-C in terms of response, survival, and toxicity. Twenty-five mg/sm of adriamycin of the original P-C were replaced by 40 mg/sm of EPI or 8 mg/sm of IDA.

Another objective of our trial was assessment of the feasibility and safety of a flexible schedule in which anthracycline doses were increased if no acute myelotoxicity was observed during the previous cycle of therapy. The rationale for adopting a flexible schedule was based on the assumption that an increase in anthracycline DI could be achieved through this modality, and that more intense treatment would result in a better outcome, as suggested by different reports (17, 27, 28). Our results confirm that the adoption of a flexible

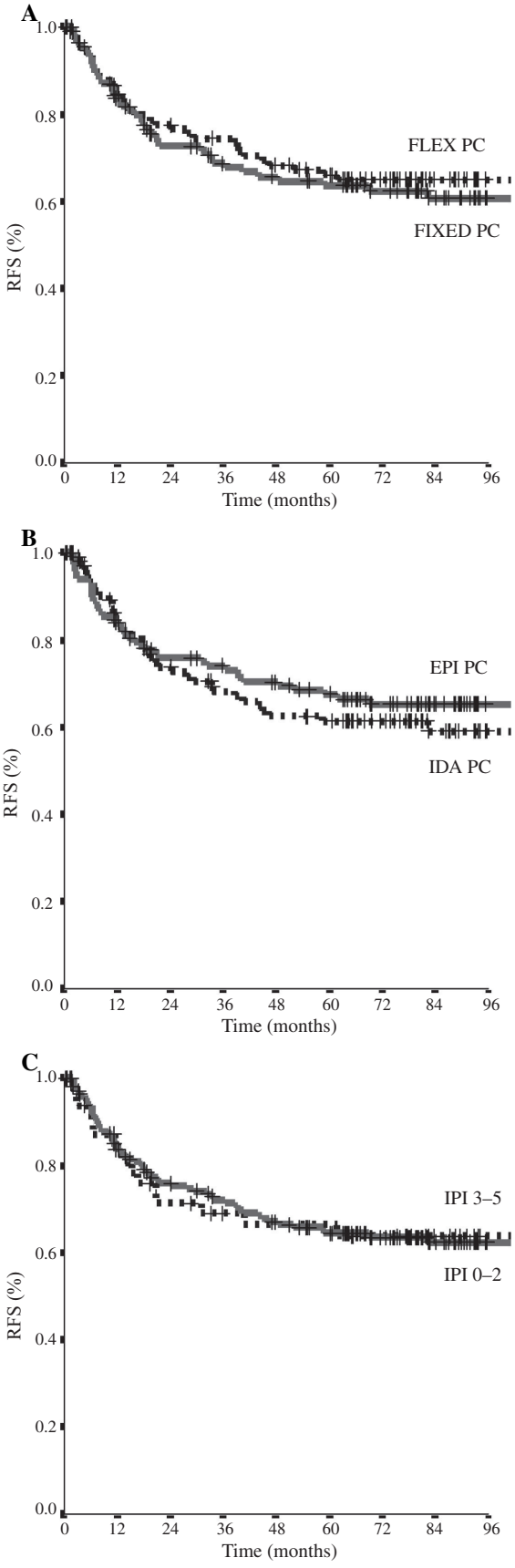

Fig. 3. (A) Relapse-free survival (RFS) according to regimen ($P = 0.614$). PC, ProMACE-CytaBOM. (B) Relapse-free survival (RFS) according to anthracycline type ($P = 0.497$). PC, ProMACE-CytaBOM; EPI, Epidoxorubicin; IDA, Idarubicin. (C) Relapse-free survival (RFS) according to simplified IPI ($P = 0.977$).

schedule is feasible and does not result in additional toxicity. Overall, patients randomized to the flexible arms received higher doses of anthracyclines, as documented by the different median DI of the two drugs in the different study arms (Table 2) with 21% patients receiving a 40% or higher dose at the fourth cycle; however, the higher anthracyclines' doses didn't result in an increase in response rate or survival. A possible explanation for these results is that the increase in DI in the flexible arm was modest and limited to only one drug. Our results are in line with that of another randomized trial comparing standard BACOP with BACOP that included escalated doses of doxorubicin; also in this study the CR rates for the two groups were 59% and 61%, respectively, without significant difference (28).

Dose escalation of more than one drug has been investigated by other authors and available data seem to confirm that this is a feasible and effective strategy for patients with aggressive lymphomas. The National Cancer Institute published in 2002 the results of a dose-adjusted EPOCH regimen for the treatment of large B-cell lymphomas in which the doses of etoposide, doxorubicin, and cyclophosphamide were adjusted 20% each cycle to achieve a nadir absoulte neutrophil count below 0.5×10^9/L. The treatment was associated with a 92% CR rate and with a 73% OS rate after a median follow-up of 62 months (29). In our opinion, these results confirm that the strategy of dose escalation should be applied to more than one effective drug and may warrant further investigation.

Other authors have investigated the efficacy of simply increasing drug doses without escalation, and based on few randomized trials it seems that this approach may be effective for patients with aggressive lymphoma. P-C regimen administered at 200% of standard dose has been evaluated by Gordon *et al.* in a phase-I and a phase-II trials; the dose intense regimen could be administered with G-CSF support with acceptable and manageable toxicity; moreover also if no phase-III trial has been performed the 72% CR rate has been considered a promising result (30). In a recent randomized trial for low risk localized aggressive lymphoma, an intensified CHOP derived regimen, namely AC-VBP, followed by sequential consolidation has determined superior results compared to CHOP

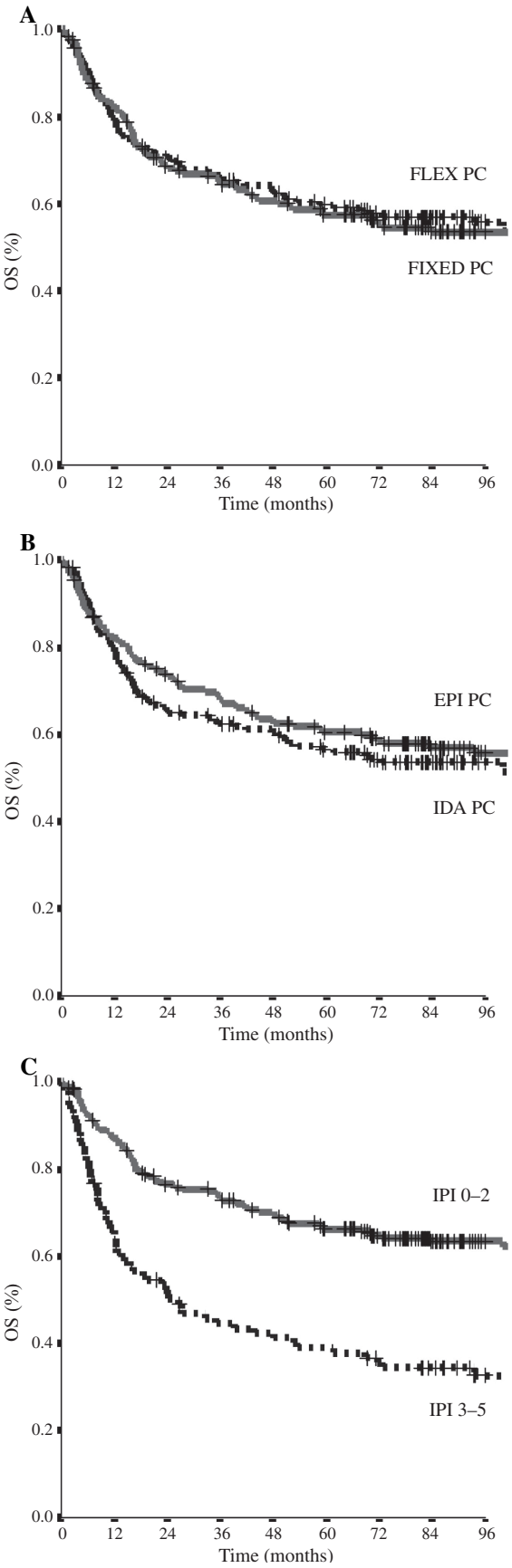

Fig. 4. (A) Overall survival (OS) according to regimen ($P = 0.852$). PC, ProMACE-CytaBOM. (B) Overall survival (OS) according to anthracycline type ($P = 0.362$). PC, ProMACE-CytaBOM; EPI, Epidoxorubicin; IDA, Idarubicin. (C) Overall survival (OS) according to simplified IPI ($P < 0.0001$).

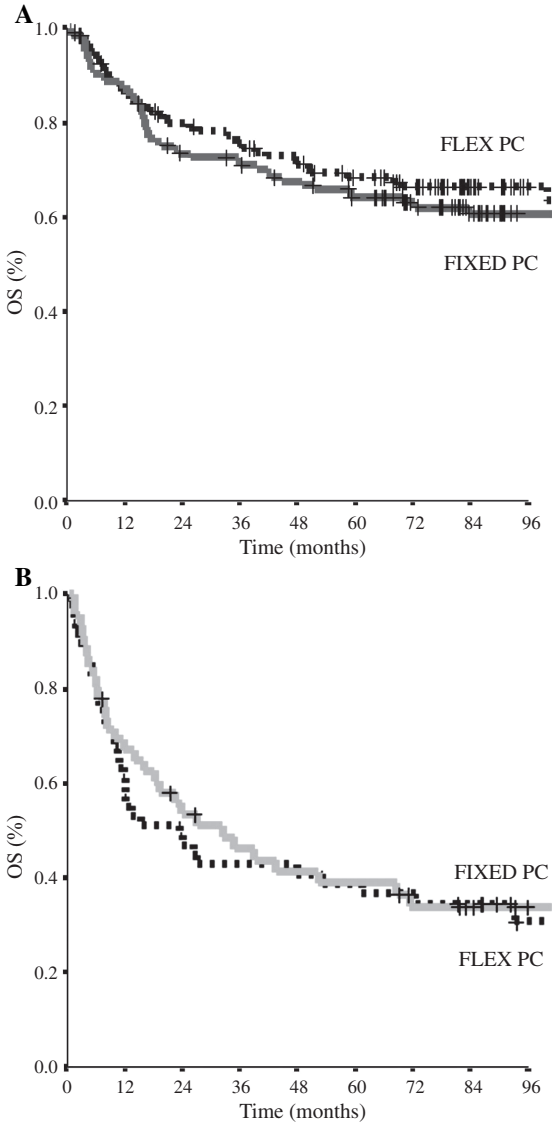

Fig. 5. (A) Overall survival (OS) for patients with IPI 0–2 according to regimen ($P = 0.473$). PC, ProMACE-CytaBOM. (B) Overall survival (OS) for patients with IPI 3–5 according to regimen ($P = 0.617$). PC, ProMACE-CytaBOM.

plus RT (31). The same ACVBP regimen has been also compared to standard CHOP by the same group as first-line treatment for patients with poor-risk aggressive lymphoma; despite higher toxicity, the ACVBP regimen was superior to standard CHOP with regard to both event-free survival and OS (26).

Table 6. Grade III–IV toxicity according to regimen

Toxicity	No. of patients (%)		*P* value
	Fixed	Flexible	
Anemia	7 (4)	14 (9)	0.17
Neutropenia	15 (9)	25 (16)	0.11
Thrombocytopenia	3 (2)	6 (4)	0.34
Lung toxicity	4 (2)	5 (3)	0.75
Infection	11 (7)	7 (4)	0.48

Very promising results in the intensification of chemotherapy regimens come from experience with dose-dense schemes, as shown in phase II studies with high-dose CHOP (32), bi-weekly CHOP (33), and VACPE, an intensified chemotherapy regimen consisting of vincristine, doxorubicin, cyclophophamide, prednisone, and etoposide (34). More recently, Pfreundschuh and colleagues have demonstrated that an intensified version of CHOP (CHOP-14) resulted in a significant improvement of cure rate in elderly patients with aggressive NHL (35, 36). Excellent results were also obtained by Vitolo *et al*. in a phase-III trial comparing a dose dense, dose intense regimen (MEGACEOP) with a high-dose therapy regimen in patients with aggressive NHL (37). These results, along with negative results obtained by simply increasing the DI, suggest that it is not only the absolute dose that should be increased to induce more tumor death but also, probably, the time over which therapy is delivered.

Finally, an important finding of our study comes from the adoption of the IPI as an initial parameter on which to base different treatment lengths. Started in 1993, the LA03 trial has been one of the first studies where IPI was used prospectively for planning therapy. Our results have shown that a conventional treatment with six cycles of P-C-based chemotherapy can be considered a good treatment for patient with aggressive NHL at low or low-intermediate risk, but that the same regimen is not enough for patient with IPI 3–5, also if additional cycles are delivered. Also, in the present study, as in our previous trials, we observed that the relapse rate was similar regardless of initial risk group, confirming that when patients do respond to treatment the quality of their response is similar, regardless of their initial risk; the problem with patients with IPI 3–5 that is a lower number of such patient achieve CR. Moreover, patients failing initial treatment tend to present an early disease progression. The achievement of an early response can thus be considered the most important goal for patients with aggressive NHL. For this reason an early assessment of response – for example, with positron emission tomography (PET), – should be considered in future studies.

Since the advent of anti-CD20 monoclonal antibody in the late 1990s, the chemo-immunotherapy combination has been demonstrated to improve survival in patients with aggressive B NHL of all age groups (12, 38). Since then, R-CHOP has been considered the standard treatment. However, when the LA03 trial was designed in 1993, data on Rituximab were not available and the optimal treatment was still chemotherapy alone.

In conclusion, our trial has demonstrated that P-C-based chemotherapy allows cure of a relevant number of patients with advanced, aggressive NHL

Table 7. Outcome of patients with aggressive NHLs

Authors	Year	Regimen	Risk group	n. pts	% CR	% OS
Martelli *et al.*	2003	MACOP-B	IPI 2–3	75	68	65 (5 yr)
Gianni *et al.*	1997	MACOP-B	All	50	70	55 (7 yr)
Zinzani *et al.*	1999	MACOP-B	All	91	70.5	61 (9 yr)
		F-MACHOP		257	72	67 (9 yr)
Jerkeman *et al.*	1999	MACOP-B	All	181	41	60 (5 yr)
		CHOP		193	37	59 (5 yr)
Tilly *et al.*	2003	ACVBP	IPI 2–3	323	58	46 (5 yr)
		CHOP		312	56	38 (5 yr)
Reyes *et al.*	2005	ACVBP	Stage I, II; IPI 0	318	93	90 (5 yr)
		CHOP		329	92	81 (5 yr)
Silingardi *et al.*	1995	ProMACE-CytaBOM	All	105	62	54 (4 yr)
		MACOP-B		103	67	61 (4 yr)
Federico *et al.*	1998	ProMECE-CytaBOM	All	128	62	56 (5 yr)
		ProMICE-CytaBOM		121	64	47 (5 yr)
Fisher *et al.*	1993	CHOP	All	225	44	54 (3 yr)
		m-BACOD		223	48	52 (3 yr)
		ProMACE-CytaBOM		233	56	50 (3 yr)
		MACOP-B		218	51	50 (3 yr)
Present study	2005	ProMECE-CytaBOM	All	183	69	60 (5 yr)
		ProMICE-CytaBOM		173	59	57 (5 yr)

CR, Complete remission; OS, Overall survival.

at low risk according to IPI, but does not seem appropriate for those at high risk. We believe that better-designed schemes, along with the use of current and future target therapies, will probably allow us to cure more patients. However, to accomplish this we still need better tools, i.e., using more sensitive prognostic factors, for the early identification of patients who will benefit from investigational therapies.

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