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Long-term Results of a Multicentre Randomised, Comparative Phase III Trial of CHOP Versus CNOP Regimens in Patients With Intermediate- and High-grade Non-Hodgkin's Lymphomas

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59 previously untreated patients with intermediate- or high-grade, stage II–IV non-Hodgkin's lymphoma (NHL) were entered into an open-label, randomised, multicentre study to compare the efficacy and safety of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) with that of CNOP (cyclophosphamide, mitoxantrone, vincristine and prednisolone). 10 patients refused treatment following randomisation. The remaining 349 patients received either the CHOP or CNOP regimen every 3 weeks for a maximum of six to eight cycles. The randomisation procedure was violated for 34 patients treated at two study centres. Data from these 34 patients were analysed separately for efficacy and survival. Data from the remaining 325 patients, 164 assigned to CHOP and 161 to CNOP, were used in the major efficacy and survival analyses. Of these 325 patients, 263 (81%) met the eligibility criteria of the protocol. Supplementary analyses of data from these 263 patients, 132 assigned to CHOP and 131 to CNOP, were conducted for efficacy and survival. Data from all 349 treated patients were analysed for safety. In the 325 randomised patients, the overall objective response rate was not significantly different between the two groups (χ_2 test, $P = 0.35$). The CHOP regimen had a 51% (83/164) complete remission (CR) rate compared with 40% (64/161) for the CNOP regimen ($P = 0.05$). Among those with CR, the median time to response was 104 days with the CHOP regimen and 77 days with the CNOP regimen, and the median duration of CR was 667 and 1833 days, respectively. The median time to progression was 449 days for CHOP patients and 564 days for CNOP patients. The median survival time was 932 days for CHOP patients and 1801 days for CNOP patients, with a risk of death on CNOP relative to CHOP of 0.93 (95% confidence interval 0.68–1.27). After 5 years, 50% of patients in the CNOP arm and 40% of patients in the CHOP arm were still alive; these differences between treatment groups were not statistically significant. The median time to treatment failure (TTF) was 285 days for patients on the CHOP arm and 282 days for patients on the CNOP arm. Separate analyses of 263 eligible randomised patients, and 34 patients in whom the randomisation procedure was not followed, yielded similar results for remission rate, TTF, duration of CR and estimated overall survival. The incidence of non-haematological events, such as severe nausea and vomiting ($P < 0.01$), mucositis ($P < 0.05$) and alopecia ($P < 0.001$), were significantly lower in patients treated with CNOP as compared with those who received the CHOP regimen. The incidence of cardiovascular toxicity of any severity was similar in the two groups. While severe and potentially life-threatening neutropenia occurred more frequently in patients treated with CNOP compared with CHOP ($0.05 > P > 0.10$), the incidence of infection of any severity was similar in both arms. We conclude that CHOP and CNOP regimens were both efficacious in patients with previously untreated aggressive NHL.

Key words: randomised trial, phase III, chemotherapy, non-Hodgkin's lymphoma
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INTRODUCTION

INITIALLY REPORTED by Gottlieb and associates [1] in 1973, the CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) chemotherapy regimen for non-Hodgkin's lymphoma (NHL) is known to produce complete remission in 44–55% of patients and cure in approximately 30% [2, 3]. Over the years, there have been numerous attempts to devise more effective regimens for NHL through the incorporation of additional chemotherapeutic agents, intensification of the schedule of administration or changes in the route of administration of certain agents. Regimens such as MACOP-B (methotrexate, cyclophosphamide, doxorubicin, vincristine, prednisolone and bleomycin), COP-BLAM (cyclophosphamide, doxorubicin, vincristine, prednisolone, bleomycin and methotrexate) and

ProMACE-cytaBOM (cyclophosphamide, doxorubicin, vincristine, prednisolone, bleomycin, leucovorin, methotrexate, cytarabine and etoposide) were reported to have superior complete remission rates, ranging from 65 to 84%, and 3–5-year relapse-free survival for complete responders ranging from 60 to 80% in several non-randomised, single-centre trials [4–8]. The patient population enrolled in these trials was, however, younger than the overall mean age for patients with NHL, and this factor may well have contributed to superior remission rates and survival. A recent prospective, randomised, multicentre study comparing NHL patients treated with either CHOP, MACOP-B, ProMACE-cytaBOM, or m-BACOD (bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone, methotrexate and leucovorin) reported no significant differences between the treatments with respect to complete remission rate, overall remission rate and 3-year disease-free survival [2]. When the toxicities of these second- and third-generation regimens are taken into consideration, CHOP remains the standard regimen for the treatment of most patients with NHL.

Mitoxantrone (Novantrone) is an anthracenedione chemotherapeutic agent with a lower risk of cardiotoxicity than doxorubicin [9]. It has activity as a single agent in patients with previously treated NHL [10] and has been reported as active when substituted for doxorubicin in the CHOP and m-BACOD regimens [11–13]. This report presents the efficacy and safety results of an international, multicentre, randomised clinical trial comparing the CHOP regimen with the CNOP (cyclophosphamide, mitoxantrone, vincristine and prednisolone) regimen in the treatment of patients with NHL. The purpose of the study was to compare differences in remission rates, time to response, time to treatment failure (TTF), time to progression, duration of complete remission, estimated overall survival and adverse effect profile, including cardiovascular toxicity, between the two regimens.

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PATIENTS AND METHODS

Eligibility criteria

This study was open to enrolment from July 1984 until October 1987 and involved 32 investigators in 14 different countries. Patients were required to be at least 16 years of age and to have a histological diagnosis of intermediate- or high-grade NHL, according to the International Working Formulation [14], and to be Ann Arbor stage II [15] or greater. Histological diagnosis was by an expert pathology panel at each participating centre. Central pathology review was not attempted because of the logistics involved. Patients were staged by standard clinical, radiological and pathological criteria, including as a minimum chest X-ray, abdominal scan (computed tomography and sonography) and bone marrow evaluation by means of bone marrow aspiration and trephine biopsy. No prior chemotherapy or extensive radiotherapy was permitted; however, prior use of single-agent glucorticoids or local radiation therapy was allowed. Additional eligibility criteria included a WHO performance status of ≤ 2; creatinine clearance >60 ml/min; serum glutamic-oxalacetic transaminase (SGOT), glutamic-pyruvic transaminase (SGPT) and alkaline phosphatase levels within twice the upper limit of normal; absolute granulocyte count $>1500/mm^3$; and platelet count $>100\,000/mm^3$. Patients with documented lymphomatous involvement of the liver or bone marrow were permitted on the study regardless of their laboratory values. Patients were required to have normal cardiac function as measured by radionuclide multiple-gated angiography (MUGA) scan or echocardiogram. Patients with a prior history of malignancy other than basal cell carcinoma of the skin or carcinoma *in situ* of the cervix were excluded. This study was approved by local ethics committees and health authorities of the respective countries; written or verbal informed consent was obtained in accordance with local regulations.

Treatment schedule and study design

Patients were randomly allocated in blocks of four to receive either the CHOP or CNOP regimen using a balanced block design. Treatment allocations were stratified according to histological grade (intermediate and high grades); disease stage (number of patients with stage IV disease and those with combined groups of stages II and III); and presence or absence of systemic symptoms, such as fever, sweats and loss of more than 10% body weight during the 6 months prior to diagnosis. The CHOP regimen consisted of cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2 and vincristine 1.4 mg/m^2, all administered intravenously on day 1, and prednisolone 50 mg/m^2 administered orally on days 1–5. In the CNOP regimen, all study drugs were the same except mitoxantrone 10 mg/m^2 was administered intravenously on day 1, in place of doxorubicin. Haematology testing was performed every week, and blood chemistry and urine analysis tests were performed before each course of chemotherapy. Dose adjustments of cyclophosphamide, doxorubicin, and mitoxantrone took into account the nadirs of white blood cell (WBC), neutrophil and platelet counts of the previous cycle of chemotherapy, as well as the results of liver function tests. Dose reduction of 25% of mitoxantrone or doxorubicin and cyclophosphamide was applied if WBC was $<1000/mm^3$ in the previous chemotherapy cycle, as determined

by weekly blood count. Doxorubicin and mitoxantrone doses were also modified by 25% for bilirubin elevations of between 1.5- and 2-fold the upper limit of normal. The entire course of treatment was repeated every 21 days provided that the WBC count had returned to at least 3000/mm^3 and the platelet count, to at least 70 000/mm^3. In the two arms of the study, the dosage modification scheme for mitoxantrone and doxorubicin was identical.

Response to therapy was assessed at the end of each cycle of treatment. A complete restaging was performed at the end of cycles three and six, and again at cycle eight for patients receiving more than six cycles of treatment.

Complete remission (CR) was defined as the disappearance of all clinical and pathological evidence of tumour, lasting a minimum of 8 weeks. Patients with lymphomatous bone marrow infiltration at baseline, who were believed to be in CR after treatment, were required to have a bone marrow assessment to confirm response.

Partial remission (PR) was defined as a 50% or greater decrease in the sum of the products of the diameters of all measurable lesions lasting for a minimum of 4 weeks. Only lesions greater than 1 cm in diameter were used for this evaluation. For liver involvement, a 30% reduction in the sum of the measurements below the costal margin constituted a PR.

Stable disease was defined as no change or a response less than a PR.

Progressive disease was defined as an increase of at least 25% in the sum of the products of all measurable lesions or the appearance of a new lesion.

Duration of response was defined as the time from achievement of response to the first sign of progressive disease.

Safety was assessed continuously from the start of treatment for all patients who received at least one dose of any chemotherapeutic agent. Haematological toxicity was monitored weekly. Cardiac function was monitored by electrocardiogram (ECG) performed every 12 weeks, and by either MUGA scan or echocardiogram. The latter was performed either at the end of treatment, as indicated by clinical signs and symptoms, or after the patient had received a cumulative dose of 80 mg/m^2 of mitoxantrone or 400 mg/m^2 of doxorubicin.

A maximum of eight cycles of chemotherapy could be administered on the study. In general, patients achieving a CR were treated for two or three additional cycles prior to cessation of treatment. Patients achieving CR at cycle three continued to a total of six cycles. Patients achieving a PR within three cycles were continued on the same treatment to six cycles. After further re-evaluation at the end of cycle six, those in PR, as well as those who had achieved CR by six cycles, received two more courses to a maximum of eight cycles of chemotherapy. Patients with stable disease at the end of the third cycle of chemotherapy were removed from the study and offered alternative treatment. Patients were withdrawn from the study at any time during the trial for progressive disease, intolerance to the therapy, at the request of the patient or at the discretion of the investigator.

Patients

A total of 359 patients were enrolled in the study, 178 to CHOP and 181 to CNOP. The randomisation procedure was violated at two investigational sites. Data from the 34 patients (14 CHOP; 20 CNOP) enrolled at these two sites are not included in the major analyses of efficacy. Of the 325 appropriately randomised patients (164 CHOP; 161 CNOP), 10 (5 in each group) were randomised but not treated. The data from these 10 patients are included in the major efficacy analyses. Of the 325 appropriately randomised patients, 263 (81%) met all eligibility criteria specified in the protocol. Supplementary analyses of efficacy were conducted on the 263 eligible patients (132 CHOP; 131 CNOP), and on the 34 incorrectly randomised patients. Safety data were analysed for all 349 patients who received treatment, regardless of whether they were correctly or incorrectly randomised.

Statistical methodology

This study was designed to assess the comparability of the two treatment regimens with regard to assessments of efficacy, survival, TTF, time to progression and remission rates. For each of these efficacy variables, the analyses were based on the null hypothesis of no difference between the two regimens versus the two-sided alternative that there is a difference between the regimens. Additionally, for each regimen, the time to achievement of a complete remission and duration of complete remission were summarised.

Objective response was assessed for each cycle, according to the previously defined criteria. The distribution of the best response for each patient was summarised for each regimen. The two regimens were compared with respect to CR, PR and overall (CR plus PR) remission rates, using the χ^2 test. Confidence intervals (CI) for the difference between remission rates of the two regimens were calculated using a normal approximation [16].

For each of the following time to event variables, survival curves (time-adjusted distribution) were estimated for each regimen, using the Kaplan–Meier method [17]. The survival interval was defined as the interval between randomisation and death (or censored at the date of last follow-up observation for survivors). Time to treatment failure was the interval from randomisation until the first occurrence of relapse (among responders with CR), progression (among partial responders or non-responders), withdrawal due to toxicity or intolerance, or death. Patients who did not experience any of these events were censored at the date of their last assessment. Time to progression was the interval from randomisation to relapse, for patients who responded to treatment or progression of disease. Patients who did not relapse or progress were censored at the date of their last assessment. Duration of CR was defined as the interval from the first documentation of a CR until relapse. It was censored at the time of last observation for patients who continued to be in CR. The treatment groups were compared with respect to TTF, time to progression, duration of CR (disease-free survival), and overall survival (OS), using the log-rank test. Additionally, for each of these variables, the hazard ratio (relative risk) and its associated 95% CI were calculated. The two regimens were also compared with respect to the frequency and severity of adverse experiences using Wilcoxon's rank sum test. The differences in the incidence of severe events between the regimens were tested using Fisher's exact test. The significance level for all tests of the hypothesis was 0.05. All statistical analyses were performed using SAS statistical software [18].

RESULTS

The demographic characteristics of the 325 patients for whom the randomisation procedure was properly followed, and the 263 eligible randomised patients are presented in Table 1. The patients were evenly distributed between groups with respect to age, sex, race, performance status, presence or absence of systemic symptoms, extranodal involvement and histological

Table 1. Demographic and disease characteristics of all randomised and eligible randomised patients according to treatment groups

Characteristics	All randomised patients		Eligible randomised patients	
	CHOP (n = 164) n (%)	CNOP (n = 161) n (%)	CHOP (n = 132) n (%)	CNOP (n = 131) n (%)
Gender				
Male	86(52)	88(55)	71(54)	71(55)
Female	78(48)	73(45)	61(46)	59(45)
Race				
White	114(70)	108(67)	93(71)	91(69)
Hispanic	40(24)	37(23)	32(24)	28(21)
Black	5(3)	6(4)	3(2)	5(4)
Other	5(3)	10(6)	4(3)	7(5)
Age (years)				
Mean	55	54	54	54
Range	19–81	14–88	19–81	16–88
<60	95(58)	90(56)	79(60)	73(56)
≥60	69(42)	70(43)	53(40)	57(44)
Unknown	0	1(1)	0	1(1)
Height (cm)				
Mean	163	164	164	163
Range	136–210	122–184	136–210	122–183
Weight (kg)				
Mean	64	65	65	65
Range	39–123	40–102	39–123	39–95
Performance status				
0	52(32)	44(27)	44(33)	36(28)
1	65(40)	67(42)	57(43)	57(44)
2	41(25)	45(28)	31(24)	38(29)
3	5(3)	4(2)	0	0
4	1(0.6)	0	0	0
Unknown	0	1(1)	0	0
Stage				
II	32(20)	49(30)	27(20)	44(34)
III	56(34)	39(24)	45(34)	33(25)
IV	75(46)	72(45)	60(46)	54(41)
Unknown	1(0.3)	1(1)	0	0
Symptoms				
Absent	96(59)	91(57)	79(60)	76(58)
Present	67(41)	69(43)	53(40)	55(42)
Unknown	1(1)	1(1)	—	—
No. of extranodal sites				
None	57(35)	64(40)	50(38)	56(43)
1	66(40)	57(35)	51(39)	44(34)
2	32(20)	29(18)	25(19)	22(17)
3	8(5)	9(6)	5(4)	7(5)
>3	1(1)	2(1)	1(1)	2(2)
Histological grade				
Intermediate	119*(73)	110†(68)	101(77)	88(67)
High	45(27)	51(32)	31(23)	43(33)

*Includes one low grade tumour. †Includes two low grade tumours.

grade. There were more patients with stage III disease in the CHOP arm as compared to the CNOP arm. Of the 325 randomised patients, 56 (34%) in the CHOP arm had stage III disease compared with 39 (24%) in the CNOP arm. The corresponding figures for stage II were 32 patients (20%) receiving CHOP versus 49 patients (30%) receiving CNOP. The number of patients with stage IV disease was similar for CNOP (46%) and CHOP (45%). A similar imbalance for disease stage existed in the 263 eligible randomised patients. The demographic characteristics of 34 patients from two sites, where the randomisation procedure was violated, were unremarkable. A total of 62 (32 CHOP; 30 CNOP) of the 325 randomised patients did not fulfil all protocol eligibility criteria. The reasons for ineligibility are listed in Table 2.

Drug exposure

Of the 325 randomised patients, 315 were treated with one of the two regimens (159 CHOP; 156 CNOP). As previously

Table 2. Summary of eligibility status

Reason for non-eligibility	CHOP	CNOP
Protocol violation		
Cardiac abnormality*	11	6
History of cardiac disease	0	3
Performance status ≥3	6	4
Low-grade lymphoma	1	2
<15 years age	0	1
History of malignancy	1	1
Lymphomatous meningitis	1	0
Concurrent malignancy	1	1
Nonmeasurable disease	1	1
Irradiated lesion	0	1
Abnormal blood chemistry/ urinary test results at baseline	2	1
Abnormal haematology test results at baseline	1	1
Absence of screening results at baseline		
Blood chemistry/urinary tests	4	6
LVEF	1	1
Biopsy	1	0
Incomplete baseline case record form book	1	1
Total	32(20%)	30(19%)

LVEF, left ventricular ejection fraction. *LVEF below 50%, ischaemia or cardiomyopathy.

mentioned, 10 patients refused the treatment to which they were randomised, and, therefore, were not included in drug exposure analyses. Seventy per cent (112/159) of the patients treated with CHOP and 66% (103/156) of the patients treated with CNOP completed at least six cycles of chemotherapy. The percentage of the protocol dose administered for each drug of the regimen ranged from 82 to 102% in the CHOP group and from 80 to 133% in the CNOP group (Table 3). In approximately 70% of the cycles, all drugs except vincristine were administered at unmodified doses, and within 27 days of the previous cycle of chemotherapy. In 30 and 24% of the cycles of the CHOP and CNOP regimens, respectively, the dose of vincristine was unmodified and administered within 27 days of the previous cycle of chemotherapy. Dose 'capping' of vincristine at a maximum dose of 2.0 mg was responsible for the high calculated rate of vincristine dose modification. It should, however, be pointed out that the alternative method of dose calculation, namely percentage of protocol dose administered, showed that vincristine dosages were in the range of 80–93%. Prednisolone doses were rounded to the nearest 5 mg to take into account tablet size. Apart from the vincristine dose 'capping' and tablet size considerations in regard to prednisolone dose, the reason for dose modification of the other drugs, namely of cyclophosphamide, doxorubicin or mitoxantrone, was haematological toxicity.

Remission rates

The remission rates for the 325 patients who were correctly randomised are shown in Table 4. 83 of 164 (51%) patients treated with CHOP and 64 of 161 (40%) patients treated with CNOP had a CR (χ^2 test, $P = 0.05$). The overall remission rates (CR and PR) for the two groups were not statistically significantly different (CHOP 65%; CNOP 60%); ($P = 0.35$). The median time to CR was 104 days for complete responders to the CHOP regimen and 77 days for complete responders to the CNOP regimen.

Survival

As of February 1994, there were 84 deaths among the 164 patients on the CHOP arm and 75 deaths among the 161 patients on the CNOP arm. Survival times ranged from 0 to 2890 days (7.9 years) on CHOP and from 0 to 2959 days (8.1 years) on CNOP. The distributions of survival times for the two treatment groups were similar with a log-rank P value of 0.62 (Figure 1). The estimated risk of death on CNOP relative to CHOP was

Table 3. Dosage summary for 315 randomised treatment patients according to treatment group

	CHOP (n = 159)		CNOP (n = 156)	
Compound	No. of cycles	% of protocol dose	No. of cycles	% of protocol dose
Total no. of cycles	888	—	862	—
Mean number of cycles/patient	5.6 ± 2		5.5 ± 2	
Doxorubicin				
Mean dose range/cycle		95–99		—
Cycles with dose unmodified	671(76%)		—	
Mitoxantrone				
Mean dose range/cycle		—		93–99
Cycles with dose unmodified	—		594(69%)	
Cyclophosphamide				
Mean dose range/cycle		93–100		93–100
Cycles with dose unmodified	623(70%)		577(67%)	
Vincristine				
Mean dose range/cycle		82–93		80–93
Cycles with dose unmodified	266(30%)		210(24%)	
Prednisolone				
Mean dose range/cycle		100–102		98–133
Cycles with dose unmodified	649(73%)		605(70%)	

Table 4. Response rates of all randomised and eligible randomised patients according to regimen

Type of response	All randomised patients CHOP (n = 164) n (%)	All randomised patients CNOP (n = 161) n (%)	Eligible randomised patients CHOP (n = 132) n (%)	Eligible randomised patients CNOP (n = 131) n (%)
Complete remission	83(51)*	64(40)	73(55)†	55(42)
Partial remission	23(14)	32(20)	21(16)	26(20)
Stable disease	15(9)	17(11)	10(8)	13(10)
Disease progression	23(14)	30(19)	16(12)	28(21)
Evaluation not possible	20(12)	18(11)	12(9)	9(7)

*χ^2 test, P = 0.05, CHOP versus CNOP. † χ^2 test, P = 0.03, CHOP versus CNOP.

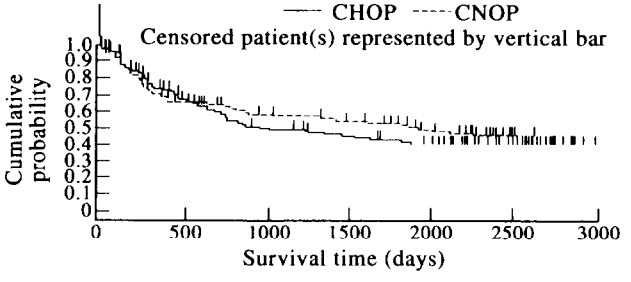

Figure 1. Kaplan–Meier estimates of overall survival of the 325 randomised patients according to treatment groups.

0.93 (95% CI 0.68–1.27). Median survival time was 932 days for CHOP patients and 1801 days for CNOP patients. This large apparent difference is primarily an artefact of the gradual slopes of the survival curves at the medians, rather than being indicative of a substantial survival advantage for CNOP (Figure 1). After 1 (365 days), 2 (730 days) and 5 years (1825 days), cumulative survival rates were 74, 56 and 40%, respectively, for CHOP and 69, 62 and 50% for CNOP.

TTF

The distributions of treatment failure times for the two treatment groups were similar (P 0.64, log-rank test). The estimated risk of treatment failure with CNOP relative to CHOP was 0.94 (95% CI 0.72–1.22) (Figure 2). The median TTF was 285 days for patients on the CHOP arm and 282 days for patients on the CNOP arm.

Duration of CR (disease-free survival)

Duration of CR was analysed for the 147 patients achieving a CR (CHOP 83; CNOP 64). The median duration of CR was 667 days for patients on the CHOP arm and 1833 days for patients on the CNOP arm (Figure 3).

Time to progression

The distributions of the time to progression for the two treatment groups were similar (P 0.49, log-rank test). The estimated risk of progression with CNOP relative to CHOP was 0.91 (95% CI 0.69–1.20). The median time to progression was 449 days (range 2–2682) for patients on the CHOP arm, and 564 days (range 10–2836) for patients on the CNOP arm.

Supplemental analyses of the 263 eligible, randomised patients and the 34 incorrectly randomised patients yielded similar results with regard to response rate, TTF, time to progression, duration of complete remission and estimated overall survival (data not shown).

Safety

Safety data were obtained for the 349 patients (CHOP 173; CNOP 176) who received a minimum of one dose of any constituent drug of either chemotherapy regimen on the study. 23 patients (CHOP 11; CNOP 12) died within 3 months of the conclusion of chemotherapy. The causes of death for these patients are summarised in Table 5.

16 (9%) of the 173 CHOP-treated patients and 10 (6%) of the 176 CNOP-treated patients were withdrawn from the study prior to completion of therapy. The reasons for withdrawal of the patients were toxicity (CHOP 10; CNOP 5), refusal of further therapy (CHOP 5; CNOP 4), lost to follow-up (CHOP 1; CNOP 0), and withdrawal to receive alternate therapy (CHOP 0; CNOP 1). 4 patients in each arm were withdrawn from the study as a result of cardiovascular toxicity.

Clinical and laboratory adverse events were summarised and graded in terms of their severity according to WHO criteria.

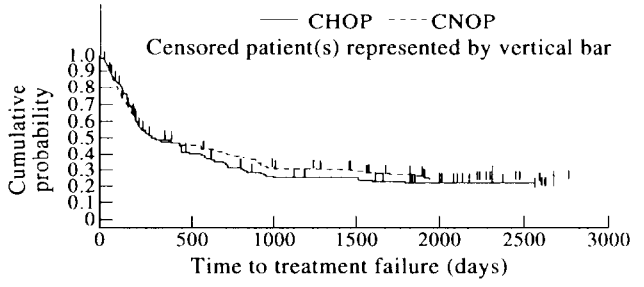

Figure 2. Time to treatment failure according to treatment group (for all 325 randomised patients).

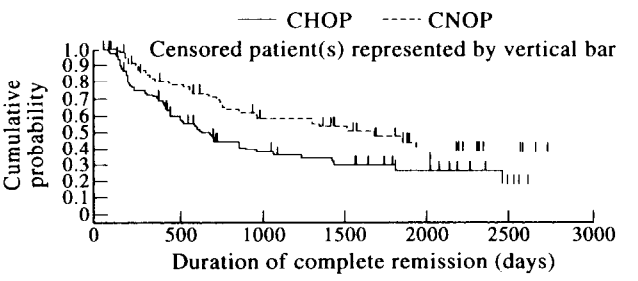

Figure 3. Duration of complete remission according to treatment group for the 147 randomised patients who had complete remissions.

Table 5. Causes of death within 90 days of last course of CHOP (n = 173) and CNOP (n = 176)

Cause of death	Number of patients CHOP	CNOP
Cardiovascular		
Acute myocardial infarction	0	1
Congestive heart failure	0	1
Cardiac and renal insufficiency	0	1
Cardiac insufficiency	1	0
Cerebrovascular accident	2	0
Disease progression	3	2
Metabolic, haemorrhagic or septic shock	1	2
Pulmonary embolism	1	1
Liver failure	1	1
Sepsis and acute renal failure	1	0
Septicaemia and pleural effusion	0	1
Ileus, paralytic	0	1
Unknown	1	1
Total	11(6%)	12(7%)

Overall, the percentage of patients experiencing at least one adverse event of any severity during the study period was similar for the two treatment groups. A total of 168 of 173 (97%) CHOP-treated patients, and 166 of 176 (94%) CNOP-treated patients experienced at least one adverse event (Table 6). The overall incidence of adverse events considered severe was significantly greater in the CHOP arm compared to the CNOP arm. Seventy-three per cent of the CHOP-treated patients experienced at least one severe adverse event compared with 43% of the CNOP-treated patients ($P < 0.001$, Wilcoxon test) (Table 6). Specifically, the CNOP-treated patients experienced a significantly lower incidence of severe alopecia ($P < 0.001$), nausea and vomiting ($P < 0.01$), and mucositis ($P < 0.05$) than did the CHOP-treated patients (Table 6).

Table 6. Safety profile for 349 patients treated with CHOP (n = 173) and CNOP (n = 176)

Adverse experience	CHOP *n* (%)	CNOP *n* (%)
Total no. of patients with		
≥1 adverse experience	168(97)	166(94)
≥1 severe adverse experience	126(73)*	76(43)
≥1 moderate adverse experience	36(21)	67(38)*
Anthracycline-associated (severe)		
Alopecia	105(61)*	25(14)
Nausea/vomiting	37(21)†	19(11)
Mucositis	9(5)‡	1(1)
Other frequent severe adverse experiences		
Infection	12(7)	10(6)
Diarrhoea	1(1)	7(4)
Peripheral neuropathy	2(1)	3(2)
Skin effect	3(2)	2(1)
Laboratory test abnormalities		
Leucopenia—WHO grade 3	57(33)	81(46)‡
Leucopenia—WHO grade 4	21(12)	28(16)
Neutropenia—WHO grade 3	38(22)	51(29)§
Neutropenia—WHO grade 4	50(29)	69(39)§
Thrombocytopenia—WHO grade 3	9(5)	4(2)
Thrombocytopenia—WHO grade 4	2(1)	4(2)

*Significantly more events, $P < 0.001$, CHOP versus CNOP. †Significantly more events, $P < 0.01$, CHOP versus CNOP. ‡Significantly more events, $P < 0.05$, CHOP versus CNOP. §$0.05 > P > 0.10$, CHOP versus CNOP. All P values were calculated using Fisher's exact test.

The incidence and distribution of severity of cardiovascular toxicity were similar between the two groups. 15 patients in the CHOP arm and 12 patients in the CNOP arm experienced a cardiovascular adverse event. The nature of these events is listed in Table 7. Cardiovascular toxicity was considered severe in 5 patients in the CHOP group and 3 in the CNOP group. In addition, 2 patients in the CHOP group and 3 patients in the CNOP group died within 30 days of chemotherapy as a result of cardiovascular toxicity (Table 7).

There was a significantly higher incidence of neutropenia and leucopenia in patients treated with the CNOP regimen. WHO grade 3 or 4 leucopenia occurred in 62% of the CNOP-treated patients compared with 45% of the CHOP-treated patients ($P < 0.05$, Fisher's exact test) (Table 6). Similarly, WHO grade 3 or 4 neutropenia occurred in 69% of the CNOP-treated patients compared with 51% of the CHOP-treated patients ($0.05 > P > 0.10$). Myelosuppression appeared to be cumulative in the two treatment groups with the nadir WBC count occurring between days 10 and 14 of each cycle of chemotherapy and recovery generally occurring by day 21. WHO grade 3 or 4 thrombocytopenia occurred less frequently (Table 6).

Despite these differences in the incidences of neutropenia and leucopenia, the overall incidence of infection was similar between the two treatment groups. Severe infection, WHO grades 3 and 4, occurred in 7% of the CHOP-treated patients and 6% of the CNOP-treated patients (Table 6). Mild or moderate infections, WHO grades 1 and 2, were reported in an additional 32% of the CHOP-treated patients and 30% of the CNOP-treated patients.

Severe abnormalities in liver and kidney function tests were rare and occurred in only 2 patients in CHOP group and 1 patient in CNOP group.

DISCUSSION

This report summarises mature clinical data from the largest comparative trial to data comparing mitoxantrone to doxorubicin

Table 7. Incidence of cardiovascular toxicity in 349 patients treated with CHOP (n = 173) and CNOP (n = 176)

Event	CHOP	CNOP
Early death (within 30 days)		
Acute myocardial infarction	0	1
Congestive heart failure	0	1
Renal and cardiac insufficiency	0	1
Cerebrovascular accident	2	0
Symptomatic congestive heart failure		
With arrhythmia	1	1
Without arrhythmia	3	2
Asymptomatic decrease in LVEF ≥ 10%	5	3
Other		
Palpitations and atrial fibrillation	2	0
Hypertension	1	0
Postural hypotension	0	1
Not specified	1	2
Total	15(9%)	12(7%)

LVEF, left ventricular ejection fraction.

as components of a combination chemotherapy regimen for aggressive NHL. Initiated in 1984, the aim of the study was to demonstrate that the CNOP regimen possessed equivalent efficacy to CHOP with an improved toxicity profile.

The two regimens induced similar overall response rates, although the CHOP regimen resulted in a greater CR rate compared to the CNOP regimen (51 versus 40%). The CR rate for CHOP is comparable to the CR rates reported from other large randomised trials using this regimen [2, 19, 20]. The two regimens were, however, equivalent with respect to the remaining efficacy end-points, specifically TTF and overall survival. The finding of equal TTF (Figure 2) for the two arms of the study, in the face of a higher CR rate in the CHOP arm, suggests either that a proportion of the CRs induced by CHOP were less durable than those in the CNOP-treated patients or, alternatively, that the PRs obtained with CNOP were of longer duration. Support for the first possibility comes from consideration of the duration of CR (Figure 3) for the two arms of the study, which shows more early failures in the CHOP arm, although the two curves later approximate so that there was no overall statistical difference in the duration of CR. The other possible explanation for these findings is that significantly more patients in the CNOP-treated arm may have been classified as PR on the basis of residual non-lymphomatous masses at re-evaluation. Whatever the explanation, the results indicate that the quality of responses to CNOP are at least equal to those obtained with CHOP.

The possible influence of other factors which may have affected the results was also examined. There were no significant discrepancies when the results were analysed by center. The exclusion of 34 incorrectly randomised patients from the analysis also appeared not to significantly bias the results. When efficacy results from a series of supplemental analyses of eligible patients and incorrectly randomised patients were compared with the results of the intent to treat analysis, all data appear internally consistent. The eligibility rate of approximately 80% for patients enrolled on the study is consistent with the usual difficulties encountered in conducting a large multicentre clinical trial. Other sources of bias cannot, however, be excluded entirely. Data on baseline lactate dehydrogenase was not required at entry, the trial having been performed prior to the definition of the International Prognostic Index. However, in a trial of this size both treatment groups should have been similarly affected by missing evaluations and, thus, we do not expect these parameters to have played a major role in the outcome of this trial. Another factor which was considered was dose intensity. There did not appear to be any imbalance between the two arms of the study, in terms of the relative dose intensity of the chemotherapy delivered.

The safety profiles of the two regimens were qualitatively different. There was far more severe nausea and vomiting, alopecia, and mucositis among the CHOP-treated patients. Indeed, twice as many patients discontinued CHOP chemotherapy due to toxicity (cardiac events 4, infection 5, nausea/vomiting 1) compared to CNOP (cardiac events 3, infection 2). In contrast, the CNOP-treated patients experienced a significantly greater incidence of severe neutropenia and leucopenia. However, this did not translate into an increased incidence of severe infections. There was no statistically significant difference between the two groups in terms of cardiovascular toxicity, a finding which is attributable to the fact that only a minority of patients on the study were at risk for cardiovascular toxicity, based on the cumulative dosages of either doxorubicin or mitoxantrone that were administered.

In conclusion, this study demonstrates that CNOP is an active regimen for the treatment of patients with intermediate- and high-grade NHL. The important finding from this study is that long-term survival outcome for the CNOP-treated patients was comparable to those treated with CHOP. The CHOP regimen resulted in an increased incidence of severe non-haematologic toxicities, which may be meaningful from a quality of life standpoint in certain patients, while the CNOP regimen resulted in an increased incidence of severe leucopenia and neutropenia. Therefore, a possible avenue of further exploration may be dose escalation of mitoxantrone with haematopoietic growth factors in patients with relapsed or refractory NHL.

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Heterogeneity of Intratumour Proliferative Activity in Primary Breast Cancer: Biological and Clinical Aspects

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The present retrospective study was undertaken to verify whether the extent of intratumour proliferative activity variation or the method of quantifying tumour proliferative activity is related to biological characteristics and clinical outcome in a series of operable node-negative breast cancer patients. For tumour proliferative activity evaluation, the ^{3}H-thymidine autoradiographic assay was used. After incubation of 3–8 samples from different areas of the equatorial section of each tumour for 1 h at 37°C with ^{3}H-thymidine, the following methods were used for evaluation of tumour cell labelling: mean tumour labelling index (LI), the highest labelling value from a specific area (LI-max), and the extent of intratumour labelling variation from several samples (LI–CV). LI-max was related to ER and PgR status, and linearly correlated with LI (c.c. = 0.92, $P < 10^{-6}$) whereas LI–CV was independent of tumour size, grade ER and PgR status, but dependent on the number of tumour samples analysed for each tumour. After 5 years of median follow-up, disease-free survival was only related to tumour size (T1 versus T2: 84 versus 64%, $P < 0.04$ by log rank analysis) and different LI values (low versus high ^{3}H-Tdr-LI: 86 versus 61%, $P < 0.03$ by log rank analysis). LI-max and LI–CV values were not significantly related to clinical outcome. Cox multivariate analysis confirmed the independent prognostic value of LI and tumour size on disease-free survival.

Key words: proliferative activity, breast cancer
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INTRODUCTION

TUMOUR PROLIFERATIVE activity, determined according to various assays, has been demonstrated to be of prognostic relevance in several human cancers [1], and in particular for operable breast cancer patients [2, 3]. One of the major criticisms against these studies is directed at a potential source of error: the variability of site to site tumour proliferative activity [4]. Moreover, this tumour variability has been demonstrated not to be artefactual and is of greater magnitude than the intra-operator counting error [5, 6].

While genetic and non-genetic factors [7, 8] have frequently been suggested to explain the heterogeneity of regional tumour cell kinetics, scarce discussion has been directed to the biological and clinical significance of these intratumour differences.

One of the first methods frequently utilised to predict the breast cancer cell proliferation rate was the *in vitro* uptake of the nucleic acid precursor ^{3}H-thymidine by tumour fragments, and

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