Original article

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Primary chemotherapy in operable breast carcinoma comparing CMF (cyclophosphamide, methotrexate, 5-fluorouracil) with an anthracycline-containing regimen: short-term responses translated into long-term outcomes

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Background: The role of anthracyclines has been extensively studied in adjuvant chemotherapy, but much less in the primary chemotherapy of early breast carcinoma. This study, comparing CMF (cyclophosphamide, methotrexate, 5-fluorouracil) with the rotational anthracycline-containing regimen CMFEV (CMF plus epirubicin and vincristine) administered as primary chemotherapy, demonstrated a significant increase in clinical complete response in premenopausal women. We report the long-term results.

Patients and methods: Two hundred and eleven patients with stage I or II palpable breast carcinoma and a tumour diameter of >2.5 cm were randomised to receive CMF or CMFEV for four cycles before surgery. After surgery, the patients in both arms received adjuvant CMF for three cycles.

Results: In the study population as a whole, there was a non-significant 20% reduction in mortality and relapse rates in the CMFEV arm. However, the effect of the experimental regimen was only found in premenopausal patients, especially in terms of relapse-free survival ($P = 0.07$) and locoregional relapse-free survival ($P = 0.0009$), thus mirroring the effect on response rates. After 10 years, the proportions of premenopausal patients free from locoregional relapse as a first event in the CMF and CMFEV groups were 68% and 97%, respectively. No relevant differences were found in postmenopausal patients.

Conclusion: The overall results of this study showed that the greater activity of the experimental anthracycline-containing combination over CMF as primary chemotherapy in premenopausal patients translated into long-term effects in the same subgroup.

Key words: anthracycline, breast carcinoma, CMF, complete response, outcome, primary chemotherapy

Introduction

A number of randomised clinical trials comparing preoperative chemotherapy with the same chemotherapy given postoperatively in patients with early breast carcinoma have failed to show an improvement in long-term outcomes [1–7]. However, there are different reasons for choosing primary (i.e. preoperative) chemotherapy, including the possibility of performing conservative surgery when it was not initially indicated because of large tumours [3], and the ability to document tumour chemosensitivity *in vivo* [3, 8].

Fewer randomised clinical trials have compared different primary chemotherapy regimens and, to the best of our knowledge, none have compared cyclophosphamide, methotrexate and 5-fluorouracil (CMF) with an anthracycline-containing regimen.

We report here the long-term results of a prospective randomised trial involving patients with operable breast carcinoma who were treated with four preoperative CMF cycles or

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four preoperative cycles of an anthracycline-containing combination (rotational CMFEV: CMF plus epirubicin and vincristine) designed by us. The rotational technique allowed the addition of epirubicin (and vincristine) to the three CMF agents two at a time, without the subtraction of any and without any decrease in dose when administered.

The previously reported short-term results of this study [9] indicated that our anthracycline-containing regimen was superior to CMF in terms of complete (CR) plus partial response (PR) rates, and clinical CR rates. Although these differences did not reach statistical significance in the study population as a whole, the premenopausal patients showed a statistically significant increase in objective responses (CR plus PR) and in CR. The increase in the objective responses was entirely accounted for by the increase in CR rates, whereas the PR rates remained the same.

Patients and methods

Eligibility criteria, diagnosis and staging

The main eligibility criteria were: (i) a palpable tumour mass of >2.5 cm, or a palpable tumour mass of ≤2.5 cm with cytologically-proven positive axillary node involvement; (ii) clinical stage I or II according to the AJCC/UICC (American Joint Committee on Cancer/Union International contre le Cancer) [10]; (iii) age <70 years; (iv) the absence of distant metastases following a complete staging process; (v) the absence of additional primary tumours; and (vi) adequate bone marrow, kidney, liver and heart function. Patients with clinical stage III tumours (i.e. T3 N1, or T4 any N, or any T N2) were not eligible.

Breast carcinoma was diagnosed by means of fine needle aspiration (FNA) biopsy. We considered that the probability of the occurrence of *in situ* histology in palpable tumours would be negligible. In order to include as many patients as possible with proven axillary lymph node involvement, an ultrasound-guided FNA biopsy was performed on echographically assessable axillary lymph nodes. All of the patients underwent complete hemogram, blood chemistry and electrocardiographic examinations.

The study protocol was approved by the Ethics Committees of the participating institutions, and all of the patients gave their informed consent.

Study design and treatment

This multi-institutional study was carried out at the Medical Oncology Units of Parma, Reggio Emilia, Terni, Perugia, Piacenza and Fermo of the Italian Oncology Group for Clinical Research (GOIRC); Parma and Reggio Emilia contributed the vast majority (93%) of the enrolled patients. The study design is shown in Figure 1.

The patients were centrally randomised via a telephone call to the operational office of GOIRC in Parma within strata defined by clinical centre, menopausal status (pre-/postmenopause), clinical tumour diameter (≤3.5/>3.5 cm) and clinical axillary node status (negative/positive). They were assigned to receive four cycles of CMF (arm A) or four cycles of CMFEV (arm B) and then, after their clinical response had been evaluated, underwent surgery (quadrantectomy and axillary dissection, or mastectomy and axillary dissection), thus allowing the assessment of a pathological complete response (pCR) in all patients. The patients in both arms received the same adjuvant chemotherapy (CMF for three cycles); the postmenopausal women also received oral tamoxifen 20 mg/day for 2 years, regardless of their ER and/or PgR status. At the end of adjuvant chemotherapy, postoperative radiation was administered to the patients treated with conservative surgery. In patients treated with mastectomy, radiation was not normally given, but was recommended in the case of ≥4 positive axillary nodes.

The CMF combination consisted of monthly cycles of cyclophosphamide 600 mg/m^2 i.v. on days 1 and 8; methotrexate 40 mg/m^2 i.v. on days 1 and 8; and 5-fluorouracil 600 mg/m^2 i.v. on days 1 and 8. In the CMFEV group, epirubicin (E) and vincristine (V) were added in such a way that each of the four cycles was administered as a four-drug combination by means of the sequential omission of E, F, M and C (thus effectively becoming CMFV, CMEV, CFEV and MFEV). The C, M and F doses and times of administration were the same as those used in arm A; the doses of E and V were respectively 40 mg/m^2 i.v. (days 1 and 8) and 1.4 mg/m^2 i.v. (day 1) (Table 1).

Response and toxicity evaluation

Clinical objective responses were assessed just before surgery using the World Health Organisation (WHO) criteria [11]. All of the patients underwent a clinical examination and mammography and, in the case of disagreement, the final response was attributed on the basis of previously described criteria [12]. Pathological responses were assessed at the time of surgery; pCR means the absence of any residual infiltrating or non-infiltrating tumour in the breast and axilla. Toxicity was evaluated according to the WHO criteria [11], and the patients were classified on the basis of the worst degree of treatment complication.

Statistical methods

The χ^2 test and Fisher's exact test were used to compare the distribution of patient characteristics, response rates and toxicities in the two treatment groups.

Given the exploratory nature of this trial, mistakenly randomised ineligible patients were excluded from the response rate assessment, as were patients not evaluated for response and those who refused further

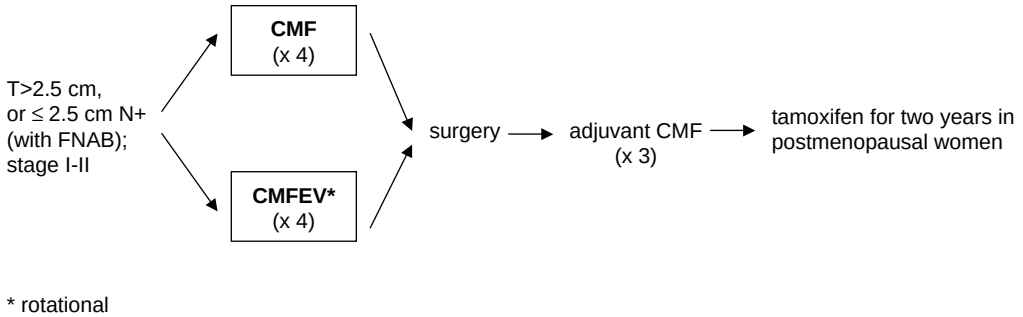

Figure 1. Study design.

Table 1. Doses and schedules

Schedule	
CMF	
Cyclophosphamide	600 mg/m^2, i.v. short infusion, days 1 and 8
Methotrexate	40 mg/m^2, i.v. bolus, days 1 and 8
5-fluorouracil	600 mg/m^2, i.v. bolus, days 1 and 8 (every 4 weeks)
CMFEV (rotational)	
CMFV combination	
Cyclophosphamide	600 mg/m^2, i.v. short infusion, days 1 and 8
Methotrexate	40 mg/m^2, i.v. bolus, days 1 and 8
5-fluorouracil	600 mg/m^2, i.v. bolus, days 1 and 8
Vincristine	1.4 mg/m^2, i.v. bolus, day 1 (every 4 weeks)
CMEV combination	
Cyclophosphamide	600 mg/m^2, i.v. short infusion, days 1 and 8
Methotrexate	40 mg/m^2, i.v. bolus, days 1 and 8
Epirubicin	40 mg/m^2, i.v. bolus, days 1 and 8
Vincristine	1.4 mg/m^2, i.v. bolus, day 1 (every 4 weeks)
CFEV combination	
Cyclophosphamide	600 mg/m^2, i.v. short infusion, days 1 and 8
5-fluorouracil	600 mg/m^2, i.v. bolus, days 1 and 8
Epirubicin	40 mg/m^2, i.v. bolus, days 1 and 8
Vincristine	1.4 mg/m^2, i.v. bolus, day 1 (every 4 weeks)
MFEV combination	
Methotrexate	40 mg/m^2, i.v. bolus, days 1 and 8
5-fluorouracil	600 mg/m^2, i.v. bolus, days 1 and 8
Epirubicin	40 mg/m^2, i.v. bolus, days 1 and 8
Vincristine	1.4 mg/m^2, i.v. bolus, day 1 (every 4 weeks)

chemotherapy after the first cycle. All of the eligible patients were included in the evaluation of long-term outcomes, and all of the randomised patients were included in the calculation of overall survival (OS) according to the intention-to-treat principle.

In the calculation of relapse-free survival (RFS), local or distant relapses, or deaths due to breast carcinoma without a previous clinical diagnosis of relapse, were considered as events. In the calculation of OS, deaths from any cause were considered as events. In the calculation of locoregional relapse-free survival (LRRFS), the first relapse of breast carcinoma in the same breast, the homolateral chest wall, or the homolateral axillary, supraclavicular or internal mammary lymph nodes were considered as events. In this analysis, the patients with distant relapses or death as a first event were censored at the time of the events. In the calculation of distant metastases relapse-free survival (DMRFS), the first relapse in any distant site was considered an event. In this analysis, the patients with locoregional relapse or death as a first event were censored at the time of the events. In both the LRRFS and DMRFS analyses, the patients who developed a contralateral primary breast carcinoma or a second primary malignancy were censored at the time of the first competing events.

It has to be pointed out that the comparisons of the long-term results with short-term responses were not affected by the usual bias affecting studies attempting to correlate objective response with survival, because all of the patients were homogenously assessed for response after the completion of primary chemotherapy (i.e. 4 months after randomisation).

The time-to-event analyses used Kaplan and Meier's product-limit method for descriptive purposes [13]. The differences in survival distributions were evaluated using the log-rank test. Multivariate logistic regression was used to assess the presence of a significant influence of menopausal status on the activity of the experimental treatment (i.e. response rate), and Cox's proportional hazard regression was used to adjust for possible imbalances in prognostic factors [14]. Hazard ratios of less than 1 favour CMFEV chemotherapy. Two-sided P values and 95% confidence intervals (95% CI) are given; unless stated otherwise, 'significant' indicates P values of less than 0.05. SPSS software was used for all of the analyses. No adjustments of the P values for multiple comparisons were made because of the exploratory nature of the study.

Results

Between November 1990 and April 1995, 211 patients were randomised to receive CMF (107) or CMFEV (104). Six

Table 2. Characteristics of the randomised patients by treatment arm

Characteristics	CMF		CMFEV	
	No.	%	No.	%
Total no.	107	100	104	100
Age				
Median	51.5		52	
Range	27–73		32–69	
Menopausal status				
Premenopause	48	45	52	50
Postmenopause	59	55	52	50
Clinical tumour size				
≤2.5 cm	10	9	13	13
2.6–3.5 cm	43	40	41	39
3.6–5.0 cm	40	38	42	40
>5 cm	12	11	7	7
Unknown	2	2	1	1
Clinical axillary node status				
Negative	68	64	59	57
Positive	39	36	45	43
Estrogen receptor status				
Positive	57	53	47	45
Negative	31	29	34	33
Unknown	19	18	23	22

CMF, cyclophosphamide, methotrexate, 5-fluorouracil; CMFEV, cyclophosphamide, methotrexate, 5-fluorouracil, epirubicin, vincristine.

patients were not eligible: four in the CMF group (stage III disease) and two in the CMFEV group (one aged >70 years and one with distant metastases). Eight patients were not evaluable for response: four in each group. The cut-off date for follow-up was 30 April 2003. The median follow-up was 116 months, range 84–146 months. Table 2 shows the main characteristics of the randomised patients.

Summary of short-term results [9]

Table 3 shows the previously published short-term response results [9]. The proportions of objective responses (CR plus PR) and clinical CR were higher in the anthracycline-containing arm (73% versus 66%, and 21% versus 12%), but the differences were not statistically significant. However, the differences among the premenopausal patients were striking (80% versus 54%, and 26% versus 4%) and statistically significant ($P = 0.007$; $P = 0.004$); there were no remarkable differences among the postmenopausal patients. The number of pCRs was low but the differences between the two arms followed the same pattern as that of clinical CRs: the overall proportions were 6% in the CMFEV group and 2% in the CMF group; the proportions among premenopausal patients were 8% versus 0%, and those among postmenopausal patients 4% versus 4%. The proportions of patients treated with conservative surgery were not significantly different: 55% in the CMF and 62% in the CMFEV group.

In order to assess formally the modifying effect of menopausal status on the relative activity of the chemotherapies, a multivariate logistic regression model was fitted to the data with the probability of clinical CR as the dependent variable, and menopausal status, type of chemotherapy and the interaction term as covariates. The results indicated the presence of a significant interaction between menopausal status and the type of chemotherapy in determining the probability of achieving CR (odds ratio = 0.11; 95% CI 0.02–0.71; $P = 0.02$). As a consequence, a seven-fold increase in the odds of a CR was predicted in premenopausal women using

Table 3. Response to treatment in patients as a whole, and by menopausal status

Efficacy variable	CMF		CMFEV	
	No./Total	%	No./Total	%
Clinical objective response (CR plus PR)				
All patients	65/99	66	72/98	73
95% CI (%)		57–75		69–82
Premenopausal	25/46[a]	54	40/50[a]	80
95% CI (%)		40–68		69–91
Postmenopausal	40/53	75	32/48	67
95% CI (%)		69–81		59–75
Clinical complete response				
All patients	12/99	12	21/98	21
95% CI (%)		6–18		13–29
Premenopausal	2/46[b]	4	13/50[b]	26
95% CI (%)		0–10		14–38
Postmenopausal	10/53	19	8/48	17
95% CI (%)		8–50		6–28
Pathological complete response				
All patients	2/98	2	6/97	6
Premenopausal	0/46	0	4/50	8
Postmenopausal	2/52	4	2/47	4

[a] $P = 0.007$,

[b] $P = 0.004$.

CMF, cyclophosphamide, methotrexate, 5-fluorouracil; CMFEV, cyclophosphamide, methotrexate, 5-fluorouracil, epirubicin, vincristine; CR, complete response; PR, partial response; CI, confidence interval.

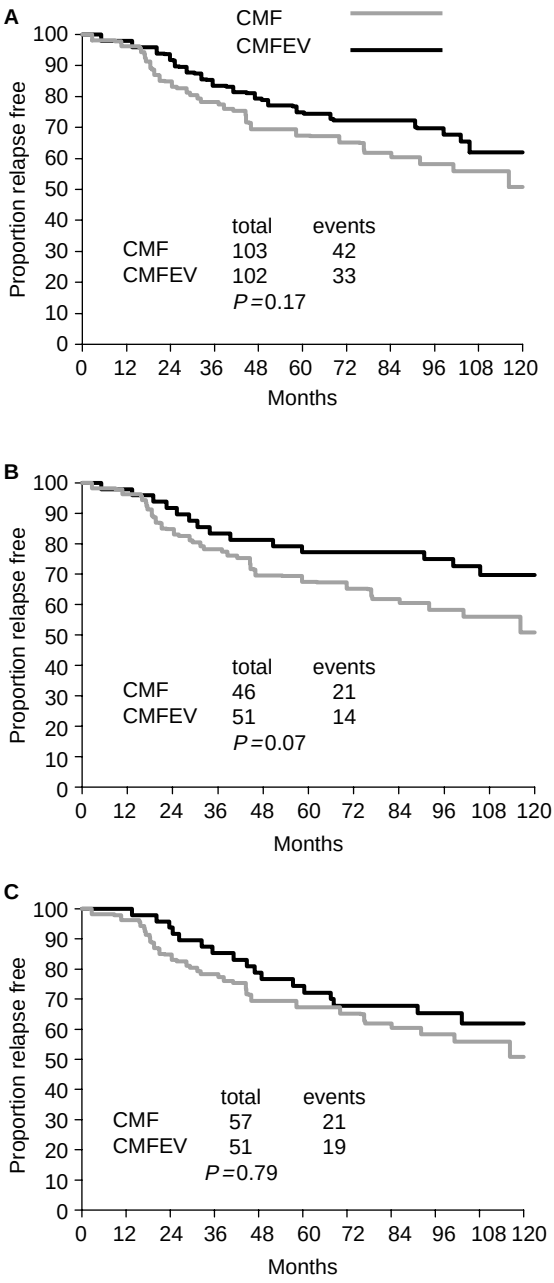

Figure 2. Relapse-free survival by treatment. (**A**) All patients; (**B**) premenopausal; (**C**) postmenopausal.

the anthracycline-containing regimen (OR = 7.7; 95% CI 1.6–36.3), whereas no effect was predicted in postmenopausal women [9].

Long-term results by treatment and menopausal status

There were three cases of controlateral breast cancer and eight of a second primary malignancy in the CMF group, compared with six and two in the CMFEV group. These differences were not statistically significant.

Figure 2 shows RFS in the patients as a whole by treatment arm and menopausal status. In the study population as a whole, there was a non-significant improvement in RFS ($P = 0.17$) in the experimental arm. The difference was more marked among the premenopausal patients and approached statistical significance ($P = 0.07$), whereas RFS in the postmenopausal patients was similar in the two arms.

Figure 3 shows LRRFS by treatment and menopausal status. There was a statistically significant ($P = 0.0029$) difference in favour of the anthracycline-containing arm in the overall study population, which was almost entirely due to the striking improvement in the premenopausal patients ($P = 0.0009$); the LRRFS curves of the postmenopausal patients were very similar in the two treatment arms ($P = 0.38$).

The three graphs of the Figure 2 and Figure 3 offer a simple visualisation of the fact that the advantages of the experimental regimen in terms of RFS (non-statistically significant) and LRRFS (statistically significant) in the patients as a whole were entirely due to its effects in the premenopausal patients.

There was no difference in DMRFS between the two treatment arms in the study population as a whole, or in the menopausal subgroups (data not shown). OS was also similar in the two arms, whether assessed in the population as a whole or in the two menopausal subgroups (data not shown).

Table 4 shows the hazard ratios in the CMFEV arm compared with the CMF arm in terms of RFS, LRRFS, DMRFS and OS in a Cox model including clinical node status, clinical response and menopausal status. All of the unadjusted and adjusted hazard ratios favoured CMFEV over CMF, but the difference was statistically significant ($P = 0.011$) only for LRRFS.

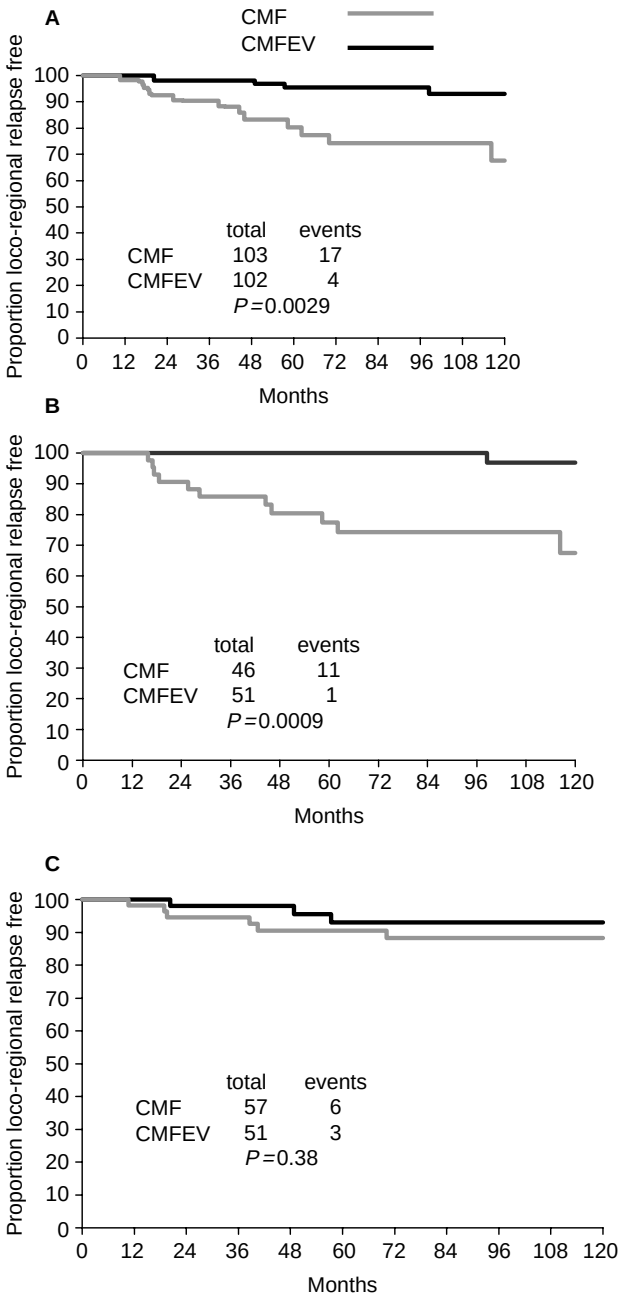

Figure 3. Locoregional relapse-free survival by treatment. (**A**) All patients; (**B**) premenopausal; (**C**) postmenopausal.

Long-term results by type of short-term response

Figure 4 shows the effect of the type of clinical short-term response on RFS. The difference between complete responders, partial responders and non-responders was statistically significant ($P = 0.014$) mainly because of the very good RFS of the complete responders (10-year RFS close to 80%); the long-term outcome of the partial responders was not markedly different from that of the non-responders.

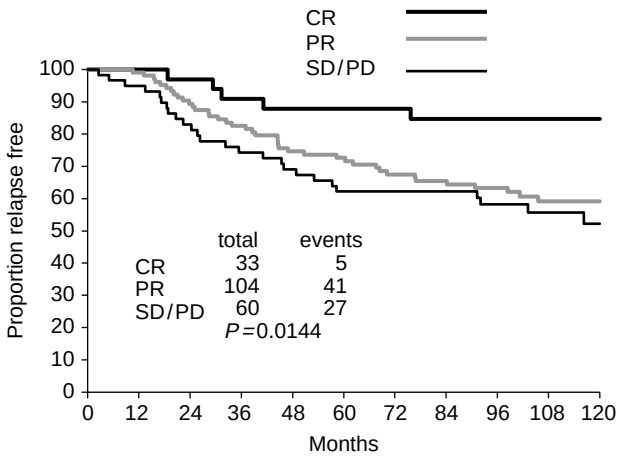

Figure 4. Relapse-free survival by type of clinical short-term response.

Table 4. Hazard ratios in the CMFEV arm compared with the CMF arm[a]

End point	Unadjusted		Adjusted	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
RFS			0.80 (0.50–1.27)	0.35
Premenopausal	0.73 (0.46–1.15)	0.17	0.54 (0.28–1.07)	0.08
Postmenopausal			0.96 (0.51–1.78)	0.89
LRRFS			0.24 (0.08–073)	0.011
Premenopausal	0.22 (0.07–0.66)	0.007	0.07 (0.009–0.55)	0.012
Postmenopausal			0.52 (0.13–2.09)	0.355
DMRFS			1.08 (0.63–1.85)	0.79
Premenopausal	1.07 (0.62–1.81)	0.81	1.08 (0.47–2.46)	0.86
Postmenopausal			1.12 (0.55–2.26)	0.76
OS			0.80 (0.47–1.37)	0.41
Premenopausal	0.77 (0.45–1.31)	0.38	0.72 (0.31–1.67)	0.45
Postmenopausal			0.84 (0.42–1.68)	0.63

[a]A Cox model including clinical node status (negative; positive), menopausal status (premenopause; postmenopause), clinical response (clinical CR; other) was used to estimate the adjusted hazard ratios; *P* values were estimated using the log-rank test. Hazard ratios of less than 1 favour CMFEV chemotherapy

CMF, cyclophosphamide, methotrexate, 5-fluorouracil; CMFEV, cyclophosphamide, methotrexate, 5-fluorouracil, epirubicin, vincristine; CR, complete response; CI, confidence interval; RFS, relapse-free survival; LRRFS, locoregional relapse-free survival; DMRFS, distant metastases relapse-free survival; OS, overall survival.

The same relationship was observed between the type of response and OS, but these differences were not statistically significant ($P = 0.27$).

Discussion

The concept that primary chemotherapy can have cytoreductive effects on primary tumours and even micrometastases has been repeatedly proposed [15, 16], and the hypothesis is supported by the similar OS results reported in randomised studies comparing primary with adjuvant chemotherapy [1–7], as well as by the very favourable outcome reported in patients achieving pCR after primary chemotherapy [3, 17, 18].

Randomised studies comparing two different chemotherapies administered in the neoadjuvant setting [9] make it possible to verify whether or not differences in short-term responses translate into long-term effects. Our study addresses this issue by comparing an anthracycline-containing regimen with CMF.

The short-term results showed that the clinical CR rate was higher in the patients receiving the anthracycline-containing CMFEV regimen, but this benefit was restricted to premenopausal women.

Before discussing the long-term results, we need to consider the limitations of this study. First, it was designed with objective responses as the primary end point, and the evaluation of long-term outcomes as a secondary objective; it is therefore by definition underpowered to estimate with acceptable precision the plausible risk reductions in RFS and particularly OS when comparing an anthracycline-containing regimen with CMF in the adjuvant setting. Secondly, given the multiplicity of the tests of statistical significance, the associated *P* values should be considered merely indicative and devoid of any formal value. Consequently, the results of this study should be considered as hypothesis-generating.

The long-term results are consistent with the objective response data, insofar as they show that the anthracycline-containing regimen offers a benefit in premenopausal women. With regard to 10-year RFS, the anthracycline-containing regimen was superior to CMF in all patients (76% versus 55%), and particularly in the premenopausal patients (70% versus 51%) in whom that difference reached a statistical trend ($P = 0.07$). With regard to 10-year OS, the anthracycline-containing regimen was also superior to CMF in all patients (75% versus 70%), and even more so in the premenopausal patients (80% versus 72%). However, these differences were not statistically significant.

The most significant finding of this study concerns LRRFS. The 10-year LRRFS rates in the patients receiving CMFEV and CMF were, respectively, 95% and 79% in the population as a whole ($P = 0.0029$), and 97% and 68% in the premenopausal patients ($P = 0.0009$); once again, there was no between-treatment difference among the postmenopausal patients. These findings were reproduced in a Cox model in which the adjusted hazard ratio in premenopausal patients treated with the anthracycline-containing CMFEV regimen was extremely low in comparison with CMF (0.07; range 0.009–0.55), and statistically significant ($P = 0.012$).

To the best of our knowledge, our results are the first to show parallelism between short-term clinical CR rates and at least one of the long-term outcome parameters (LRRFS), and need to be discussed in the context of other randomised studies comparing adjuvant chemotherapies with and without

anthracyclines. Some other authors have also reported data favouring anthracycline-containing regimens limited to premenopausal patients. The Oncofrance study, which compared 12 cycles of CMF with 12 cycles of AVCF (V = vincristine) in patients with positive axillary nodes, reported an overall significant advantage of the latter in terms of DFS and OS. However, a subgroup analysis revealed that the differences were statistically significant only in premenopausal patients [19]. Furthermore, a Scandinavian study comparing nine cycles of CMF with nine cycles of FEC in 1195 patients with positive axillary nodes or at high risk with negative axillary node tumours reported a significant OS advantage in favour of the anthracycline-containing regimen, but only in the premenopausal subgroups [20]. It is also worth noting that other trials showing differences in favour of the anthracycline-containing arm enrolled only premenopausal patients, and that most of the patients included in the overview comparisons of CMF and anthracyline-containing regimens were relatively young. These findings support the hypothesis that premenopausal patients may be more chemosensitive to anthracycline, but the biological basis for this is still unknown.

The type of anthracycline-containing regimen should also be discussed. We have previously shown [21] that regimens in which the anthracycline 'replaced' all or nearly all of the agents administered in the conventional arm (typically the AC or EC regimens) failed to show any significant advantage over CMF [22], whereas those in which the anthracycline was 'added' to all or nearly all of the agents in the conventional arm (typically the FAC or FEC, and CAF or CEF regimens) frequently had greater antitumour effects [19, 20, 23–26]. Bearing this in mind, our CMFEV regimen could be considered optimal, insofar as epirubicin was added to all the three agents of the CMF regimen.

The rotational strategy included in our regimen was introduced in the 1980s as an innovative and favourable compromise between the sequential strategy and the alternate strategy, which were supported at that time by some preclinical evidence. Like the sequential strategy (but somewhat earlier), it allowed the administration of full doses of multiple agents whose toxicity prevented their combined administration and, like the alternate strategy (but with more continuity), it allowed the administration of multiple agents in a short period of time in order to avoid or delay acquired resistance to chemotherapy. We do not know whether our present results were due to the addition of anthracycline, or to the rotational strategy, or both. In any case the 27% reduction in the 10-year risk of relapse (39% in premenopausal patients) found in this study is much higher than the overall risk reduction of 12% reported in the overview [27]. But it must be remembered that the overview also considered the studies of what can be considered suboptimal regimens on the basis of our concept [21].

One unique aspect of our study was the finding that the long-term benefit of the anthracycline-containing regimen was achieved with only four preoperative cycles (the three adjuvant CMF cycles were identical in the two arms), as opposed to the six cycles generally regarded as conventional in the adjuvant chemotherapy setting. As a result of the rotational drug administration schedule, the anthracycline was administered in only three of the four cycles, but it is worth noting that our regimen also included the vinca alkaloid, vincristine, in all four cycles. The role of this agent is unclear but, although its use has declined and is currently considered obsolete, it has to be remembered that a few randomised trials have found that it has a positive effect in the adjuvant setting [28], and that the other vinca alkaloid, vinorelbine, is now considered to be one of the most active agents in the treatment of metastatic breast carcinoma [29]. Furthermore, the anthracycline-containing regimen in the above-mentioned Oncofrance randomised trial (which found significant differences in DFS and OS) included vincristine and doxorubicin in the experimental arm [19].

Finally, the benefit of the CMFEV regimen was restricted to LRRFS and did not significantly extend to RFS. This finding is currently unexplainable, but it is known that initial locoregional relapses in early breast carcinoma are almost invariably followed by further and even distant metastases and, finally, death. For this reason, locoregional soft tissue sites may offer a very sensitive scenario in which to document early differences in the activity of different neoadjuvant treatments.

Our study reported rather low proportions of pCR, in line with the high and statistically significant heterogeneity reported in randomised trials of primary chemotherapy [7]. One important finding of this study is the confirmation of the long-term prognostic relevance of an initial clinical CR to neoadjuvant chemotherapy [17]. Our results suggest that a clinical CR may represent a surrogate end point of long-term effects, although this hypothesis will need to be validated in a larger randomised neoadjuvant trial. If it were to be confirmed, any difference in short-term clinical CRs would be an unbiased predictor of long-term adjuvant effects, thus allowing a substantial reduction in the time (5–10 years) needed to evaluate adjuvant regimens, particularly those including new agents.

In conclusion, the results of this study suggest that our anthracycline-containing regimen is more active than CMF in premenopausal patients, and possibly more effective in terms of long-term outcomes. However, before it can be considered a standard primary chemotherapeutic regiment, our results need to be confirmed in a larger patient population. Furthermore, it remains to be established whether similar or different results can be achieved using other anthracycline-containing regimens.

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