

## A Prospective Randomized Trial Comparing Epirubicin Monochemotherapy to Two Fluorouracil, Cyclophosphamide, and Epirubicin Regimens Differing in Epirubicin Dose in Advanced Breast Cancer Patients

By the French Epirubicin Study Group

The French Epirubicin Study Group carried out a randomized trial comparing epirubicin alone 75 mg/m<sup>2</sup> with fluorouracil (5FU) 500 mg/m<sup>2</sup>, cyclophosphamide 500 mg/m<sup>2</sup>, and epirubicin 50 mg/m<sup>2</sup> (FEC 50) and 5FU 500 mg/m<sup>2</sup>, cyclophosphamide 500 mg/m<sup>2</sup>, and epirubicin 75 mg/m<sup>2</sup> (FEC 75) as first treatment for advanced breast cancer patients. Patients were stratified according to whether or not there were bone metastases only. Four hundred twelve patients entered this trial; 378 were assessable for tolerability and 365 for efficacy. The overall response rates were comparable between FEC 50 (44.6%) and FEC 75 (44.7%), but both were better than the epirubicin alone (30.6%) ( $P = .04$  and  $P = .0006$ , respectively). The complete response rate was better in FEC 75 (15.5%) than in FEC 50 (7%) ( $P = .025$ ) or epirubicin (4%) ( $P = .002$ ). Similar results were obtained in the group of patients without bone-only metastases. No difference in the three treatments was observed in the patients with bone metastases only. Mean durations of

response were similar in the three groups, being 412 days, 440 days, and 350 days for FEC 50, FEC 75, and epirubicin, respectively. Patients without previous adjuvant chemotherapy fared better than those with previous treatment (without anthracyclines). Tolerability was fair in the three groups. Overall, the epirubicin alone group showed better tolerance than the two other groups, which did not differ significantly. Time to progression and survival were not different among the three groups, but more early relapses occurred in the epirubicin and FEC 50 groups; survival seemed to be better during the first 8 months in the FEC 75 group, and the survival difference between the epirubicin group and the FEC 75 group was of borderline significance. No difference in survival was observed between epirubicin- and FEC 50-group patients, even though the response rate was significantly worse in the monochemotherapy group.

*J Clin Oncol* 9:305-312. © 1991 by American Society of Clinical Oncology.

**A**DRIAMYCIN (doxorubicin; Adria Laboratories, Columbus, OH) and epirubicin are the most effective drugs in human breast cancer. In phase II trials, Adriamycin induced a 40% response rate in previously untreated patients<sup>1,2</sup> and epirubicin a 37% response rate in 344 treated patients.<sup>4</sup> One of the most frequently used Adriamycin-containing combinations is the fluorouracil (5-FU), Adriamycin, and cyclophosphamide (FAC) regimen; the response rates to this regimen ranged from 43%<sup>5</sup> to 64%.<sup>6</sup> The Italian and French Epirubicin Study Groups recently carried out a phase III trial comparing the FAC and FEC regimens.<sup>7,8</sup> The only difference was the replacement of doxorubicin by the same dose (50 mg/m<sup>2</sup>) of epirubicin. The two trials gave comparable results; in both studies, the response rates were not different for the two regimens, and no differences were observed in duration of response, time to progression, and survival. However, tolerability was significantly better in the FEC groups.

The French Epirubicin Study Group has carried out a clinical trial in previously untreated advanced breast cancer patients comparing the FEC

50 regimen (5-FU 500 mg/m<sup>2</sup>, cyclophosphamide 500 mg/m<sup>2</sup>, and epirubicin 50 mg/m<sup>2</sup>) to epirubicin alone (75 mg/m<sup>2</sup>) and to FEC 75, in which epirubicin is given at a dose of 75 mg/m<sup>2</sup>. The rationale for this trial was to determine whether a 50% higher epirubicin dose was more effective in the FEC regimen; the second point was to see whether epirubicin alone could be as effective and less toxic than FEC (either 50 or 75).

### PATIENTS AND METHODS

#### Patients

Four hundred twelve patients from 13 institutions entered this trial. All patients had histologic evidence of breast cancer with recurrent or metastatic disease. Eligibility criteria included age 70 years or younger, performance status (PS)  $\leq 2$  (World Health Organization [WHO] scale),

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0732-183X/91/0902-0009\$3.00/0



progressive disease with measurable or assessable lesions. Patients could have had prior adjuvant chemotherapy without anthracycline but no prior chemotherapy for advanced disease. Blood counts and blood chemistry had to be within normal limits (absolute granulocyte count [AGC]  $> 2,000/\mu\text{L}$ , platelets  $> 100,000/\mu\text{L}$ , bilirubin  $< 35 \mu\text{mol/L}$ , creatinine  $< 130 \mu\text{mol/L}$ ). Informed consent was obtained from each patient according to the standard procedures followed at each participating institution. Patients were not included if they had a history of preexisting heart disease, determined by clinical signs of cardiac failure and/or coronary artery disease, ECG abnormalities, left ventricular hypertrophy, or left bundle branch block or right bundle branch block with left anterior or posterior hemiblock, or coronary artery disease signs, and left ventricular ejection fraction (LVEF) less than 40% if measured by echography, or less than 50% if measured by angioscintigraphy. One of these parameters was enough for a patient to be ineligible. Patients were not included if they had a history of other malignancy (except for skin cancer or carcinoma in situ of the cervix) or active infection.

### Therapeutic Regimens

Patients were randomly allocated to one of the three treatment regimens shown in Table 1. A stratification was carried out according to whether or not there were bone-only metastases. Treatments were repeated every 21 days, all drugs being delivered intravenously (IV) on day 1 of each cycle. Patients received the treatment until there was evidence of disease progression and/or unacceptable toxicity, or until a cumulative dose of epirubicin of  $825 \text{ mg/m}^2$  was reached. The protocol contained the option of discontinuing therapy after six cycles of treatment for patients with stable disease.

If the AGC at day 21 was between 1,500 and  $2,000/\mu\text{L}$  and/or platelet count between 75 and  $100,000/\mu\text{L}$ , the doses for all three drugs in either regimen were reduced by 25%. If the AGC was between 1,000 and 1,500 cells per microliter or the platelet count between 50 and  $75,000/\mu\text{L}$ , the doses were reduced by 50%. Lower blood counts led to a treatment delay of 1 week or more until the above criteria were satisfied. A maximum delay of 3 weeks was permitted. The epirubicin dose was reduced by 50% if the serum bilirubin was between 35 and  $50 \mu\text{mol/L}$  and was discontinued if the bilirubin was greater than  $50 \mu\text{mol/L}$ .

Response and toxicity were defined according to WHO criteria. To ensure consistency in the recording and report-

ing of results, the trial coordinator visited each trial center and checked every patient file with the clinical investigator.

### Statistical Methods

To test for baseline comparability of treatment groups, the patient characteristics and prognostic factors were compared using the two-tailed  $\chi^2$  tests for categorical variables<sup>9</sup> and the analysis of variance tests for continuous variables (age and disease-free interval).<sup>10</sup>

Comparison of response rates in the three study arms was performed by the  $\chi^2$  adjusted<sup>11</sup> for the variable of stratification. Confidence intervals for response rates were computed using the normal approximation of the binomial distribution.

Toxicity incidence was compared using the Cochran<sup>12</sup> and Armitage<sup>13</sup> tests and the  $\chi^2$  for trend.<sup>13</sup> The calculation of life probability and time to progression was performed by the Kaplan-Meier method.<sup>14</sup> The Mantel-Haenszel (log-rank) test<sup>15,16</sup> and the adjusted log-rank test<sup>17</sup> were used to compare the survival curves.

## RESULTS

Of 412 patients who entered this study, 365 were assessable for efficacy and 378 for toxicity (Table 2).

The reasons for ineligibility were other malignant tumor (two), cardiac failure before treatment (one), PS less than 2 (five), absence of measurable or assessable lesion (four), clinically evident CNS metastases (one), ECG abnormality (one), impossible follow-up (four), physician error in randomization (two), and prior anthracycline therapy (one).

To be assessable for efficacy, the patients had to have received at least two cycles of therapy if the disease progressed, otherwise three cycles of therapy were required. The reasons for not being assessable for efficacy were early death (six), loss to follow-up (seven), rapid alteration of PS (two), protocol deviations (nine), treatment refusal after two cycles (one), and only one course given because of high bilirubin (one). The reasons for not being eligible or assessable were well balanced in the three groups.

Table 1. Therapeutic Regimens

	Dosage (IV route) ( $\text{mg/m}^2$ )
<b>FEC 50 every 3 weeks</b>	
Epirubicin	50
Fluorouracil	500
Cyclophosphamide	500
<b>FEC 75 every 3 weeks</b>	
Epirubicin	75
Fluorouracil	500
Cyclophosphamide	500
Epirubicin every 3 weeks	75

Table 2. Patient Treatment Distribution

	FEC 50	FEC 75	Epirubicin	Total
Entered	135	137	140	412
Eligible	129	130	132	391
Assessable				
Effectiveness	121	123	121	365
Toxicity	126	127	125	378



Table 3. Characteristics of Patient Populations

	FEC 50	FEC 75	Epirubicin	P
Eligible patients	129	130	132	
Median age (range)	53 (30-70)	51 (22-70)	53 (26-70)	NS
Performance status				
0	30	35	32	
1	51	59	55	NS
2	48	36	45	
Prior adjuvant CMF	19	31	30	NS
Prior adjuvant radiotherapy*	66	71	75	NS
Relapse-free interval†	27.9 ± 5.7	35.4 ± 6.5	38.1 ± 8.7	NS
Tumor site (%)				
Soft tissue	67 (52)	55 (42)	53 (40)	NS
Lymph nodes	61 (48)	43 (33)	44 (33)	<.02
Bone	62 (48)	61 (47)	73 (55)	NS
Lung	29 (23)	35 (27)	31 (23)	NS
Liver	38 (30)	37 (29)	39 (30)	NS
No. of organ sites/patient (%)				
≤ 2	92 (71)	104 (80)	103 (78)	NS
≥ 3	37 (28)	26 (20)	29 (22)	NS

Abbreviations: CMF, cyclophosphamide, methotrexate, and fluorouracil; NS, not significant.

\*CO<sup>60</sup> left parasternal field.

†Months ± SE.

#### Patient Characteristics

The pretreatment characteristics of the eligible patients are shown in Table 3. The only difference in the three groups was the higher frequency of lymph node metastases in the FEC 50 patients.

#### Response to Therapy

As previously mentioned, randomization was stratified according to the presence or absence of bone-only metastases. Results are given for the whole group and separately for the non-bone-only metastases and the bone-only metastases groups. Results are shown in Table 4 for all the patients;

Table 4. Response Rates (all patients)

	FEC 50	FEC 75	Epirubicin
CR	8	19	5
PR	46	36	32
NC	50	55	51
PD	17	13	33
Total	121	123	121
CR + PR (%)	44.6 ± 9.0	44.7 ± 9.0	30.6 ± 8.4

NOTE. Overall, the response rates were different between the three groups ( $P = .0006$ ). When considered two by two, epirubicin was not as good as either FEC 50 ( $P = .04$ ) or FEC 75 ( $P = .0006$ ). The CR rate was better in the FEC 75 arm (overall,  $P = .005$ ); FEC 50 v FEC 75,  $P = .025$ ; FEC 75 v epirubicin,  $P = .002$ . PD was more frequent in the epirubicin than in the FEC 75 group ( $P = .0006$ ).

Abbreviations: CR, complete response; PR, partial response; NC, no change; PD, progressive disease.

overall, the response rates obtained with the three regimens were significantly different ( $P = .0006$ ) after adjustment for the variable of stratification; when compared two by two, the difference was significant in epirubicin alone, FEC 75 ( $P = .0006$ ), and FEC 50 ( $P = .04$ ). The complete response rate was significantly higher in the FEC 75 than in the FEC 50 group ( $P = .025$ ) or the epirubicin group ( $P = .002$ ). Progressive disease was more frequent in the epirubicin-alone group than in the FEC 75 group ( $P = .0006$ ). There was no significant difference between the FEC 50 and FEC 75 groups with regard to overall response. When considering the response rates of all eligible patients it was 41.9% in the FEC 50, 42.3% in the FEC 75, and 28% in the epirubicin group.

When considering the response rates in patients without bone-only metastases (Table 5), the FEC 75 group was better than the FEC 50 ( $P = .02$ ) and epirubicin ( $P = .00003$ ) groups. The complete response rate was higher in the FEC 75 group than in the FEC 50 ( $P = .05$ ) and epirubicin ( $P = .005$ ) groups (overall,  $P = .01$ ); progressive disease was more frequent in the epirubicin-alone group (overall,  $P = .003$ ); FEC 50 versus epirubicin ( $P = .06$ ), FEC 75 versus epirubicin ( $P = .0006$ ).

Progression before the second course of treatment among the patients treated with FEC 50 was more than twice as high as that among patients treated with FEC 75 (FEC 50, 16 patients; FEC



Table 5. Response Rates in Patients Without Bone-Only Metastases

	FEC 50	FEC 75	Epirubicin
CR	8	19	5
PR	40	32	27
NC	37	43	38
PD	16	7	29
Total	101	101	99
CR + PR (%)	47.5 ± 10.0	50.5 ± 10.0	32.5 ± 9.5

NOTE. Overall, the response rates were different between the three groups ( $P = .0001$ ). When considered two by two, FEC 75 was better than FEC 50 ( $P = .02$ ) and epirubicin ( $P = .00003$ ). The CR rates were better in the FEC 75 group (overall,  $P = .01$ ); FEC 50 v FEC 75,  $P = .05$ ; FEC 75 v epirubicin,  $P = .005$ . Progressive disease was more frequent in the epirubicin group (overall,  $P = .003$ ); FEC 50 v epirubicin,  $P = .06$ ; FEC 75 v epirubicin,  $P = .0006$ .

75, seven patients). Analysis of this subpopulation showed that 15 of the 16 FEC 50 patients and four of the seven FEC 75 patients had two or more different sites of disease, while 10 of 16 FEC 50 and six of seven FEC 75 patients presented with visceral involvement (FEC 50: eight liver, five lung; FEC 75: four liver, two lung).

The response rates observed in bone-only metastases patients were, respectively, 30% ± 20%, 18% ± 16%, 23% ± 18% for FEC 50 ( $n = 20$ ), FEC 75 ( $n = 22$ ), and epirubicin ( $n = 22$ ). The difference in these three groups was not significant. The number of patients was obviously too small to draw any conclusion.

Patients with previous adjuvant treatment (without anthracyclines) ( $n = 76$ ) had a lower response rate than those without ( $n = 288$ ) ( $P = .025$ ). The comparison of the response rates in the three arms after adjustment for adjuvant chemotherapy showed a statistically significant difference ( $P = .005$ ). However, within each treatment group, the difference in response rates among patients with and without adjuvant treatment was not significant, respectively: FEC 50, 31.8% ± 19.9% ( $n = 22$ ) and 47.5% ± 10% ( $n = 99$ ); FEC 75, 34.5% ± 17.7% ( $n = 29$ ) and 47.9% ± 10.3% ( $n = 94$ ); epirubicin, 20% ± 16% ( $n = 25$ ) and 33.3% ± 9.6% ( $n = 96$ ). The absence of a significant difference was probably due to the small number of patients in each group.

The response rates at each tumor site were not different in the three groups (Table 6).

Table 6. Response Rate According to Tumor Site

CR + PR (%)	FEC 50	FEC 75	Epirubicin
Soft tissue	51.6 ± 12.7 $n = 62$	61.5 ± 13.5 $n = 52$	32 ± 13.2 $n = 50$
Node	56.1 ± 13.1 $n = 57$	64.3 ± 14.8 $n = 42$	61.5 ± 15.6 $n = 39$
Lung	33.3 ± 16.1 $n = 27$	50 ± 17.1 $n = 34$	28.6 ± 17.1 $n = 28$
Liver	37.5 ± 17.1 $n = 32$	35.1 ± 15.7 $n = 37$	36.4 ± 16.8 $n = 33$
Bone	26 ± 11.9 $n = 54$	20.4 ± 11.0 $n = 54$	17.8 ± 9.7 $n = 62$

NOTE. The response rates were not different in the three groups whatever the tumor site.

#### Duration of Response

Median and range of duration of response was not different in the three groups, respectively: FEC 50, 378 days (84 to 1,008); FEC 75, 395 days (22 to 1,139); and epirubicin, 315 days (84 to 1,107). Time to response was not earlier in the FEC 75 group.

#### Time to Progression and Survival

No difference was seen among the three arms with regard to time to progression (Fig 1). However, early relapses before the third cycle were more frequent in the epirubicin (27.3%) group than in the FEC 50 (14.1%) or the FEC 75 (10.6%) groups.

The survival of patients receiving FEC 75 (Fig 2) seemed to be slightly better than the survival of patients in the epirubicin group ( $P = .06$ ). During the first 8 months, the survival was better in patients in the FEC 75 group (FEC 75, 92%; FEC 50 and epirubicin, 79%). No difference in survival was noticed according to a previous adjuvant chemotherapy ( $P = .182$ ).

#### Toxicity

The treatment had to be stopped because of cardiac toxicity in 15 patients (three in the FEC 50, five in the FEC 75, seven in the epirubicin group) because of (1) a decrease in the LVEF, measured either by echocardiography or angioscintigraphy, without any clinical symptoms in 11 patients; (2) cardiac failure after cumulative doses of 575, 664, and 668 mg/m<sup>2</sup> in three patients, and (3) ventricular extrasystoles in one patient. In five patients, cardiac abnormalities appeared after cessation of



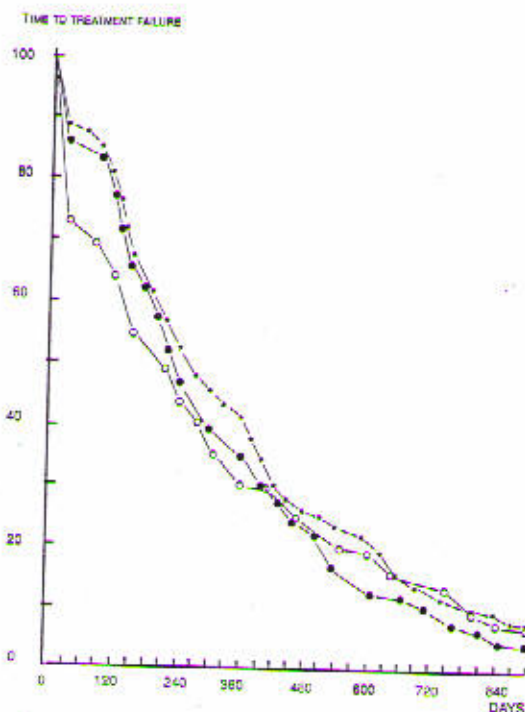


Fig 1. Time to treatment failure ( $n = 365$ ). No difference was seen among the three curves ( $P = .47$ ). The number of early relapses was more frequent in the epirubicin group than in the two other groups. (●—●) FEC 50, (▲—▲) FEC 25, (○—○) epirubicin 75.

treatment; in two patients there was a decrease in LVEF with no clinical symptoms (1 month and 6 months after the end of chemotherapy); in the other three patients, clinical signs of cardiac failure appeared, respectively, 1 month, 1½ months, and 1 year after the end of treatment after 825, 825, and 802 mg/m<sup>2</sup> of epirubicin, respectively. Overall, six cases of cardiac failures (1.6%) were seen during or after chemotherapy; they were all controlled by symptomatic treatment.

Granulopenia incidence was lower in the epirubicin group than in the FEC 50 ( $P = .007$ ) or FEC 75 ( $P = .0001$ ) groups (Table 7), and no difference was noted between the FEC 50 and FEC 75 groups. Thrombopenia was rare, and no differences were observed in the three groups.

Nausea and vomiting (Table 8) were more frequent in the FEC 75 group than in the epirubicin group ( $P = .0006$ ); no difference was noted between FEC 50 and FEC 75 or between FEC 50 and epirubicin.

Patients wearing a cooling cap ( $n = 107$ ) and those who did not ( $n = 235$ ) were considered

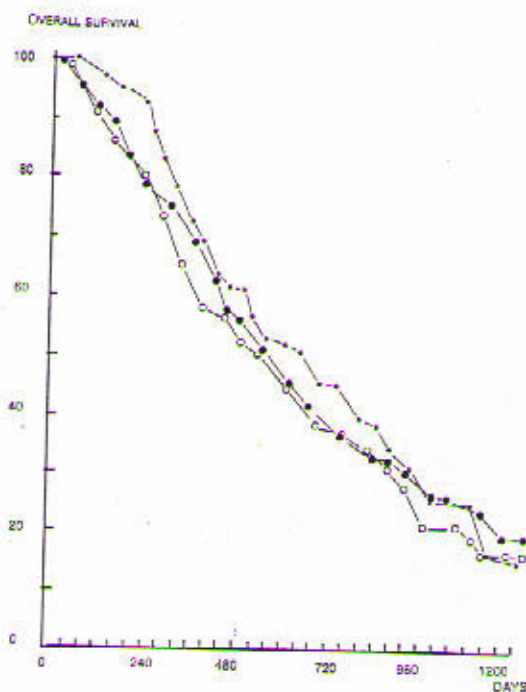


Fig 2. Overall survival ( $n = 391$ ). No difference was seen among the three curves ( $P = .46$ ). During the first 8 months, survival plateaued in the FEC 75 group. (●—●) FEC 50, (▲—▲) FEC 75, (○—○) epirubicin.

separately. Among the first, grade 3 alopecia was noted in 11.8% of patients in FEC 50 and FEC 75 and 18% in epirubicin (NS). In patients who did not wear the cooling cap, grade 3 alopecia was observed, respectively, for FEC 50, FEC 75, and epirubicin patients in 55.3%, 76%, and 50% of the cases (NS).

When all the patients were considered together, grade 3 alopecia was more frequent in the FEC 75 arm than in the epirubicin arm ( $P = .03$ ).

## DISCUSSION

This study shows that the three treatment arms differ significantly with regard to the response

Table 7. Percentage of Granulopenia in 2,706 Courses

	WHO Grade			
	0	1	2	3 and 4
FEC 50 ( $n = 979$ )	73	14.4	8.7	3.9
FEC 75 ( $n = 935$ )	71.8	13.7	9.7	4.8
Epirubicin ( $n = 787$ )	80.4	11.3	6.6	1.7

NOTE. Overall granulopenia was different in the three groups ( $P = .00005$ ). The epirubicin group demonstrated less myelotoxicity than did the FEC 50 ( $P < .007$ ) and FEC 75 ( $P = .0001$ ) groups.



Table 8. Percentage of Nausea and Vomiting in 2,786 Courses

	WHO Grade			
	0	1	2	3 and 4
FEC 50 (n = 1,018)	25.7	32.2	27.1	15
FEC 75 (n = 957)	23.8	26.3	33.8	16.1
Epirubicin (n = 811)	27.5	32.9	27.3	12.3

NOTE: Overall, nausea and vomiting were comparable in the three groups. When considered two by two, the only difference was between FEC 75, which was more poorly tolerated, and epirubicin ( $P = .0006$ ).

rates. The epirubicin-alone group had a significantly worse response than either the FEC 50 or FEC 75 groups. Complete responses were more frequently observed in the FEC 75 than in the other two groups. It is interesting to note that the higher epirubicin dose only achieved a higher complete response rate with FEC 75, whereas the overall response rate was the same in both the FEC 75 and FEC 50 groups, suggesting that an increase in the epirubicin dose of 50% could not overcome the resistance to this drug.

It must be stressed that the response rate observed in the FEC 50 group was somewhat lower than the one obtained in the Italian and French FAC-FEC trials,<sup>7,8</sup> 53.6% and 50.4%, respectively, and not very different from the results obtained with epirubicin alone in phase II trials.<sup>4</sup> The same trend was obtained when excluding bone-only metastases patients. The rationale for doing such a stratification was the poor response rate generally observed in bone metastases and the difficulty in assessing the effectiveness of a treatment at this site.

The FEC 75 regimen demonstrated the best response rate (especially the complete response rate) of the three arms; however, although significant, the difference was not great. The relative dose intensity of FEC 75 to FEC 50 according to Hryniuk and Bush<sup>18</sup> was 1.17, which was probably not great enough to significantly increase the response rate. The high epirubicin dose used was probably not sufficient to obtain such high response rates as observed by Antman and Gale<sup>19</sup> in their literature review of patients receiving high-dose chemotherapy and bone marrow autotransplants. In this study, the doses actually administered (mean value/course) were very close in the three arms, for FEC 50, FEC 75, and epirubicin, 90.4%, 88.3%, and 92.9%, respectively. The ratio

between delivered and theoretic doses was close in the three groups.

Hortobagyi et al<sup>20</sup> recently published the results of a randomized study comparing standard FAC and high-dose FAC; at the third course of the high-dose FAC, Adriamycin dosage was two times, FU 2.5 times, and cyclophosphamide three times the standard dose. However, no difference was observed in the response rates (which were high with the standard regimen: 78%), the time to progression, and the survival; side effects were significantly more frequent in high-dose FAC. Jones et al<sup>21</sup> simultaneously published results obtained in 26 patients who received escalating doses of Adriamycin (up to 135 mg/m<sup>2</sup>; median, 99 mg/m<sup>2</sup>). The overall response rate was 85% with a complete response rate of 38%, which is more than the commonly reported rates obtained with conventional Adriamycin dosage but with substantial toxicity. Carmo-Pereira<sup>22</sup> randomized 48 Adriamycin-treated patients in two arms: 70 mg/m<sup>2</sup> every 3 weeks (eight courses) versus 35 mg/m<sup>2</sup> every 3 weeks (16 courses); the response rates were, respectively, 58% and 25% ( $P < .02$ ) (four complete responses in the first arm and one in the second one); the median duration of response was, respectively, 14 and 6 months ( $P < .005$ ), and the median duration of survival, 20 and 8 months ( $P < .01$ ).

The duration of response and time to treatment failure were not different in the three groups, as was also noted by Hortobagyi et al.<sup>20</sup> The survival curves were not statistically different; the survival curve of the patients on the FEC 75 regimen presented a shoulder, as if survival had been better for the first 8 months; if confirmed, this observation could justify a more intensive regimen during the first months of treatment. This is the rationale for the ongoing trial of the French Epirubicin Study Group comparing FEC 75 with four courses of FEC 100 (same doses of 5-FU and cyclophosphamide and 100 mg/m<sup>2</sup> epirubicin) and FEC 50.

The results obtained in the epirubicin group were not as good as in the FEC groups. The response rate observed in the monochemotherapy group was in the range of the published results,<sup>4</sup> whereas the response rate observed with the FEC regimens was at the lower range of previous reports of FAC<sup>18</sup> or FEC regimen.<sup>7,8</sup> However, the duration of response and the time to progression



were not different in the epirubicin group and the FEC groups. Survival was slightly better, albeit not significantly, in the FEC 75 than in the epirubicin group. Ahmann et al<sup>23</sup> recently analyzed the survival results of 131 patients in three clinical trials comparing monochemotherapy (lomustine, Adriamycin, or ifosfamide) to polychemotherapy (cyclophosphamide, 5-FU, and prednisone [CFP]  $\pm$  vincristine) in advanced breast cancer patients; overall, no significant survival benefit was observed with polychemotherapy. However, when comparing Adriamycin to CFP, the difference in favor of CFP was significant when using the Smirnov test ( $P = .02$ ) but not when using the log-rank test ( $P = .10$ ). However, the number of patients was very small preventing the demonstration of a slight difference; furthermore, the polychemotherapy regimen did not include Adriamycin.

Chlebowski et al<sup>24</sup> analyzed the results of two separate trials comparing concomitant combination treatment and the sequential use of the same drugs given as single agents (cyclophosphamide, methotrexate, 5-FU, and prednisone). Overall, no difference of survival was observed. A significant benefit ( $P < .05$ ) for survival was observed with polychemotherapy in the 81 patients with liver metastasis. Such a difference in our study seems unlikely since the response rate of patients with liver involvement was comparable in the three groups. A better survival had never been observed in the published trials comparing monochemotherapy versus polychemotherapy as reviewed by Chlebowski et al. The therapeutic benefit of the chemotherapy (in terms of objective and subjective response and of survival) has to be weighed against the side effects, which are more numerous often with polychemotherapy. However, since patients given epirubicin alone relapsed earlier, and since the difference in survival between epirubicin and FEC 75 was of borderline significance, it seems wise to use polychemotherapy.

Treatment had to be stopped due to cardiac alterations more often in the epirubicin-only and FEC 75 arms than in the FEC 50 arm. This is probably due to higher cumulative doses in these groups. However, no fatal complications were noted. Three reversible cardiac failures were observed. In two cases, the patients had been treated for hypertension. In the third case, the ventricular ejection rate was at the lower limit of the normal range before treatment. In three other cases, cardiac insufficiency was observed 1 month to 1 year after the end of treatment.

Hematologic side effects (neutropenia) as well as alopecia were comparable in the FEC 50 and FEC 75 arms. Epirubicin alone was less toxic than FEC 75 (FEC 75 and FEC 50 for neutropenia). Overall, the three arms were well tolerated.

The important question at the end of this study could be, Is a higher complete response rate worth the routine use of a moderately higher dose of epirubicin? The tolerability of the FEC 75 regimen was fair. The lower relapse rate during the first months of treatment with FEC 75 was an important observation. However, overall survival did not differ between the two FEC groups. It is not possible at present to know if a complete response leads to a better survival, even if some correlation might exist between response rates and median survival.<sup>25</sup>

Considering these results, it appears wise to keep the FEC 50 regimen for routine use. Nevertheless, taking into account the significantly better complete response rate, the shoulder of the survival curve during the first 8 months, and the early progression rate of the disease, the FEC 75 regimen could be useful for patients suffering from large tumors and visceral metastatic sites.

#### ACKNOWLEDGMENT

The authors are indebted to Richard Gams for his advice and to Y. Vendel for her excellent secretarial assistance.

#### APPENDIX

Participants in the French Epirubicin Study Group trial were as follows: Drs Ph. Bastit, B. Chevallier: Centre Henri Becquerel, Rouen; J. Bonnetierre: Centre Oscar Lambret, Lille; P. Fargeot, J. Guerrin: Centre G.F. Leclerc, Dijon; J.P. Armand, M. Hayat: Institut Gustave Roussy, Villejuif; A. Monnier: Centre Hospitalier General, Montbéliard; H. Roché: Centre Claudius Regaud, Toulouse; J. Chauvergne, M. Durand, L. Mauriac: Fondation Bergonié, Bordeaux; M. Namer: Centre Antoine Lacassagne, Nice; J.F. Bosset, P. Hurloup: Farmitalia Carlo-Erba Medical Department, Paris; Ph. Montcuquet, S. Schraub: Centre Hospitalier Regional, Besançon; N. Guiochet, R. Keilling: Hospices Civils, Strasbourg; P. Fumoleau, O. Godin: Centre René Gauducheau, Nantes; R. Metz, B. Weber: Centre Alexis Vautrin, Nancy; Ph. Chollet, R.



## APPENDIX Continued

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