PERGAMON

European Journal of Cancer 38 (2002) 2279–2288

European Journal of Cancer

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Epirubicin versus CMF as adjuvant therapy for stage I and II breast cancer: a prospective randomised study☆

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Received 26 February 2002; received in revised form 14 June 2002; accepted 9 August 2002

Abstract

We compared a relatively short regimen of monochemotherapy with epirubicin versus polychemotherapy with CMF (cyclophosphamide, methotrexate, 5-fluorouracil) as adjuvant treatment for stage I and II breast cancer patients. 348 patients with oestrogen receptor negative (ER−) node negative and ER− or ER+ node-positive with <10 nodes were accrued. CMF was given intravenously (i.v.) on days 1 and 8, every 4 weeks, for six courses; epirubicin was given weekly for 4 months. Postmenopausal patients received tamoxifen for 3 years. The primary endpoints were overall survival (OS), relapse-free survival (RFS) and event-free survival (EFS). Outcome evaluation was performed both in eligible patients and in all randomised patients according to the intention-to-treat principle. 8 randomised patients were considered ineligible. At a median follow-up of 8 years, there was no difference in OS (Hazard Ratio (HR) = 1.11, 95% Confidence Interval (CI): 0.77–1.61, $P = 0.58$), EFS (HR = 1.14, 95% CI: 0.78–1.64, $P = 0.48$), and RFS (HR = 1.14, 95% CI: 0.8–1.64, $P = 0.48$) between the two arms for all of the patients. At 8 years, the RFS percentages (±Standard Error (S.E.)) were 65.4% (±4%) in the CMF arm and 62.7% (±4%) in the epirubicin arm; for EFS these were 64.2% (±4%) for CMF and 60.8% (±4%) for epirubicin, respectively. A significant difference in RFS ($P = 0.015$) was observed in patients with 4–9 positive nodes in favour of the CMF arm. Toxicity in the two arms was superimposable except for more frequent grade 3 alopecia in the epirubicin-treated patients ($P = 0.001$). Overall, at a median follow-up of 8 years, there were no differences between the two arms in terms of OS, EFS and RFS.

Keywords: Adjuvant therapy; Breast cancer; Epirubicin; CMF; Randomised study

1. Introduction

During the past 20 years, it has been demonstrated that adjuvant systemic treatments with chemotherapy, endocrine therapy, or a combination of both benefit women with operable primary breast cancer [1]. A combination of cyclophosphamide, methotrexate and 5-fluorouracil (CMF) has been used as a standard regimen

☆ The preliminary results of this trial were presented at the 33rd Annual Meeting of the American Society of Clinical Oncology Meeting, Denver, CO, USA, 17–20 May 1997.

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0959-8049/02/$ - see front matter
PII: S0959-8049(02)00452-5

in Europe and in the USA since the first published results [2].

Doxorubicin was considered the most effective single agent in the treatment of advanced breast cancer until a few years ago, when the taxanes were also proven to be active. Recent evidence suggests that as a single agent doxorubicin causes regression of breast cancer in metastatic disease and in neoadjuvant treatment as often as the best combinations [3–5].

The initial reluctance to use doxorubicin in the adjuvant treatment of breast cancer was due to the potential risk of late cardiac damage and alopecia. When it appeared that the optimal duration of adjuvant treatment could be limited to approximately 6 months, however, the drug was introduced in clinical trials. Several studies have been published on anthracycline-containing regimens, but the evaluation of these studies was difficult because they included variations in dose intensity, dose schedule, number of courses, different combinations of drugs, and in the risk profile of selected patients. Nevertheless, by the end of the 1980s, anthracycline-containing regimens were proven to be at least as effective, if not superior, to the CMF or CMF-derived regimens in the adjuvant setting. It was also shown that relatively short regimens such as doxorubicin plus cyclophosphamide for four courses (2 months) were as effective as the conventional CMF given for 6 months and more acceptable to patients [6].

Furthermore, epirubicin, a stereoisomer of doxorubicin, had similar therapeutic activity in advanced breast carcinoma with a better therapeutic index on a molar basis due to reduced haematological and cardiac toxicity [7–9].

Another possible approach to reduce the chronic cardiac toxicity of an anthracycline is to modify the peak drug concentration by altering the administration schedule. In metastatic breast cancer weekly administration of doxorubicin at a low dose showed the same efficacy as the 3-week schedule and, at least in two studies, less cardiotoxicity [10–13].

While the Early Breast Cancer Trialist's Collaborative Group (EBCTCG) overview [1] established the superiority of combination over single agent chemotherapy, an anthracycline, as a single agent, has not previously been evaluated. On the basis of these considerations, in 1990 we decided to evaluate the efficacy in terms of overall survival (OS), relapse-free survival (RFS), event-free survival (EFS) and the toxicity of mono-chemotherapy with epirubicin delivered weekly for 4 months in comparison to CMF (intravenous (i.v.) on days 1 and 8 every 4 weeks) for six courses, in patients with stage I and II breast cancers [14,15]. Tamoxifen was administered concomitantly to all postmenopausal women. At that time, the optimal duration of tamoxifen administration as adjuvant treatment was unknown, but it appeared that more than 2 years was superior to less than 2 years [1], so we decided to give it for 3 years.

2. Patients and methods

2.1. Study design

This study is a randomised multicentre clinical trial designed and performed by the Italian Oncology Group for Clinical Research (GOIRC). Patients were enrolled from 11 centres. Randomisation was performed by telephoning the data coordinating centre in Parma. Patients were stratified according to menopausal status (pre, post $\leqslant 60$ years, post >60 years), nodal status (negative, 1–3 and 4–9 positive nodes), tumour size (T1, T2, T3), and hormonal receptor status (positive, negative, unknown). Patients were randomly assigned using a permuted block randomisation procedure to one of the two treatment arms: CMF (i.v. on days 1 and 8)$\times$6 courses or epirubicin weekly$\times$16 weeks plus tamoxifen for postmenopausal women in both arms.

All patients had undergone modified radical mastectomy or conservative surgery (quadrantectomy) plus full axillary dissection for unilateral stage I or II histologically confirmed carcinoma of the breast. Adjuvant chemotherapy was scheduled to start within 5 weeks following surgery.

Elegible patients were: N− if oestrogen receptor (ER)-negative or node-positive with $\leqslant 9$ metastatic nodes. Other eligibility criteria included: age between 18 and 70 years, Eastern Cooperative Oncology Group (ECOG) performance status 0-1, adequate bone marrow, renal and liver function, normal cardiac function with normal electrocardiogram (ECG) and left ventricular ejection fraction (LVEF) measurement. No previous or concomitant cancer was permitted except adequately treated basal cell carcinoma of the skin or *in situ* cervical cancer.

ER and progesterone receptor (PgR) determination was made using biochemical assays or immunohistochemical procedures. Patients with amenorrhoea for 2 years or more were considered to be postmenopausal. Patients with previous hysterectomy without concomitant oophorectomy were considered to be postmenopausal if aged 52 years or more. In doubtful cases, elevated circulating levels of follicle-stimulating hormone were required.

The study was approved by the ethics committee of the Group and an informed consent was obtained from all of the patients enrolled in the study.

CMF was given i.v. as follows: cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, 5-fluorouracil 600 mg/m^2 on days 1 and 8 every 28 days for six courses. Epirubicin was delivered at a dose of 30 mg/m^2 weekly for 16 weeks.

Tamoxifen was given in a dosage of 20 mg by mouth daily for 3 years to all postmenopausal patients concurrently with chemotherapy. For patients receiving breast conserving surgery, radiotherapy was delivered at the end of chemotherapy. 50 Gy were administered to

the breast in 25–28 fractions followed by a boost of 10 Gy to the tumour bed by electron beam therapy.

The World Health Organization (WHO) criteria were adopted for evaluation of toxicity [16].

A complete blood cell count was required before each administration of chemotherapy. If the platelet count was less than $100\,000\times10^9$ cells/l or the white blood cell (WBC) count less than 3500×10^9 cells/l on day 1 of a CMF scheduled course, treatment was postponed, but after 1 week, drug doses were reduced if full recovery had not occurred. If on day 8 the WBC count was less than 2500×10^9 cells/l or the platelet count was less than $75\,000\times10^9$ cells/l, doses were omitted, while, if the WBC count was between 2500 and 3500×10^9 cells/l and/or the platelet count between 75 000 and $120\,000\times10^9$ cells/l, only 50% of each drug was administered. For epirubicin, if the WBC count was between 3000 and 3500×10^9 cells/l and/or the platelet count was between 100 000 and $120\,000\times10^9$ cells/l, the dose was reduced by 25%; if the WBC was between 2500 and 3000×10^9 cells/l and/or the platelet count between 75 000 and $100\,000\times10^9$ cells/l, the dose was reduced by 50%; if the WBC count was less than 2500×10^9 cells/l and/or the platelet count less than $75\,000\times10^9$ cells/l, the dose was postponed for 1 week. Appropriate dose reductions were used for gastrointestinal, hepatic or renal toxicities.

2.2. Follow-up

Follow-up evaluation was performed by physical examinations and biochemical analysis every 3 months for 2 years then every 6 months until the fifth year and once a year thereafter. Chest X-ray, mammography, liver sonography and bone scan were carried out every year throughout the first 5 years, then physical examination and mammography annually and the other examinations every 2 years.

ECG and LVEF measurement by sonography or multigated angiogram (MUGA scan) were performed before the administration of epirubicin, at the end of the treatment, and yearly thereafter.

The definition of primary treatment failure was the evidence of new disease manifestation as documented through clinical, radiological, and when feasible, histological means. The classification of first treatment failure was as follows: locoregional area(s) that included homolateral axillary adenopathy, chest wall, and in patients treated with breast-conserving surgery the homolateral breast; distant site(s); contralateral breast cancer.

2.3. Statistical analysis

This trial was originally planned to be a three-arm study comparing CMF (conventional arm) to two experimental arms (epirubicin weekly for 4 months or CMF for six courses followed by two late re-inductions). The aim was to test for a ratio of median relapse-free survival (RFS) of 1.5 (33% reduction of the risk of relapse) between CMF and either of the two experimental arms. The required sample was 118 patients per arm (α error $=0.05$, $\beta=0.20$) and considering a possible 15% withdrawal rate this number was increased to 400 patients overall. The third arm with CMF for six courses followed by late re-inductions was never activated and the study was closed in January 1994 after a recruitment of 348 patients into the two arms.

Association (comparison of baseline patient characteristics) was tested with Chi square or Fisher's Exact test. Follow-up information was updated as of 05/03/00 and thus the minimum follow-up time was 6.4 years.

RFS, event-free survival (EFS) and overall survival (OS) were estimated according to the Kaplan–Meier method [17]. For EFS, measured from the randomisation date, the following events were considered failures: local, regional, or distant recurrence, recurrence of the tumour in the ipsilateral breast following quadrantectomy, second primary cancer, or death without recurrence of cancer. For OS, measured from the randomisation date, death from any cause was the end point of interest. For all analyses, time was censored at the last follow-up date if no event/death was observed. Differences in time distributions (RFS, EFS and OS) were evaluated using the log-rank test [18] and the Cox proportional hazard regression [19]. Multivariate analysis was performed to evaluate the effect of treatment on outcome in the presence of other covariates. Hazard Ratios (HR) (with 95% Confidence Intervals (CI) and P values) were estimated with respect to the reference category for each covariate using binary variables. Outcome (RFS, EFS, OS) evaluation was performed in all randomised patients according to the intention-to-treat principle. Safety was analysed considering only the treated patients. The absolute cumulative dose (especially relevant for epirubicin) is the sum of all received doses: it is calculated for each drug and is expressed in mg/m^2. Delivered dose intensity (DDI) was defined as the total amount (in mg) of drug delivered during treatment, divided by the patient's body surface area and divided again by the total number of weeks of therapy received (therefore calculated as mg/m^2/week) [20]. The ratio between delivered and planned (according to protocol) DI was used as an indicator of treatment feasibility and compliance. Wilcoxon's test was used to compare the proportion of intended doses in the two arms [21]. All P values are derived from two-sided tests of significance. Statistical Analysis System (SAS) software was used for statistical analyses [22].

3. Results

A total of 348 patients were enrolled from November 1990 to January 1994. 8 randomised patients were

considered ineligible (4 in CMF arm and 4 in epirubicin arm). The reasons for patient ineligibility in the CMF arm were: node-negative and ER+(1), metastatic disease (2), node-positive >9 (1); in the epirubicin arm: node-negative ER+ (2), first degree A-V block (1), previous contralateral breast cancer (1) (Fig. 1).

174 eligible patients were randomised to the CMF arm and 166 to the epirubicin arm. One patient (CMF arm) refused treatment. 2 patients randomised to epirubicin were treated with CMF, but were evaluated for outcome according to their randomised group and for toxicity to the treatment received. For 1 patient (CMF arm), only haematological toxicity was reported.

Characteristics of eligible patients are reported in Table 1 and are well balanced between the two arms. The median age was 50 years in the CMF arm (range 30–69 years) and 50 years in the epirubicin arm (range 30–70 years). An infiltrating ductal carcinoma was reported in 151 patients in each arm.

The median follow-up is 8 years (range 6.4–9.5 years) for the current evaluation.

The median number of courses of CMF was six and the median number of weeks of epirubicin was 16. In the CMF arm, 97% of patients (168/174) received six courses; in the epirubicin arm, 88% of patients (146/166) received 16 weeks of treatment. The median treat-

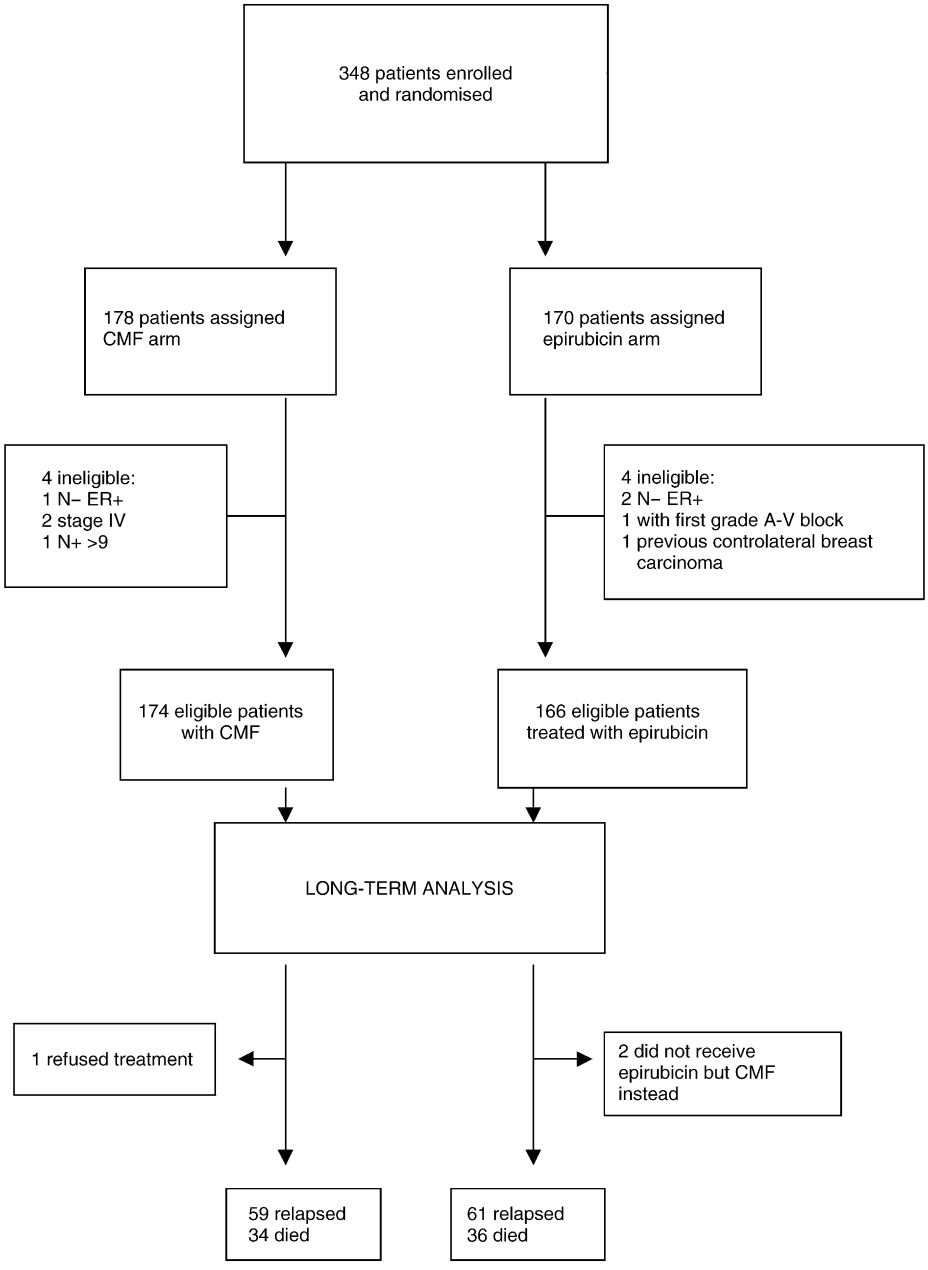

Fig. 1. N–, node-negative; N+, node-positive; ER, Oestrogen Receptor; CMF, cyclophosphamide, methotrexate, 5-fluorouracil.

Table 1
Characteristics of eligible patients

Characteristic	CMF ($N=174$) No. of pts (%)	Epirubicin ($N=166$) No. of pts (%)
Age (years)		
<40	21 (12)	14 (8)
40–50	68 (39)	72 (43)
>50	85 (49)	80 (48)
Premenopausal	92 (53)	89 (54)
Postmenopausal	82 (47)	77 (46)
Tumour size (cm)		
Unknown	5 (3)	7 (4)
⩽2	87 (50)	86 (52)
2–5	80 (46)	72 (43)
>5	2 (1)	1 (1)
No. of involved nodes		
0	34 (20)	38 (23)
1–3	102 (59)	90 (54)
4–9	38 (22)	38 (23)
Histological grade		
Unknown	70 (40)	64 (39)
G1	20 (11)	13 (8)
G2	50 (29)	58 (35)
G3	34 (20)	31 (19)
Type of surgery		
Mastectomy	102 (59)	90 (54)
Quadrantectomy	72 (41)	76 (46)
Days from surgery to entry		
Median (range)	28 (11–51)	28 (13–63)
Receptor status		
ER+PgR+	86 (49)	71 (43)
ER+PgR−	10 (6)	11 (7)
ER+PgR unknown	2 (1)	2 (1)
ER- PgR+	21 (12)	26 (16)
ER−PgR−	37 (21)	37 (22)
Unknown	18 (10)	19 (11)

G, grade; ER oestrogen receptor; PgR, progesterone receptor; pts, patients; CMF, cyclophosphamide, methotrexate, 5-fluorouracil.

ment duration was 24 weeks (range 12–30 weeks) in the CMF arm and 16 weeks (range 2–23 weeks) in the epirubicin arm. The planned and delivered dose intensities (mg/m^2/week) were calculated for each drug and the median ratio between the delivered/planned dose was 0.93 for epirubicin and 0.92 for each drug of the CMF combination.

The number of events that have occurred so far is low: 120 with 59 relapses in the CMF arm and 61 in the epirubicin arm, 34 deaths in the CMF arm and 36 in the epirubicin arm.

No significant differences in RFS (HR = 1.14, 95% CI: 0.8–1.64, $P=0.48$; Fig. 2), EFS (HR = 1.14, 95% CI: 0.78–1.64, $P=0.48$) and OS (HR = 1.11, 95% CI: 0.77–1.61, $P=0.58$; Fig. 3) were observed between the two arms (Table 2). At 8 years, the RFS percentages (±S.E.) were 65.4% (±4%) in the CMF arm and 62.7% (±4%) in the epirubicin arm, for EFS the values were 64.2% (±4%) in the CMF arm and 60.8% (±4%) in the epirubicin arm, and for OS 81.4% (±3%) and 77.8% (±3%), respectively.

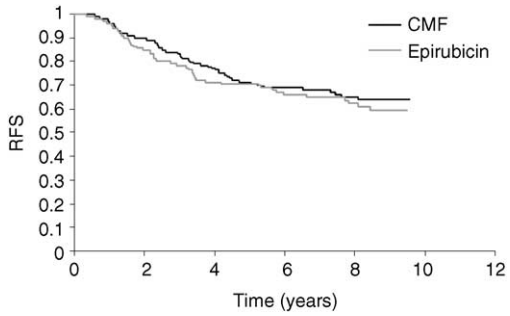

Fig. 2. Relapse-free survival for all patients.

No significant differences in RFS and OS existed between the two arms in either pre- or postmenopausal patients (Table 3).

In the subgroup analysis according to nodal status, no differences in terms of OS between the two treatment arms were observed. However, in the subset of patients with 4–9 positive nodes, CMF was superior to epirubicin in terms of RFS (HR = 2.5; $P=0.015$, 95% CI: 1.25–4.4).

Results were confirmed in a multivariate model adjusted for age, menopausal status, and number of positive nodes. The HR for RFS was 1.14 (95% CI: 0.8–1.72, $P=0.48$).

No statistically significant differences were evident in the distribution of locoregional and distant failures in the two treatment groups (Table 4).

We observed 10 second primary tumours: five in the CMF arm (two endometrial, one kidney, one ovary and one acute myeloid leukaemia) and five in the epirubicin arm (one non-small cell lung cancer, one rectum, one leiomyosarcoma of the small bowel, one nasopharyngeal and one endometrial). Two of the three endometrial cancers were observed in postmenopausal women treated with tamoxifen.

When the analysis was performed according to the intention-to-treat principle, the results were almost the same.

3.1. Toxicity

338 patients were evaluable for toxicity. Leucopenia and anaemia were the most frequent haematological toxicities, but no statistically significant differences were reported between the two arms. Leucopenia grades 3 and 4 was observed in 12 patients (7%) in the CMF arm and in 9 patients (5%) in the epirubicin arm. The worst degree of non-haematological toxicities at any time during treatment are reported in Table 5. No statistically

significant differences were observed between the two arms except for alopecia grade 3 that was more common in the epirubicin arm ($P=0.001$). Nausea and vomiting (grade 1-2) occurred in 72% of patients in the CMF arm and in 77% of patients in the epirubicin arm ($P=$NS).

2 patients died of treatment-related toxicity, 1 in each arm. One premenopausal 48-year-old patient developed neutropenic septic shock and grade 4 mucositis after administration of the fifth course of CMF. A postmenopausal 68-year-old patient who suffered from essential hypertension treated with angiotensin-converting enzyme (ACE) inhibitors developed fatal congestive heart failure 3 weeks after epirubicin treatment was completed; the patient had a normal basal ECG and LVEF measured by echocardiography. Aside from this case of toxic death, cardiotoxicity was not significantly different in the two arms. We observed a reduction of LVEF in 1 patient after a dose of 300 mg/m^2 of epirubicin. Paroxysmal supraventricular tachycardia occurred in 2 patients in the CMF arm and in 3 patients in the epirubicin arm. In 1 of these latter patients, the administration of epirubicin was discontinued after two doses.

Amenorrhoea (cessation of menses for at least 6 months during or after the administration of chemotherapy) was

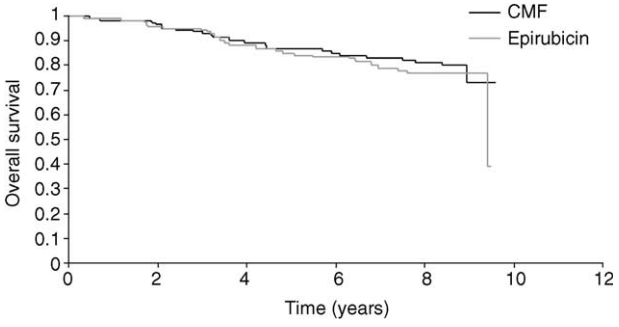

Fig. 3. Overall survival for all patients.

Table 4
Sites of first relapse

	CMF	Epirubicin
	No. (%)	No. (%)
Total	59/174	61/166
Local-regional alone	16 (27)	23 (38)
Distant		
Soft tissue	7 (12)	8 (13)
Bone	15 (25)	8 (13)
Viscera	15 (25)	14 (23)
Contralateral breast	6 (10)	8 (13)

Table 2
Relapse-free survival, event free survival, and overall survival

	CMF	Epirubicin	Logrank *P* value	Hazard ratio
Relapse-free survival				
Failures/total	59/174	61/166	0.48	1.14
8-year % failure-free (S.E.)	65.4±4%	62.7±4%		(95% CI: 0.8–1.64)
Event-free survival				
Events/total	66/174	67/166	0.48	1.14
8-year % event free (S.E.)	64.2±4%	60.8±4%		(95% CI: 0.78–1.64)
Overall survival				
Deaths/total	34/174	36/166	0.58	1.11
8-year % alive (S.E.)	81.4±3%	77.8±3%		(95% CI: 0.77–1.61)

SE, Standard Error; 95% CI, 95% Confidence Interval.

Table 3
RFS and OS by menopausal status

RFS	CMF		Epirubicin		*P* value (Logrank)	Hazard ratio (95% CI)
	Failures/total	8-year% (S.E. %)	Failures/total	8-year% (S.E. %)		
Pre	32/92	63.7 (5)	32/89	64.3 (5)	0.7	1.11 (0.64—1.92)
Post	27/82	67.4 (6)	29/77	60.8 (6)	0.53	1.16 (0.74—1.84)
OS	CMF		Epirubicin		*P* value (Logrank)	Hazard ratio (95% CI)
	Deaths/total	8 year % (S.E. %)	Deaths/total	8 year % (S.E. %)		
Pre	15/92	82.8 (4)	16/89	81.3 (4)	0.73	1.12 (0.63—1.99)
Post	19/82	79.9 (5)	20/77	73.8 (5)	0.74	1.1 (0.68—1.78)

Table 5
Patient worst non-haematological toxicity (WHO)

	CMF	Epirubicin	*P* value
	No. pts (%)	No. pts (%)	
Nausea and vomiting			
1	70 (40)	70 (43)	
2	56 (32)	48 (29)	N.S.
3	19 (11)	11 (7)	
4	2 (1)	0	
Diarrhoea			
1	8 (5)	7 (4)	
2	4 (2)	1 (1)	N.S.
3	1 (1)	0	
4			
Mucositis			
1	34 (20)	35 (21)	
2	15 (9)	18 (11)	N.S.
3	6 (3)	5 (3)	
4	2 (1)	1 (1)	
Cardiotoxicity			
1	2 (1)	3 (2)	
3	0	2 (1)	N.S.
4	0	1	
Alopecia			
1	36 (21)	10 (6)	
2	62 (36)	60 (37)	
3	6 (3)	57 (35)	0.001
Total patients	174	164	

pts, patients; N.S., non-significant.

reported in 48 of 92 patients (52%) in the CMF arm and in 52 of 89 patients (58%) in the epirubicin arm (P = NS).

4. Discussion

Individual trial results and the overview have established that adjuvant CMF prolongs DFS and OS [1].

When we planned the present study, the role of anthracyclines in the adjuvant setting was undefined and no study had evaluated anthracyclines as a single agent. Several adjuvant trials have compared anthracycline-containing combinations to CMF or CMF-derived regimens. Their interpretation is difficult because of a number of variables introduced in the different trials. In some of these trials no significant benefit from the anthracycline regimens was observed [6,23–27].

By contrast, in at least five randomised trials the anthracycline combinations appear to be superior. One study (B11) by the National Surgical Adjuvant Breast and Bowel Project (NSABP) group [25] compared the use of doxorubicin, melphalan and fluorouracil with melphalan and fluorouracil alone in 697 patients with positive axillary nodes who were considered unresponsive to tamoxifen. This study demonstrated that the addition of doxorubicin significantly improved DFS and OS, at a median follow-up of 6 years. However, the two groups differ in the number of cytotoxic drugs received. Bonadonna and colleagues [28] showed that four cycles of doxorubicin followed by eight cycles of CMF produces a better outcome for patients with four or more involved nodes than two cycles of CMF alternated with one cycle of doxorubicin for a total of 12 cycles. At a 10-year follow-up, there was a significant DFS and OS advantage for the sequential arm and the authors outlined the importance of specific timing of doxorubicin administration. 4 cases of congestive heart failure (1 fatal) were observed in doxorubicin-treated patients who received postoperative irradiation to the left breast.

In another trial, the Cancer and Leukemia Group B (CALGB) [29] compared cyclophosphamide, methotrexate, 5-fluorouracil, vincristine, prednisone (CMFVP) for 14 months with CMFVP for 8 months followed by a combination of vinblastine, doxorubicin, thiotepa and fluoxymesterone (VATH) for 6 months in 945 node-positive patients. A significant benefit in DFS and OS was reported in patients who had more than four positive nodes with the sequential schedule.

Misset and colleagues [30] have reported the final results of a trial comparing a combination of cyclophosphamide, doxorubicin, fluorouracil and vincristine (AVCF) with CMF for 12 cycles in 249 node-positive patients with a 16-year median follow-up. A significantly longer DFS and OS was observed with the anthracycline-based combination. When analysed according to menopausal status, the differences remained significant only for premenopausal patients, but this is probably because the postmenopausal population was too small.

An intensive cyclophosphamide, epirubicin and 5-fluorouracil (CEF) regimen was compared with CMF in premenopausal node-positive patients by Levine and colleagues [31]. At a median follow-up of 59 months, a significant improvement in DFS and OS was shown with CEF, but a greater haematological toxicity was also reported.

The EBCTCG overview [32] demonstrated that the anthracycline-containing regimen significantly reduced the annual risk of recurrence and death in comparison with CMF and these results have been confirmed recently (EBCTCG overview 2000, not yet published).

To our knowledge, the single trial that has compared monochemotherapy with anthracyclines with CMF was reported only as an abstract. The study was performed in 302 patients aged 55 years or younger with locally advanced breast cancer (stage IIIA). After local treatment with radiotherapy and radical mastectomy the patients were randomised to doxorubicin 50 mg/m^2 on days 1 and 8 every 4 weeks for five courses or to CMF for six courses. A statistically significant increase in DFS and OS was observed with doxorubicin at a median follow-up of 6.3 years [33].

Another very recent trial has shown that epirubicin, administered weekly for 3 weeks every 28 days, in combination with tamoxifen in operable, node-positive elderly breast cancer patients, results in a DFS advantage compared with tamoxifen alone with a good tolerability [34].

Our study is the first randomised trial that has compared monochemotherapy with epirubicin to polychemotherapy in the adjuvant treatment of stage I and II breast cancers. At a median follow-up of 8 years, there was no statistically significant difference in RFS, EFS, and OS between the epirubicin and CMF arms. This was true for all patients and for both pre- and postmenopausal patients.

A significant difference in RFS was observed in patients with 4–9 positive nodes in favour of the CMF arm. However, the limited number of patients precludes us from drawing definitive conclusions.

No significant difference in toxicity was observed between the two arms, except for alopecia that was more common in the epirubicin arm. Two toxic deaths were reported, one in each arm. We had chosen a weekly administration of epirubicin in an attempt to reduce the cardiac toxicity, but we observed two instances of significant toxicity, one fatal congestive heart failure and one reduction of LVEF ($<50\%$). The incidence of cardiac toxicity was similar to that reported by others [35].

No difference in the incidence of second primary tumours was observed. One endometrial cancer occurred during tamoxifen administration, but it was a grade 2 stage Ib tumour, and the patient is alive and disease-free after a hysterectomy.

We had anticipated a superior result in the epirubicin arm. However, the dose used could be considered too low. In treatment of metastatic breast cancer anthracyclines appear to have a positive dose–response relationship, although the benefit has not been associated with an improvement in OS [36,37]. A higher response rate, and a prolonged time to progression was found by increasing the dose of epirubicin from 40 to 90 mg/m^2. Nevertheless, no increase in efficacy was observed from 90 to 135 mg/m^2 in a study in which 287 patients with metastatic breast cancer were randomised to receive either 40, 60, 90 or 135 mg/m^2 of epirubicin every 3 weeks as first-line cytotoxic therapy [38]. It is still unknown if increasing the dose above a threshold effect could enhance efficacy [39]. In the adjuvant setting, the optimal dose intensity of epirubicin is undefined [40–42] and the results from ongoing multicentric studies comparing standard dose regimens with dose intensified epirubicin-containing regimens will help to clarify its importance.

Dose intensity remains an important determinant of the response to chemotherapy, and its reduction is clearly associated with decreased response rates and decreased survival in cases with metastatic disease [43]. The concept of dose intensity does not allow us to understand other features of drug administration that may be related to tumour response such as dose rate, peak level, schedule and total duration. The dose rate (mg/m^2/min) refers to the rate of drug administration at the time each dose is given to the patient [44]; we utilised a low dose rate for epirubicin. The schedule chosen could be important: when we planned our study a weekly schedule of epirubicin was not inferior to 3-weekly administrations in the treatment of metastatic disease. In a subsequent trial [45], weekly FEC compared with a conventional every 4-week regimen in metastatic breast cancer showed lower efficacy and lower toxicity despite an identical dose intensity. Last, but not least, we compared a monochemotherapy with anthracyclines to a polychemotherapy with CMF and now we know that only three-drug anthracycline-based regimens are superior to CMF.

In conclusion, the present randomised trial with a quite long follow-up shows no difference between the two arms in terms of OS, EFS, and RFS and a good tolerability for both arms. The good tolerability and efficacy profile of anthracycline monochemotherapies could warrant further applications, especially in the treatment of elderly patients, a patient population which has not been adequately considered in the past.

5. Participating investigators

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