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ORIGINAL REPORT

Sequential Adjuvant Epirubicin-Based and Docetaxel Chemotherapy for Node-Positive Breast Cancer Patients: The FNCLCC PACS 01 Trial

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ABSTRACT

Purpose
The PACS 01 trial compared six cycles of fluorouracil, epirubicin, and cyclophosphamide (FEC) with a sequential regimen of three cycles of FEC followed by three cycles of docetaxel (FEC-D) as adjuvant treatment for women with node-positive early breast cancer.

Patients and Methods
Between June 1997 and March 2000, 1,999 patients with operable node-positive breast cancer were randomly assigned to either FEC every 21 days for six cycles, or three cycles of FEC followed by three cycles of docetaxel, both given every 21 days. Hormone-receptor–positive patients received tamoxifen for 5 years after chemotherapy. The primary end point was 5-year disease-free survival (DFS).

Results
Median follow-up was 60 months. Five-year DFS rates were 73.2% with FEC and 78.4% with FEC-D (unadjusted $P = .011$; adjusted $P = .012$). Multivariate analysis adjusted for prognostic factors showed an 18% reduction in the relative risk of relapse with FEC-D. Five-year overall survival rates were 86.7% with FEC and 90.7% with FEC-D, demonstrating a 27% reduction in the relative risk of death (unadjusted $P = .014$; adjusted $P = .017$). The incidence of grade 3 to 4 neutropenia, the need for hematopoietic growth factor, and incidence of nausea/vomiting were higher with FEC. Docetaxel was associated with more febrile neutropenia in the fourth cycle, stomatitis, edema, and nail disorders. Though rare overall, there were fewer cardiac events after FEC-D ($P = .03$), attributable mainly to the lower anthracycline cumulative dose.

Conclusion
Sequential adjuvant chemotherapy with FEC followed by docetaxel significantly improves disease-free and overall survival in node-positive breast cancer patients and has a favorable safety profile.

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INTRODUCTION

Anthracyclines and taxanes are the most active cytotoxic drugs for the treatment of breast cancer. In the adjuvant setting, the pivotal role of anthracycline-based chemotherapy has been established in successive overviews by the Early Breast Cancer Trialists' Collaborative Group.[1] Compared with the combination of cyclophosphamide, methotrexate, and fluorouracil, anthracycline-based regimens reduce the annual breast cancer death rate by approximately 38% in women younger than 50 years, and by approximately 20% for those age 50 to 69 years.

Taxanes were introduced in the 1990s for treatment of advanced breast cancer. First-line single-agent docetaxel (D) 100 mg/m^2 resulted in an overall response rate (ORR) of 67.7%, and showed a dose-effect relationship at doses between 75 mg/m^2 and 100 mg/m^2.[2] As second-line therapy, D resulted in ORRs ranging from 53% to 57% in anthracycline-resistant patients.[3,4] Recent results of a randomized trial that directly compared docetaxel and paclitaxel in advanced breast cancer showed the superiority of docetaxel over paclitaxel.[5]

These results have led to the evaluation of various taxane-anthracycline regimens aimed at optimizing efficacy. Phase II trials confirmed the high activity of taxane-anthracycline combinations, with ORRs ranging from 57% to 94%.[6-18] As first-line treatment for advanced breast cancer, randomized

trials demonstrated significant and constant improvements in ORRs for anthracycline-taxane combinations compared with anthracycline minus taxane regimens, as well as increased time to tumor progression in half of the trials.[19-26] In general, the concomitant use of an anthracycline and a taxane resulted in higher toxicity, requiring dose reduction of both agents.

In the adjuvant setting, three major trials have shown a significant improvement in disease-free survival (DFS) when a taxane was added sequentially or concomitantly to an anthracycline regimen.[27-29] Presently, the optimal strategy for combining an anthracycline with a taxane in the adjuvant setting has not been completely defined in terms of timing (sequential or concomitant), number of cycles, anthracycline (doxorubicin or epirubicin), taxane (docetaxel or paclitaxel), or doses. Based on the results of the French Adjuvant Study Group (FASG) 05 trial, the FEC regimen (fluorouracil, epirubicin [100 mg/m^2], and cyclophosphamide) was considered to be one of the reference treatments for node-positive breast cancer.[30] Previously, the FASG-01 trial showed that six cycles of FEC significantly improved 10-year DFS compared with three cycles of FEC in premenopausal node-positive patients.[31]

Based on these data, we initiated the PACS 01 trial to evaluate our reference adjuvant chemotherapy regimen of six cycles of FEC compared with a sequential regimen of three cycles of FEC followed by three cycles of D in patients with node-positive breast cancer. Our aim was to use optimal doses of epirubicin and docetaxel and limit adverse effects, while using a six-cycle regimen.

PATIENTS AND METHODS

Study Population

Women eligible for the study were between 18 and 64 years old and had undergone primary surgery with clear margins (ie, modified mastectomy or tumorectomy) plus axillary dissection for unilateral operable carcinoma of the breast (stage $<$ T4a). Pre- and postmenopausal women with histologically proven axillary lymph-node involvement (at least five nodes removed) were included. Main eligibility criteria included WHO performance status less than 2; adequate hematologic (granulocyte count $\geq 2 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L) and hepatic (transaminases $\leq$ 1.5$\times$ the upper limit of normal [ULN], alkaline phosphatases $\leq$ 2.5$\times$ ULN, and bilirubin $\leq$ ULN) tests; and normal cardiac function (baseline left ventricular ejection fraction [LVEF] $\geq$ ULN for each center).

Exclusion criteria included pregnancy, documented history of cardiac disease contraindicating anthracyclines, previous cancer (except treated basal cell and squamous cell carcinoma of the skin or cancer of the uterine cervix), previous radiation therapy, hormone therapy, or chemotherapy for breast cancer, or if more than 42 days had passed since initial breast cancer surgery.

Potentially eligible patients underwent bone scan, chest x-ray, abdominal ultrasound, and contralateral mammography. Written informed consent was obtained before randomization. The protocol was reviewed and approved by the ethics committee/institutional review board and the study was conducted according to the Declaration of Helsinki and European Good Clinical Practice requirements.

Study Design and Treatment

This was a randomized multicenter open-label phase III study. Randomization procedures were centralized and balanced per block. Patients were assigned to receive fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2 (FEC) intravenously on day 1 every 21 days for six cycles or the same regimen of FEC for three cycles followed by D 100 mg/m^2 intravenously on day 1 every 21 days for three cycles. Stratification was by age ($<$ 50 and $\geq$ 50 years), number of positive axillary nodes (1 to 3, and $>$ 3), and center. To prevent docetaxel-related hypersensitivity or fluid retention, patients received premedication with six doses of corticosteroids—each equivalent to 50 mg of prednisolone—starting 12 hours before and ending 18 hours after the docetaxel infusion. Primary prophylaxis with granulocyte colony-stimulating factors (G-CSF) and antibiotics was prohibited. Antiemetics (5-HT$_3$ receptor antagonists) were prescribed routinely before each cycle.

Treatment was interrupted for at least 1 week in the event of an absolute granulocyte count less than 1.5 $\times$ 10^9/L and/or a platelet count less than 100 $\times$ 10^9/L on day 21. G-CSF (filgrastim 5 μg/kg/d on days 4 to 11) was prescribed for all subsequent chemotherapy cycles. If G-CSF was prescribed during the first three cycles of FEC, it was withdrawn for the first cycle of D. In the event of febrile neutropenia, G-CSF was added after the first episode. If a second episode occurred, the doses of epirubicin or docetaxel were reduced by 25%. The docetaxel dose was reduced by 25% for transaminases more than 1.5$\times$ ULN, alkaline phosphatases more than 2.5$\times$ ULN, and/or bilirubin more than ULN.

Table 1. Baseline Characteristics of Patients and Tumors

Characteristic	FEC (n = 996) No. of Patients	FEC (n = 996) %	FEC-D (n = 1,003) No. of Patients	FEC-D (n = 1,003) %
Age, years				
Median	50		50	
Range	26-67		25-65	
$<$ 50	505	50.7	500	49.8
Premenopausal*	613	62.4	598	60.4
Premenopausal and $\geq$ 50 years*	131	13.3	129	13.0
Surgery				
Breast conservation	510	51.2	531	52.9
Modified mastectomy	486	48.8	472	47.1
Histologic tumor size, cm				
$<$ 2	313	34.5	360	39.1
2-5	524	57.7	490	53.3
$\geq$ 5	71	7.8	70	7.6
Missing	88		83	
SBR grade				
I	102	10.4	126	12.8
II	438	44.9	430	43.7
III	389	39.9	385	39.1
Not gradable	47	4.8	44	4.5
Missing	20		18	
No. of positive nodes				
1 to 3	611	61.3	626	62.4
$>$ 3	385	38.6	377	37.6
Hormone receptors†				
Positive (ER and/or PR)	760	77.4	802	80.7
Negative (ER and PR)	222	22.6	192	19.3
Missing	14		9	
Estrogen receptor†				
Positive	707	71.4	765	76.5
Negative	283	28.6	235	23.5
Missing	6		3	
Progesterone receptor				
Positive	635	64.6	648	65.1
Negative	348	35.4	347	34.9
Missing	13		8	

Abbreviations: FEC, fluorouracil, epirubicin, and cyclophosphamide; FEC-D, fluorouracil, epirubicin, and cyclophosphamide followed by docetaxel; SBR, Scarff–Bloom Richardson; ER, estrogen receptor; PR, progesterone receptor.
*Percentages were calculated among patients for whom information on menopausal status was available (983 patients in the FEC group and 990 in the FEC-D group).
†P = .02.

Table 2. Analysis of Events in the ITT Population

Event	FEC (n = 996) No. of Patients	FEC (n = 996) %	FEC-D (n = 1,003) No. of Patients	FEC-D (n = 1,003) %	HR	95% CI	P*
First event†	264	26.5	218	21.7	0.80	0.67 to 0.96	.012
Relapse of breast cancer	235	23.6	190	18.9	0.78	0.64 to 0.94	.010
Local only	40	4.0	28	2.8			
Regional (with or without local)	15	1.5	12	1.2			
Distant (with or without local or regional)	180	18.1	150	14.9			
Contralateral breast cancer	23	2.3	21	2.1			
Death	6	0.6	7	0.7			
Contralateral breast cancer	30	3.0	24	2.4	0.80	0.47 to 1.37	.43
Second cancer	25	2.5	17	1.7	0.65	0.35 to 1.21	.17
Any death	135	13.5	100	10.0	0.73	0.56 to 0.94	.017
Of breast cancer	123	12.3	89	8.9			
Of second cancer	5	0.5	3	0.3			
Due to toxic effects	3	0.3	4	0.4			
Other causes	4	0.4	4	0.4			

Abbreviations: ITT, intent-to-treat; FEC, fluorouracil, epirubicin, and cyclophosphamide; FEC-D, fluorouracil, epirubicin, and cyclophosphamide followed by docetaxel; HR, hazard ratio.
*Log-rank test adjusted for nodal involvement and age.
†First event defined according to the disease-free survival criteria (ie, local relapse, regional relapse, distant relapse, contralateral breast cancer, death of any cause).

Discontinuation of treatment was required for disease progression, unacceptable toxicity, WHO grade 3 to 4 cardiac event, or fluid retention associated with weight gain. Treatment could also be discontinued at the discretion of the patient or investigator.

Adjuvant Treatment After Chemotherapy Completion

Tamoxifen 20 mg/d was started after chemotherapy completion and continued for 5 years. Initially, tamoxifen was required for postmenopausal women with hormone receptor (HR) –positive (estrogen [ER] and/or progesterone [PR] receptors) tumors. Tamoxifen was given at the investigator's discretion for patients with HR-negative tumors; however, the policy had to be similar for both treatment arms at each center. In December 1998, the study protocol was amended to require tamoxifen treatment for premenopausal women with HR-positive tumors. HR status was assessed by immunohistochemistry or biochemistry.

Radiotherapy was initiated within 4 weeks after the last cycle of chemotherapy and was mandatory for all patients who had undergone breast-conserving surgery. Radiation to the chest wall, supraclavicular area, and internal mammary chain was recommended following mastectomy. Irradiation of the axilla was prohibited. Radiotherapy procedures had to be similar for both arms at a given center.

Evaluations

The tolerability of chemotherapy was evaluated before each cycle. In addition, an ECG and an absolute blood count were performed on day 21, and nonhematologic toxicity was evaluated during the period between cycles. Toxicity was graded according to WHO criteria and serious adverse events were defined according to International Conference on Harmonization guidelines. The resting LVEF was measured by radioisotopic or echocardiographic methods at baseline, within 3 weeks after completion of adjuvant chemotherapy, and then after 1 and 5 years. A physical examination was performed every 4 months for the first 2 years, then every 6 months for the following 3 years. Imaging studies (ie, mammography, chest x-ray, liver ultrasound, and bone scan) were performed 1 year after the initial surgery, then yearly thereafter for 5 years. Beyond this period, a mammography was performed annually.

Sample Size Determination and Statistical Analysis

The primary end point was 5-year DFS. DFS was defined as the time from randomization until first relapse (local, regional, or distant), contralateral breast cancer, or death from any cause. This trial was designed to detect a 7.5% difference in DFS with 90% power and a two-sided type I error of 5%. These hypotheses required enrolling 1,600 patients, and 469 events. Because the accrual rate was higher than expected, the sample size was expanded to 2,000 patients to increase the power of the trial from 90% to 95%. Data were analyzed according to the intent-to-treat (ITT) principle.

Table 3. Cox Regression Model Analysis for Disease-Free Survival in the ITT Population

Factors	HR	95% CI	P
Arm			
FEC	1		
FEC-D	0.82	0.69 to 0.99	.034
Age, years			
< 50	1		
≥ 50	0.86	0.72 to 1.04	.123
Positive nodes			
1 to 3	1		
> 3	2.13	1.77 to 2.55	< .001
Histologic tumor size, mm			
< 20	1		
≥ 20	1.75	1.39 to 2.20	< .001
SBR grade			
1	1		
2	1.98	1.24 to 3.15	.004
3	2.53	1.58 to 4.03	< .001
Hormone receptor			
ER−/PR−	1		
ER−/PR+	1.20	0.80 to 1.80	.38
ER+/PR−	1.39	1.01 to 1.90	.041
ER+/PR+	0.89	0.67 to 1.17	.40
Tamoxifen			
No	1		
Yes	0.57	0.45 to 0.73	< .001

Abbreviations: ITT, intent-to-treat; HR, hazard ratio; FEC, fluorouracil, epirubicin, and cyclophosphamide; FEC-D, fluorouracil, epirubicin, and cyclophosphamide followed by docetaxel; SBR, Scarff-Bloom Richardson; ER, estrogen receptor; PR, progesterone receptor.

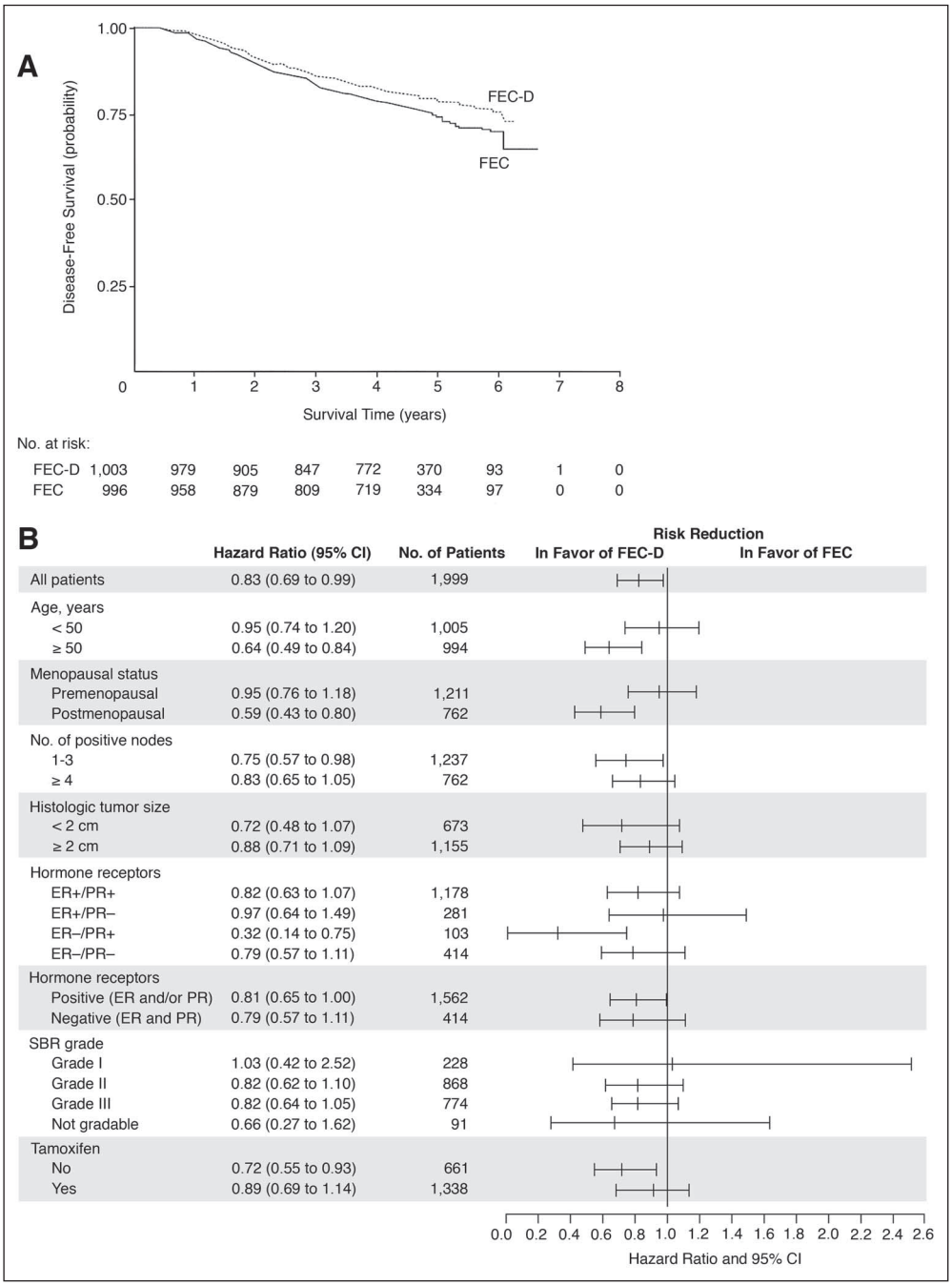

Fig 1. Disease-free survival: (A) Kaplan-Meier estimates; (B) hazard ratios and 95% CIs in different subgroups (Forest plot analysis). FEC, fluorouracil, epirubicin, and cyclophosphamide; FEC-D, fluorouracil, epirubicin, and cyclophosphamide, followed by docetaxel; ER, estrogen receptor; PR, progesterone receptor; SBR, Scarff–Bloom Richardson.

Secondary end points were overall survival (OS), defined as the time from randomization until death from any cause, and safety. Patients who received at least one dose of study drug were analyzed for safety.

The DFS and OS rates were calculated by the Kaplan-Meier method. Treatment arms were compared using a log-rank test stratified for the number of positive axillary lymph nodes (N) and age. A supportive multivariate analysis (Cox regression model) was preplanned, and was adjusted for age, N, histologic tumor size, HR status, Scarff–Bloom Richardson (SBR) grade, and tamoxifen. Each interaction between variables and DFS has been explored.

One interim efficacy analysis was prospectively planned at 2 years after the recruitment of the last patient. This was conducted conservatively with a type I error of .001 in order to maintain an overall type I error of 5%.[32] All analyses were presented to an independent data monitoring committee.

RESULTS

Patient Characteristics

Between June 1997 and March 2000, 85 centers in France and Belgium enrolled 1,999 women (996 on the FEC arm; 1,003 on the FEC-D arm). Three patients did not receive treatment (1 FEC; 2 FEC-D). A total of 1,944 patients were eligible (976 FEC; 968 FEC-D) for treatment, and of these 1,827 received the complete protocol-specified treatment and were considered the per protocol population (928 FEC; 899 FEC-D). Baseline characteristics were well balanced between treatment arms, except for combined

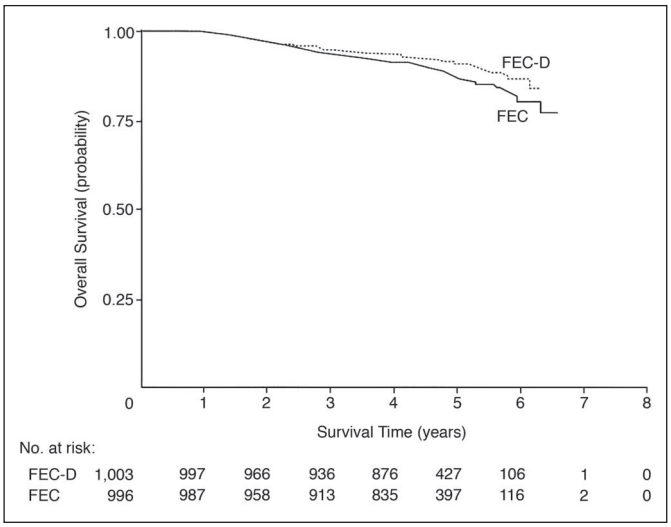

Fig 2. Kaplan-Meier estimates of overall survival. FEC, fluorouracil, epirubicin, and cyclophosphamide; FEC-D, fluorouracil, epirubicin, and cyclophosphamide, followed by docetaxel.

hormone-receptor status (HR) and estrogen-receptor status ($P = .02$; Table 1).

Treatment Characteristics

Six treatment cycles were completed by 97% of patients in the FEC group and by 96.1% of the patients in the FEC-D group. In the FEC group, four patients received docetaxel instead of FEC in the last three cycles. In the FEC-D group, 29 patients received FEC instead of D, and of those patients, 20 received FEC in cycles 5 or 6. Almost all treated patients received radiotherapy. Tamoxifen use was well balanced between arms (65.5% in the FEC arm and 68.4% in the FEC-D arm; $P = .16$), including both premenopausal (younger than and older than 50 years) and postmenopausal women.

Efficacy Results

The cutoff date for this analysis was September 2004 and the median follow-up time was 60 months from randomization. In the ITT population, 482 patients relapsed (Table 2). The 5-year DFS rates were 73.2% on the FEC arm and 78.4% on the FEC-D arm (unadjusted $P = .011$; adjusted $P = .012$). This difference was due mainly to the reduction in distant metastasis with FEC-D (Table 2). Similar results were observed in the eligible and per protocol populations. The multivariate analysis adjusted for prognostic factors showed a 18% reduction in the relative risk of relapse with FEC-D (hazard ratio [HR] = 0.82; 95% CI, 0.69 to 0.99; $P = .034$; Table 3; Fig 1A). Figure 1B shows the treatment effect in different subgroups. In the subgroup of patients with one to three positive nodes, FEC-D significantly reduced the risk of relapse compared with FEC ($P = .04$). In the subgroup of patients with more than three involved nodes, the benefit was almost the same showing a 17% reduction in the risk of relapse with FEC-D ($P = .12$; Fig 1B). Women age 50 years or older derived significant benefit in DFS from treatment with FEC-D ($P = .001$), but this advantage was not found in younger women ($P = .65$). Using the Cox regression model, a significant interaction between age and treatment was shown ($P = .028$), suggesting a heterogeneity of the treatment effect in the two age groups. Patients receiving tamoxifen showed improved DFS rates, irrespective of age.

Table 4. Adverse Events Experienced per Patient

Event	% of Patients FEC (n = 995)	% of Patients FEC-D (n = 1,001)	P
Hematologic grade 3-4			
Neutropenia on day 21	33.6	28.1	.008
Cycles 4-6	20.2	10.9	< .001
Febrile neutropenia	8.4	11.2	.03
Cycles 4-6	3.7	7.4	.005
Cycle 4	1.0	4.6	
Cycle 5	1.5	2.3	
Cycle 6	1.7	1.2	
G-CSF	27.0	22.2	.01
Cycles 5 and 6	24.8	9.5	< .001
Infection	1.6	1.6	.99
Anemia	1.4	0.7	.12
Thrombocytopenia	0.3	0.4	.71
Nonhematologic			
Nausea-vomiting grade 3-4	20.5	11.2	< .001
Cycles 4-6	11.0	1.6	< .001
Stomatitis grade 3-4	4.0	5.9	.054
Cycles 4-6	2.3	4.0	.03
Alopecia grade 3	83.9	82.6	.40
Edema moderate or severe, cycle 4-6	0.3	4.8	< .001
Nail disorder moderate or severe, cycle 4-6	1.0	10.3	< .001
Chemotherapy-induced amenorrhea	72.4	68.4	.13
Cardiac			
Any events reported as SAE	1.3	0.4	.03
CHF	0.4	0.0	
Decrease in LVEF	0.4	0.1	
Cardiac death	0.1	0.1	
Other	0.4*	0.2†	
Changes in LVEF at the end of chemotherapy			
Below ULN	10.9	9.9	.48
Decrease > 20% of baseline value	7.0	6.5	.63
Changes in LVEF at one year‡			
Below ULN	13.2	10.0	.03
Decrease > 20% of baseline value	10.0	7.8	.09

Abbreviations: FEC, fluorouracil, epirubicin, and cyclophosphamide; FEC-D, fluorouracil, epirubicin, and cyclophosphamide followed by docetaxel; G-CSF, granulocyte colony-stimulating factor; SAE, serious adverse event; CHF, congestive heart failure; LVEF, left ventricular ejection fraction; ULN, upper limit of normal.

*Arrhythmia (n = 2), myocardial infarction (n = 1), dyspnea (n = 1).

†Pericarditis (n = 1), menace syndrome (n = 1).

‡Changes in LVEF at the end of chemotherapy were evaluated for 947 and 941 patients in the FEC and FEC-D groups, respectively, and changes at 1 year were evaluated for 356 and 330 patients, respectively.

Of the 235 deaths, 135 were in the FEC group and 100 were in the FEC-D group (Table 2). The 5-year OS rates were 86.7% with FEC and 90.7% with FEC-D, demonstrating a 27% reduction in the relative risk of death for FEC-D (HR = 0.73; 95% CI, 0.56 to 0.94; Fig 2).

Acute and Delayed Toxic Effects

At least one serious adverse event occurred in 13.9% of patients in the FEC group and in 15.1% of patients in the FEC-D group ($P = .38$). The incidence of grade 3 or 4 neutropenia on day 21 was higher with FEC, whereas the incidence of febrile neutropenia was higher with D at cycle 4 (Table 4). Use of G-CSF was highest in the FEC group. In the

FEC and FEC-D groups, respectively, G-CSF was administered to 27.0% and 22.2% of patients overall ($P = .01$) and to 24.8% and 9.5% of patients at cycles 5 and 6 ($P < .001$). Grade 3 or 4 nausea and vomiting were more frequent with FEC, and an increase in grade 3 or 4 stomatitis was reported with D. Docetaxel-related toxicities such as edema and nail disorders were reported as expected when full doses were given for three cycles (Table 4). No early toxic deaths occurred.

Although cardiac events were uncommon in both treatment arms, there were significantly fewer cardiac events after FEC-D (Table 4). One delayed cardiac death was reported in each treatment arm, but neither event could be clearly related to chemotherapy.

Three cases of acute myeloid leukemia occurred in the FEC group and one occurred in the FEC-D group. Other hematologic malignancies were one case each of lymphoma (FEC), myeloma (FEC-D), and chronic myeloid leukemia (FEC-D). Three patients who received adjuvant tamoxifen presented with an endometrial carcinoma. Nineteen other second cancers were reported after FEC and 13 were reported after FEC-D.

DISCUSSION

The PACS 01 trial of adjuvant chemotherapy in node-positive breast cancer patients showed that the sequential use of the epirubicin-based regimen FEC followed by docetaxel significantly improved DFS and OS after 5 years of follow-up. Our results highlight several important issues when considered in context with previous clinical trials of taxanes in the adjuvant setting. First, we compared two six-cycle regimens of equal treatment duration, which is similar to the strategy used in the Breast Cancer International Research Group (BCIRG) 001 trial.[29] However, in trials that evaluated the addition of paclitaxel to an anthracycline, the treatment duration was longer in the paclitaxel arms of the study, and this could partially explain the improved outcomes.[27,28] In contrast, in our trial, the reference treatment regimen (FEC) provided higher 5-year DFS and OS durations than the reference regimens used in other adjuvant trials involving taxanes. Moreover, a side-by-side comparison of FEC and docetaxel/doxorubicin/cyclophosphamide (TAC) yielded similar results.[33] Four cycles of doxorubicin plus cyclophosphamide, although effective, were probably of too short duration in node-positive breast cancer.[27,28,34]

Subgroup analysis revealed a treatment benefit in favor of FEC-D for patients age 50 years and older but not for younger patients. Furthermore, the treatment benefit with FEC-D was superior to FEC in postmenopausal women but not in premenopausal women, even though it has been shown that adjuvant chemotherapy provides a greater benefit in terms of DFS and OS for premenopausal women.[1] We searched for any potential bias in prognostic factors, but identified no important imbalances between age groups, except a higher rate of SBR grade 3 tumors and a higher rate of PR-positive status in women younger than 50 years old (data not shown). The proportion of women receiving tamoxifen was similar in both groups, as well as in the premenopausal subgroups of each treatment arm. The incidence of chemotherapy-induced amenorrhea was similar between arms. However, subgroup analyses should be considered exploratory and underpowered as illustrated by the large confidence intervals framing the estimates of relative risk. Our findings with respect to treatment effect and nodal status were similar to those of the BCIRG 001 trial, in which a greater benefit of adding docetaxel was observed in patients with fewer than four involved nodes.[29]

Although fewer episodes of severe neutropenia and nausea and vomiting were observed with FEC-D, the higher rate of febrile events occurring mainly during the first D cycle could be prevented with G-CSF primary prophylaxis. Despite administering lower doses of each drug, combination therapy is generally associated with more severe acute toxicities. Using systematic antibiotic prophylaxis, TAC is associated with a high rate of grade 3 and 4 neutropenia and febrile neutropenia requiring G-CSF.[29] A reduction in the epirubicin cumulative dose from 600 mg/m^2 to 300 mg/m^2 may reduce long-term toxicities (ie, cardiac toxicity and secondary acute leukemia).[30,35-37] In our trial, after 5 years of follow-up, FEC-D was associated with a significantly lower rate of cardiac events (0.4% *v* 1.3%) and less secondary leukemia (1 case *v* 3 cases) compared with FEC. This observation is probably related to a 50% reduction in anthracycline total dose in the FEC-D group, but longer follow-up is required to further evaluate this trend.

In conclusion, sequential adjuvant chemotherapy with three cycles of FEC followed by three cycles of D significantly improves DFS and OS in patients with node-positive breast cancer. This regimen could be adjusted in terms of number of cycles and the addition of trastuzumab. Although the magnitude of the benefit observed with FEC-D is lower in some subgroups of patients, differences in the toxicity profiles of FEC and FEC-D may influence the choice of treatment for patients with node-positive early breast cancer.

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members 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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