A Prospective, Randomized Phase III Trial Comparing Combination Chemotherapy with Cyclophosphamide, Doxorubicin, and 5-Fluorouracil with Vinorelbine plus Doxorubicin in the Treatment of Advanced Breast Carcinoma

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This study was conducted according to GCP standards.

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BACKGROUND. A prospective, multicenter, randomized, Phase III trial comparing the efficacy of combination chemotherapy with 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) with a combination of vinorelbine and doxorubicin (NA) in the treatment of patients with advanced breast carcinoma was undertaken.

METHODS. One hundred and seventy-seven patients who previously were untreated for recurrent or metastatic breast carcinoma were entered into the study; 7 patients could not be assessed. The final analysis relates to 85 patients who were treated with FAC and 85 patients who were treated with NA, of whom 21 (25%) and 44 (52%), respectively, had received prior adjuvant chemotherapy.

RESULTS. The overall response rates were similar for the two treatments and were unaffected by prior exposure to adjuvant therapy; overall response rate (ORR) for FAC was 74% (95% confidence interval [95% CI], 65–83%), and the ORR for NA was 75% (95% CI, 66–84%). The activity of NA in patients with liver involvement was greater than that of FAC in terms of survival. Overall survivals were similar, with a median of 17.3 months for patients receiving FAC and 17.8 months for patients receiving NA. Severe toxicity was uncommon with World Health Organization Grade 3–4 neutropenia affecting only 7% of patients in each arm of the study. NA was associated with a higher incidence of mild to moderate constipation, neurotoxicity, and phlebitis, whereas FAC produced a slight excess of mild cardiotoxicity.

CONCLUSIONS. The efficacy of these two regimens is very similar, although NA may be more active in a subset of patients with visceral metastatic disease, particularly liver involvement. It is clear that, in a direct comparison with an established three-drug regimen, the newer two-drug combination of NA demonstrated equivalent activity with no significant excess of Grade 3–4 toxicity. ***Cancer* 1999;85: 1091–7.** © *1999 American Cancer Society.*

KEYWORDS: advanced breast carcinoma, combination chemotherapy, randomized controlled trials.

Approaches to the treatment of metastatic breast carcinoma involving doxorubicin-based regimens generally have a somewhat higher overall response rate than methotrexate-based regimens.[1] In an analysis of 1581 patients treated at the M. D. Anderson Cancer

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Center with anthracycline regimens (mainly using 5-fluorouracil, doxorubicin, and cyclophosphamide [FAC] for induction therapy), 16.6% of patients achieved complete responses (CRs), and 48.5% of patients achieved partial responses (PRs; overall response rate, 65.1%).[2]

New compounds are now available for the management of metastatic breast cancer, among these vinorelbine (Navelbine; Pierre Fabre Médicament, Boulogne, France) is the newest and most active inhibitor of mitotic tubulin polymerization. It differs from the classic periwinkle derivatives by modification of the catharanthine moiety of the molecule.[3] This modification has led to an increase in clinical activity and an alteration in the typical pattern of toxicity with vinca-alkaloids with significantly reduced peripheral neuropathy when compared with vincristine.[4] The assessment of vinorelbine in the management of breast carcinoma has been extensive and was initiated after promising results were obtained in Phase II trials in which the response rates ranged from 40% to 60% in previously untreated patients.[5–11] Encouraging results for vinorelbine in combination therapy have been obtained with vinorelbine 25 mg/m^2 on Days 1 and 8 and doxorubicin 50 mg/m^2 on Day 1. Of 89 patients, 74% responded to the therapy with 21% CRs. High response rates were observed in visceral metastatic sites: liver, 50% (13% CRs); lung, 68% (21% CRs). The median duration of response was 12 months (range, 2.4–40.5 months), and the median survival was 27.5 months (range, 4–46 months).[12]. Based on the above data and the encouraging response rate and duration achieved with the combination of vinorelbine and doxorubicin (NA), a Phase III trial was initiated to compare this combination with the well established FAC regimen.

METHODS

Patients

One hundred and seventy-seven patients from 15 institutions entered in this trial from April, 1991, to July, 1994. All patients had histological evidence of breast carcinoma with recurrent or metastatic disease. Eligibility criteria included age $\leq$ 70 years, performance status (PS) $\leq$ 2 (World Health Organization [WHO] scale), and progressive disease with measurable or assessable lesions. Patients who had adjuvant treatment with or without anthracyclines were eligible if they were disease free for at least 6 months after completing treatment. Patients who were treated with hormones as adjuvant therapy or for metastatic disease were included only with clear evidence of progression. Blood counts and chemistry were within normal limits: absolute leukocytes count (white blood cells [WBC]) $\geq$ 3000/mm^3, granulocyte count (AGC) $\geq$ 1500/mm^3, platelets $\geq$ 100,000/mm^3, bilirubin $<$ 1.5 mg/dL, prothrombin time (PT) $>$ 70%, and creatinine $<$ 2 mg/dL. Patients were excluded if they had a history of preexisting heart disease, including clinical or electrocardiography (ECG) signs of cardiac failure or coronary artery disease, left ventricular hypertrophy, left bundle branch block, right bundle branch block with left anterior or posterior hemiblock, and left ventricular ejection fraction (LVEF) $<$ 70% measured by echocardiography. Patients with a history of other malignancy (except for skin carcinoma or carcinoma in situ of the cervix), active infection, or signs of leptomeningeal and brain involvement were excluded.

TABLE 1
Therapeutic Regimens

Regimen	Dosage (mg/m^2 IV)	21-Day schedule
FAC		
5-Fluorouracil	500	Day 1
Doxorubicin	50	Day 1
Cyclophosphamide	500	Day 1
NA		
Vinorelbine	25	Days 1 and 8
Doxorubicin	50	Day 1

IV: intravenous; FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide; NA: vinorelbine and doxorubicin.

The protocol was designed following the recommendations of the Helsinki Declaration and was approved by the Ethics Committee of each participating center. Written or witnessed oral informed consent was obtained from each patient according to the standard procedures at each participating institution.

Therapeutic Regimens

Patients were allocated randomly to one of the two treatment regimens shown in Table 1. Treatments were repeated every 21 days. All drugs were delivered intravenously (IV) on Day 1 except vinorelbine, which was delivered on Days 1 and 8. The standard FAC regimen was used [13–15]. Patients were treated until there was evidence of disease progression or unacceptable toxicity or until a cumulative doxorubicin dose of 550 mg/m^2 was reached. Beyond this dose, the treatment was administered only with close cardiac monitoring. Discontinuing the treatment two cycles after obtaining a CR was optional.

No dose reductions were permitted. Low blood counts at Day 21 led to treatment delays of 1 or 2 weeks until blood recovery (WBC $\geq$ 3000/mm^3, AGC $\geq$ 1500/mm^3, and platelets $\geq$ 100,000/mm^3). A maxi-

mum delay of 3 weeks was permitted, beyond which the treatment was discontinued. For other toxic manifestations, the same rule was applied. Monitoring of the full blood count before Day 21 was not undertaken routinely, and nadir counts, therefore, were not documented.

Assessments of response were performed according to WHO criteria [16] after every two cycles of therapy with repeat of those clinical and routine imaging procedures that had been used to define the extent of disease at presentation. A CR was defined as the disappearance of all known lesions on two separate measurements at least 4 weeks apart, a PR was defined as a reduction of each lesion by at least 50%, stable disease was defined as a decrease of less than 50% or an increase of less than 25% with no new lesions, and progressive disease was defined as an increase of greater than 25% or the appearance of new lesions. Duration of CR and PR were calculated from the day on which treatment was initiated to the day on which progression was first noted.[17]

Toxicity also was assessed by using the WHO criteria[16] every 21 days, with clinical evaluation, biochemical analysis, and cardiac monitoring by LVEF. ECG was repeated at the end of treatment and was reported in the case report form. To ensure consistency in the recording and reporting, the trial monitor visited each center to check every patient file with the investigator.

Statistical Methods

All patients were registered when they entered the study and were randomized into two groups in cohorts of four patients each (e.g., A-B-A-B). All data from participating centers were registered in the Data File of the "Grupo Oncológico Argentino," and an intention to treat analysis was performed.

All qualitative variables were compared between both arms by tables of contingency tests (chi-square test, Yates, Fisher's exact test). All quantitative variables were compared by using the non parametric Mann–Whitney test.

Comparison of response rates in the two arms was performed by using the chi-square test adjusted for the variable of significance. Confidence intervals for response rates were computed by using the normal approximation of the binomial distribution.

The time event curves (duration of response, time to progression, and survival) were drawn up by using the Kaplan–Meier method. Both groups were compared by using the two-tailed log-rank test. All statistical analyses were done using SPSS 6.3. 1 software (SPSS Inc.).

The sample size was calculated from the proposal that a 20% difference in response rate above or below a proposed response rate for FAC of 50% was required. The total number of patients required (α 0.05 and β 0.20) was 103 patients per arm. An interim analysis after 3 years, which was stipulated by the protocol, with more than 85% of patients included showed no differences between the treatments, and this finding led to termination of the study on the grounds that further accrual would not demonstrate an advantage for either treatment.

RESULTS

Of 177 patients who entered this study, 170 patients were evaluable for response. Four patients were considered lost to follow-up immediately after inclusion, 1 patient had received previous treatment for metastatic disease, 1 patient received vinorelbine and epirubicin instead of NA, and 1 patient received intensive chemotherapy for bone marrow transplantation. Therefore, 85 patients were evaluable in each arm.

Patient Characteristics

The pretreatment characteristics of the eligible patients are shown in Table 2. The only difference in the two groups was the higher frequency of patients who were treated with adjuvant chemotherapy in the NA group ($P = 0.00047$); this feature was not stratified at the time of randomization and represents an unexpected imbalance between the two arms of the study. Patient distribution according to the tumor target and previous treatment is shown in Table 3, and all other patient characteristics were well balanced in both groups.

Treatment

All patients received at least one cycle of therapy, and the median number of cycles administered was five (range, 1–10 cycles) for the FAC group and four (range, 1–10 cycles) for the NA group (P not significant). Dose intensity of the study regimens reflected the need for delays in treatments. For the FAC schema, the median dose of doxorubicin was 15 mg/m^2/week (range, 7.8–18.4 mg/m^2/week), and the mean dose intensity was 90.3% of the intended dose of 50 mg/m^2. For the NA arm, the mean dose of vinorelbine per injection was 13.2 mg/m^2/week (range, 6.2–17.5 mg/m^2/week), leading to a dose intensity of 79% of the scheduled dose. For doxorubicin, the median administered dose was 13.8 mg/m^2/week (range, 7.3–20.2 mg/m^2/week), leading to a dose intensity of 82.7%.

Of 429 cycles administered to the FAC group and 389 cycles administered to the NA group, treatment was delayed in 75% (FAC) and 81% (NA) of the cycles. Delays usually were due to Grade 1–2 neutropenia and

TABLE 2
Patient Characteristics

Characteristics	FAC (%)	NA (%)	*P* value
Median age in yrs (range)	54 (30–71)	53 (28–71)	NS
Performance status			NS
0	43 (51)	31 (36)	
1	31 (36)	41 (48)	NS
2	11 (13)	13 (16)	
Premenopausal	20 (24)	26 (31)	NS
Postmenopausal	65 (66)	59 (69)	NS
Hormonal receptors			
Positive	20 (23)	19 (22)	NS
Negative	9 (11)	18 (21)	NS
Unknown	56 (66)	48 (57)	NS
Prior adjuvant therapy	21 (25)	44 (52)	0.00047
With anthracyclines	2	11	0.04
Without anthracyclines	13	13	NS
Details not known	6	20	
Hormonal therapy	46 (54)	36 (42)	NS
Prior radiotherapy	46 (54)	55 (65)	NS
Tumor involvement			
Skin, bone, and lymph nodes	43	37	NS
Liver alone	16	21	NS
Lung alone	22	22	NS
Liver and lung	4	5	NS
Number of sites			
1	16	13	NS
2	35	33	NS
≥3	34	39	NS

FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide; NA: vinorelbine and doxorubicin; NS: not significant.

were relatively brief. In some cycles of NA, the Day 8 of vinorelbine was omitted because of phlebitis in relation to the Day 1 dose.

A subset analysis of anthracycline treatment intensity in relation to prior adjuvant treatment therapy reveals that this had an effect in both arms of the study. The administered dose of doxorubicin in FAC was reduced from 15.7 mg/m^2/week to 14.8 mg/m^2/week for those patients who had previously received adjuvant treatment and from 14.0 mg/m^2/week to 13.6 mg/m^2/week in those patients who received NA.

Toxicity

Severe toxicity was uncommon with either regimen, although, at Day 21, 7% of patients who received FAC and 7% of patients who received NA (Table 3) experienced Grade 3–4 neutropenia. Nadir counts, as stated above, were not documented.

Mild to moderate constipation and peripheral neurotoxicity were seen significantly more frequently in patients who received NA, whereas mild cardiotoxicity was slightly more common in those patients who received FAC. Phlebitis at Grade 1 or 2 was seen at a significantly greater rate in those who received NA (51% vs. 16%; $P = 0.0001$). Both regimens were well tolerated from the point of view of renal and hepatic toxicity. The incidence of Grade ≥2 infection was not significantly different between the two treatments (NA 8% vs. FAC 8%). The degree of alopecia was similar in both arms of the study.

Response to Therapy

Overall response rates for all patients are shown in Table 4, which compares the treatments. FAC and NA overall response rates were not statistically different (FAC: 74% [95% CI, 65–83%]; NA: 75% [95% CI, 66–84%)]. Response rates also were unaffected by prior exposure to adjuvant therapy, even when the distribution of disease was taken into consideration, although the activity of NA was better than that of FAC against visceral metastases (this did not reach statistical significance due to the small size of the groups).

Survival, Duration of Responses, and Time to Progression

The time dependent features of this study are reported in the context of a complete patient review that was undertaken by an external review panel in November, 1997, to clearly define durations of response and the impact of both treatments on survival. The median overall survival (adjusted to adjuvant treatment; Cox's proportional hazard model) was 17.3 months (range, 2–40 months) for patients who were treated with FAC and 17.8 months (range, 1–50 months) for patients who were treated with NA, results that were not statistically different ($P = 0.16$) and are shown in Figure 1. There also was no significant difference in the time to progression between the FAC arm at 9 months (range, 0.7–59 months) and the NA arm at 7.5 months (range, 0.5–47 months), as shown in Figure 2 ($P = 0.21$).The durations of response also were similar at 11 months (range, 0.5–15 months) for the FAC arm and at 10.5 months (range, 0.5–12 months) for the NA arm. The improved response results obtained with NA against liver metastases also are reflected in the survival of this group of patients: 13.2 months compared with 8.5 months in the FAC arm ($P = 0.04$; Fig. 3).

DISCUSSION

The result of this prospective randomized Phase III study comparing a standard three-drug regimen (FAC) with the two-drug NA combination appears to have generated a "nonpositive" outcome, in that no advantage has been established for the novel combination over the established approach to treatment; however, in the context of the palliative treatment of advanced

TABLE 3
Toxicity

	FAC						NA						
		WHO Grade (%)						WHO Grade (%)					
Toxicity	No.	0	1	2	3	4	No.	0	1	2	3	4	*P* value
Hematologic toxicity													
Neutrophils	84	35 (42)	29 (34)	14 (17)	2 (2)	4 (5)	85	39 (46)	32 (38)	7 (8)	5 (6)	1 (1)	NS
Platelets	84	57 (68)	23 (27)	2 (2)	2 (2)	—	84	61 (73)	21 (25)	2 (2)	—	—	NS
Nonhematologic toxicity													
Alopecia	63	3 (5)	6 (10)	31 (49)	23 (36)	—	74	5 (7)	11 (15)	36 (49)	22 (30)	—	NS
Cardiac	62	55 (89)	6 (10)	1 (1)	—	—	74	73 (98)	1 (2)	—	—	—	0.029
Constipation	63	61 (97)	2 (3)	—	—	—	74	54	17 (23)	2 (3)	1 (1)	—	0.0002
Peripheral neuropathy	64	63 (98)	—	1 (2)	—	—	63	61 (82)	7 (10)	3 (4)	1 (1)	1 (1)	0.001
Diarrhea	63	56 (88)	5 (8)	2 (4)	—	—	71	2 (4)	1 (1)	—	—	—	NS
Phlebitis	63	53 (84)	10 (16)	—	—	—	74	34 (46)	29 (39)	9 (12)	2 (3)	—	0.0001
Hepatic	63	60 (95)	2 (3)	1 (2)	—	—	74	74 (100)	—	—	—	—	NS
Hemorrhage	63	62 (98)	—	—	—	1 (2)	74	73 (99)	1 (1)	—	—	—	NS
Infection	62	53 (86)	4 (6)	4 (6)	1 (2)	—	74	56 (76)	12 (16)	4 (6)	2 (2)	—	NS
Mucositis	63	46 (73)	11 (17)	4 (6)	2 (4)		73	50 (68)	16 (23)	5 (7)	2 (2)	—	NS
Nausea/Vomiting	63	8 (13)	30 (48)	24 (38)	1 (2)	—	74	15 (20)	41 (55)	16 (22)	2 (3)	—	NS
Skin	63	63 (100)	—	—	—	—	73	67 (92)	5 (7)	—	—	2 (1)	0.004

FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide; NA: vinorelbine and doxorubicin; WHO: World Health Organization; NS: not significant.

TABLE 4
Overall Response

Treatment arm	CR (OR)	PR	Total
FAC			
According to treatment			
Previous adjuvant treatment	1 (71)	14	21
No previous adjuvant treatment	12 (75)	36	64
Localization			
Nonvisceral (%)[a]	10 (86)	27	43
Visceral (%)[b]	3 (62)	23	42
NA			
According to treatment			
Previous adjuvant treatment	2 (75)	31	44
No previous adjuvant treatment	4 (75)	26	40
Localization			
Nonvisceral (%)[a]	4 (78)	25	37
Visceral (%)[b]	2 (71)	32	48

CR: complete response; OR: overall response; PR: partial response; FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide; NA: vinorelbine and doxorubicin.

[a] Skin, bones, and lymph nodes.

[b] Liver and lungs.

breast carcinoma, important issues are raised by the conclusions.

First, can the number of agents used be reduced without loss of efficacy? If so, then can patients' tolerance of the treatment be improved? This study has established that no reduction in the effectiveness of treatment resulted from the use of a two-drug regimen. This implies that the contribution made by vinorelbine in the NA arm is at least as great as that made by the cyclophosphamide and fluorouracil in the FAC arm, especially considering that the dose intensity of doxorubicin was less in NA than in FAC (82.7% vs. 90.3%). The reasons for the reduction in the administered dose of doxorubicin must be related to the comparative toxicity of the two regimens as planned and may reflect the process of gaining confidence with the use of NA, but a global view of the WHO grading criteria indicates that they are virtually identical with regard to hematologic toxicity and have only minor differences in nonhematologic parameters. Therefore, although there are no clear advantages to the tolerance of NA compared with FAC, the only disadvantage relates to an increased incidence of mild neurotoxicity.

Second, it is appropriate to examine the impact of the conventional prognostic factors that have been used to predict response to treatment of metastatic breast carcinoma in this patient population. The presence of visceral and especially hepatic metastases has been shown in several series to have an adverse effect on outcome, and this certainly is borne out by the results from the FAC arm, in which response rates of

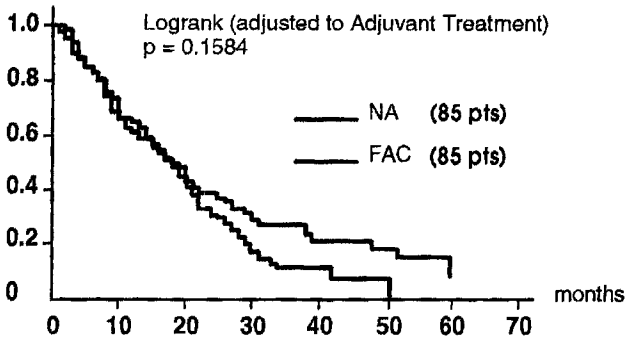

FIGURE 1. Overall survival in patients who received combination chemotherapy consisting of vinorelbine and doxorubicin (NA; n = 85) and in patients who received combination chemotherapy consisting of 5-fluorouacil, doxorubicin, and cyclophosphamide (FAC; n = 85).

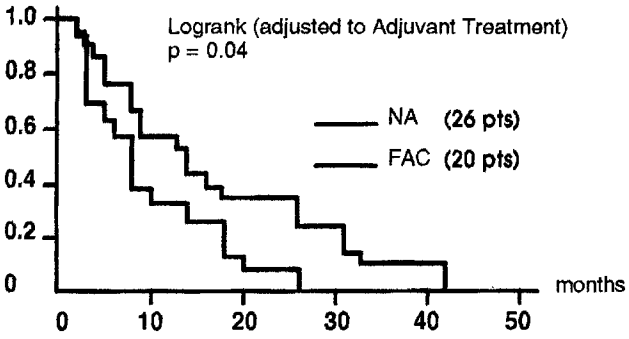

FIGURE 2. Survival in patients with liver involvement who received NA (n = 26) and in those who received FAC (n = 20).

86% (36 of 43 patients; 95% CI, 69–93%) were seen in patients with nonvisceral sites of disease compared with 62% (26 of 42 patients; 95% CI, 46–76%) in the group with liver and/or lung disease ($P = 0.0024$). However, a comparable analysis of patients treated with NA reveals that this distinction is much smaller, with a response rate of 78% (29 of 37 patients; 95% CI, 61–89%) in patients with nonvisceral sites of disease and 71% (34 of 48 patients; 19% CI, 58–84%) in those with involvement of visceral sites ($P = 0.636$). Similar results have been reported in previous trials of vinorelbine/doxorubicin[12,18–20], but, in this study, it is associated with improvements in the survival of these patients compared with those treated with FAC, and, although this observation is based on a small number of patients, it is of sufficient interest to require confirmation in a larger study.

Although prior exposure to adjuvant therapy is a less well established adverse prognosticant,[21,22] some large collaborative group studies suggest that it reduces the chances of achieving a response[23] and restricts the range and intensity of treatment for metastatic disease. We did not find that prior adjuvant therapy reduced responses to subsequent treatment, although the numbers are too small to confidently exclude an adverse effect of prior exposure to anthracyclines. In conclusion, NA was found to be as active as FAC in the primary treatment of metastatic breast carcinoma and may be more effective for visceral metastases.

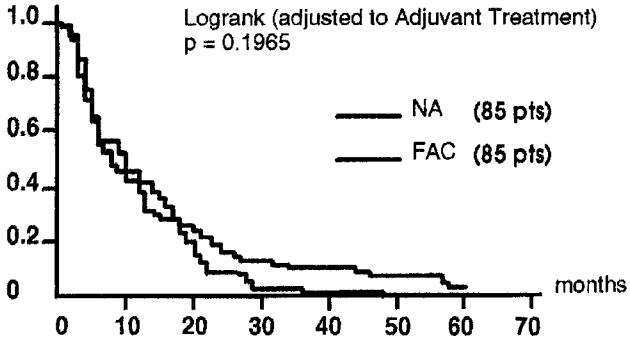

FIGURE 3. Time to progression in patients who received NA (n = 85) and in those who received FAC (n = 85).

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