# Dose-Dense Sequential Chemotherapy With Epirubicin and Paclitaxel Versus the Combination, as First-Line Chemotherapy, in Advanced Breast Cancer: A Randomized Study Conducted by the Hellenic Cooperative Oncology Group

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***Purpose:*** **To compare the efficacy of two different schedules of epirubicin and paclitaxel, as first-line chemotherapy, in patients with advanced breast cancer (ABC).**

***Patients and Methods:*** **From October 1997 until May 1999, 183 eligible patients with ABC entered the study. Chemotherapy in group A (93 patients) consisted of four cycles of epirubicin at a dose of 110 mg/m$^2$ followed by four cycles of paclitaxel at a dose of 225 mg/m$^2$ in a 3-hour infusion. All cycles were repeated every 2 weeks with granulocyte colony-stimulating factor support. The therapeutic regimen in group B (90 patients) consisted of epirubicin (80 mg/m$^2$) immediately followed by paclitaxel (175 mg/m$^2$ in a 3-hour infusion) every 3 weeks for six cycles.**

***Results:*** **In total, 79 patients (85%) in group A and 72 patients (80%) in group B completed treatment. The median relative dose-intensity of epirubicin was 0.96 in both groups, and that of paclitaxel was 0.96 and 0.97 in groups A and B, respectively. The complete response rate was higher in group A (21.5% *v* 9% *P* = .02). Nevertheless, there was no significant difference in the overall response rate between the two groups (55% *v* 42%, *P* = .10). Severe neutropenia was more frequently observed with concurrent treatment. After a median follow-up of 16.5 months, median time to progression was 10 months in group A and 8.5 months in group B (*P* = .27), and median survival was 21.5 and 20 months, respectively (*P* = .17).**

***Conclusion:*** **The present study failed to demonstrate a significant difference in overall response rate between dose-dense sequential administration of epirubicin and paclitaxel compared with the combination of the two drugs given on the same day, even though the sequential treatment resulted in a significantly higher complete response rate.**

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THE ANTHRACYCLINES doxorubicin and epirubicin are two of the most active drugs in the treatment of advanced breast cancer (ABC). Epirubicin seems to be equally effective but less toxic (especially in terms of cardiotoxicity) than its parent compound.[1] Moreover, paclitaxel was shown to demonstrate significant activity in ABC, even in anthracycline-pretreated patients.[2-4] This lack of complete cross-resistance between epirubicin and paclitaxel makes them an attractive combination for the treatment of ABC. Two phase I studies with this combination in ABC revealed that its maximum-tolerated dose was epirubicin 60 to 90 mg/m$^2$ followed by paclitaxel 200 mg/m$^2$ as a 3-hour infusion.[5,6]

Dose-dense sequential chemotherapy theoretically offers the advantages over conventional chemotherapy of slowing tumor-cell regrowth between cycles (by shortening the interval between them) and of inhibiting the development of resistant clones by changing drugs after completion of a few cycles. Additionally, sequential chemotherapy is more dose-dense and is hypothesized to be more effective than alternating chemotherapy, at least in the adjuvant treatment of breast cancer.[7] However, the experience with the use of dose-dense sequential chemotherapy in advanced disease is rather limited. The Hellenic Cooperative Oncology Group (HeCOG) tested the feasibility of dose-dense sequential administration of epirubicin and paclitaxel in a phase II study of 41 patients with ABC.[8] Chemotherapy consisted of four cycles of epirubicin (110 mg/m$^2$) followed by four

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cycles of paclitaxel (225 mg/m$^2$ as a 3-hour infusion). All cycles were delivered every 2 weeks with granulocyte colony-stimulating factor (G-CSF) support. The regimen was well tolerated and demonstrated an overall response rate (ORR) of 56% and a 19.5% complete response (CR) rate.

Since the optimal schedule of administering epirubicin and paclitaxel has not yet been defined, our group conducted a randomized study (HE 11b/97) comparing dose-dense sequential chemotherapy with epirubicin and paclitaxel versus the combination with paclitaxel infused immediately after epirubicin every 3 weeks. The main objective of the study was to compare the efficacy of the two regimens, given as first-line chemotherapy, in patients with ABC. Secondary end points were to compare acute severe toxicities, time to progression (TTP), and survival between the two groups of patients. We report in this article the final results of this study.

## PATIENTS AND METHODS

### *Eligibility Criteria*

To be eligible for the study, women had to have histologically proven ABC, life expectancy of 12 weeks or more, age at least 18 years, Eastern Cooperative Oncology Group performance status (PS) of 2 or less, measurable or assessable lesion(s) outside preirradiated areas (unless a subsequent progression was documented), adequate bone marrow, hepatic, and renal function, and a left ventricular ejection fraction of 50% or greater (measured either by multigated scan or ultrasonography). They also had to provide informed consent. Patients with a history of treatment with adjuvant chemotherapy were allowed to enter the study if the interval between completion of adjuvant chemotherapy and first relapse was 12 months or more. Anthracycline-pretreated patients could not have received cumulative doses of more than 360 mg/m$^2$ for doxorubicin, more than 450 mg/m$^2$ for epirubicin, or 72 mg/m$^2$ for mitoxantrone. Patients with lytic osseous metastases as the only metastatic site and receptor-positive status were eligible if they progressed after at least one hormonal manipulation and had an indicator lesion greater than or equal to 1 cm in size depicted in plain x-rays. Exclusion criteria were symptomatic brain metastases, history of other malignancy (except curatively resected nonmelanoma skin cancer or in-situ cervical cancer), myocardial infarction within the last 6 months, or other serious illness that would impair the ability of the patient to receive protocol treatment. Previous chemotherapy for advanced disease was not allowed. However, patients pretreated with hormonal therapy or radiation either in the adjuvant setting or for metastatic disease were eligible, provided that any treatment was stopped at least 4 weeks before study entry. The protocol was approved by the HeCOG Protocol Review Committee and the local human investigation committees in participating institutions; informed consent was obtained from all patients.

### *Treatment Plan*

Randomization was performed at the HeCOG Data Office, in Athens, and it was based on a random number list. Patients were stratified according to the history of previous adjuvant chemotherapy (no *v* yes with or without an anthracycline-containing regimen) and risk category in a modified version of the method used by Cavalli et al.[9] Risk categories were based on the following criteria: (a) free interval from initial radical surgery to first recurrence of more than 5 years with only osseous or with only locoregional metastasis, (b) free interval of 1 to 5 years and absence of visceral metastases, and (c) all others.

Patients randomized to group A were treated with four cycles of epirubicin at a dose of 110 mg/m$^2$ every 2 weeks followed by four cycles of paclitaxel at a dose of 225 mg/m$^2$ in a 3-hour infusion every 2 weeks. G-CSF (filgrastim, 5 $\mu$g/kg daily) was administered prophylactically on days 2 to 10 of each cycle. Patients randomly assigned to group B were treated with epirubicin 80 mg/m$^2$ in a 15-minute infusion followed immediately by paclitaxel 175 mg/m$^2$ in a 3-hour infusion every 3 weeks for six cycles. Ondansetron was given as antiemetic treatment in all cycles.

### *Dose Modification*

Blood counts were measured on the day of treatment. In case of granulocytopenia or thrombocytopenia on the first day of the cycle, treatment was delayed until the absolute neutrophil count was 1,500/$\mu$L or higher and the platelet count was 100,000/$\mu$L or higher, respectively. In the case of grade 3 or 4 granulocytopenia and/or thrombocytopenia, the doses of epirubicin and paclitaxel were reduced by 25% and 40%, respectively, in all subsequent cycles. In the case of grade 2 or 3 mucositis, the dose of epirubicin was reduced by 40% and that of paclitaxel by 25%. In the case of grade 2 neurologic toxicity, the dose of paclitaxel was reduced by 40%. If any grade 4 nonhematologic toxicity occurred, treatment was interrupted permanently and the patient was taken off study. G-CSF was introduced for all subsequent cycles to all patients of group B who developed severe granulocytopenia, febrile neutropenia, or severe mucositis. Toxicity criteria were those adopted by the World Health Organization.

### *Response Evaluation and Follow-Up*

Standard Eastern Cooperative Oncology Group criteria were used to define measurable disease, assessable disease, and response.[10] CR was defined as the complete disappearance of all clinical symptoms and signs of disease for a minimum of 4 weeks. Partial response (PR) was defined as a reduction by 50% or more in the sum of the products of the largest perpendicular diameters of the measurable lesions and of the measurable parameter of the assessable lesions, in the absence of any new or progressive tumor lesions. Stable disease (SD) was defined as an objective response not satisfying the criteria of a PR or an increase of 25% or less in the tumor measurements in the absence of any new lesion. Progressive disease was defined as an increase by more than 25% in the above measurements or the appearance of a new lesion.

CR of bone disease was defined as remineralization of all lytic lesions documented radiologically and disappearance of all areas of positive uptake on bone scan. PR was defined as remineralization of 50% or more of lytic lesions without an increase in size of any lytic lesion or the appearance of new lesions. SD was defined as remineralization of less than 50% of lytic lesions and no new lesions and progressive disease as a measurable increase in size of any lytic lesions or the appearance of new lesions. Blastic bone disease was not considered measurable and was not used to assess response.

Response was evaluated at midtherapy and after the completion of chemotherapy. All patients were followed at the clinic every 3 months with physical examination, complete blood count, and biochemistry and every 6 months with chest x-rays, bone scans, and computed tomography scans, as indicated. All imaging material pertinent for

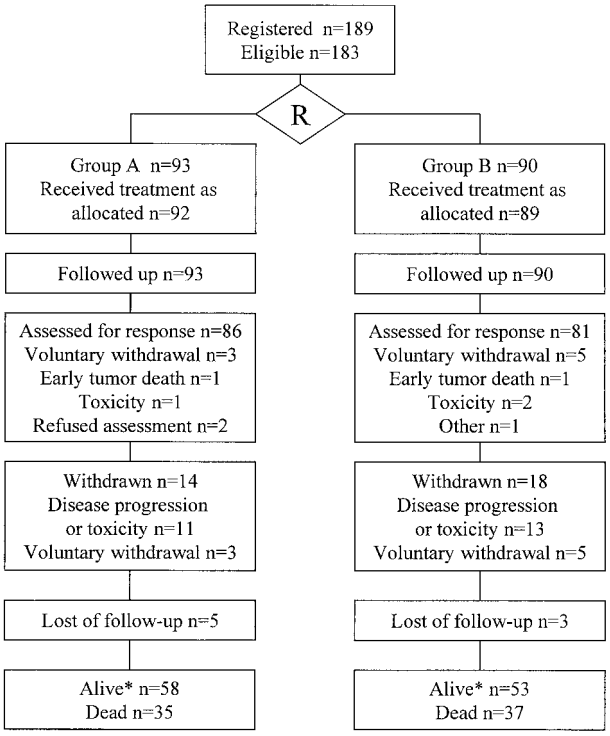


**Fig 1. Progress through the various stages of the trial. The asterisk (*) indicates that the survival status was known as of January 15, 2000. R, randomized.**

tumor response to chemotherapy was scanned (by a Mirage II scanner, maximum resolution 9.800 × 9.800 dpi; UMAX Data Systems Inc, Hsinchu, Taiwan) and evaluated after the completion of the study by a panel of three independent radiologists.

### *Statistical Analysis*

The main end point for sample-size determination was ORR. In order to detect a ± 20% difference to a baseline rate of 60%, 88 patients were required per group, so as to have 80% power at the 5% significance level. Taking into consideration 3% withdrawal rate, we increased the total number of patients to 182. No interim analysis was planned or carried out, and the results are reported on an intent-to-treat basis (all patients were used to estimate response percentages, with patients listed as not assessed for response [in Fig 1] counted as nonresponders). The posthoc power of the study if response was calculated using the number of assessable patients (167) was 78%, while it was very small for any meaningful differences in survival or TTP. According to World Health Organization criteria,[11] duration of response was calculated in the case of a CR from the date when the CR was documented until the date of progression and in the case of PR from initiation of chemotherapy until the date of progression. Because of the relatively long follow-up of this study, we decided to also perform a TTP and survival analysis. TTP was calculated from the initiation of treatment to the date progression of the disease was first documented (nonassessable patients were considered as treatment failures at the time they discontinued treatment, whereas all patients are on the TTP plot), and survival was calculated from the initiation of treatment to the date of last contact or to the date of death. Patients who were progression-free or alive on the day of last update were censored. Patients who died from causes probably related to treatment were considered to have had had tumor progression at the time of death. Patients who died from causes unrelated to the tumor or to the treatment were censored (two patients from group B died from stroke and pulmonary edema), as they were progression-free at that time (therefore, they were not included as deaths). All patients without the corresponding event by January 15, 2000, were considered censored.

The Kruskal-Wallis exact test[12] and the Fisher's exact test[13] were used for comparing patients' characteristics, response, and toxicity. The Kaplan-Meier method[14] was used to calculate TTP, survival, and duration of response curves; the log-rank test, stratified by PS,[15] was used to compare time to event distributions. Prognostic factor analyses were performed with logistic regression (CR as well as PR as the response)[16] and the Cox proportional hazards model.[17] A backward selection procedure identified the subclass of significant variables among the following: age ($\leq$ 56 *v* $>$ 56 years), PS (0 *v* 1 *v* 2), menopausal status (pre- and perimenopausal *v* postmenopausal), relapse-free interval ($<$ 1 year *v* 1 to 5 years *v* $>$ 5 years, as two indicator variables), number of metastatic sites ($<$ three *v* $\geq$ three), existence of visceral metastases, previous adjuvant chemotherapy, and previous adjuvant hormonal therapy. Estrogen receptor status was not included in the analysis because of the large amount of missing data. The significant factors were kept in the model if the maximum likelihood ratio criterion had a *P* value below .10. To adjust for covariates when evaluating treatments, we kept treatment in the model and applied backward regression to the other variables. Partial[18] and Martingale[19] residuals were used to assess the final Cox model, while the Hosmer-Lemeshow[16] goodness-of-fit test and the Pearson[16] residuals were used to assess the final logistic regression model. All two-way interactions between treatment and other factors were tested and the reported *P* values were two sided. Exact confidence intervals were used to determine the 95% upper and lower confidence limits of response rate.

## RESULTS

### *Patient Population*

From October 1997 until May 1999, 189 patients were randomized and 183 were considered eligible. The reason for noneligibility was the presence of nonmeasurable or nonassessable disease at the time of randomization. Patient characteristics are listed in Table 1. Almost two thirds of patients in both groups presented with visceral metastases. Hepatic involvement was noticed in 34 patients (37%) in group A and in 25 patients (28%) in group B. The progress of patients through the various stages of the trial is shown in Fig 1 according to the Consolidated Standards of Reporting Trials.[20]

### *Compliance With Treatment and Toxicity*

A total of 1,154 cycles of chemotherapy were delivered, 90% of them at full dose in group A and 84% at full dose in group B (Table 2). Also, 79 patients (85%) in group A and 72 (80%) in group B completed treatment. The median relative dose-intensity (DI) of epirubicin was 0.96 in both groups and that of paclitaxel was 0.96 and 0.97 in groups A

**Table 1. Selective Patient and Tumor Characteristics**

| | Group A (E→P) (n = 93) | Group B (EP) (n = 90) |
|---|---|---|
| Age, years | | |
| Median | 57.5 | 54.5 |
| Range | 26-77 | 35-77 |
| Relapse-free interval, % | | |
| < 1 year | 79 | 86 |
| 1-5 years | 16 | 11 |
| > 5 years | 5 | 3 |
| PS, % | | |
| 0 | 64 | 48 |
| 1 | 29 | 40 |
| 2 | 7 | 12 |
| Menopausal status, % | | |
| Premenopausal | 36 | 39 |
| Postmenopausal | 64 | 61 |
| Receptor status, % | | |
| Positive | 44 | 36 |
| Negative | 22 | 27 |
| Unknown | 34 | 37 |
| Adjuvant CT, % | | |
| No | 56 | 57 |
| Yes | 44 | 43 |
| Anthracycline-containing | 17 | 15 |
| Adjuvant RT, % | | |
| No | 63 | 72 |
| Yes | 37 | 28 |
| Adjuvant HT, % | | |
| No | 55 | 67 |
| Yes | 45 | 33 |
| Previous HT for AD, % | | |
| No | 75 | 78 |
| Yes | 25 | 22 |
| No prior treatment, % | 33 | 33 |
| LRR, % | | |
| Axilliary nodes | 31 | 30 |
| Skin | 22 | 23 |
| Breast | 22 | 13 |
| Supraclavicular nodes | 19 | 20 |
| Distant relapse, % | | |
| Bone | 36 | 49 |
| Soft tissue | 22 | 19 |
| Visceral | 60 | 64 |
| Other breast | 12 | 4 |
| LRR only, % | 17 | 15 |
| Distant relapse only, % | 45 | 53 |
| LRR + distant relapse, % | 38 | 32 |
| One metastatic site, % | 33 | 38 |
| ≥ Three metastatic sites, % | 39 | 30 |

Abbreviations: E, epirubicin; P, paclitaxel; CT, chemotherapy; RT, radiation therapy; HT, hormonal therapy; AD, advanced disease; LRR, locoregional relapse.

and B, respectively. In terms of toxicity, both regimens were generally well tolerated, and severe (grade 3 or 4) side effects were infrequent. The most common severe toxicities in groups A and B were leukopenia (12% *v* 18%, $P = .3$), neutropenia (8% *v* 19%, $P = .03$), anemia (7% *v* 4%), thrombocytopenia (2% *v* 2%), nausea/vomiting (3% *v* 3%), peripheral neuropathy (4% *v* 0%), and hypersensitivity reactions (2% *v* 2%). Febrile neutropenia occurred in four patients (4%) in group A and in eight (9%) in group B ($P = .24$). Alopecia was universal. No case of acute cardiotoxicity was recorded. G-CSF administration was required in all group A patients (according to the protocol) and 61% of group B, mainly for maintaining DI, ie, to administer subsequent cycles on time. Also, 21% of these patients received G-CSF for severe toxicity. Furthermore, antibiotics were administered to 15 patients (16%) in group A and 16 (18%) in group B. Twelve patients (13%) from group A and eight (9%) from group B were transfused with packed RBCs, and three (4%) from group B were transfused with platelets.

*Response to Treatment and Survival*

Results of the response evaluation by the external review committee were sent to the principal investigator of the study on May 15, 2000, and are reported here (Table 3). Sixteen patients (seven in group A and nine in group B) were not assessed for response because of early tumor-related death (two patients), early treatment-related death (one patients), patient refusal (two patients), and treatment discontinuation before response evaluation (11 patients).

Median time to CR was 17.8 weeks (range, 10 to 33.5 weeks) for group A and 18.2 weeks (range, 9 to 25 weeks) for group B ($P = .5$). Median duration of response was 9 months (range, 4 to 22.5+ months) in group A and 10 months (range, 1.5 to 23.5+ months) in group B ($P = .39$), if the curves were estimated from initiation of therapy for CRs as well. Logistic regression analysis revealed that treatment ($P = .01$), visceral metastases ($P = .05$), and number of metastatic sites ($P = .0007$) were significant prognostic factors for CR; visceral metastases were significant for ORR ($P = .03$) as well. Regarding duration of response, PS was the only significant variable in Cox analysis (overall, $P = .08$; 0 *v* 1, $P = .045$; and 2 *v* 0, $P = .145$).

As of January 15, 2000, after a median follow-up of 16.5 months (range, 0.5 to 25.5+ months), 131 patients (72%) demonstrated progressive disease (63 in group A and 68 in group B) and 72 died (35 and 37, respectively). The median TTP was 10 months (range, 0 to 25.5+ months) in group A and 8.5 (range, 0 to 23.5+ months) in group B ($P = .27$) (Fig 2); whereas median survival was 21.5 months (range, 0.5 to 26+ months) and 20 months (range, 0.2 to 24+ months), respectively ($P = .17$) (Fig 3). However, follow-up has not yet been long enough to have good estimates of median survival (39% of patients dead thus far). Median survival of patients with CR has not been reached yet,

**Table 2. Selective Treatment Characteristics**

| | Group A (E→P) (n = 93) | | Group B (EP) (n = 90) | |
|---|---|---|---|---|
| Interval between cycles, days | | | | |
| Median | 14 | | 21 | |
| No. of cycles delivered | 681 | | 473 | |
| Percent of cycles at full dose | 90 | | 84 | |
| | E | P | E | P |
| Cumulative dose, mg/m$^2$ | | | | |
| Planned | 440 | 900 | 480 | 1,050 |
| Median delivered | 438 | 892 | 466 | 1,000 |
| % of patients with ≥ 80% | 85 | 74 | 69 | 66 |
| DI, mg/m$^2$/wk | | | | |
| Planned | 55 | 113 | 27 | 58 |
| Median delivered | 53 | 108 | 26 | 56 |
| Median relative DI | 0.96 | 0.96 | 0.96 | 0.97 |

compared with 20 months for those with PR or SD ($P$ = .01). In multiple Cox analyses, PS (overall, $P$ = .003; 0 *v* 1, $P$ = .03; and 2 *v* 0, $P$ = .001), history of adjuvant chemotherapy ($P$ = .07), and group B for patients with fewer than three metastatic sites ($P$ = .055) were identified as significant adverse prognostic factors for TTP. Also, PS (overall, $P$ = .003; 0 *v* 1, $P$ = .024; and 2 *v* 0, $P$ = .001) was identified as a significant adverse prognostic factor and history of adjuvant hormonal therapy ($P$ = .015) as a favorable prognostic factor for survival.

## DISCUSSION

In the present randomized phase II study, we compared the efficacy of two different schedules of administration of epirubicin and paclitaxel in ABC. The results showed that there was no significant difference in ORR between the two regimens.

Dose-dense chemotherapy, ie, the administration of anticancer drugs sequentially at an adequate dose, was introduced as a model for increasing DI for the treatment of breast cancer. Doxorubicin and paclitaxel have been tested in a dose-dense sequential schedule mainly as adjuvant treatment of "high-risk" patients with operable breast cancer.[21,22] The encouraging results of these pilot studies led to the design of large randomized studies, on both sides of the Atlantic, which are currently in progress. This therapeutic strategy is also being evaluated as neoadjuvant treatment in operable breast cancer. An interesting randomized study comparing sequential administration of doxorubicin and docetaxel versus the combination was recently published.[23] Although clinical responses were similar in both groups, with an ORR of 87%, including 20% clinical CR, patients who received sequential therapy had fewer positive lymph nodes during the operation. Grade 4 myelosuppression was more common in patients who received the combination of the two drugs.

Nevertheless, the experience with dose-dense sequential chemotherapy with an anthracycline and a taxane in advanced disease is limited. The present study is, to our knowledge, the first reported study to directly compare the administration of epirubicin and paclitaxel in a dose-dense sequential fashion with the combination of the two drugs given on the same day every 3 weeks.

**Table 3. Best Response to Treatment**

| | Group A (E→P) | | Group B (EP) | | |
|---|---|---|---|---|---|
| | RR* | 95%CI | RR* | 95%CI | *P* |
| CR | 21.5 (20) | 14-31 | 9 (9) | 4-14 | .02 |
| PR | 33 (34) | 24-43 | 33 (34) | 24-44 | |
| SD | 27 (26) | 18-37 | 32 (31) | 23-43 | |
| PD | 11.5 (12) | 6-20 | 17 (17) | 10-26 | |
| NA | 8 | 3-15 | 9 | 4-17 | |
| ORR | 55 | 44-65 | 42 | 32-53 | .10 |

Abbreviations: RR, response rate; PD, progressive disease; NA, nonassessable; CI, confidence interval

*Response rates as given by the review committee. Numbers in parentheses indicate response rates as given by the investigators. The difference in CR rates according to the analysis of the investigators' results was of borderline significance ($P$ = .06). All numbers are percentages.

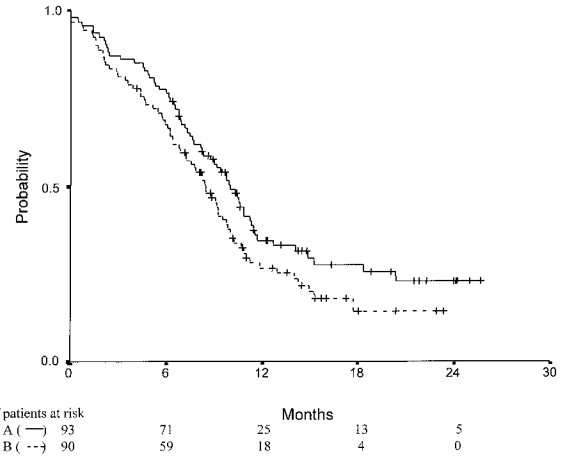


**Fig 2. TTP of patients treated with dose-dense sequential chemotherapy with epirubicin followed by paclitaxel (——) or the combination of the two drugs given on the same day (dashed line).**

As previously mentioned, our group has completed a phase II study with dose-dense sequential chemotherapy with four cycles of epirubicin followed by four cycles of paclitaxel. The ORR of 56% with a 19.5% CR rate reported in that study is remarkably similar to that achieved in group A of the present study. However, the 42% ORR observed with the combination of the two drugs in group B is considerably lower than that reported in initial dose-finding studies[5,24,25] that tested the combination of either doxorubicin or epirubicin with paclitaxel. This disturbing difference is due to patient selection, which usually characterized initial single-institution studies. For this reason, subsequent

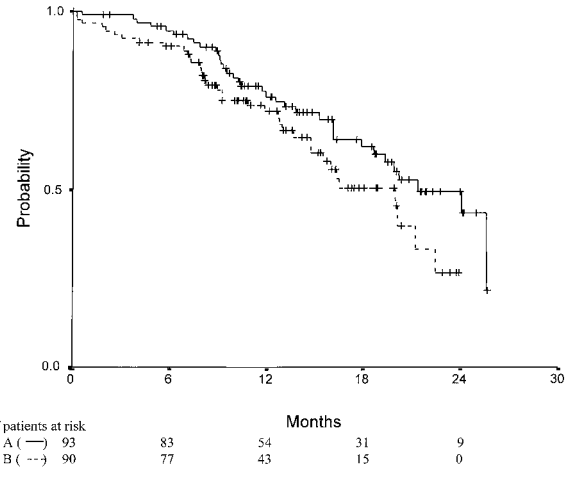


**Fig 3. Survival of patients treated with dose-dense sequential chemotherapy with epirubicin followed by paclitaxel (——) or the combination of the two drugs given on the same day (– – –).**

multi-institutional studies failed to achieve the initial reported high response rates.[26,27] Despite the fact that the DI of the both drugs was almost double with the dose-dense sequential treatment (group A), the ORR was not significantly different between the two arms. However, a significant difference in CR rate in favor of the sequential treatment was observed. Similarly, a significant difference in CR rate in favor of the dose-dense chemotherapy was also recorded in a previous randomized study conducted by our group (HE 11/93),[28] in which patients with ABC were treated with epirubicin 110 mg/m$^2$ either every 2 or every 4 weeks. The CR rate in the group of patients treated every 2 weeks was 17%, compared with 5% in those treated every 4 weeks ($P = .011$). However, ORR (53% *v* 49%), TTP (7.4 months *v* 7.2 months), and survival (14.9 months *v* 14.6 months) were not significantly different in the two groups. From these two randomized trials, in which the issue of dose-dense (and sequential) chemotherapy was addressed, it may be postulated that the number of CRs may be significantly increased with this therapeutic strategy, although a survival benefit could not be demonstrated, because both studies were statistically underpowered to detect small but clinically relevant differences.

Another reason for the lack of statistically significant differences in the results of the two study arms may be that a limited number of cycles of therapy were given in each arm. It has previously been shown that with continued treatment, CR rates increase.[29] However, four cycles were chosen arbitrarily in order to maintain a similar cumulative dose of epirubicin and paclitaxel and similar treatment duration in both arms (Table 2). Although some patients may have benefited by receiving more cycles of epirubicin, it is difficult to design a randomized study that permits individualization of the number of cycles in one arm while maintaining a set number of cycles in the second arm. Furthermore, the duration of treatment has to be similar in both arms.

Overall, the two arms were designed to differ only in schedule and intensity. In the results, we did not find a difference in our primary end point, which was ORR between the sequential (E→P) versus the concurrent (EP) administration of epirubicin and paclitaxel. Indeed, clinical research with the concurrent combination is extensive. There are several randomized studies comparing the epirubicin (or doxorubicin) and paclitaxel doublet with other combinations frequently used in ABC, such as the fluorouracil, doxorubicin, and cyclophosphamide or the epirubicin and cyclophosphamide combination.[30,31] Motivated by the results of our two previously published phase II studies[32,33] with the combination of paclitaxel and carboplatin in ABC, we are currently conducting a randomized phase III study

(HE 11b/99) to compare six cycles of the paclitaxel/epirubicin combination, as it was given in the present study, with six cycles of the paclitaxel/carboplatin doublet.

Another important end point of our study was the comparison of acute severe toxicities between the two regimens. Both treatments turned out to be well tolerated, and severe side effects, with the exception of neutropenia, were infrequent. Notably, no serious acute cardiac adverse events were observed during the whole treatment period. Overall, the sequential arm seemed to be somewhat better tolerated than the concurrent arm, although the differences in toxicity incidence did not achieve statistical significance. The relatively low toxicity seen in both arms may be attributed in part to the use of epirubicin instead of doxorubicin, the small number of patients who had received adjuvant anthracycline-containing chemotherapy, the sequential use of epirubicin and paclitaxel in one arm, or the low cumulative dose of epirubicin in both arms of the study.

In conclusion, the present study failed to detect a suppositional difference of 20% in ORR between dose-dense sequential chemotherapy with epirubicin and paclitaxel versus the combination of the two drugs given on the same day, even though the CR rate was significantly increased with sequential treatment. Both regimens were well tolerated, and no serious cardiotoxicity was recorded. It is hoped that ongoing randomized trials will provide persuasive answers to key questions, such as the role of dose-dense and/or sequential chemotherapy with a taxane and an anthracycline and, eventually, the optimal regimen to be used as first-line chemotherapy in patients with ABC.

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