Benefit of a High-Dose Epirubicin Regimen in Adjuvant Chemotherapy for Node-Positive Breast Cancer Patients With Poor Prognostic Factors: 5-Year Follow-Up Results of French Adjuvant Study Group 05 Randomized Trial

By the French Adjuvant Study Group

Purpose: **To determine the influence of the epirubicin dose in operable node-positive breast cancer patients with factors of poor prognosis.**

Patients and Methods: **Between April 1990 and July 1993, 565 operable breast cancer patients with either more than three positive nodes or between one and three positive nodes with Scarff Bloom Richardson grade ≥ 2 and hormone receptor negativity were randomized after surgery to receive either fluorouracil 500 mg/m², epirubicin 50 mg/m², and cyclophosphamide 500 mg/m² every 21 days for six cycles (FEC 50) or the same regimen except with epirubicin dose of 100 mg/m² (FEC 100). Postmenopausal patients received tamoxifen 30 mg/d for 3 years at the beginning of chemotherapy. Radiotherapy was delivered at the end of chemotherapy in both groups.**

Results: **The median follow-up was 67 months. The 5-year disease-free survival (DFS) was 54.8% with FEC 50 and 66.3% with FEC 100 ($P = .03$). The 5-year overall survival (OS) was 65.3% and 77.4%, respectively ($P = .007$). The mean relative dose-intensity was similar in the two groups (90.3% and 86.1%, respectively). Neutropenia and anemia were significantly more frequent in FEC 100 ($P < 10^{-3}$), as were nausea-vomiting ($P = .008$) and stomatitis and alopecia ($P < 10^{-3}$). Nine cases of grade 3 infection occurred only with FEC 100, and no toxic deaths occurred. Three cases of acute cardiac toxicity were observed (FEC50 = 1, FEC100 = 2) and 10 patients (FEC50 = 6, FEC100 = 4) presented delayed cardiac dysfunctions. Two cases of secondary leukemia were observed (acute lymphatic leukemia with FEC 50 and acute myelogenous leukemia with FEC 100).**

Conclusion: **After 5 years of follow-up, the increased epirubicin dose led to a significant benefit in terms of DFS and OS, with a high survival rate among patients with poor-prognosis breast cancer.**

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THE USE OF ADJUVANT chemotherapy in axillary node-positive breast cancer is well established. Its efficacy has been demonstrated on both disease-free survival (DFS) and overall survival (OS) in this setting. In an overview of the National Surgical Adjuvant Breast and Bowel Project (NSABP) clinical trials, the benefit in terms of survival and DFS was only observed among patients younger than 50 years and with fewer than three involved lymph nodes.[1] Then, two meta-analyses have been published. The first pooled results from different groups using various therapeutic regimens and compared them with those of a natural-history database from three centers.[2,3] The second was the first meta-analysis published by the Early Breast Cancer Trialists' Collaborative Group.[4] The conclusions of these two studies were similar: the benefit of chemotherapy was observed both in patients with fewer than three involved lymph nodes and in patients with more extensive lymph node involvement.

Anthracyclines are among the most active drugs in advanced breast cancer[5-8] and in the adjuvant setting.[9-12] In advanced breast cancer, results of randomized trials had shown higher response rates with fluorouracil, doxorubicin, and cyclophosphamide (FAC) compared with the regimen of cyclophosphamide, methotrexate, and fluorouracil (CMF).[6-8] Then, several studies comparing an anthracycline-containing regimen and CMF in adjuvant setting were initiated.[13-16] The French Epirubicin Study Group demonstrated that epirubicin was as effective as and less toxic than doxorubicin when administered at equimolar doses (50 mg/m²) to patients with advanced breast cancer.[17] These results were confirmed by the Italian Multicentre Breast Study comparing the same regimens.[18] In 1986, the French Adjuvant Study Group (FASG) initiated a phase III study, FASG 01, involving 602 premenopausal patients with node-positive operable breast cancer to determine the optimal dose and duration of epirubicin-based adjuvant chemotherapy, comparing fluorouracil 500 mg/m², epirubicin 50 mg/m², and cyclophosphamide 500 mg/m² every 21 days for six cycles (6 FEC 50) with FEC 50 and FEC 75 for three cycles each (3 FEC 50 and 3 FEC 75, respectively). After 8 years of follow-up, 6 FEC 50 significantly improved the

Collaborators and their affiliations are listed in Appendix.

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Address reprint requests to Jacques Bonneterre, MD, PhD, Département de Sénologie et Cancérologie Gynécologique, Centre Oscar Lambret, 3 Rue Frédéric Combemale, 59020 Lille, Cedex, France; email: j-bonneterre@o-lambret.fr.

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DFS compared with 3 FEC 50 ($P = .018$) or 3 FEC 75 ($P = .04$), and OS was also significantly better in the group receiving 6 FEC 50 than in those receiving 3 FEC 50 (67.4% *v* 60.8%; $P = .04$).[19] These results, both in the metastatic and the adjuvant setting, led us to consider 6 FEC 50 as our adjuvant standard treatment in node-positive breast cancer patients.

The dose-response relationship of epirubicin-based chemotherapy for advanced breast cancer has been examined in two randomized phase III trials comparing FEC 50 with this same regimen except with epirubicin dose of 100 mg/m^2 (FEC 100), with a significant improvement in the response rate, response duration, and time to progression in favor of FEC 100.[20,21] In the adjuvant setting, the dose-intensity studies conducted by Hryniuk et al[22] established a correlation between the mean dose-intensity and the 3-year DFS rate.

At the beginning of the 1990s, four different groups initiated trials in the adjuvant setting to test intensive chemotherapy regimens; they comprised the Cancer and Leukemia Group B trial (CALGB 8,541),[23] the NSABP B-22 trial,[24] the National Cancer Institute of Canada (NCIC) trial designed to compare a high dose of epirubicin in the FEC regimen (120 mg/m^2 every 4 weeks ie, 30mg/m^2/wk) with a classic CMF in premenopausal patients with node-positive operable breast cancer,[14] and our study (FASG 05).

The FASG 05 study compared 6 FEC 50 with 6 FEC 100 every 3 weeks (16.7 mg/m^2/wk *v* 33.3 mg/m^2/wk) to determine the effect of epirubicin dose and dose-intensity on DFS and OS in patients with poor prognostic factors, ie, extensive lymph node involvement ($N > 3$) or one to three positive nodes with Scarff Bloom Richardson (SBR) grade ≥ 2 and hormone receptor negativity (both estrogen and progesterone).

PATIENTS AND METHODS

Patient Population

Between April 1990 and July 1993, 565 women, recruited from 20 institutions in France, with operable breast cancer who had undergone modified radical mastectomy or lumpectomy plus axillary dissection were enrolled onto the study. Premenopausal and postmenopausal women with histologically proven axillary lymph node involvement (at least five axillary nodes resected) with more than three positive nodes or between one and three positive nodes with SBR grade ≥ 2 and hormone receptor negativity (both estrogen and progesterone) were studied. Postmenopausal status was defined as an amenorrhea for at least 1 year. The main eligibility criteria were age between 18 and 64 years, World Health Organization (WHO) performance status ≤ 2, normal hematologic (granulocyte count $\geq$ 2,000/mm^3, platelet count $\geq$ 100,000/mm^3), hepatic (bilirubin ≤ 35 μmol/L) and renal (serum creatinine level ≤ 130 μmol/L) functions, no cardiac dysfunction (baseline left ventricular ejection fraction [LVEF] $\geq 50\%$). LVEF was measured at rest by radioisotopic or ultrasonographic methods. Patients were excluded from the study if they had evidence of metastases, a documented history of cardiac disease or previous cancer (except treated basal cell and squamous cell carcinoma of the skin or cancer of the uterine cervix), a serious underlying medical illness or psychiatric disorder, inflammatory or locally advanced breast cancer before surgery, previous radiation therapy, hormonotherapy or chemotherapy for breast cancer, or were more than 42 days from initial surgery for breast cancer.

Potentially eligible patients also underwent bone scan, chest radiograph, abdominal ultrasound or computed tomographic scan, and contralateral mammography. Written or oral informed consent was obtained from each patient in a standard procedure at each participating institution. The study protocol was approved by the ethical committee of the coordinating center according to the French loi Huriet.

Treatment Regimens

Patients were randomized to receive intravenously one of the following chemotherapy regimens: arm A, fluorouracil 500 mg/m^2, epirubicin 50 mg/m^2, and cyclophosphamide 500 mg/m^2 every 21 days for six cycles (6 FEC 50),or arm B, fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2 every 21 days for six cycles (6 FEC 100). Stratification was by number of positive axillary nodes (one to three, four to 10, and > 10 nodes).

Preventive use of colony-stimulating factors (CSF) and antibiotics was prohibited. Antiemetic treatment was prescribed routinely before each cycle. A cooling cap could be used, according to the usual practices of each institution.

The allocated treatment was started within 42 days after initial surgery. An absolute granulocyte count less than 2,000/mm^3 and/or a platelet count less than 100,000/mm^3 on day 21 led to a treatment interruption of at least 1 week. Treatment was stopped if hematologic recovery took more than 3 weeks. The epirubicin dose was reduced by 50% if serum bilirubin levels were 35 to 50 μmol/L, and treatment was stopped if bilirubin levels exceeded 50 μmol/L. In postmenopausal patients, tamoxifen 30 mg/d was prescribed at the first chemotherapy cycle, for 3 years. In case of hormone receptor negativity, tamoxifen administration was left to the discretion of the investigators, but the policy had to be similar for both arms in a given center. Locoregional radiotherapy was delivered within 30 days after the last chemotherapy cycle according to standard procedures. After mastectomy, radiation to the chest wall, supraclavicular area, internal mammary chain, and, in case of pN1 tumor, to the axillary area was delivered and consisted of 50 Gy in 25 fractions for each target. Patients who underwent lumpectomy received local radiation to the breast that consisted of 55 Gy in 27 fractions plus a complementary breast irradiation of 10 to 15 Gy and to the supraclavicular area, internal mammary chain, and axillary area (in case of pN1 tumor) consisting of 50 Gy in 25 fractions for each target. The tolerability of chemotherapy was evaluated before each cycle: an ECG and an absolute blood count were performed on day 21, and nonhematologic toxicity was evaluated during the period between each cycle, according to WHO criteria. LVEF was assessed at the end of chemotherapy. Subjects underwent clinical, biochemical, and radiologic assessments every 6 months during the 5-year follow-up period and yearly thereafter.

Statistical Analysis

All assessable patients were entered onto an intention-to-treat analysis using SPSS software (SPSS, Inc, Chicago, IL). The χ^2 test was used to compare baseline categorical variables and the incidence of adverse events in the two groups.[25] Continuous variables were compared by using analysis of variance.[26] Relative dose-intensity was calculated based on the ratio of the drug doses actually delivered in the originally expected time over the expected dose in the expected time.[27]

Table 1. Patients Eligible for Evaluation

	FEC 50	FEC 100	Total
Randomized	289	276	565
Not eligible & not assessable			
Metastatic disease	13	5	18
No breast cancer	0	2	2
Lost to follow-up	5	3	8
Not treated	6	5	11
Assessable for safety	278	268	546
Assessable for efficacy	271	266	537

DFS was defined as the time from randomization until first relapse (local, regional, and distant). A contralateral breast cancer was considered a new primary malignancy. OS was defined as the time from randomization until death, related or not to breast cancer. All survival and DFS rates were computed according to the Kaplan-Meier method, and survival curves were compared with the log-rank test or the stratified log-rank test as appropriate.[28,29] The prevalence of the following classic prognostic factors was analyzed: menopausal status (pre- *v* postmenopausal), surgery (conservative *v* radical), number of involved lymph nodes (one to three *v* > three), tumor size (< 20 mm *v* ≥ 20 mm), SBR grade (1 *v* 2 *v* 3), and estrogen and progesterone receptor status (positive *v* negative). Estrogen receptor and progesterone receptor positivity was defined as a value greater than 10 fmol/mg proteins. Cox regression methods were used to determine whether known clinical prognostic variables confounded the treatment effect.[30] Statistical analysis has been performed double blinded both by Pharmacia & Upjohn France (Saint-Quentin en Yvelines, France) and by an independent biostatistician.

RESULTS

Patient Characteristics

Five hundred sixty-five patients were enrolled onto the study. Of these, 20 (3.7%) were ineligible (because of advanced or metastatic disease, n = 18, or no breast cancer, n = 2), and eight (1.4%) were lost to follow-up after randomization (Table 1): these patients were excluded from the efficacy analysis (n = 537). The safety and compliance analysis involved all the treated patients (n = 546) (Table 1). All the protocol violations were well balanced between the two arms, as were baseline characteristics (Table 2). Major protocol violations were included in the analysis and were as follows: age ≥ 65 years (n = 9), less than four positive nodes and hormone receptor positivity (n = 14), neutrophil count less than 2,000/mm^3 at baseline (n = 6), LVEF less than 50% (n = 11), ECG abnormalities (n = 4), interval between surgery and treatment outset exceeding 42 days (n = 19), and wrong treatment arm allocation (n = 6). As regards hormone therapy, the protocol violations were as follows: concomitant luteotropin-releasing hormone agonist (n = 10), postmenopausal patients not treated with tamoxifen (n = 19), and premenopausal patients treated with tamoxifen (n = 24). In hormone receptor–negative postmenopausal patients (n = 94), 70 (74.5%) received tamoxifen with no difference between the two arms. At the cutoff date for analysis (October 1998), the median follow-up period was 67 months (range, 2 to 96 months).

Treatment

Among the 546 treated patients (FEC 50 = 278, FEC 100 = 268), the mean number of cycles administered was 5.9 with FEC 50 and 5.85 with FEC 100. Twenty-eight patients (12 with FEC 50 and 16 with FEC 100) stopped treatment prematurely. The main reasons were the patient's refusal (n = 7), nonhematologic toxicity (n = 7), cardiac toxicity (n = 4), persistent neutropenia (n = 1), disease progression (n = 1), late discovery of initial metastatic disease (n = 1), death (n = 2; stroke and pleural involvement), catheter obstruction (n = 1), traffic accident (n = 1), and unknown (n = 3). The mean epirubicin dose received was 298.2 mg/m^2 (intended dose, 300 mg/m^2) in FEC 50 and 589.8 mg/m^2 (intended dose, 600 mg/m^2) in FEC 100. The mean epirubicin relative dose-intensity was 15.1 mg/m^2/wk, ie, 90.3% (± 10.2) in FEC 50 and 28.7 mg/m^2/wk ie, 86.1% (± 11.8) in FEC 100 with no significant difference between the two regimens.

DFS

Recurrence was evaluated in 537 patients, of whom 222 had relapsed at the cutoff date for analysis (123 [45.4%] of 271 in FEC 50 and 99 [37.2%] of 266 in FEC 100). The 5-year DFS rates were 54.8% (95% confidence interval [CI95], 48.9% to 60.7%) with 6 FEC 50 and 66.3% (CI95, 60.6% to 72.0%) with 6 FEC 100, with a significant difference in favor of 6 FEC 100 (P = .03, Fig 1). The site of first recurrence for FEC 50 patients was: breast only, n = 10 (3.7%); soft tissues only, n = 3 (1.1%); regional nodes only, n = 7 (2.6%); distant only, n = 66 (24.3%); and multiple sites of recurrence, n = 37 (13.6%). The corresponding data for the FEC 100 regimen were as follows: eight (3.0%), two (0.7%), three (1.1%), 65 (24.4%), and 21 (7.9%) patients, respectively. No statistically significant difference was detected in the pattern of recurrences between treatment groups. However, patients who received FEC 100 were characterized by tendency to develop fewer multiple sites of recurrence than those who received FEC 50 (21.2% *v* 30.1%, P = .07). The 5-year DFS rates for the subgroups of patients with one to three and more than three positive nodes are listed in Table 3. For DFS, the hazards ratios for FEC 50 compared with FEC 100 were 0.74 (P = .43; CI95, 0.35 to 1.55) for the one-to-three node group, with only 28 events in 98 patients, and 1.50 (P = .005; CI95, 1.13 to 2.00) for the more than three node group. There was no interaction between lymph node involvement and treatment (P = .48). When a Cox proportional hazards

Table 2. Clinical and Pathologic Characteristics of the 565 Randomized Patients

Characteristic	FEC 50 (n = 289)		FEC 100 (n = 276)		P
	No. of Patients	%	No. of Patients	%	
Age at randomization, years					
Mean	50.4		50.8		
Range	25-66		23-68		NS
Menopausal status					NS
Premenopausal	147	52.5	127	47.0	
Postmenopausal	133	47.5	143	53.0	
Unknown	9		6		
Surgery					NS
Conservative	126	44.8	134	49.6	
Radical	155	55.2	136	50.4	
Unknown	8		6		
Clinical tumor stage					NS
T0-T1-T2	210	76.1	210	80.5	
T3-T4	66	23.9	51	19.5	
Tx	13		15		
Pathologic tumor size					NS
< 20 mm	70	25.6	76	29.0	
≥ 20 mm	203	74.4	186	71.0	
Unknown	16		14		
No. of positive nodes					NS
1-3	52	18.5	46	17.0	
4-10	180	64.1	176	64.5	
> 10	49	17.4	49	18.1	
Unknown	8		5		
SBR grade					NS
1	13	5.2	18	7.3	
2	113	45.0	108	44.1	
3	125	49.8	119	48.6	
Unknown	38		31		
Tumor ER status					NS
Positive	139	54.7	147	57.9	
Negative	115	45.3	107	42.1	
Unknown	35		22		
Tumor PR status					NS
Positive	146	57.2	150	59.0	
Negative	109	42.8	104	41.0	
Unknown	34		22		

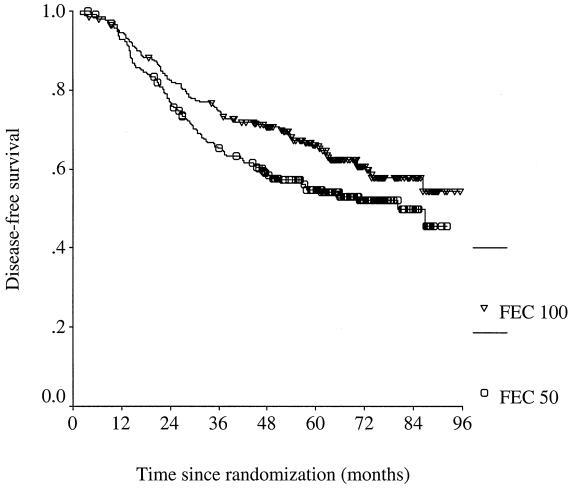
NOTE. Percentages exclude unknowns.

Abbreviations: ER, estrogen receptors; PR, progesterone receptors; NS, not significant.

model was performed, which adjusted for any imbalance in baseline prognostic factors, the relative risk (RR) for relapse with FEC 50 compared with FEC 100 was 1.37 ($P = .02$; CI95, 1.05 to 1.79). In this analysis, the number of positive nodes was an independent prognostic factor for relapse, with an RR of 0.60 ($P = .01$; C195, 0.40 to 0.89) for patients with one to three involved nodes compared with patients with more than three involved nodes. Neither age nor menopausal status was found to be an independent prognostic factor.

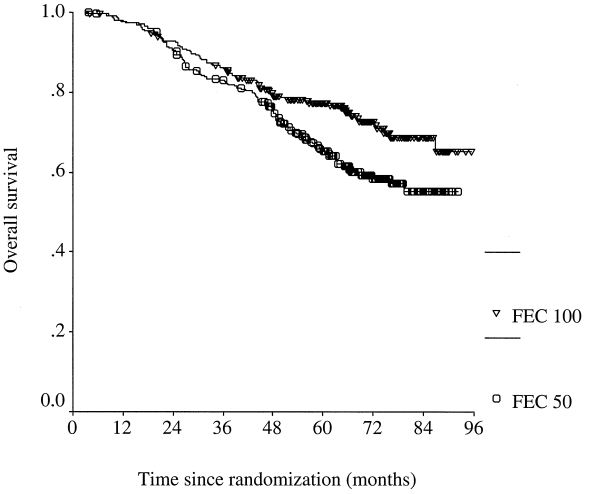
Survival

There were 171 deaths, involving 101 (37.3%) of the 271 patients in FEC 50 and 70 (26.3%) of the 266 patients in FEC 100. Nine (3.3%) of the FEC 50 patients died before recurrence because of the following: second cancer (four patients: two colorectal carcinomas, one gastric carcinoma, and one nasal fossa cylindroma), acute leukemia (one patient), myocardial infarct (one patient), stroke (one patient), and unknown reason (two patients). Six (2.3%) of the FEC 100 patients died, the causes of death being as follows: pancreatic carcinoma (one patient), acute leukemia (one patient), stroke (one patient), suicide (two patients), cardiovascular collapse (one patient included with an anteroseptal necrosis on ECG). The 5-year OS rates were 65.3% (CI95, 59.6% to 71.0%) with 6 FEC 50 and 77.4% (CI95, 72.4% to 82.4%) with 6 FEC 100, with a highly significant difference



Number of patients at risk							
6 FEC 50	248	204	169	143	104	51	17
6 FEC 100	248	215	194	171	126	63	23

Fig 1. DFS, $P = .03$. Abbreviations: FEC 50, fluorouracil 500 mg/m^2, epirubicin 50 mg/m^2, and cyclophosphamide 500 mg/m^2 every 21 days; FEC 100, fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2 every 21 days.



Number of patients at risk							
6 FEC 50	262	242	217	189	131	61	19
6 FEC 100	258	243	225	193	152	80	27

Fig 2. OS, $P = .007$.

in favor of 6 FEC 100 ($P = .007$, Fig 2). The 5-year OS rates for the subgroups of patients with one to three and more than three positive nodes are listed in Table 3. For OS, the hazards ratios for FEC 50 compared with FEC 100 were 0.81 ($P = .63$; CI95, 0.34 to 1.91) for the one-to-three node group, with only 21 events in 98 patients, and 1.71 ($P = .001$; CI95, 1.23 to 2.38) for the more than three node group. In the Cox model, the RR for death with FEC 50 compared with FEC 100 was 1.55 ($P = .005$; CI95, 1.14 to 2.10). In this analysis, the number of positive nodes was an independent prognostic factor for death, with an RR of 0.60 ($P = .03$; CI95, 0.38 to 0.94) for patients with one to three involved nodes compared with patients with more than three involved nodes.

Acute Toxicity

Toxicity was evaluated in 546 patients according to WHO criteria. Table 4 shows the adverse events per patient. Neutropenia and anemia were significantly less frequent in FEC 50 ($P < 10^{-3}$). Nine cases of grade 3 infection occurred (FEC 50, n = 0; FEC 100, n = 9) and comprised neutropenic fever (n = 7), vaginitis (n = 1), and an undocumented infection (n = 1). Two of these patients received CSF during subsequent cycles. Patients in FEC 50 were also significantly less likely to have severe nausea/vomiting ($P = .008$), stomatitis ($P < 10^{-3}$), and alopecia ($P < 10^{-3}$). Other grades 3 to 4 clinical side effects occurred in six patients (FEC 50, n = 2; FEC 100, n = 4), with grade 3 asthenia (n = 3) and grades 3 (n = 2) and 4 (n = 1) injection site injuries related to extravasation. No toxic deaths occurred.

Thirteen cardiac abnormalities were diagnosed during chemotherapy (FEC 50, n = 6; FEC 100, n = 7). These included three grade 2 conditions requiring treatment interruption (one case of left ventricular hypertrophy on the ECG in FEC 50, one LVEF decrease from 68% at baseline to 41% without clinical signs in FEC 100, and one left ventricular insufficiency on the ECG plus LVEF = 45% with no baseline measurement in FEC 100).

Delayed Cardiac Toxicity

Ten cases were reported (FEC 50, n = 6; FEC 100, n = 4), and all patients had undergone regional radiation. Two of these patients received only adjuvant chemotherapy: the first died from a myocardial infarct 17 months after a cumulative epirubicin dose of 300 mg/m^2, and the second had an LVEF decrease from 44% (abnormal value at baseline) to 20% 63 months after a cumulative epirubicin dose of 577 mg/m^2; this last patient is awaiting a heart transplantation. Eight patients developed delayed cardiac effects (FEC 50, n = 5; FEC 100, n = 3) after chemotherapy for metastatic disease; three had received doxorubicin, three mitoxantrone, and two epirubicin as first-line chemotherapy for metastatic disease (Table 5). These patients had an LVEF decrease or developed congestive heart failure. One died from global heart failure after 100 mg/m^2 mitox-

Table 3. Five-Year DFS and OS Rates

Group	DFS			OS		
	FEC 50 (%)	FEC 100 (%)	*P*	FEC 50 (%)	FEC 100 (%)	*P*
All patients	54.8	66.3	.03	65.3	77.4	.007
1-3 Nodes	77.6	71.0	.42	83.8	78.2	.63
> 3 Nodes	49.6	65.3	.005	60.9	77.2	.001

antrone, five patients died from disease progression, and two had normalization of heart function.

Second Malignancies

Second malignancies occurred in 37 patients. Twenty-one patients developed contralateral breast cancer (14 in FEC 50, seven in FEC 100) after a median period of 24 months (range, 10 to 79 months) in FEC 50 and 45 months (range, 23 to 89 months) in FEC 100. Two cases of acute leukemia occurred. One woman in FEC 50 developed acute lymphoblastic leukemia with the t(9;22) translocation, 55 months after randomization and after a cumulative epirubicin dose of 300 mg/m^2; she died of acute lymphoblastic leukemia 1 year after its diagnosis. One woman in FEC 100 developed acute myeloblastic leukemia (AML) French American British 4 with t(8;16) and del(17q21), 9 months after randomization and after a cumulative epirubicin dose of 600 gm/m^2; she died of AML 1 month after its diagnosis with disseminated intravascular coagulation. Fourteen patients developed second malignancies (seven in FEC 50, seven in FEC 100) after a median period of 44 months (range, 23 to 77 months) in FEC 50 and 33 months (range, 18 to 67 months) in FEC 100. These cases were as follows: endometrial carcinomas occurred in three patients treated with tamoxifen (one of whom also developed concomitant basocellular carcinoma), colorectal carcinomas in three, pancreatic carcinoma in one, stomach carcinoma in one, lung carcinoma in one, bladder carcinomas in two, basocellular carcinoma in one, nasal fossa cylindroma in one, and cheek histiocytoma in one.

Table 4. Treatment-Related Adverse Effects (WHO grade) by Chemotherapy Regimen

Adverse Effect	FEC 50 (n = 278)		FEC 100 (n = 268)		
	No.	%	No.	%	*P*
Neutropenia					$< 10^{-3}$
Grade 0	123	45.4	117	44.7	
Grade 1-2	118	43.5	79	30.1	
Grade 3-4	30	11.1	66	25.2	
Not evaluated	7		6		
Anemia					$< 10^{-3}$
Grade 0	240	88.9	151	57.6	
Grade 1-2	30	11.1	109	41.6	
Grade 3	0	0.0	2	0.8	
Not evaluated	8		6		
Nausea/vomiting					.008
Grade 0	41	15.1	19	7.3	
Grade 1-2	167	61.6	152	58.0	
Grade 3-4	63	23.3	91	34.7	
Not evaluated	7		6		
Stomatitis					$< 10^{-3}$
Grade 0	250	92.2	189	72.1	
Grade 1-2	21	7.8	63	24.1	
Grade 3-4	0	0.0	10	3.8	
Not evaluated	7		6		
Alopecia					$< 10^{-3}$
Grade 0	67	25.5	14	5.5	
Grade 1-2	143	54.4	40	15.7	
Grade 3	53	20.1	201	78.8	
Not evaluated	15		13		
Infection					.003
Grade 0	228	84.1	208	79.4	
Grade 1-2	43	15.9	45	17.2	
Grade 3	0	0.0	9	3.4	
Not evaluated	7		6		

NOTE. Percentages exclude "not evaluated."

DISCUSSION

We observed a significant improvement in 5-year DFS (66.3% *v* 54.8%, $P = .03$) and OS (77.4% *v* 65.3%, $P = .007$) with FEC 100 regimen relative to FEC 50. These results are noteworthy, even in the patients treated with FEC 50, because all the patients had factors of poor prognosis and one half were premenopausal. Even if this study was not powered for a subset analysis, it is worth noting that the difference was significant only in patients with more than three positive nodes. Moreover, the mean epirubicin relative dose-intensity was excellent with both regimens (90.3% and 86.1% for FEC 50 and FEC 100, respectively) and better than the results obtained with FEC 120 days1 to 8, every 4 weeks, in the study by Levine, in which the mean epirubicin relative dose-intensity was only 77%.[18] As regards safety, FEC 100 was more toxic than FEC 50, but these adverse events were acceptable and no toxic deaths occurred.

The place of anthracyclines in adjuvant treatment of breast cancer is well established. The latest results of the Early Breast Cancer Trialists' Collaborative Group demon-

Table 5. Delayed Cardiac Effects

	Adjuvant EPI Dose (mg/m^2)	ABC Protocol	ABC Anthra Dose (mg/m^2)	Event	Age at Event (years)	Time From Discontinuation of Adjuvant CT at Event (months)	Outcome
FEC 50							
	300			Myocardial infarct	64	17	Died of MI
	300	FEC	550	ECG abnormalities	67	62	Alive
	300	VDS-MTX-MTZ	150	Left ventricular impairment	45	34	DOD
	300	FAC	675	LVEF decrease	44	24	DOD
	298	MTZ-VNR	100	CHF	33	34	Died of CHF
	294	EPI-VNR	300	LVEF decrease from 69% to 49%	69	44	DOD
FEC 100							
	577			LVEF decrease from 44% to 20%	39	63	Alive
	609	VDS-MTX-MTZ	90	CHF	38	43	DOD
	581	PCT-DXR	240	CHF + LVEF decrease from 50% to 26%	37	29	DOD
	593	FAC	400	LVEF decrease from 62% to 48%	46	26	Alive

Abbreviations: ABC, advanced breast cancer; EPI, epirubicin; VDS, vindesine; MTX, methotrexate; MTZ, mitoxantrone; VNR, vinorelbine; DXR, doxorubicin; PCT, paclitaxel; Anthra, anthracyclines/anthracenediones; CHF, congestive heart failure; CT, chemotherapy; MI, myocardial infarct; DOD, died of disease.

strate the advantage of anthracycline-containing regimens over CMF in 11 randomized trials, with a 5-year absolute benefit in terms of DFS (3.2%, $2P = .006$) and OS (2.7%, $2P = .02$).[31] The reduction in the annual risk with anthracycline-containing regimens is 12% ± 4% ($2P = .006$) for relapse and 11% ± 5% ($2P = .02$) for death.

The use of FEC is supported by the results of several studies comparing FEC and CMF. In 1996, Coombes et al[13] used two alternative schedules of FEC versus CMF according to the participating centers, and no significant benefit for the anthracycline-containing regimen was observed. FEC1 (fluorouracil 600 mg/m^2 d1 intravenously [IV], epirubicin 50 mg/m^2 d1 IV, cyclophosphamide 600 mg/m^2 d1 IV, eight cycles every 3 weeks) and CMF1 (cyclophosphamide 100 mg/m^2 d1 to d14 orally, methotrexate 40 mg/m^2 d1 and d8 IV, fluorouracil d1 and d8 IV, six cycles every 4 weeks) were of similar efficacy. However, FEC2 (fluorouracil 600 mg/m^2 d1 and d8 IV, epirubicin 50 mg/m^2 d1 IV, cyclophosphamide d1 and d8 IV, six cycles every 4 weeks) improved DFS and OS compared with CMF2 (cyclophosphamide 600 mg/m^2 d1 and d8 IV, methotrexate d1 and d8 IV, fluorouracil 600 mg/m^2 d1 and d8 IV, six cycles every 4 weeks). Recently, Mouridsen et al[15] compared IV CMF to FEC 60 in premenopausal node-negative and node-positive patients and observed a significant improvement in 6-year OS with FEC 60 compared with CMF (76% *v* 69%, $P = .01$). Di Leo et al[16] compared a classic oral CMF regimen with EC 60 and high-dose EC (epirubicin 100 mg/m^2, cyclophosphamide 830 mg/m^2) in 777 node-positive breast cancer patients: no difference was observed among the three treatment groups after a median follow-up of 50 months, but longer follow-up and a larger number of patients are required to confirm these results. Finally, Levine et al[14] compared FEC 120 every 4 weeks with a classic CMF regimen and showed the superiority of FEC over CMF in terms of both 5-year DFS (63% *v* 53%, $P = .009$) and OS (77% *v* 70%, $P = .03$) in premenopausal women with axillary node-positive breast cancer. In this study, the epirubicin dose-intensity was higher than in the other trials (30 mg/m^2/wk).

Given the clear advantage of an anthracycline-containing adjuvant regimen, the benefit of dose intensification has been studied. Recently, Hryniuk et al[32] and Frei et al[33] tried to construct a scale using the concept of summation dose-intensity (SDI), ie, integrating the contributions of the individual agents within a combination regimen. They defined the unit dose-intensity as the dose of each drug required to produce a 30% objective response rate. In the single-agent trials, dose-response relationships were linear when the studies covered a range of dose-intensities. In randomized trials testing dose-intensity in metastatic disease, response rates and median survival correlated linearly with the SDI of the treatment arms. The results in metastatic disease were negative if the difference between the arms was less than 0.54 SDI units. Adjuvant trials testing a difference in dose-intensity of less than 0.65 SDI units were also negative. In our study, the increment of 0.65 SDI units was calculated by the authors with 1.16 and 1.82 SDI units for FEC 50 and FEC 100, respectively.[32] In comparison, the commonly used AC regimen has a total of 1.91 SDI units, the 4-week FAC regimen using 2 weeks of daily oral cyclophosphamide has 2.10 units, and the FEC regimen used by Levine et al has 1.96 SDI units. Furthermore, these regimens contain amounts of anthracycline similar to those in FEC 100. In the adjuvant setting, three major teams initiated intensive chemotherapy studies during the same period as our own study. The NCIC study compared six cycles of FEC 120 days1 to 8, every 4 weeks, to six cycles of classic CMF in premenopausal node-positive patients.[14] The FEC regimen had a comparable intended epirubicin

dose-intensity to that of our FEC 100 regimen every 21 days (30 *v* 33 mg/m^2/wk, ie, a 10% difference), but the actual doses delivered were 23.1 and 28.7 mg/m^2/wk, with an increase of 24% in our study. This could explain why both FEC regimens gave similar results for both 5-year DFS (63% *v* 66.3%) and OS (77% *v* 77.4%), despite the fact that more than 60% of patients had one to three involved axillary nodes in the NCIC trial, whereas 80% of our patients had at least four positive nodes. The CALGB 8,541 study examined three different doses of cyclophosphamide, doxorubicin, and fluorouracil in node-positive breast cancer patients: after long-term follow-up, this trial showed the greatest benefit with the most dose-intense adjuvant therapy, but the standard treatment (cyclophosphamide 300 mg/m^2, doxorubicin 30 mg/m^2, fluorouracil 300 mg/m^2 $\times$ 2, for four cycles) was probably underdosed.[34] The subsequent CALGB trial (CALGB 9,344) studied doxorubicin dose intensification (60, 75, and 90 mg/m^2) plus cyclophosphamide 600 mg/m^2, with or without paclitaxel consolidation. After 18 months of follow-up, there was no benefit of dose intensification,[35] but this follow-up period was short. Indeed, after 3 years of follow-up, we observed an advantage in favor of FEC 100 in terms of DFS ($P = .02$) but no difference as regards OS.[36] The NSABP B-22 and B-25 trials showed no significant benefit of a cyclophosphamide dose intensification from 600 to 2,400 mg/m^2.[37,38] The results of our study and of these dose intensification studies demonstrate a potential value of higher anthracycline doses but fail to show an advantage of increasing the cyclophosphamide dose-intensity. Moreover, in several retrospective studies, the efficacy of anthracycline-containing regimens has been correlated with the overexpression of the c-*erb*B-2 oncogene.[39-41] Moreover, the CALGB found a dose-effect of doxorubicin for relapse-free survival.[39] Also, the FASG initiated a retrospective study to determine the correlation between the c-*erb*B-2 status and the epirubicin dose in terms of DFS and OS.

Regarding, hematologic toxicity, FEC 100 is more toxic than FEC 50. The incidence of neutropenic fever was low (2.7%) with FEC 100, without CSF support or antibiotic prophylaxis, compared with 8.5% with FEC 120 days1 to 8 and antibiotic prophylaxis in Levine's study.[14] We conclude that our days 1 to 21 schedule is better than days 1 to 8 every 4 weeks in terms of hematologic safety and that it allows a better relative dose-intensity. On the other hand, nonhematologic toxicity was similar to that observed in Levine's study.[14]

The risk of cardiac toxicity was low, with only two cases (0.4%) occurring after adjuvant treatment and eight (1.4%) cases after anthracycline or anthracenedione-containing chemotherapy for advanced disease. Three recent studies of cardiac toxicity after doxorubicin and epirubicin in the adjuvant setting have been published. The study by Shapiro et al[42] compared the incidence of cardiac events after five and 10 cycles of AC (cumulative doxorubicin dose, 225 or 450 mg/m^2). After a median follow-up of 6 years, six events (4.3%) had occurred after 5 AC, compared with 16 (11.8%) after 10 AC (RR = 3.6, $P < .0003$), mainly in patients who had received locoregional radiotherapy. In the study by Basser et al[43] of long-term cardiac effects after high-dose chemotherapy with epirubicin-cyclophosphamide (200 mg/m^2 + 4 g/m^2 for three cycles, with CSF support), there were four cases (4%) of cardiac toxicity. Finally, Gianni et al[44] studied cardiac sequelae in operable breast cancer patients after CMF with or without doxorubicin (75 mg/m^2, four cycles): after 12 years, the incidence of systolic dysfunction was significantly higher in patients who received doxorubicin (7.9% *v* 0.7% with CMF, $P < .01$). It is now well established that epirubicin has better cardiac safety than doxorubicin,[17,18,45] but cardiac outcome in long-term survivors remains controversial. For this reason, we have initiated a prospective study of long-term cardiac function involving the patients treated in the present study.

An increased incidence of AML after chemotherapy with alkylating agents and/or topoisomerase II inhibitors has been described in a number of studies. The secondary AML arising in patients treated with alkylators is generally of the M1-M2 French American British subtype, whereas secondary AML arising in patients treated with topoisomerase II inhibitors is generally of the M4-M5 subtypes. In the present study, one case (0.2%) of AML 4 with t(8;16) and del 17q21 occurred a short time after treatment completion, and the case of acute lymphoblastic leukemia is not strongly related to the chemotherapy. In Levine's study, after 5 years of follow-up, four cases of AML had occurred in 351 patients treated with FEC (1.1%).[14] A 10-year follow-up review of the M.D. Anderson experience in six adjuvant or neoadjuvant trials with the FAC regimen gave an estimated leukemia rate of 1.5%, which increased to 2.5% when radiotherapy was added.[46] After a short follow-up period in the study by the Scandinavian Breast Cancer Study Group, there were seven cases of AML/myelodysplastic syndrome in patients receiving the tailored FEC regimen.[47] On the other hand, there were no cases of secondary AML in the OncoFrance trial after 13 years of follow-up among patients treated with the AVCF regimen as adjuvant therapy.[48] The NSABP B-22 and B-25 studies showed a high rate of secondary leukemias correlating with the cumulative dose of cyclophosphamide, with six cases (0.26%) in 2,305 patients at 5 years and 16 cases (0.63%) in 2,548 patients at 4 years, respectively.[37,49] Acute leukemia is rare in patients treated with CMF. Valagussa et al[50] reported a 0.23% cumulative rate of acute leukemia over 15 years in 2,465 patients who received CMF. In our study, FEC was associ-

ated with a low risk of secondary leukemia, and the benefits of this regimen greatly outweighed the risk of treatment-related leukemia.

The dose-response relationship of epirubicin-based chemotherapy for advanced breast cancer has been examined previously in two randomized trials comparing FEC 50 with FEC 100, with a significant improvement in the response rate, response duration, and time to progression.[20,21] Our study is the first to demonstrate a strong benefit in terms of DFS and OS when the epirubicin dose is increased from 50 mg/m^2 to 100 mg/m^2, and confirms the epirubicin dose-effect in the adjuvant setting, as previously observed in advanced disease. We conclude that women with operable breast cancer benefit more from FEC 100 than from FEC 50. At this epirubicin of dose 100 mg/m^2, the safety profile is acceptable, without CSF or antibiotic prophylaxis, when administered every 3 weeks for six cycles.

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APPENDIX

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