Pergamon

European Journal of Cancer Vol. 33, No. 8, pp. 1195–1201, 1997

Printed in Great Britain
0959-8049/97 $17.00 + 0.00

PII: S0959-8049(97)00051-8

Original Paper

CHOP-based Chemotherapy is as Effective as Alternating PEEC/CHOP Chemotherapy in a Randomised Trial in High-grade Non-Hodgkin's Lymphoma

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The aim of this study was to test whether survival for patients with high-grade non-Hodgkin's lymphoma (NHL) can be improved with a non-cross-resistant regimen as compared to a CHOP-based regimen. This is a multicentre study comprising 325 adult patients, median age 58 years, with high-grade non-Hodgkin's lymphoma: patients of any age and performance status were eligible provided they were able to receive the drugs in the regimens. Patients were randomised to either B-CHOP-M (bleomycin, cyclophosphamide, doxorubicin, vincristine, prednisolone and methotrexate) or PEEC-M (methylprednisolone, vindesine, etoposide, chlorambucil and methotrexate) alternating with B-CHOP-M. At a median follow-up of 9 years, there was no significant difference in overall survival or disease-free survival between the two arms. Toxicities for the two regimens were equivalent. This study confirms that for relatively unselected patients with high-grade non-Hodgkin's lymphoma, an alternating multidrug regimen does not improve upon the results obtained with B-CHOP-M.

Key words: CHOP, non-Hodgkin's lymphoma, randomised trial, survival

Eur J Cancer, Vol. 33, No. 8, pp. 1195–1201, 1997

INTRODUCTION

DURING THE 1970s it became clear that treating high-grade non-Hodgkin's lymphoma with combination chemotherapy such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) would result in approximately one-third of patients being cured [1–3]. The next decade saw the development, particularly in North America, of more intensive regimens, such as M-BACOD (methotrexate, bleomycine, doxorubicin, cyclophosphamide, vincristine, dexamethasone) [4], MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisolone, bleomycin) [5] and ProMACE-CytaBOM (cyclophosphamide, doxorubicin, etoposide, methotrexate–cytarabine, bleomycin, vincustine, methotrexate) [6]. In the single institutions in which they were developed, such regimens produced higher response rates and actuarial disease-free survival compared with the historical series of patients treated with CHOP. At the same time, Goldie and Coldman [7] developed the theoretical basis for such approaches, having shown in 1982 that correct use of non-cross-resistant chemotherapy might overcome resistance to some of the drugs being used and thus increase the chance of cure [7].

However, these new regimens were associated with an increase in toxicity, and only ProMACE-CytaBOM introduced any new drugs — in particular etoposide, which was

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Received 16 Oct. 1995; revised 4 Dec. 1996; accepted 16 Jan. 1997.

shown to have activity in high-grade NHL by Cabanillas and associates in 1982 [8].

After a pilot study involving 30 patients [9], the Scotland and Newcastle Lymphoma Group felt that it was reasonable to test such a 'non-cross-resistant' regimen including etoposide, but administered with no more toxicity than CHOP.

PATIENTS AND METHODS

Patients

The Scotland and Newcastle Lymphoma Group includes the majority of haematologists and oncologists working in both district general and teaching hospitals in the North of England and Scotland, as well as a number of interested histopathologists within the same regions. All patients presenting with high-grade NHL between 1 December 1984 and 23 October 1991 were eligible for consideration for the study, and were treated and followed up at their local hospital, with a median follow-up time of 9 years. Patients were required to give verbal informed consent to the trial, as specified by their local ethical committee.

Table 1. Numbers (percentages) for main characteristics in each arm

	Arm A ($n = 167$)	Arm B ($n = 158$)	Total ($n = 325$)
ECOG/PS			
0	54(32)	60(38)	114(35)
I	73(44)	69(44)	142(44)
II	26(16)	21(13)	47(15)
III	10(6)	6(4)	16(5)
IV	2(1)	2(1)	4(1)
NK	2(1)	0(0)	2(1)
Clinical stage			
I	13(8)	12(8)	25(8)
II	45(27)	47(30)	92(28)
III	28(17)	32(20)	60(19)
IV	81(49)	67(42)	148(46)
B Symptoms	83(50)	76(48)	159(49)
Bulk ≥ 5 cm	95(57)	103(65)	198(61)
Age* (years)			
<30	14(8)	10(6)	24(7)
30–39	13(8)	08(5)	21(7)
40–49	25(15)	20(13)	45(14)
50–59	40(24)	45(28)	85(26)
60–69	57(34)	61(39)	118(36)
>69	18(11)	14(9)	32(10)
Prognostic index			
Good prognosis	52(31)	63(40)	115(35)
Intermediate	56(34)	50(32)	106(33)
Worst prognosis	51(31)	39(25)	90(28)
NK (missing data)	8(5)	6(4)	14(4)
Working formulation (WF)			
A (small lymphocytic)	2(1)	1(1)	3(1)
B/C (follicular small/mixed cell)	5(3)	9(6)	14(4)
D (follicular large cell)	0(0)	1(1)	1(<0.5)
E/F (diffuse small/mixed cell)	31(19)	24(15)	55(17)
G (diffuse large cell)	71(43)	71(45)	142(44)
H (immunoblastic)	27(16)	21(13)	48(15)
I (lymphoblastic)	9(5)	10(6)	19(6)
Unclassifiable in WF	18(11)	18(11)	36(11)
Not NHL on review	4(2)	3(2)	7(2)

*Median age of all 325 patients was 58 years.

12 cases were unclassifiable at external review. These cases have been classified as at entry to the trial.

Inclusion criteria were a histological diagnosis of NHL in any of the Intermediate or High-grade categories of the Working Formulation (see list in Table 1) [10], together with the fitness of the patient to receive the chemotherapy. Patients were staged in the usual way, and although the trial recommended minimum staging criteria (see Table 1), inadequately staged patients were included if they met the other criteria. Any patient with other than stage 1A disease who was considered by their clinician to require chemotherapy was eligible. Prior radiotherapy was allowed provided it was either given with radical intent to apparently localised disease which had failed, or it was given as an emergency but not in such a way as to compromise the patient's ability to receive chemotherapy as per protocol.

There were intentionally only a few exclusion criteria including pregnancy, prior chemotherapy or a history of other malignancy (other than basal cell carcinoma of the skin or *in situ* carcinoma of the cervix). Table 1 shows the characteristics of the patients, and confirms that there were no significant differences between the two groups in terms of factors that were likely to affect outcome, including our own previously validated prognostic index [11]. Serum LDH (lactate dehydrogenase) was not measured in most patients and thus outcome by the recently published International Index could not be assessed [12].

Treatment

Patients entered into the study were randomised between two treatment arms, after stratification by bulk disease, which was defined as measurable disease >5 cm in one diameter in at least one site.

Arm A consisted of six cycles of B-CHOP-M, administered every 3 weeks. Arm B consisted of six cycles of alternating PEEC-M/B-CHOP-M (see Figure 1). At the end of the first four cycles, patients were evaluated by repeating all positive base-line investigations. Those in arm B with CR (complete response), PR (partial response) or without progression of unmeasurable disease continued on their original arm for a further two cycles. Any who had less than PR could be given second-line therapy at the clinician's discretion. Those in arm A who were in CR, or without progression of unmeasurable disease, also continued for a further two cycles; all others were switched to a final two cycles of PEEC-M. Dose modifications were done on the basis of the full blood count on the day of intended treatment (see Table 2).

Following chemotherapy, megavoltage radiotherapy could be given to sites of initial bulk disease only, as per the normal practice of the patient's local radiotherapy centre. Those in complete remission were given 2500 cGy in 10 fractions over 12–14 days; those with residual disease at sites of initial bulk disease were given at least 3500 cGy in 20 fractions over 26–28 days. In both cases, critical organ shielding was used as appropriate. Final evaluation was 1 week after final methotrexate or radiotherapy, and consisted of repeating all positive baseline investigations. Thereafter patients were followed up monthly for 3 months, 3 monthly for a further 15 months, and 6 monthly thereafter. All treatment, toxicity and follow-up data were forwarded to the SNLG secretariat, who also did the initial randomisation by telephone.

External pathological review was achieved in 91% of cases and the Working Formulation categories of the

DAY	ARM A		ARM B	
1	B-CHOP M		PEECM	
21	B-CHOP M		B-CHOP M	
42	B-CHOP M		PEECM	
63	B-CHOP M		B-CHOP M	
	EVALUATE		EVALUATE	
	CR or no progression of unmeasurable disease ↓	Less than CR ↓	CR or PR or no progression of unmeasurable disease ↓	Less than PR ↓
84	B-CHOP M	PEECM	PEECM	2nd line therapy of clinician's choice
105	B-CHOP M	PEECM	B-CHOP M	

B-CHOP M:	**Cyclophosphamide**	**750 mg/m²**	**Day 1**
	Doxorubicin	**45 mg/m²**	**Day 1**
	Vincristine	**1.4 mg/m²**	**Day 1 (max 2 mg)**
	Bleomycin	**7.5 mg/m²**	**Day 1 (max 10 mg)**
	Prednisolone	**40 mg daily**	**Days 1-5**
	Methotrexate	**200 mg/m²**	**Day 15**
	Folinic Acid	**15 mg/m²**	**Day 16 (6-hourly x 4)**
PEEC M:	**Methylprednisolone**	**250 mg**	**Day 1**
	Vindesine	**3 mg/m²**	**Day 1 (max 5 mg)**
	Etoposide	**100 mg/m²iv**	**Day 1**
	Etoposide	**200 mg/m²po**	**Days 2 & 3**
	Chlorambucil	**20 mg/m²**	**Days 1 - 3 (max 30 mg)**
	Methotrexate	**200 mg/m²**	**Day 15**
	Folinic Acid	**15 mg/m²**	**Day 16 (6-hourly x 4)**

Figure 1. Arms A and B — chemotherapy regimens.

patients shown in Table 1 are those applicable after such review. Table 3 lists the pathological types of those patients whose tumours could not at review be classified within the Working Formulation. For survival analysis, deaths identified as 'treatment-related' include all those in which treatment was at least part of the cause of death. A death is

Table 2. Dose modification protocol

If WBC ($\times 10^9$) (on day of treatment)	>3.5	>3 to ≤3.5	>2.5 to ≤3.0	≤2.5
Or platelets ($\times 10^{12}$)	>100	>75 to ≤100	>50 to ≤75	≤50
Action (doses of all drugs except steroids)	100%	75%	50%	Delay 7 days

categorised as due to lymphoma even if other factors are considered to have been involved as well; all other deaths are termed 'other'.

Statistical design and analysis

The size of the study was not based upon formal power calculations. It was anticipated that 35–50 patients could be recruited annually, and a 3 year entry was proposed. An entry of 100 patients would yield a standard error for the difference between rates in the two treatment arms, which would always be 10% or less. In practice, after 3 years, recruitment was at the upper range of our expectations and as no trial had been proposed to replace the present trial, entry was allowed to continue. At the time of trial closure, there was an 80% power to detect a difference of 15% in the complete remission rates, or 5 year survival rates at the 5% level of significance.

All patients who were considered eligible at the time of their first treatment were included in the study. Time to treatment failure or death was measured from the date of randomisation and the rates of treatment failure were analysed by the methods of Kaplan and Meier [13] with the log-rank test [14] being used to compare treatment groups. Comparison of toxicities and responses were done using chi-squared tests.

RESULTS

Response

Objective response rates were similar for the two arms of the trial, both at the first and final assessments, as shown in Table 4. The observed difference in CR rates was only 3% in favour of arm A, with 95% confidence limits from −8% to 13%. Furthermore, overall survival (Figure 2) and relapse-free survival (Figure 3) were not significantly different, with median survival times in arms A and B of 42 months and 36 months, respectively. Omitting patients considered at pathological review to have been retrospectively ineligible did not alter these conclusions. Similarly, there was no difference in outcome between the two arms for the patients over 60 years of age.

Insufficient data on serum LDH in particular prohibited application of the International Index [12] in this data set.

Table 3. Pathology unclassifiable in working formulation

	Arm A	Arm B	Total
Pleomorphic T-cell	3	4	7
Mycosis fungoides	0	2	2
High-grade large cell	4	5	9
High-grade T-cell anaplastic	1	0	1
High-grade B-cell	2	2	4
High-grade unclassifiable	2	3	5
High-grade mixed small and large cell	1	0	1
T-zone	2	1	3
Burkitt's	1	0	1
No diagnostic pathology	2	1	3
Total	18	18	36

However, as Table 1 confirms, there was no difference between the patients in the two arms in terms of their prognostic grouping as defined by our previously devised [11] and validated [15] index. Furthermore, there is no statistically significant interaction between the two arms of the trial and the prognostic groups ($\chi^2 = 2.1$, df = 2, $P = 0.35$), confirming the equal efficacy of the two arms, irrespective of the patients' pretreatment prognosis.

Treatment

Table 4 shows that the proportion of patients in each arm who received at least 90% of their intended dose was similar, as was the toxicity for the two drug regimens (see Table 5). The proportion of patients in each arm who achieved CR and PR was not different depending on the proportion of drug actually administered.

There were 28 patients in arm A for whom the protocol required a switch to PEEC-M because of an inadequate response after four cycles of B-CHOP-M. 15 of those patients switched as per protocol, with 7 achieving CR and 1 PR. A further 2 patients switched beyond the fourth cycle, with 1 achieving CR. Of those 10 who did not switch, 4 remained on B-CHOP-M, 2 achieving a CR and 1 PR. There was no

Table 4. Treatment and follow-up details (percentages in parentheses)

	Arm A (n = 167)	Arm B (n = 158)	Total (n = 325)
Completing four courses	124(74)	125(79)	249(77)
Chemotherapy given cycles 1–4			
B-CHOP ≥90%	85(51)	92(58)	177(54)
other	82(49)	66(42)	148(46)
PEEC ≥90%	*2(1)	106(67)	108(33)
other	165(99)	52(33)	217(67)
Response at first evaluation (after four courses)			
CR/PR	113(68)	101(64)	214(66)
Static/progressed	16(10)	28(18)	44(14)
Not evaluable	36(22)	27(17)	63(19)
Data missing	2(1)	1(1)	4(1)
Chemotherapy given cycles 5 and 6			
B-CHOP ≥90%	61(37)	68(43)	129(40)
other	106(63)	90(57)	196(60)
PEEC ≥90%	11(7)	79(50)	90(28)
other	156(93)	79(50)	235(72)
Response at end of treatment			
CR	72(43)	69(44)	141(43)
PR	25(15)	23(15)	48(15)
Static	8(5)	7(4)	15(5)
PD	14(8)	9(6)	23(7)
Ever achieved CR	106(63)	96(61)	202(62)
Status at 31 March 1996			
Alive	68(41)	51(32)	119(37)
NED	56(34)	44(28)	100(31)
Dead: cause lymphoma	72(43)	72(46)	144(44)
treatment	8(5)	9(6)	17(5)
other	18(11)	25(16)	43(13)
not known	1(1)	1(1)	2(1)

*i.e. Protocol violations.

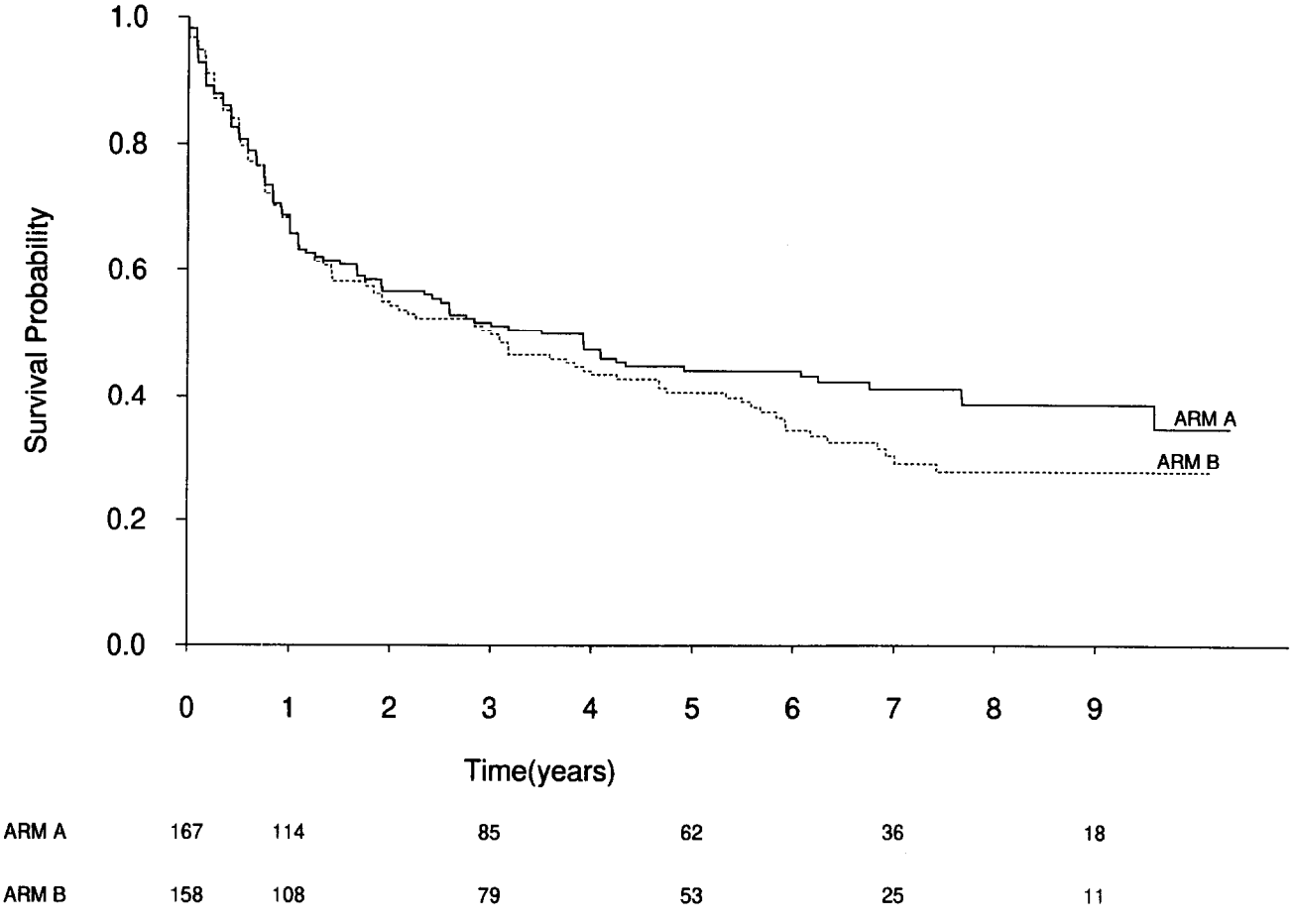

Figure 2. Survival curve for 325 patients comparing the two treatment arms A and B. Median survival time — arm A = 42 months, arm B = 36 months, $P = 0.23$.

difference in survival between the 15 who switched as per protocol and the remaining 13, nor was there any difference statistically in the response rates between the 17 receiving PEEC-M and the 4 who remained on B-CHOP-M (9/17 versus 3/4).

DISCUSSION

At the time that this trial was initiated, data largely from North America suggested that third-generation regimens for treating high-grade NHL had a higher response rate and probably improved survival, despite the increased toxicity. However, the SNLG felt that the Goldie–Coldman non-cross-resistant hypothesis should be tested in a setting where the toxicity was anticipated to be no more than that seen with CHOP, in an attempt to improve upon the latter's response rate.

Since then the SWOG/ECOG trial, with a median follow-up of only 35 months, has shown that the third-generation regimens M-BACOD, ProMACE-CytaBOM and MACOP-B are not significantly better than CHOP when tested in a multicentre phase III setting, and has also confirmed their significantly increased toxicity [16]. This is confirmed by the current study which, in contrast to the flurry of non-randomised trials performed in the 1980s (later refuted by the SWOG/ECOG trial [16]), reports mature follow-up data so that the results are highly likely to represent actual, and not just actuarial, survival. However, the particular combination used here is no more toxic, although there were more toxic deaths in both arms of this study than the CHOP arm of the SWOG/ECOG study, which probably reflects the relatively unselected nature of patients included in this study.

Etoposide has increasingly been used in the treatment of NHL, both in primary regimens such as ProMACE-CytaBOM [6], as part of a high-dose conditioning regimen [17], and also palliatively as a continuous oral regimen [18]. This study shows that half the CHOP cycles can safely be replaced with an etoposide-containing combination, without any significant alteration in toxicity or response. This may yet prove to be useful, in view of the well-established short- and long-term cardiac morbidity and mortality seen with doxorubicin use [19]. It may also prove a useful alternative to offer to patients who have, or develop, contraindications to anthracyclines and yet require potentially curative chemotherapy for high-grade NHL. Furthermore, although the numbers were small, there were three complete responses amongst those patients who were crossed over to PEEC-M after failing to achieve a complete response to CHOP; it might be interesting to test the PEEC combination for longer in such patients in the future, as the alternative third-generation regimens are more toxic, and the outlook for such non-responding patients is worse. One specific toxicity, renal failure, which in one case was fatal, was attributed to methotrexate [20]. This was despite normal serum creatinines, high oral fluid intake and folinic acid rescue.

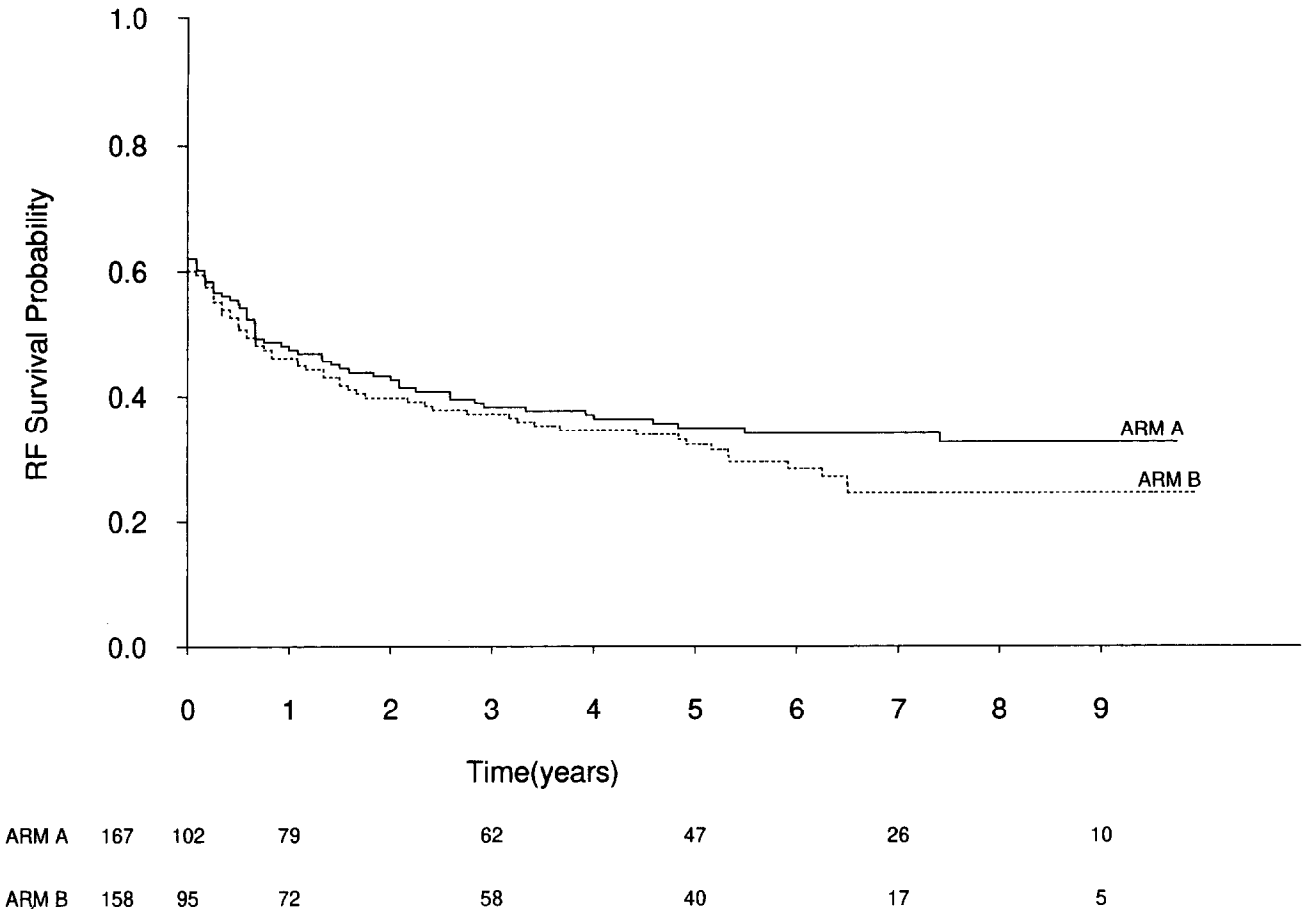

Figure 3. Relapse-free survival curve for 325 patients grouped by the two treatment arms A and B. 65 patients out of 167 in arm A and 63 out of 158 in arm B did not achieve any remission. $P = 0.34$.

Table 5. WHO trade toxicity (percentages in parentheses)

		Arm A ($n = 167$)	Arm B ($n = 158$)	Total ($n = 325$)
Infection				
No infection	0	100(60)	95(60)	195(60)
Fever	1	20(12)	12(8)	32(10)
Local infection	2	21(13)	29(18)	50(15)
Bacteria	3	10(6)	13(8)	23(7)
Septic	4	6(4)	2(1)	8(2)
Dead	5	1(1)	0(0)	1(<0.5)
Recorded grade nk		4(2)	5(3)	9(3)
Not known		5(3)	2(1)	7(2)
Nausea/vomiting				
None	0	59(35)	55(35)	114(35)
Nausea	1	28(17)	23(15)	51(16)
Trans vomiting	2	40(24)	44(28)	84(26)
Vomit (therapy)	3	22(13)	27(17)	49(15)
Vomit (intract)	4	6(4)	2(1)	8(3)
Recorded grade nk		7(4)	5(3)	12(4)
Not known		5(3)	2(1)	7(2)
Other toxicity specified				
Alopecia		51(31)	47(30)	98(30)
Renal failure		4(2)	4(3)	8(2)
Treatment delay				
↓WBC		71(43)	86(54)	157(48)
Total delayed		149(89)	139(88)	288(89)

The application of a prognostic indicator is not necessarily helpful unless it leads to either a more effective treatment or less toxicity. The validity of the SNLG prognostic index for high-grade NHL has been previously shown in this group of patients [15] — and the more mature data in this report confirm that the index is not regimen-specific. This is important as it would strengthen the argument that those in a poor prognostic group should receive more intensive treatment initially, since the two regimens are equivalent in toxicity and intensity. Whether an increased dose intensity can impact upon survival remains uncertain, partly because the third-generation regimens developed in North America in the 1980s failed to improve upon the survival seen with CHOP when tested outside the teaching centres [16]. What is required is a prospective study of a significantly increased dose intensity as compared with CHOP in poor prognostic patients.

Because of the problem of transferring the apparently superior results of third-generation regimens into non-teaching hospitals, we felt it important to design a study which encompassed the broad range of patients with high-grade NHL so that any conclusions would automatically be applicable to patients managed in different types of institutions. The consequence of this is that numerous subgroups exist within the 325 patients in this study (for example, only 59% are truly diffuse large cell; only 64% are stage III and IV

disease). There is thus the potential for missing a benefit for one or another regimen within such a narrower definition of high-grade NHL. However, such subgroups are equally distributed between the two arms and thus it is unlikely that a survival benefit of significant magnitude has been overlooked. Equally, some patients had received radiotherapy, either before entry or as consolidation. Such patients were equally distributed between the two arms and thus their inclusion does not alter the conclusion as to the efficacy of the two treatment arms. Furthermore, a clinician working with perhaps less than ideal staging or pathological facilities can still be confident that CHOP is an appropriate regimen for his/her patient.

This study was designed to test a CHOP-based regimen against a hybrid regimen where the PEEC arm was intended to be non-cross-resistant. The evidence for this is partly the efficacy of etoposide in patients who had relapsed after initial combination chemotherapy [8], as well as our prior experience with both PEEC and alternating PEEC-CHOP [9]. In that pilot study, complete responses were seen in 3 out of 4 previously treated patients who were given PEEC (with or without CHOP) on relapse.

Consistent with the precepts that underpinned the design of the NCI ProMACE-MOPP protocol [22], it was further anticipated that the patients in arm A who were switched to PEEC-M after failing to achieve a PR with four cycles of B-CHOP-M would demonstrate this non-cross-resistance. However, their response rate was not statistically different from that seen in the 4 patients who erroneously continued with B-CHOP-M after a similarly inadequate response.

In the 10 years since this study was conceived, the Goldie–Coldman hypothesis [22] has not been validated. Furthermore, it is doubtful whether any truly non-cross-resistant regimens can be designed for NHL. Thus, the negative conclusion of this study is perhaps not a surprise. What is clear, however, is that one can substitute etoposide for doxorubicin in half the cycles of a multidrug regimen without compromising either toxicity or survival. Since predictors for anthracycline-induced cardiotoxicity are currently unavailable, this offers an alternative therapeutic strategy for patients in whom even 300 mg/m^2 of doxorubicin might be thought too hazardous.

The results of randomised treatment trials are important, but it is necessary to be circumspect in drawing general conclusions from them. Nowhere is this truer than in trials in malignant lymphoma where optimum results derive from studies where the follow-up is short and patient entry restricted by pathological subgroup (basically large cell lymphoma) and in effect by age. The strength of this trial lies in the fact that it is a much closer test of the sorts of treatment in the sorts of patients seen in day-to-day practice by clinicians managing high-grade lymphomas.

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Acknowledgements—The authors are grateful to Ms C. D. Martin for data management help.