Eur J Cancer, Vol. 29A, No. 1, pp. 37–43, 1993.
Printed in Great Britain

0964–1947/93 $5.00 + 0.00

A Pilot Study of Intensive Cyclophosphamide, Epirubicin and Fluorouracil in Patients with Axillary Node Positive or Locally Advanced Breast Cancer

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A multicentre pilot study has been conducted to determine an intensive regimen of cyclophosphamide, epirubicin, and fluorouracil which was tolerable and acceptable to patients with node positive breast cancer. Consecutive patients with operable axillary node positive breast cancer (T1-3, N1-2, M0), 266 patients, or locally advanced breast cancer (T4), 22 patients, were treated with cyclophosphamide post-operatively for 14 days and epirubicin and flourouracil, both intravenously on days 1 and 8. Each cycle was repeated monthly for 6 months. Dosages were increased according to predetermined guidelines. Outcome measures were admission to hospital for febrile neutropenia and change in cardiac function as assessed by radionucleide angiography. The first 46 patients were treated at the doses of cyclophosphamide = 75 mg/m², epirubicin = 50 mg/m², fluorouracil = 375 mg/m² (level 1), then 42 patients at cyclophosphamide = 75 mg/m², epirubicin = 50 mg/m² and fluorouracil = 500 mg/m² (level 2), 69 patients at cyclophosphamide = 75 mg/m², epirubicin = 60 mg/m², and fluorouracil = 500 mg/m² (level 3), and 42 patients at cyclophosphamide = 75 mg/m², epirubicin = 70 mg/m², and fluorouracil = 500 mg/m² with concurrent antibiotics (level 4). The rates of febrile neutropenia were 8.7% (level 1), 7.1% (level 2), 18.8% (level 3), and 31% (level 4), respectively, $P = 0.002$. Accrual to level 4 was discontinued according to study guidelines and a further 89 patients were recruited at level 3 dosages with antibiotic prophylaxis (level 3a), resulting in a 5.6% rate of febrile neutropenia. The difference in febrile neutropenia rates between levels 3 and 3a was statistically significant. There were no toxic deaths and 2 cases of heart failure. In conclusion, through a careful dose-finding study in patients with operable or locally advanced breast cancer, an intensive epirubicin-containing adjuvant regimen has been established which is presently being compared with standard CMF (cyclophosphamide,methotrexate, 5-fluorouracil) chemotherapy in a randomised trial. In addition, this study suggests that antibiotic prophylaxis reduces the risk of febrile neutropenia in breast cancer patients receiving intensive chemotherapy.
Eur J Cancer, Vol. 29A, No. 1, pp. 37–43, 1993.

INTRODUCTION

ADJUVANT CHEMOTHERAPY decreases recurrence and improves survival in women with axillary node positive breast cancer [1, 2]. Previous randomised trials have demonstrated that a number of chemotherapy treatment regimens are effective [1, 2], that multi-agent drug combinations are more effective than single doses [3], and that maximal efficacy is observed in premenopausal node positive patients [2]. However, the optimal management of patients with operable axillary node positive breast cancer is unknown and despite adjuvant chemotherapy many of these women still continue to relapse and die of their disease [1, 2, 4].

Doxorubicin is one of the most active single agents in stage IV breast cancer [5] and, in combination with other drugs, has produced higher response rates and improved survival compared with non-doxorubicin combinations [6, 7]. However, its routine use in the adjuvant setting has been limited by its potential for cardiotoxicity. Nonetheless, a number of recent studies have been conducted examining the role of adjuvant doxorubicin in women with node positive breast cancer [8–14]. Epirubicin, has been developed as an analogue of doxorubicin and is reported to be less cardiotoxic than doxorubicin, with no loss of antitumour activity [15–22].

In order to improve the prognosis of patients with axillary node positive breast cancer, a multicentre phase I/II pilot study has been conducted in Ontario to determine the most intensive regimen of cyclophosphamide, epirubicin, and 5-fluorouracil (5-FU) (CEF), which is tolerable and acceptable in these patients for use in a subsequent phase III evaluation in node positive patients. The intention was to also maximise the dose of epirub-

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Presented in part at the ECCO 6 Meetings 1991.
Revised 9 June 1992; accepted 17 June 1992.

icin delivered. The CEF pilot regimen development was based on the concepts that anthracyclines are the most active chemotherapeutic agents in advanced breast cancer and that increasing the dose intensity of chemotherapy may improve outcome [23]. The basis of the experimental regimen was cyclophosphamide, doxorubicin, and 5-FU, one of the most active combinations in advanced breast cancer, as first reported by Bull and Tormey [6].

The primary outcome measure for our pilot study was hospitalisation for febrile neutropenia.

PATIENTS AND METHODS

Patient population

We studied consecutive patients 60 years of age or less who had either operable axillary node positive breast cancer (T1-3, N1-2, M0) or inoperable locally advanced breast cancer (T4). Patients with axillary node positive disease were either premenopausal (any oestrogen receptor) or postmenopausal with oestrogen receptor negative tumours. Patients with operable axillary node positive disease underwent either modified radical mastectomy or a segmental mastectomy plus axillary node dissection. Patients with locally advanced disease underwent biopsy only. The patients were treated at the Ontario Cancer Treatment and Research Foundation Regional Cancer Centres in Hamilton, London, Ottawa, Windsor, and Toronto Bayview; and at the Princess Margaret, Mount Sinai, Women's College, Toronto Western, and Humber Memorial Hospitals.

Patients were excluded from the study if they had evidence of metastases; had a documented history of previous cancer (except basal cell carcinoma of the skin or early cervical carcinoma), or cardiac disease (arrhythmias requiring treatment, congestive heart failure, or coronary artery disease as shown by history or electrocardiogram); had inadequate renal function (as indicated by a serum creatinine greater than 140 mmol/l); had a bilirubin > 25 mmol/l, or a white cell count $< 3.0 \times 10^9$/l, or a platelet count $< 100 \times 10^9$/l; had an underlying serious medical illness, psychiatric or addictive disorder; or were more than 8 weeks from primary breast surgery.

Informed consent was obtained from eligible patients prior to treatment. The study protocol was approved by the Institutional Review Boards of all participating centres.

Treatment regimens

Patients with operable axillary node positive disease were treated with cyclophosphamide orally for 14 days and epirubicin and 5-FU, both intravenously, on Days 1 and 8. Each cycle was repeated monthly for 6 months. Breast irradiation for patients whose primary treatment was a segmental mastectomy was given after completion of chemotherapy.

Patients with inoperable locally advanced disease were treated with cyclophosphamide, epirubicin, and 5-FU as described above, but initial treatment was monthly for 3 months. After three cycles disease reponse was evaluated according to standard UICC response criteria [24]. If the disease was stable or responding, therapy was continued for a total of at least six full cycles. Then, at the discretion of the investigator, chemotherapy with CEF could be continued for three more cycles (for a total of nine cycles) or changed to standard (Bonadonna) CMF in which methotrexate 40 mg/m^2 was substituted for epirubicin [4]. For those patients who received nine cycles of CEF and were to continue on chemotherapy, CMF was used subsequently. If local radiotherapy or surgery was felt to be indicated in patients who were stable or responding, this was performed after at least six cycles of CEF. Patients with progressive disease after three cycles of CEF chemotherapy were treated at the discretion of the investigator, but followed for cardiotoxicity.

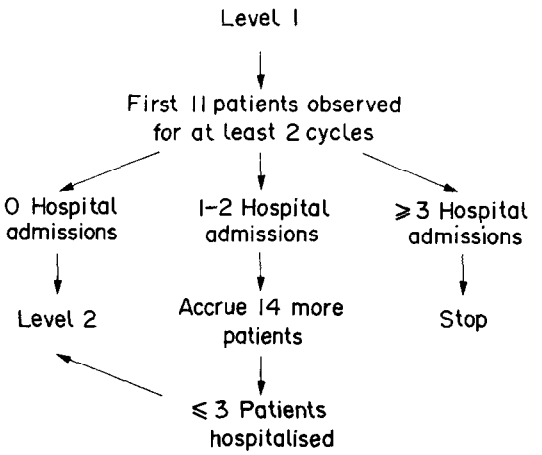

Fig. 1. Dose escalation scheme.

Dosage escalation scheme

Dosages were increased according to predetermined guidelines. There was no within-patient escalation, but dose escalation occurred after consecutive groups of patients. Data was forwarded to the Methods and Coordination Centre at McMaster University in a timely fashion and monitored carefully in an ongoing manner. This centre was notified within 24 h of any hospital admission. Prior to each escalation to a higher drug dosage level, a meeting of investigators was convened to review the toxicity data.

The dose escalation scheme is presented in Fig. 1. Briefly, at least 11 patients were to be entered at the first dose level and were to be observed for a minimum of two cycles each before escalating to the next dose level. Thus, after a total of at least 22 cycles in at least 11 patients, escalation to the next level could occur provided there were no hospital admissions for febrile neutropenia and not more than 5 patients had a nadir granulocyte count of less than 0.2×10^9/l, or of $< 0.5 \times 10^9$/l persisting for 2 consecutive weeks. If no infections were observed in these 11 patients then a febrile neutropenia rate of greater than 20% could be excluded with 90% confidence.

If these conditions were not met and if less than 3 of these 11 patients developed neutropenia, then an additional 14 patients were to be accrued and observed for a minimum of two cycles each. However, if 3 or more of the initial 11 patients developed febrile neutropenia, the protocol would be suspended with no further recruitment. If not more than 3 of the 14 subsequent patients were hospitalised for febrile neutropenia and if less than 50% of all patients developed a nadir granulocyte count of $< 0.2 \times 10^9$/l or of $< 0.5 \times 10^9$/l for 2 consecutive weeks, then escalation could occur to level 2. This escalation scheme was repeated for each subsequent level.

It should be emphasised that although the decision to proceed to the next level was based on the experience of between 11 and 25 patients at the preceding level, recruitment at each level did not stop, but continued until this initial group of patients had all been followed for two cycles. Thus, each group contains > 25 patients.

Dosage modifications

Complete blood count (CBC), platelet count, and differential were performed weekly. Dosage modifications were performed

Day 1 Counts	Nadir	Dose adjustment
P+B ≥ 1.5 x 10⁹/l and Plts ≥ 100 x 10⁹/l	(1) P+B ≥ 0.2 x 10⁹/l and Plts ≥ 50 x 10⁹/l	100% of day 1 of previous cycle
	(2) P+B < 0.2 x 10⁹/l or Plts < 50 x 10⁹/l or Feb. Neut	75% of day 1 of previous cycle
P+B < 1.5 x 10⁹/l or Plts < 100 x 10⁹/l		Delay 1 week, then (1) If P+B ≥ 1.5 x 10⁹/l and Plts ≥ 100 x 10⁹/l use nadirs (2) If P+B 1.0–1.5 x 10⁹/l and Plts ≥ 100 x 10⁹/l give 75% of day 1
Day 8		
P+B ≥ 1.5 x 10⁹/l and Plts ≥ 100 x 10⁹/l		same as day 1
P+B 1.0–1.499 x 10⁹/l and Plts ≥ 100 x 10⁹/l		75% of day 1
P+B < 1.0 x 10⁹/l or Plts < 100 x 10⁹/l		No treatment

P+B = polymorphs + bands
Plts = platelets

Fig. 2. Dosage modifications.

according to guidelines presented in Fig. 2. Once there had been a dose reduction for granulocyte or platelet nadirs then for all subsequent doses the reference dose became 100% of the de-escalated dose. There was no re-escalation. If an episode of hospitalisation for febrile neutropenia occurred, then chemotherapy was to be resumed at 75% of the initial dose as soon as the total granulocyte count reached 1.5×10^9 l, and subsequently remained at the 75% level. Colony stimulating factors were not allowed.

If patients developed severe mucositis (ECOG Grade 3), the chemotherapy could be delayed by one week and once the symptoms had resolved, the chemotherapy was administered if blood counts permitted at the investigator's discretion, but at 75% of the initial dose and kept at 75% provided blood counts permitted.

Follow-up studies

After completion of chemotherapy, patients were seen every 3 months until the end of the second year, then every 6 months thereafter. At each follow-up visit the patient underwent a history and physical examination and all the following tests were performed: CBC, platelet count, liver function tests, creatinine, and electrolytes. Chest X-ray and mammogram were performed once a year. Serial radionucleide cardiac scans were performed at baseline and at 9, 12, 18, and 24 months post-initiation of chemotherapy.

Outcome assessment

The major outcome measure for this study for the establishment of the maximally tolerated dose was admission to hospital for febrile neutropenia. Other important outcome measures were development of clinical congestive heart failure and change in cardiac function as assessed by serial radionucleide angiography. A detailed presentation of the cardiac scan data will be the subject of a subsequent report. Febrile neutropenia was deemed to be present if the absolute granulocyte count was $< 1.0 \times 10^9$/l and the temperature was ≥ 38.5°C. All episodes of hospitalisation for febrile neutropenia were adjudicated by a panel unaware of dosage level.

Toxicity was assessed according to the ECOG toxicity criteria [25].

Table 1. Drug dosages

Level	Patient no.	Cyclophosphamide (mg/m²) post operatively days 1–14	Epirubicin (mg/m²) intravenously days 1 and 8	Fluorouracil (mg/m²) intravenously days 1 and 8
1	46	75	50	375
2	42	75	50	500
3	69	75	60	500
4 *	42	75	70	500
3a *	89	75	60	500

*Antibiotic prophylaxis with clotrimoxazole two tablets twice a day or ciprofloxacin 500 mg post operatively twice a day if clotrimoxazole not tolerated.

Statistical analysis

Ninety-five per cent confidence limits for the rate of febrile neutropenia at each dose level were calculated according to standard methods [26]. The χ^2 test for linear trend was used to compare febrile neutropenia rates across levels [27]. Repeated measures analysis of variance was used to compare mean drug doses across levels [28]. Repeated measures analysis of variance was also used to examine change in granulocyte counts over time and to compare granulocyte counts between levels.

RESULTS

Trial execution

Initially it was planned that the experimental CEF regimen derived from the pilot study would be compared in a phase III trial against CMF, a regimen commonly used by many practising oncologists as standard adjuvant chemotherapy for stage II breast cancer patients [4]. Hence, in order to ensure that the CEF regimen would be as close to the cyclophosphamide and fluorouracil in CMF on a mg for mg basis, we started with doses of cyclophosphamide = 100 mg/m², epirubicin = 50 mg/m² and fluorouracil = 500 mg/m². However, when 3 of the first 8 patients entered were admitted to hospital with febrile neutropenia, it was decided to restart the study with lower doses of drug, but trying to maintain the highest dose of epirubicin (which was felt to potentially be the most effective component) at the possible expense of the other two drugs in the combination. The results of these 8 patients are not included in the analysis.

Patient population and dosage regimens

266 consecutive patients with operable axillary node positive breast cancer and 22 patients with locally advanced breast cancer who underwent biopsy only were treated with CEF chemotherapy. The trial started in December 1987 and the last patient was entered in January 1990. The drug dosages for each level are presented in Table 1. The first 46 patients were treated at the doses of cyclophosphamide = 75 mg/m², epirubicin = 50 mg/m², fluorouracil = 375 mg/m² (level 1). The next 42 patients were treated at higher levels of drug: cyclophosphamide = 75 mg/m², epirubicin = 50 mg/m², and fluorouracil =

Table 2. Baseline characteristics

Factor	Dose level 1 $n = 46$ (%)	2 $n = 42$ (%)	3 $n = 69$ (%)	4 $n = 42$ (%)	3a $n = 89$ (%)
Age					
< 50 years	35 (76.1)	33 (78.6)	54 (78.3)	31 (73.8)	70 (78.7)
No. of positive nodes					
≤ 3	14 (30.4)	24 (57.1)	28 (40.6)	12 (28.6)	34 (38.2)
4–9	22 (47.8)	14 (33.3)	27 (39.2)	19 (45.2)	34 (38.2)
≥ 10	5 (10.9)	2 (4.8)	9 (13.0)	6 (14.3)	13 (14.6)
Surgery type					
Modified radical	24 (52.2)	26 (61.9)	37 (53.6)	20 (47.6)	55 (61.8)
Lumpectomy	17 (36.9)	15 (35.7)	27 (39.1)	18 (42.9)	26 (29.2)
Biopsy only	5 (10.9)	1 (2.4)	5 (7.3)	4 (9.5)	8 (9.0)
Tumour size					
< 2 cm	7 (15.2)	9 (21.4)	9 (13.0)	3 (7.2)	11 (12.3)
Oestrogen receptor					
< 10	19 (41.3)	18 (42.9)	26 (37.7)	15 (35.7)	31 (34.8)
Progesterone receptor					
< 10	17 (37.0)	16 (38.1)	18 (26.1)	14 (33.3)	37 (41.6)

500 mg/m^2 (level 2). 69 patients were treated with: cyclophosphamide = 75 mg/m^2, epirubicin = 60 mg/m^2, and fluorouracil = 500 mg/m^2 (level 3), and finally, 42 patients were entered at level 4: cyclophosphamide = 75 mg/m^2, epirubicin = 70 mg/m^2, and fluorouracil = 500 mg/m^2 with concurrent prophylactic antibiotics (clotrimoxazole two tablets twice a day orally or ciprofloxacin 500 mg twice a day orally if clotrimoxazole was not tolerated). The antibiotics were taken daily throughout each monthly cycle. Accrual to level 4 was discontinued according to study guidelines because of excessive febrile neutropenia, and a further 89 patients were recruited at level 3 dosages with antibiotic prophylaxis (level 3a).

The treatment cohorts were reasonably comparable in terms of baseline characteristics such as age, number of positive axillary nodes, type of surgery, tumour size, and levels of oestrogen and progesterone receptor (Table 2).

Febrile neutropenia

4 (8.7%) of the 46 patients in level 1, 3 (7.1%) of the 42 patients in level 2, 13 (18.8%) of the 69 patients in level 3 and 13 (31%) of the 42 patients in level 4 were admitted to hospital with febrile neutropenia (Table 3). Accrual to level 4 was discontinued because the criteria for not proceeding to a higher dose were fulfilled. This increase in febrile neutropenia rates across levels was statistically significant, $P = 0.002$. Following the discontinuation of accrual to level 4, we continued to accrue at level 3 dosages but also used concurrent antibiotic prophylaxis. A further 89 patients were recruited at level 3a dosages, with 5 admissions, a 5.6% rate of frebrile neutropenia. The comparison of rates between level 3 and level 3a was statistically significant, $P = 0.01$. None of the patients died as a result of a febrile neutropenic episode.

Table 3. Hospitalisation for febrile neutropenia

Level	Start date	No. of patients	Febrile neutropenia (n (%)	95% CI (%)
1	Dec. 1987	46	4 (8.7)	2.4–20.8
2	June 1988	42	3 (7.1)	1.5–19.5
3	Oct. 1988	69	13 (18.8)	10.4–30
4	Mar. 1989	42	13 (31)	17.6–47
3a	June 1989	89	5 (5.6)	1.9–12.6

1 vs. 2 vs. 3 vs. 4: $P = 0.002$.
3 vs. 3a: $P = 0.01$.

Toxicity

There were 2 patients who developed clinical cardiac dysfunction. The first patient who received level 4 drug doses, presented with fatigue and exertional dyspnoea 3 months after completion of chemotherapy. She received a total of 741 mg/m^2 of epirubicin. Chest X-ray showed cardiac dilatation and increased vascularity. Radionucleide cardiac scan revealed a left ventricular ejection fraction of 40%. On echocardiogram, she was found to have an atrial septal defect with a significant left to right shunt, which was felt to have contributed in part to the heart failure. Her clinical condition improved on diuretics. However, 6 months later she developed sudden ventricular tachycardia which resulted in neurologic impairment.

The second patient who received level 3 doses, presented with exertional dyspnoea 10 months after completion of chemotherapy. She had locally advanced breast cancer and had received 6 months of chemotherapy followed by radiation to the left breast and supraclavicular area which was then followed by 3 more months of chemotherapy. Her total dose of epirubicin was 1080 mg/m^2. Chest X-ray revealed cardiac dilatation, radionucleide scan showed an ejection fraction of 36%, and echocardiogram showed increased left ventricular dimensions and decreased contractility. Her clinical condition improved markedly on digoxin and diuretics.

The worst toxicity grades experienced by each patient according to ECOG toxicity criteria are summarised in Table 4. There

*Table 4. Incidence of toxicity: % of patients experiencing worst toxicity grade at each dose level**

	Level 1				Level 2				Level 3				Level 4				Level 3a			
Toxicity grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Haematological †		18	43	39	5	14	31	50		7	38	55	0	2	7	88		2	23	75
Nausea	34	48	7		45	43	7		35	48	6		32	54	12		39	44	12	
Stomatitis ‡	30	16	5		38	19	2		55	20	6		39	32	10		43	15	15	
Diarrhoea	21	9	2		38	5			30	7	1		15	7			39	5		
Neurologic (CNS)	21	23	7		24	38	2		26	30	3		32	27			32	26	1	
Alopecia		100			5	95			1	97			2	95				97		

*Within each toxicity type, numbers represent the percentage of patients for whom the worst recorded toxicity was at this grade.
†1 vs. 2 vs. 3 vs. 4 $P = 0.0002$; 3 vs. 3a $P = 0.02$.
‡1 vs. 2 vs. 3 vs. 4 $P = 0.02$; 3 vs. 3a N.S.

was a statistically significant difference between dose levels for haematologic toxicity and stomatitis.

CBC and platelet counts were measured weekly for the 6 months of treatment (data not shown). For each cycle there was a statistically significant decrease in mean white blood cell (WBC) nadir and mean absolute granulocyte nadir as the dose level increased from 1 to 4. It is of interest that at each week except pretreatment, the mean WBC and mean absolute granulocyte counts were statistically significantly different between levels 3 and 3a (Fig. 3). No statistically significant difference was detected between levels 3a and 4 for these parameters. For each level there was a statistically significant decrease in mean WBC and mean absolute granulocyte counts over the six cycles of treatment.

Drug dosage received and treatment delays

The analysis of the amount of drug received was based on 284 patients, as 4 patients with locally advanced disease who received only 3 months of chemotherapy and then went on to radiation or surgery were excluded from analysis. The mean of the total amount of each drug received, by dose level, is shown in Table 5 and the mean of the received dose intensity (mg/m²/week), by dose level, is shown in Table 6. The comparison of levels 1, 2, 3 and 4 revealed that the observed decrease in cyclophosphamide and increase in epirubicin over these levels were statistically significant. It is of interest that the mean dose of epirubicin at level 3 was 1043 mg which dropped to 968 mg at level 3a. This difference was statistically significant. Similarly, there was a statistically significant drop in the mean dose intensity of epirubicin received between level 3 and level 3a.

Table 5. Total dose of drug received, mean (S.D.)

Level	Patient no.	Cyclophosphamide (mg)	Epirubicin (mg)	Fluorouracil (mg)
1	44	9755 (1310)	936 (125)	7090 (1085)
2	42	9344 (2491)	889 (207)	8881 (2069)
3	69	9346 (1697)	1043 (188)	8739 (1620)
4	41	8200 (1930)	1047 (267)	7550 (1897)
3a	88	8985 (1799)	968 (211)	8263 (1669)
1 vs. 2 vs. 3 vs. 4		$F = 5.4$	$F = 7.3$	$F = 12.9$
		$P = 0.001$	$P = 0.0001$	$P < 0.0001$
3 vs. 3a		$F = 1.6$	$F = 5.4$	$F = 3.2$
		$P = 0.2$	$P = 0.02$	$P = 0.07$

The mean number of cycles of chemotherapy (Days 1 and 8) received per patient, by dose level is presented in Table 7. No difference was detected between levels. The number of treatment delays for Days 1 and 8 treatments is presented in Table 7. The observed increase in the percentage delays over levels 1 and 4 was statistically significant. In addition, there was a statistically significant increase in percentage delays between levels 3 and 3a.

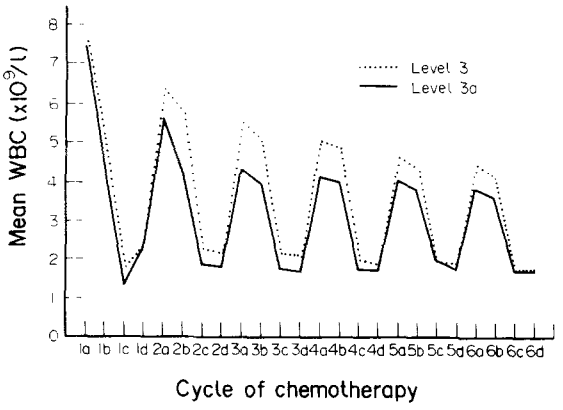

Fig. 3. White blood cells (mean) over six cycles for levels 3 and 3a.

Table 6. Dose intensity (mg/m²/week)

Level	Patient no.	Cyclophosphamide	Epirubicin	Fluorouracil
1	44	241.1	23.1	174.6
2	42	233.3	22.2	222.0
3	69	235.8	26.2	219.7
4	41	210.3	26.7	192.8
3a	88	217.5	23.7	201.7
1 vs. 2 vs. 3 vs. 4		$P = 0.015$	$P < 0.001$	$P < 0.001$
3 vs. 3a		$P = 0.005$	$P < 0.001$	$P < 0.001$

Table 7. Chemotherapy cycles and treatment delays

Level	Patient no.	Cycles* mean (S.D.)	No. of delays	Total no. of treatments*	% Delay
1	44	5.9 (0.47)	39	260	15.0
2	42	5.7 (0.98)	37	239	15.5
3	69	5.8 (0.73)	54	402	13.4
4	41	5.7 (1.10)	56	235	23.8
3a	88	5.9 (0.59)	116	516	22.5
1 vs. 2 vs. 3 vs. 4		$P = 0.48$			$P = 0.04$
3 vs. 3a		$P = 0.72$			$P = 0.001$

*Refers to Days 1 and 8 of chemotherapy.

DISCUSSION

The objective of our study was to develop an acceptable intensive epirubicin-containing chemotherapy regimen which would ultimately be compared in a randomised trial to a standard adjuvant chemotherapy regimen. In addition, we wanted to determine the highest possible dose of epirubicin combined with cyclophosphamide and 5-FU. Traditionally, dose finding studies in cancer are conducted in a single institution in patients with advanced malignancy, are often limited to a single drug and use the outcomes of response and survival [29]. This study differed in that it was multi-centre, contained more than one drug, included patients with early but not end-stage cancer, and used the outcomes of hospital admission for febrile neutropenia and change in cardiac function. This approach led to the rapid recruitment of a consecutive cohort of patients and to the rapid establishment of the maximally tolerated regimen.

In the present study we elected to use epirubicin because of its potential for lesser cardiotoxicity than doxorubicin without loss of antitumour efficacy [15–22]. It was also decided to escalate the epirubicin (possibly at the expense of the other two drugs) because anthracyclines are probably the most active group of drugs in metastatic breast cancer and because escalation of a single agent seemed more practical than escalating all three drugs [5–7].

There was a statistically significant increase in the rates of hospitalisation for febrile neutropenia between levels. However, there were no fatalities related to febrile neutropenic episodes.

The introduction of concurrent antibiotic prophylaxis at level 4 failed to provide protection against infection, suggesting that the degree of myelosuppression was too great to allow antibiotic prophylaxis to be effective. However, when prophylactic antibiotics were added to level 3 drug dosages, the rate of hospitalisation for febrile neutropenia was reduced substantially. This suggests that with this lower drug dosage, the threshold beyond which antibiotics would not be effective was not exceeded. In addition, the comparison of the febrile neutropenia rates between level 3 (without antibiotics) and 3a suggests that antibiotic prophylaxis is efficacious in patients with breast cancer receiving aggressive chemotherapy. We recognise that there are limitations to such a comparison because the patients were not randomly allocated to receive or not receive antibiotics. Nonetheless, we feel that bias was minimised because consecutive eligible patients were recruited, there were no significant differences in baseline patient characteristics between levels, and all episodes of hospitalisation for febrile neutropenia were adjudicated by a panel unaware of dosage level. In addition, we did not observe more non-protocol dosage reductions or delays in patients who received level 3a compared with level 3. Although there is evidence from clinical trials which supports the efficacy of prophylactic antibiotics in patients undergoing induction chemotherapy for acute leukaemia, there is a paucity of such data supporting their role in patients with solid tumours receiving chemotherapy [30].

There was a statistically significant increase in both the mean total dose and dose intensity of epirubicin received between levels 2 and 3. However, we were unable to increase the amount of epirubicin received by escalating to level 4. This was probably due to a combination of factors including increased myelosuppression, toxicity, and febrile neutropenia. It is of interest that even though prophylactic antibiotics reduced the rate of febrile neutropenia associated with level 3 doses, the total amount of epirubicin received was significantly lower in level 3 with antibiotics compared with level 3 without antibiotics. A possible explanation for this is that the clotrimoxazole which interferes with folate metabolism led to increased myelosuppression.

It is of interest that when the total dose and dose intensity of drugs delivered are compared between the initial level (level 1) and the final accepted regimen (level 3a), only the 5-FU was substantially increased. The dose of cyclophosphamide was decreased and that for epirubicin increased only slightly. The objective of our study design was to escalate the dose of epirubicin. It is possible that the magnitude of increase in the dose intensity of epirubicin with level 3a will be insufficient to improve outcome compared to standard CMF chemotherapy in the adjuvant setting. However we feel that the final intended total dose (and dose intensity) of level 3a is sufficiently intensive by present day standards to justify comparison with CMF in a randomised trial.

Only 2 patients (0.7%) have developed clinical congestive heart failure. 1 patient had an underlying atrial septal defect and the other patient received local regional radiation and 1080 mg/m^2 of epirubicin for locally advanced disease. The regimen that we have chosen for stage II patients has a dose of epirubicin of 720 mg/m^2. No cardiotoxicity was observed at this level. A recent study in patients with metastatic breast cancer suggested that only when the dose of epirubicin exceeds 1000 mg/m^2 does the risk of cardiac dysfunction increase significantly [31].

Increased dose-intensity chemotherapy can be administered with either haematopoietic growth factor support or autologous marrow transplantation. Their efficacy in delivering substantially higher dose-intensity chemotherapy is presently being evaluated in randomised trials. Our study was conducted before such modalities were readily available. In addition, it is not practical for economic reasons to administer intensive adjuvant chemotherapy to all breast cancer patients under growth factor coverage or with autologous transplantion. Hence, alternative dose intense regimens such as ours need to be evaluated.

Thus, through a careful dose-finding study, an intensive epirubicin-containing adjuvant regimen has been determined which is acceptable to our oncologists. The total intended dose of epirubicin delivered in this regimen is 720 mg/m^2 over six months. If this regimen is demonstrated to decrease recurrence and improve survival compared with a more standard adjuvant chemotherapy regimen in women with axillary node positive breast cancer, then this could have a major impact on the management of this disease.

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Acknowledgements—We would like to acknowledge the contribution of participating oncologists who entered patients on the study, particularly S. Verma and T. Vandenberg; the contribution of L. Dickson, S. DePauw, M. Goodyear, R. Roberts and D. Marcellus for data management and analyses.