Concomitant versus Sequential Administration of Epirubicin and Paclitaxel as First-Line Therapy in Metastatic Breast Carcinoma

Results from the Gruppo Oncologico Nord Ovest Randomized Trial

Pier Franco Conte, M.D.[1]
Valentina Guarneri, M.D.[1]
Paolo Bruzzi, M.D.[2]
Tiziana Prochilo, M.D.[1]
Barbara Salvadori, M.D.[1]
Angelo Bolognesi, M.D.[3]
Daniela Aldrighetti, M.D.[3]
Marco Venturini, M.D.[4]
Riccardo Rosso, M.D.[4]
Serafina Mammoliti, M.D.[5]
Flavio Carnino, M.D.[6]
Piergiorgio Giannessi, M.D.[7]
Massimo Costantini, M.D.[2]
Alfredo Moyano, M.D.[8]
Editta Baldini, M.D.[1]
On behalf of the Gruppo Oncologico Nord Ovest.

[1] Division of Medical Oncology, St. Chiara University Hospital, Pisa, Italy.

[2] Unit of Clinical Epidemiology and Trials, National Cancer Research Institute, Genoa, Italy.

[3] Department of Oncology, S. Raffaele Institute, Milan, Italy.

[4] Division of Medical Oncology, National Cancer Research Institute, Genoa, Italy.

[5] Department of Oncology, Galliera Hospital, Genoa, Italy.

[6] Department of Oncology, St. Anna Hospital, Turin, Italy.

[7] Division of Medical Oncology, Civil Hospital, Livorno, Italy.

[8] Department of Oncology, Ramon y Cajal Hospital, Madrid, Spain.

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Address for reprints: Pier Franco Conte, M.D., Department of Oncology and Hematology, University of Modena and Reggio Emilia, Modena, Italy; Fax: (011) 39-059-4224429; E-mail: conte.pierfranco@unimore.it

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BACKGROUND. The authors performed a randomized trial comprising patients with metastatic breast carcinoma (MBC). They used a noninferiority design to evaluate whether the results of sequential administration of epirubicin and paclitaxel were not markedly worse than the concomitant administration in terms of objective response rates (ORRs). Toxicity profile, quality of life (QOL), and pharmacoeconomic evaluations were evaluated as well.

METHODS. In the current study, 202 patients with MBC were randomized to receive either the combination of epirubicin at a dose of 90 mg/m^2 plus paclitaxel at a dose of 200 mg/m^2 for 8 cycles (concomitant arm, $n = 108$) or epirubicin at a dose of 120 mg/m^2 for 4 cycles followed by paclitaxel at a dose of 250 mg/m^2 over 3 hours for 4 cycles every 21 days (sequential arm, $n = 94$).

RESULTS. The authors rejected the null hypothesis that the sequential treatment is less active than the standard concomitant regimen (ORRs: concomitant = 58.5%, sequential = 57.6%). The median progression-free and overall survival periods were 11.0 months (95% confidence interval [95% CI], 9.7–12.3) and 20.0 months (95% CI, 17.2–22.6), respectively, in the concomitant arm and 10.8 months (95% CI, 7.9–13.6) and 26 months (95% CI, 18.1–33.8), respectively, in the sequential arm (P = not significant). Patients who received the sequential regimen experienced a higher incidence of Grade 3/4 (according to the World Health Organization grading system) neutropenia (62.2% of courses vs. 50.62%; $P = 0.003$) and Grade ≥ 2 neuropathy (45.5% vs. 30.4% of patients; $P = 0.03$), whereas 6 patients who received the concomitant regimen developed Grade II cardiotoxicity according to New York Heart Association criteria. QOL analyses failed to provide clear differences.

CONCLUSIONS. The sequential administration of epirubicin and paclitaxel at full doses was found to be as active as their association. Therefore, both the sequential and the combined administration were acceptable options. ***Cancer* 2004;101: 704–12.** © *2004 American Cancer Society.*

KEYWORDS: metastatic breast carcinoma, concomitant administration, sequential administration, epirubicin, paclitaxel.

Although the prognosis of patients with early breast carcinoma who receive current treatments is generally very good, metastatic disease is still incurable. In the case of hormone-resistant tumors, chemotherapy provides clinical benefit in terms of symptom control. Moreover, the patients who achieve an objective response can experience a prolonged progression-free and overall survival.[1,2] More recently, the combination of doxorubicin with taxanes induced a further increase in activity at the cost of higher cardiotoxicity and myelotoxicity.[3–6] This excess of toxicities was not observed when epirubicin was used in combination with paclitaxel.[7,8] Different phar-

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macokinetic interferences between the two anthracycline analogs and paclitaxel account for these differences in clinical toxicities.[9–11] Unfortunately, randomized trials comparing anthracycline/taxane combinations with anthracycline-containing regimens have failed to show a clear-cut advantage. Anthracycline/taxane regimens produce higher response rates, which occasionally are associated with prolonged progression-free survivals, but to our knowledge a significant survival advantage has been observed only rarely.[12–22] Moreover, the more active combinations were often associated with more severe toxicities. These data, and the data from randomized trials comparing combination chemotherapy with sequential single agents, have questioned the assumption that combination chemotherapy must represent the standard approach for patients with metastatic breast carcinoma (MBC).[12,23–25]

To further clarify whether the sequential administration of anthracyclines/taxanes was associated with an activity similar to that of the combined regimen, we performed a randomized trial that compared the epirubicin/paclitaxel combination with the sequential administration of single-agent epirubicin followed by single-agent paclitaxel. The dose of single-agent epirubicin was chosen on the basis of trials demonstrating a dose-response effect[26–28] and single-agent paclitaxel was given at its maximum tolerated dose (MTD).[29]

The primary goal of the current study was to determine whether the sequential (experimental) regimen was not worse in efficacy than the standard concomitant regimen. Secondary aims were to confirm the lower toxicity expected in the sequential arm and to compare the two regimens with regard to the proportion of complete responses (CR), response rates after four and after eight cycles of chemotherapy, and progression-free and overall survivals. Ancillary studies were performed to study quality of life (QOL) and pharmacoeconomic parameters in the two different schedules of treatment. Based on the cost of cytotoxic drugs only, the sequential arm was 37% less expensive than the combination treatment. The complete results of the pharmacoeconomic analysis will be reported separately.

MATERIALS AND METHODS

Eligibility Criteria

To be eligible for the study, women were required to have MBC; a life expectancy of ≥t 6 months; a Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≥ 2; measurable or assessable disease; normal hematologic, hepatic, and renal functions; and a left ventricular ejection fraction (LVEF) of ≥ 50% (measured either by multigated scan or echocardiogram). Previous adjuvant chemotherapy was allowed only if it was ended ≥ 1 year before study entry. In the case of previous adjuvant anthracyclines, the cumulative doses permitted were 240 mg/m^2 for doxorubicin and 360 mg/m^2 for epirubicin. Previous chemotherapy for metastatic disease was not allowed, and only one line of hormonal therapy was permitted. Pregnant or lactating women were excluded. Sexually active patients of child-bearing potential adopted adequate contraceptive measures during study participation. Exclusion criteria were other past or concomitant tumors except for nonmelanoma skin cancer or curatively treated in situ carcinoma of the cervix, documented myocardial infarction within 6 months preceding study entry or a history of second or third-degree block or heart failure, active infections, or other serious underlying medical conditions, and brain metastases. The local human investigation committees of participating institutions approved the protocol. Written informed consent was obtained from all patients before study partcipation.

Treatment Plan

In the current Phase III, multicenter, open-label trial, patients were randomized to receive either concomitant or sequential epirubicin and paclitaxel. Randomization was performed centrally at the Department of Clinical Epidemiology and Trial Office of the National Cancer Research Institute in Genoa by phone call. A separate randomization list for each center was prepared with permuted blocks of varying size in random sequence.

Patients randomized to Arm A (concomitant regimen) were treated with 8 cycles of epirubicin at a dose of 90 mg/m^2 and paclitaxel at a dose of 200 mg/m^2. Patients assigned to Arm B (sequential regimen) received 4 cycles of epirubicin at a dose of 120 mg/m^2 followed by 4 cycles of paclitaxel at a dose of 250 mg/m^2. In both arms, the courses of chemotherapy were administered every 3 weeks. Paclitaxel was administered as a 3-hour infusion and epirubicin was administered as a bolus infusion (immediately before paclitaxel in the concomitant arm). To prevent hypersensitivity, patients were premedicated 30 minutes before paclitaxel with dexamethasone given at a dose of 20 mg intravenously (i.v.), diphenidramine given at a dose of 40 mg intramuscularly, and ranitidine given at a dose of 150 mg i.v. All patients received antiemetic premedication.

Patients who experienced disease progression during concomitant treatment or while receiving paclitaxel during sequential treatment were released from the study. Patients whose disease progressed while

they were receiving epirubicin treatment were given paclitaxel at a dose of 250 mg/m^2.

The prophylactic use of hemopoietic factors was not allowed. The use of granulocyte–colony-stimulating factor (G-CSF; given at a total dose of 300 μg subcutaneously) was suggested if there was febrile neutropenia or Grade (according to the World Health Organization) 4 neutropenia lasting $>$ 72 hours.

Chemotherapy was administered if the leukocyte count was $\geq$ 3.5/μL and/or the absolute neutrophil count (ANC) was $\geq$ 1500/μL, and the platelet count was $\geq$ 100,000/μL. If these criteria were not met on the day of recycle, treatment was delayed until recovery. If the delay was $>$ 3 weeks, patients were released from the study. For the combination regimen, paclitaxel was reduced to a dose of 175 mg/m^2 and the dose of epirubicin was not modified when patients developed febrile neutropenia, Grade 4 neutropenia lasting $>$ 7 days (in spite of the use of G-CSF from the third day onward), or an ANC $<$ 100/μL lasting $>$ 3 days. When there was a reappearance of one of the previously reported toxicities (in spite of a paclitaxel dose reduction), Grade 4 thrombocytopenia, or any Grade $\geq$ 3 nonhematologic toxicity (excluding alopecia and emesis), paclitaxel was reduced to a dose of 175mg/m^2 and epirubicin to a dose of 75 mg/m^2.

In the sequential regimen, single-agent epirubicin was reduced to a dose of 90 mg/m^2 and single-agent paclitaxel was reduced to a dose of 200 mg/m^2 if patients developed febrile neutropenia, Grade 4 neutropenia lasting $>$ 7 days (in spite of the use of G-CSF from the third day onward), an ANC $<$ 100/μL lasting $>$ 3 days, Grade 4 thrombocytopenia, or any Grade $\geq$ 3 nonhematologic toxicity (excluding alopecia and emesis). Single-agent epirubicin was reduced to a dose of 75 mg/m^2 and single-agent paclitaxel was reduced to a dose of175 mg/m^2.when there was reappearance of one of the previously reported toxicities (in spite of an epirubicin/paclitaxel dose reduction).

In case of Grade 4 neutropenia, all patients received prophylaxis with oral antibiotics (ciprofloxacin given orally at a dose of 500 mg/day) and antimicotics (fluconazol given orally at a dose of 50 mg/day) for a total of 6 days.

In both treatment arms, epirubicin was discontinued if patients developed Grade II or worse congestive heart failure (CHF) according to the New York Heart Association criteria or a $\geq$ 20% decrease in LVEF.

Pretreatment and Study Evaluation

To determine the extent of disease, standard surveillance including a physical examination, PS, routine hematology, biochemistry analysis, cardiac evaluation, and appropriate radiologic assessments were performed within 4 weeks before enrollment. Toxicity was assessed every cycle. Tumor response and cardiac evaluation were assessed every two cycles by imaging techniques identical to those used at baseline. Tumor responses were assessed locally using standard ECOG criteria.[30] A CR was defined as the disappearance of all clinical evidence of tumor, determined by 2 observations not less than 4 weeks apart. A partial response (PR) was defined as a $\geq$ 50% decrease in the sum of the products of the largest dimension of the target lesions, determined by 2 observations no less than 4 weeks apart, in the absence of any new or progressive tumor lesions. Stable disease was defined as the steady state of response less than PR or progression less than progressive disease (PD) for $\geq$ 4 weeks duration and no appearance of new lesions. PD was defined as an increase of $\geq$ 25% in the product of measured lesions and/or the appearance of new lesions.

Overall survival was calculated from the date of randomization to the date of death or last follow-up. Progression-free survival was calculated from the date of randomization to documented PD or death.

QOL evaluation was performed by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30). The QLQ-C30 is a 30-item self-administered questionnaire that assesses five functional domains (physical, role, emotional, cognitive, and functional), an overall quality of life domain, eight symptom domains (fatigue, nausea and emesis, pain, dyspnea, sleep disturbance, appetite loss, constipation, and diarrhea), and the perceived financial impact of disease and treatments.[31] All scales were linearly transformed to a 0–100 scale. For the six functional scales, a higher score represents a better level of functioning. For the symptom scales, a higher score represents a higher level of symptoms. QOL assessments were performed at baseline, then during the second, fourth, and eighth cycle of chemotherapy.

Statistical Methods

It was assumed that, due to its lower costs and to its postulated more favorable tolerability, the sequential regimen could become the treatment of choice if it was associated with a reduction no $>$ 15% in the overall response rate (ORR) compared with the combined regimen. The choice of the noninferiority delta of 15% was based on the considerations that treatment for MBC has mainly palliative aims and that 10–15% increases in response rates translate into negligible or null effects on overall survival. As a consequence, a treatment associated with significant improvements in toxicity and QOL may become the

treatment of choice unless the decrease in response rate is > 15%. Based on these premises, the study was designed as a noninferiority trial aimed at testing the null hypothesis that the sequential regimen was indeed associated with a 15% reduction in ORR. For an 80% power under the alternative hypothesis that ORR in the experimental arm is not lower than that in the concomitant arm, and setting alpha error = 0.05 (one-sided), 133 patients were needed in each treatment arm.[32,33]

The primary study end point was the ORR (i.e., the proportion of responses observed in the whole treatment period, defined as the best response observed in each patient, confirmed no less than 4 weeks apart). In a secondary analysis, the proportion of CR and the response status after four and eight courses of therapy in the two arms were compared. In all these analyses, early PD and death were classified as failures. Patients in the sequential arm who developed PD while receiving epirubicin were classified as failures, independently of their response to paclitaxel. All analyses were conducted according to the intention-to-treat principle. The proportions of responses were compared using the Mantel–Haenszel test with center as a stratification factor. Overall and progression-free survivals were compared in the two groups using log-rank test. No interim analyses or stopping rules were foreseen in the study protocol and the study was monitored only for toxicity.

Statistical Methods for Quality of Life

Eight of 18 centers agreed to participate in the QOL part of the study. A linear mixed model for each EORTC scale was fitted to the data. The three QOL assessments after baseline were coded as dummy variables. The model included QOL baseline scores as covariate and time-varying covariates to model the drop-out process. For each patient, this variable was coded as +1 if the QOL assessment was the last available before the patients dropped out and as −1 if the QOL assessment was not the last available for that patient.

RESULTS

Patient Population

Between December 1996 and June 2001, 202 patients from 18 institutions (15 Italian and 3 Spanish institutions) were enrolled in the study. Of these patients, 108 patients and 94 patients were randomized to receive concomitant and sequential treatment, respectively. At that time, periodic analyses were conducted with the aim of monitoring the toxicity profiles of the two regimens. Contrary to expectations, the experimental regimen was not associated with a decreased, but possibly with an increased toxicity, with similar or increased rates of Grade 3–4 neutropenia and Grade 2–4 neuropathy.

This observation undermined the rationale of the current noninferiority trial (lower toxicity and similar activity) and induced the steering committee of the study to end patient accrual before the planned sample size of 266 patients. Two patients in the concomitant arm and two patients in the sequential arm withdrew their informed consent and were lost to follow-up immediately after randomization. They were excluded from all analyses, leaving 198 patients (106 in the sequential arm and 92 in the concomitant arm).

Patient characteristics were well balanced in the two treatment arms (Table 1). The median age of the entire group was 58 years (range, 30–73 years). The majority of patients (76%) had an ECOG PS score of 0. Forty-nine percent of patients had received adjuvant

TABLE 1
Patient Characteristics[a]

Characteristics	Concomitant arm A (n = 106) (%)	Sequential arm B (n = 92) (%)
Median age, (yrs) (range)	58 (36–73)	58 (30–73)
PS		
0	79 (74.5)	72 (78.3)
1	22 (20.8)	19 (19.6)
2	5 (4.7)	2 (2.2)
Disease status at presentation		
Metastatic	29 (27.3)	14 (15.2)
Recurrence after surgery[b]	76 (71.7)	77 (83.7)
Unknown	1 (0.9)	1 (1.1)
Nb of metastatic sites		
1	40 (37.7)	38 (41.3)
2	30 (28.3)	35 (38.0)
> 2	36 (33.9)	19 (20.6)
Dominant metastatic site		
Viscera	80 (75.4)	67 (72.8)
Bone	12 (11.3)	12 (13.0)
Soft tissue	14 (13.2)	13 (14.1)
Receptor status		
ER+ and/or PgR+	54 (50.0)	54 (58.7)
Negative	30 (28.3)	17 (18.5)
Unknown	22 (20.7)	21 (22.8)
Previous adjuvant therapy		
None or RT only	44 (41.5)	32 (34.7)
HT ± RT	13 (12.2)	11 (11.9)
CT ± HT ± RT	49 (46.2)	49 (53.2)
If CT: Epirubicin	27 (55.1)	23 (46.9)
Previous metastatic therapy		
None or RT only	91 (85.8)	73 (79.3)
HT ± RT	15 (14.1)	19 (20.6)

PS: performance status; RT: radiotherapy; HT: hormonal therapy; CT: chemotherapy; ER: estrogen receptor; PgR: progesterone receptor.

[a] Two patients in Arm A and two patients in Arm B were not evaluable.

[b] Median disease-free interval (range): Arm A: 28.5 months (0–209 months); Arm B: 36.6 months (0–275 months).

TABLE 2
Objective Response Rate

	Epirubicin plus paclitaxel (n = 106) (%)[a]		Epirubicin followed by paclitaxel (n = 92) (%)[b]	
Characteristics	4 cycles	8 cycles	4 cycles	8 cycles
CR[c]	5 (4.7)	12 (11.3)	1 (1.1)	10 (10.9)
PR	49 (46.2)	50 (47.2)	38 (41.3)	43 (46.7)
SD	39 (36.8)	30 (28.3)	42 (45.6)	27 (29.3)
PD	13 (12.3)	14 (13.2)	11 (12.0)	12 (13.0)
ORd	54 (50.9)	62 (58.5)	39 (42.4)	53 (57.6)

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; OR: overall response.
[a] Arm A.
[b] Arm B.
[c] P = 0.22, comparison between the two arms at four cycles.
[d] P = 0.23, comparison between the two arms after four cycles.

chemotherapy, which included epirubicin in 50.5% of patients. The majority of patients (74.2%) had viscera as the dominant metastatic sites.

Response

Objective responses (CR and PR) were recorded in 62 patients (58.5%) in the concomitant arm and in 53 patients (57.6%) in the sequential arm. The probability of the observed 0.9% difference in ORR under the null hypothesis of a 15% difference in favor of the combination arm was 0.023. In both arms, 13% of patients experienced PD (Table 2). Among responding patients, 87% achieved the best response within 4 cycles in the concomitant arm versus 76% in the sequential arm. The median progression-free survivals were 11 months (95% confidence interval [95% CI], 9.7–12.3) and 10.8 months (95% CI, 7.9–13.6), respectively, in the concomitant and sequential arms (P = not significant [NS]) (Fig. 1). The median overall survivals were 20 months (95% CI, 17.2–22.6) and 26 months (95% CI, 18.1–33.8), respectively, in the concomitant and sequential arms (P = NS) (Fig. 2).

Compliance with Treatment and Toxicity

Sixty patients (56.6%) in the concomitant arm and 60 patients (65.2%) in the sequential arm completed the planned treatment. Of these, 15 (14.1% of 106 patients) in the combination arm and 31 (33.7% of 92 patients) in the sequential arm completed all cycles without protocol modifications (P = 0.001). A median of eight courses (range, zero to eight courses) was administered in both treatment arms. One patient in the concomitant arm was never treated because of an increase in the level of serum bilirubin above the accepted value immediately before the initiation of chemotherapy (Table 3).

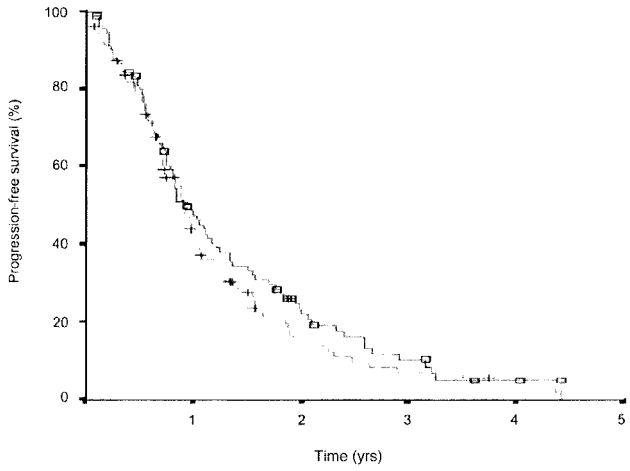

FIGURE 1. Kaplan-Meier progression-free survival (PFS). The median PFS in Arm A was 11 months (range, 9.7–12.3 months) and the median PFS in Arm B was 10.8 months (range, 7.9–13.6 months). -+-: Arm A (concurrent); -square: -Arm B (sequential).

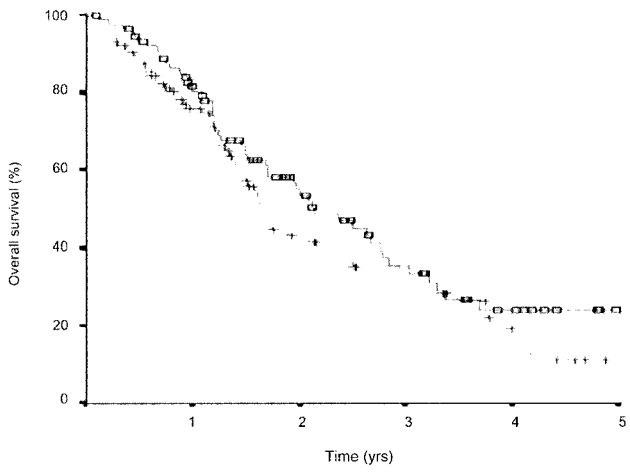

FIGURE 2. Kaplan-Meier overall survival. The median overall survival in Arm A was 20 months (range, 17.2–22.6 months) and the median overall survival in Arm B was 26 months (range, 18.1–33.8 months; P value was not significant). -+-: Arm A (concurrent); -square: -Arm B (sequential).

In terms of toxicity, both regimens were well tolerated and severe side effects were uncommon. The most common severe toxicity (Grade 3–4) was neutropenia, which occurred in 49.3% of cycles in the concomitant administration, 62.2% of cycles during single-agent epirubicin, and 24% of cycles with single-agent paclitaxel. After 4 cycles of treatment, Grade 3–4 neutropenia was reported to occur in 50.6% of courses in the concomitant arm and in 62% of cycles in the sequential arm (P = 0.003). Grade 2–4 neuropathy occurred in 30.4% of patients in the concomitant arm

TABLE 3
Compliance with Treatment[a]

Characteristics	Eight cycles of epirubicin plus paclitaxel (n = 106) (%)	Eight cycles of epirubicin followed by paclitaxel (n = 92) (%)
Completed	60 (56.6)	60 (65.2)
As protocol	15 (14.1)[b]	31 (33.7)[b]
With delay	28 (26.4)	16 (17.4)
With dose reduction	17 (16.6)	13 (14.1)
Terminated early	45 (42.4)	32 (34.8)
Toxicity	11 (10.4)	15 (16.3)
PD	14 (13.2)	12 (13.0)
Death	4 (3.8)	3 (3.2)
Refusal	8 (7.5)	1 (1.1)
Other	8 (7.5)	1 (1.1)
Never treated[a]	1 (0.9)	0 (0)

PD: progressive disease.
[a] Two patients in Arm A and two patients in Arm B withdrew their consent after randomization, before the initiation of treatment, and were excluded from all analyses.
[b] P = 0.001.

TABLE 4
Toxicity (percent Incidence of Events for 1296 Cycles)

	Concomitant arm A			Sequential arm B					
	Epirubicin + paclitaxel (667 cycles)			Epirubicin (342 cycles)			Paclitaxel (287 cycles)		
WHO grade	2	3	4	2	3	4	2	3	4
Anemia	13.7	2.2	0	9.3	2.7	0	4.0	0	0
Neutropenia[a]	14.1	22.3	27.0	11.4	25.6	36.6	10.6	14	10
Mucositis	4.3	0.6	0.1	9.6	1.7	0	1.7	1.3	0
Infection	0.4	0	0	0.8	0	0	0	0.3	0
Cardiac toxicity	0	0.9	0.1	0	0	0	0	0	0
Neuropathy	9.9	1.5	0	1.7	0	0	23	4.5	0.3
Febrile neutropenia	0	1.3	0	0	1.7	0	0	0	0

WHO: World Health Organization.
[a] Grade 3/4 neutropenia after four cycles: 50.6% in Arm A and 62% in Arm B (P = 0.003).

and in 45.5% of patients in the sequential arm (P = 0.03) (Tables 4 and,5). Nine patients in the concomitant arm and eight patients in the sequential arm experienced a serious adverse event. In particular, six patients had CHF, two patients had Grade 3 mucositis, and one patient had an episode of febrile neutropenia that required hospitalization during concomitant treatment. Three of the six patients who developed CHF had received previous adjuvant epirubicin. The cumulative dose for developing a cardiac event was 1080 mg/m^2 of epirubicin. Five of these patients fully recovered from CHF with appropriate treatment. In the sequential arm, two patients experienced febrile neutropenia requiring hospitalization, two patients developed infection, one patient experienced Grade 3 mucositis, and three patients required hospitalization for Grade 3–4 neuropathy. Four possible treatment-related deaths were reported, namely, one patient each with CHF, hepatorenal syndrome, and multiorgan failure in the concomitant treatment arm and one patient with pulmonary embolism in the sequential arm.

TABLE 5
Toxicity (Percentage of Patients)

	Eight cycles of epirubicin + paclitaxel (n = 96)			Eight cycles of epirubicin followed by paclitaxel (n = 87)		
WHO grade	2	3	4	2	3	4
Anemia	26.0	7.3	0	18.4	6.9	0
Neutropenia	9.4	20.8	58.3	4.6	20.7	66.7
Mucositis	16.7	2.9	1	24.4	7.8	0
Infection	2.9	0	0	3.3	1.1	0
Cardiac toxicity	0	5.9	0.9	0	0	0
Neuropathy	26.5	3.9	0	32.2	12.2	1.1
Febrile neutropenia	0	7.3	0	0	5.7	0

WHO: World Health Organization.

Quality of Life

Of the 164 randomized patients from the 8 centers participating in the QOL assessment, 82 (50.0%) with minimum criteria were included in the analyses (i.e., they had at least baseline evaluation and another evaluation over time). Results of the QOL analysis using the linear mixed-effect model are listed in Table 6 as the mean differences between the two arms for each EORTC scale. A negative score difference (corresponding to better function in the concomitant arm) for four functional scales (role, emotional, cognitive, and social) and for global QOL was observed. The difference was statistically significant for emotional functioning in favor of concomitant treatment (score differences, 95% CI, 3.53; −6.99 to −0.06). Conversely, a positive score difference was observed for seven symptom scales and for financial impact (corresponding to better symptom control in the concomitant arm).

DISCUSSION

In spite of an impressively high activity, the combined administration of anthracyclines and taxanes has failed to demonstrate a clear superiority over anthracycline combinations.[12–22] It is questionable whether combination chemotherapy must be considered the standard approach for all the patients with MBC. Nev-

TABLE 6
Score Differences (Means and 95% CI) in the 15 Scales of QOL between the Two Arms[a]

Functional scales	Score differences (95% CI)	*P* value
Physical functioning	0.07 (−4.48 to 4.62)	0.976
Role functioning	−1.99 (−6.35 to 2.38)	0.375
Emotional functioning	−3.53 (−6.99 to −0.06)	0.049
Cognitive functioning	−2.47 (−5.71 to 0.77)	0.140
Social functioning	−3.24 (−7.08 to 0.60)	0.102
Global QOL	−1.35 (−4.99 to 2.28)	0.468
Symptom scales		
Fatigue	2.11 (−1.62 to 5.82)	0.270
Nausea and emesis	0.45 (−2.95 to 3.86)	0.794
Pain	1.57 (−2.55 to 5.68)	0.458
Dyspnea	2.10 (−1.91 to 6.12)	0.307
Sleep disturbance	2.67 (−1.36 to 6.69)	0.198
Appetite loss	4.54 (−0.14 to 9.00)	0.061
Constipation	2.99 (−2.62 to 8.60)	0.299
Diarrhea	−1.06 (−3.70 to 1.58)	0.433
Financial impact	1.20 (−2.33 to 4.72)	0.508

CI: 95% confidence interval; QOL: quality of life.

[a] A negative score in the functional scales corresponds to better functioning in the concomitant arm. A positive score in the symptom scales corresponds to better symptom control in the concomitant arm.

ertheless, there is still considerable interest in the development of combination regimens for several reasons. First, there is evidence that polychemotherapy is significantly better than adjuvant single-agent administration.[34] Second, the superiority of combination regimens compared with single-agent regimens for patients with metastatic disease was observed in some trials.[35–38] Finally, the heterogeneity of this population, with patients developing an aggressive disease, requires a rapid reduction of tumor burden. Conversely, the study design of recently reported trials does not rule out the possibility that the sequential administration of the same agents might produce results similar to those obtained with their combination.[36,38]

In the current trial, we have tried to minimize the potential pitfalls of the comparisons between combined versus sequential single agents. The combination regimen was developed to allow the administration of active drugs at full doses[7] with reduced negative pharmacokinetic interferences[10,11] and cardiotoxicity.[8] The sequential arm was the planned sequence of the same agents given at their MTD[26–29] without a break between the two treatments.

The primary aim of the study was to assess whether the sequential regimen was equivalent to the concomitant regimen in ORR, based on the assumption that it would be significantly less toxic. ORR after eight cycles were identical in the two arms, rejecting the noninferiority hypothesis that sequential treatment is associated with a clinically relevant decrease in activity. The *P* value in this comparison should be considered with caution because it was derived from an unplanned interim analysis. However, it has to be stressed that the analysis was driven by an event unrelated to the end point (i.e., the higher than expected toxicity in the sequential arm).

Although these results confirm the high activity of anthracyclines/taxanes, they indicate that the sequential regimen is not associated with any substantial loss in activity compared with the concomitant regimen.

Tolerability and QOL were important issues. The trial design was based on the assumption that the sequential regimen would be less toxic and less expensive than the combination regimen. Toxicity data did not meet the expectations for tolerability. For example, the sequential arm induced significantly more Grade 3–4 neutropenia (62.2% of courses vs. 50.6%; $P = 0.003$) during the epirubicin administration and Grade 2–4 neuropathy (45.5 % vs. 30.4% of patients; $P = 0.03$) during paclitaxel administration. Among the four possibly treatment-related deaths, three occurred in the combination arm and one in the sequential arm.

QOL data failed to provide definite indications, even though they provide some indication of better function, symptom control, and global QOL in the concomitant arm compared with the sequential arm. The higher doses of single agents are responsible for the observed higher hematologic and neurologic toxicities and might possibly have negatively influenced the QOL of the patients treated on the sequential arm. However, most of the observed toxicities were devoid of clinical relevance and did not compromise the efficacy of the treatment. In fact, a significantly higher proportion of patients in the experimental arm completed the treatment protocol without modifications or delays.

Lower doses of sequential single agents should produce lower toxicities but their equivalent efficacy has to be proven.

Other trials have compared the sequential versus the concomitant administration of anthracyclines and taxanes. A recently published intergroup trial (E1193) has shown that the ORR for the combination of doxorubicin and paclitaxel was significantly superior to the ORR of single-agent doxorubicin and single-agent paclitaxel (47% vs. 36% vs. 34%, respectively), as was the time to treatment failure (8.0 months, 5.8 months, and 6.0 months, respectively). However the combination was not associated with prolonged survival or improvement in QOL.[12] Differences in study design (single agents administered at progression in E1193, planned sequential administration of single agents in

the current study), and in planned doses of single agents (standard doses in E1193 and MTD in the current trial), may account for the different results observed.

The Hellenic Cooperative Oncology Group has evaluated a dose-dense (i.e., every 2 weeks) regimen of sequential epirubicin and paclitaxel versus the 3 weekly combination of the 2 drugs. No differences in ORR, time to PD, and median survival were reported, even though the sequential dose-dense treatment resulted in a significantly higher CR rate.[39] More recently, the results of the GEICAM 9903 study, which compared sequential versus concomitant administration of doxorubicin and docetaxel, were presented. There were no apparent differences with regard to activity, progression-free survival, and overall survival. However, the sequential arm had a significantly lower incidence of febrile neutropenia (33.8% of patients vs. 50%; $P = 0.0203$).[25]

In the neoadjuvant setting, Miller et al.[40] evaluated the efficacy and toxicity of 4 courses of 3-weekly combination chemotherapy with doxorubicin plus docetaxel versus the sequential dose-dense (i.e., every 2 weeks) administration of 3 cycles of doxorubicin followed by 3 cycles of docetaxel. In both arms, the same total dose of doxorubicin and docetaxel was given over a 12-week period before surgery. The sequential treatment was significantly more myelotoxic (Grade 4 leukopenia, 38% vs. 11% of patients; Grade 4 neutropenia, 76% vs. 37% of patients) and induced more frequently hand–foot syndrome, but appeared to improve lymph node clearance even if the limited number of patients did not allow a statistically meaningful analysis.

The results of the current trial indicate that the sequential administration of the MTD of single-agent epirubicin and paclitaxel is not less active than their combination. However, contrary to expectations, it is not less toxic and is not associated with an improvement of QOL. On the basis of these data and data from other trials, both the combination and the sequential regimens can be considered appropriate options for the treatment of patients with MBC.

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