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Randomized Trial Comparing Cyclophosphamide, Epirubicin, and Fluorouracil With Cyclophosphamide, Methotrexate, and Fluorouracil in Premenopausal Women With Node-Positive Breast Cancer: Update of National Cancer Institute of Canada Clinical Trials Group Trial MA5

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ABSTRACT

Purpose
Certain anthracycline-containing adjuvant chemotherapy regimens are associated with improved relapse-free survival (RFS) and overall survival (OS) compared with the classic regimen of cyclophosphamide, methotrexate, and fluorouracil in women with early-stage breast cancer.

Patients and Methods
Between 1989 and 1993, 710 pre- and perimenopausal women with axillary node–positive breast cancer were randomly assigned to either cyclophosphamide 75 mg/m^2 orally days 1 through 14, epirubicin 60 mg/m^2 intravenously days 1 and 8, and fluorouracil 500 mg/m^2 intravenously days 1 and 8 (CEF) or CMF (cyclophosphamide 100 mg/m^2 orally days 1 through 14, methotrexate 40 mg/m^2 intravenously days 1 and 8, and fluorouracil 600 mg/m^2 intravenously days 1 and 8). On the basis of follow-up to May 1997 (median follow-up time, 59 months), there was a statistically significant improvement in RFS and OS for CEF compared with CMF.

Results
The trial results are now updated, with a median follow-up of 10 years for live patients. The 10-year RFS is 52% for patients who received CEF compared with 45% for CMF patients (hazard ratio [HR] for CMF *v* CEF = 1.31; stratified log-rank, $P = .007$). The 10-year OS for patients who received CEF and CMF are 62% and 58%, respectively (HR for CMF *v* CEF = 1.18; stratified log-rank, $P = .085$). The rates of acute leukemia have not changed since the original report, whereas the rates of congestive heart failure are slightly higher but acceptable (four patients [1.1%] in the CEF group *v* one patient [0.3%] in the CMF group).

Conclusion
The previously demonstrated benefit of CEF compared with CMF adjuvant chemotherapy is maintained with longer follow-up in the MA5 trial.

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INTRODUCTION

Anthracyclines are currently an important component of adjuvant chemotherapy, but this was not always the case. In 1976, the combination of cyclophosphamide, methotrexate, and fluorouracil (CMF) was first reported to be effective in women with axillary node–positive breast cancer and was soon widely used in clinical practice.[1] In the

1980s, to improve on the results of CMF, a number of trials were conducted evaluating anthracycline-containing regimens, and the results were inconsistent.[2-4] In a pilot study in women with node-positive and locally advanced breast cancer, we established the safety of an intensive regimen of cyclophosphamide, epirubicin, and fluorouracil (CEF).[5] The development of CEF was based on the concepts at that time that doxorubicin was one of the most active agents in advanced breast cancer, that epirubicin was less cardiotoxic than doxorubicin with no loss of antitumour efficacy, and that increasing the dose-intensity of chemotherapy improved outcome.[6-10] The CEF regimen was then compared with CMF in pre- or perimenopausal women with axillary node–positive breast cancer in the MA5 trial conducted by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG). Recruitment to the trial occurred between 1989 and 1993. At a median follow-up of 59 months, there was a statistically significant improvement in relapse-free survival (RFS) and overall survival (OS) for CEF compared with CMF.[11] There are few trials of adjuvant anthracycline chemotherapy that have reported long-term results of efficacy and safety. We now provide a 10-year update of the MA5 trial.

PATIENTS AND METHODS

Patient Population

Premenopausal or perimenopausal women with histologically confirmed axillary node–positive breast cancer who had undergone modified radical mastectomy or lumpectomy plus axillary dissection were studied. Menopausal status was defined according to the criteria described in our previous publication.[11] Patients were excluded from the study if they had evidence of metastases, a documented history of cardiac disease or previous cancer except skin cancer, inadequate renal function, abnormal liver function tests, a serious underlying medical illness or psychiatric disorder, inflammatory or locally advanced breast cancer before surgery, microscopic evidence of residual tumor at the resection margin of the total mastectomy, gross tumor that remained in the axilla after surgery, or previous radiation therapy or chemotherapy for breast cancer; patients were also excluded if they were more than 10 weeks from initial surgery for breast cancer.

Informed consent was obtained from eligible patients before assignment to treatment. The study protocol was approved by the institutional review board of each participating center.

Treatment Regimens

Patients were assigned to one of the regimens using stratified block randomization with a block size of four. Patients were allocated to receive CMF as first reported by Bonadonna et al[1] (cyclophosphamide 100 mg/m^2 orally days 1 through 14, methotrexate 40 mg/m^2 intravenously days 1 and 8; and fluorouracil 600 mg/m^2 intravenously days 1 and 8). CEF consisted of cyclophosphamide 75 mg/m^2 orally days 1 to 14, epirubicin 60 mg/m^2 intravenously days 1 and 8, and fluorouracil 500 mg/m^2 intravenously days 1 and 8. Patients administered CEF received antibiotic prophylaxis that consisted of cotrimoxazole two tablets orally twice a day for the duration of chemotherapy. If this could not be tolerated, then norfloxacin 400 mg orally twice a day or ciprofloxacin 500 mg orally twice a day was used. Dose modifications were performed according to predefined guidelines based on hematologic and nonhematologic toxicities.[11] Use of colony-stimulating factors was not allowed.

All patients who underwent lumpectomy received local radiation that consisted of 50 Gy in 25 fractions to the breast after completion of chemotherapy. Radiation to the chest wall after total mastectomy and radiation to the regional nodes were not permitted. Patients in both arms were not to receive tamoxifen, long-term prednisone therapy, or other hormones.

Outcomes

The primary outcome for the study was RFS. Secondary outcomes included OS and toxicity as measured by the expanded NCIC CTG Common Toxicity Criteria. The definition of these outcomes can be found in our previous publication.[11]

Statistical Analysis

RFS and OS of the treatment groups were described by Kaplan-Meier curves. The stratified log-rank test, adjusting stratification variables at baseline (node-positive disease, estrogen receptor [ER] and progesterone receptor status, and surgical type), was the primary method to compare the time-to-event data of the two treatment groups. This test gives equal weight to all time points of the survival distribution. The *P* values of the stratified Wilcoxon test, adjusting stratification variables at baseline (node-positive disease, ER and progesterone receptor status, and surgical type), were also presented. This test puts higher weights on the earlier part of the survival distribution

The hazard ratios (HRs) between CMF and CEF for recurrence and mortality and 95% CIs were obtained using the Cox proportional hazards model with a single treatment covariate. An adjusted HR was also calculated by including additional covariates, such as age (< 50 years and ≥ 50 years), tumor size (T1, T2, and T3), nodal status (one to three and $\geq$ four nodes), and ER level (< 10 and ≥ 10 fmol/mg), in the Cox model.

RESULTS

The database for the current analysis was locked in April 2002. All patients on the trial who were alive were observed for a minimum of 9 years and a median of 10 years. Seven hundred sixteen women underwent random assignment; six patients (one on CMF and five on CEF) were ineligible and, therefore, excluded. Seven hundred ten eligible patients (351 on CEF and 359 on CMF) were included in the analysis. The treatment groups were reasonably balanced for baseline characteristics, including age, axillary nodes, hormone receptor status, and type of surgery (Table 1). There was no statistically significant difference in any of the baseline characteristics between groups.

Two hundred one CMF patients have developed breast cancer recurrence compared with 162 CEF patients. The 10-year RFS for CMF patients was 45% compared with 52% for CEF patients (HR = 1.31; 95% CI, 1.06 to 1.61; stratified log-rank, $P = .007$; stratified Wilcoxon, $P = .005$; Fig 1).

Table 1. Baseline Characteristics

Factor	No. of Patients CMF (n = 359)	CEF (n = 351)
Age		
≤ 29 years	6	4
30-39 years	77	86
40-49 years	215	205
≥ 50 years	61	56
Nodes positive		
1-3	218	215
4-10	117	114
> 10	24	22
ER level, fmol/mg		
< 10	100	106
≥ 10	212	206
Surgery		
Lumpectomy	176	169
Mastectomy	183	182
Tumour stage		
T1	139	126
T2	175	193
T3	42	25

Abbreviations: CMF, cyclophosphamide, methotrexate, and fluorouracil; CEF, cyclophosphamide, epirubicin, and fluorouracil; ER, estrogen receptor.

The disease-free survival rates for nodal subgroups and subgroups based on ER status are listed in Table 2. When a Cox model was performed, which adjusted for age, tumor size, nodal status, and ER level, the HR for recurrence was 1.31 (95% CI, 1.06 to 1.61).

One hundred fifty-three CMF patients have died compared with 131 CEF patients. The 10-year survival rate for CMF was 58% compared with 62% for CEF (HR = 1.18; 95% CI, 0.94 to 1.49; stratified log-rank, $P = .085$; stratified Wilcoxon, $P = .047$; Fig 2). The corresponding survival data for nodal and ER status subgroups are listed in Table 2. In the Cox model, the adjusted HR for mortality was 1.16 (95% CI, 0.91 to 1.46).

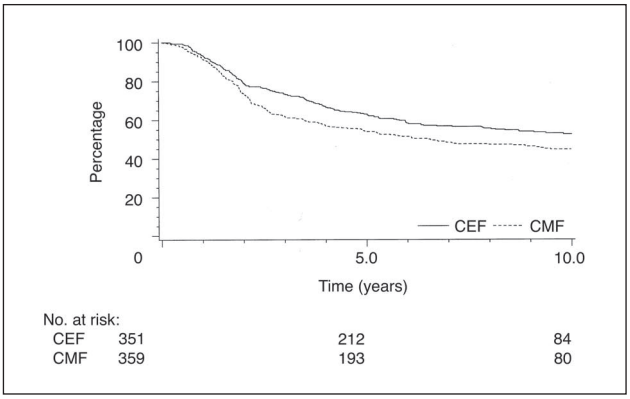

Fig 1. Ten-year relapse-free survival of cyclophosphamide, methotrexate, and fluorouracil (CMF) versus cyclophosphamide, epirubicin, and fluorouracil (CEF).

As a sensitivity analysis, we performed a failure-free survival analysis that included recurrence, second primary cancer, or death as an event. The HR was 1.25 (95% CI, 1.02 to 1.52; stratified log-rank, $P = .015$; stratified Wilcoxon, $P = .012$).

At the time of the trial publication in 1998, five patients in the CEF group experienced acute leukemia. One patient experienced congestive heart failure in the CMF group. There have been no further cases of leukemia in the CEF group, but one patient in the CMF group experienced leukemia. There have been four cases of congestive heart failure in CEF patients but no additional cases in CMF patients; these cases occurred between 16 and 58 months after study entry. One of these patients with congestive heart failure received doxorubicin for metastases to the chest wall.

DISCUSSION

The results of the MA5 trial published in 1998 demonstrated the superiority of CEF compared with classical CMF.[11] The 5-year RFS for CEF was 63% compared with 53% for CMF (HR = 1.3; 95% CI, 1.04 to 1.65). The 5-year OS for CEF and CMF were 77% and 70%, respectively (HR = 1.22; 95% CI, 0.91 to 1.64). The updated analysis shows that the previously demonstrated benefit of CEF over CMF is maintained. The CMF to CEF HRs for both RFS and OS at 5 years and 10 years are consistent with each other.

Our trial was not powered for comparison of treatment regimens in subgroups based on nodes or hormone receptor status. However, the HRs favored CEF in patients with one to three nodes and four or more nodes. This was also observed at the 5-year analysis. In our earlier publication, the results of the comparison of treatments based on ER status subgroups were not presented. In the current analysis, the HRs favored CEF in patients with ER-positive and -negative tumors. Currently, patients with hormone receptor–positive tumors often receive endocrine therapy. The results of the MA5 trial may not be readily extrapolated to today's practice because of the absence of endocrine therapy in the trial.

Serious adverse experiences, such as leukemia and heart failure, are of concern with intensive anthracycline regimens. Since the previous publication, there have been no further cases of leukemia in CEF patients. The cases previously reported occurred between 15 and 41 months after randomization. Since the previous analysis, there have been four cases of heart failure in the CEF group. All of these cases occurred before 5 years of follow-up. In fact, these cases actually occurred during the follow-up period of our 1998 publication, but data came in after the database was closed. Currently, all patients on the trial who are alive have been observed for a minimum of 9 years. Hence, it is reassuring that there seems to be no late cardiotoxicity.

Table 2. Ten-Year Disease-Free Survival and Overall Survival

Subgroup	No. of Patients		Disease-Free Survival				Overall Survival			
	CEF	CMF	CEF (%)	CMF (%)	HR	95% CI	CEF (%)	CMF (%)	HR	95% CI
All patients	351	359	52	45	1.31	1.06 to 1.61	62	58	1.18	0.94 to 1.49
No. of nodes										
1-3	215	218	60	56	1.24	0.92 to 1.66	69	66	1.17	0.84 to 1.63
≥ 4	136	141	40	28	1.41	1.05 to 1.89	51	45	1.20	0.86 to 1.67
ER status*										
ER negative	160	100	55	47	1.26	0.84 to 1.88	60	52	1.21	0.80 to 1.84
ER positive	206	212	50	42	1.37	1.06 to 1.78	65	57	1.39	1.02 to 1.90

Abbreviations: CEF, cyclophosphamide, epirubicin, and fluorouracil; CMF, cyclophosphamide, methotrexate, and fluorouracil; HR, hazard ratio; ER, estrogen receptor.
*ER status was unknown in 39 patients treated with CEF and 47 patients treated with CMF.

There has been only one other adjuvant trial of an anthracycline regimen compared with classic CMF, and this trial has a much shorter follow-up than our trial.[12] Although anthracycline-containing regimens are now commonly used as adjuvant therapy, there are relatively few publications concerning long-term efficacy and safety results of trials that evaluated such agents a number of years ago.[13,14] Currently, taxanes are often incorporated into anthracycline regimens.[15,16] It is unknown how CEF compares with an anthracycline/taxane regimen. Presently, CEF is being compared with doxorubicin and cyclophosphamide followed by paclitaxel and with dose-dense high-dose epirubicin and cyclophosphamide followed by paclitaxel in a large multicenter trial conducted by the NCIC CTG with the participation of the US Intergroup. Recently the combination of docetaxel, doxorubicin, and fluorouracil has been reported to have better RFS and OS but increased febrile neutropenia compared with fluorouracil, doxorubicin, and cyclophosphamide.[17] There are limitations in comparing fluorouracil, doxorubicin, and cyclophosphamide with CEF because the regiments contain different anthracyclines and are administered through different schedules.

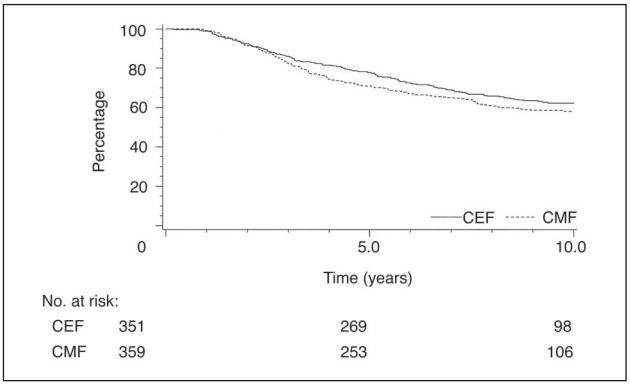

Fig 2. Ten-year overall survival of cyclophosphamide, methotrexate, and fluorouracil (CMF) versus cyclophosphamide, epirubicin, and fluorouracil (CEF).

In conclusion, the long-term superiority of CEF compared with CMF in the MA5 trial is maintained. It is reassuring that no further late toxicity has occurred. This provides important information that serves as a foundation as current research in adjuvant therapy is evaluating incorporating new potentially cardiotoxic agents into anthracycline regimens.

Authors' Disclosures of Potential Conflicts of Interest

Although all authors have completed the disclosure declaration, the following author or their immediate family members has indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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