Randomized phase III trial comparing docetaxel plus epirubicin versus docetaxel plus capecitabine as first-line treatment in women with advanced breast cancer


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Background: The purpose of this study was to compare docetaxel plus epirubicin versus docetaxel plus capecitabine combinations as front-line treatment in women with advanced breast cancer (ABC).

Patients and Methods: Previously untreated patients with ABC were randomly assigned to receive docetaxel 75 mg/m² plus epirubicin 75 mg/m² (DE) on day 1 or docetaxel 75 mg/m² on day 1 plus capecitabine 950 mg/m² orally twice daily on days 1–14 (DC) in 21-day cycles. Previous anthracycline-based (neo)-adjuvant chemotherapy was allowed if completed >1 year before enrollment. The primary objective of the study was to compare time to disease progression (TTP).

Results: One hundred and thirty-six women were treated on each arm and median TTP was 10.6 versus 11.0 months (P = 0.7), for DE and DC, respectively. According to RECIST criteria we observed 15 (11%) versus 11 (8%) complete responses and 55 (40%) versus 61 (45%) partial responses (P = 0.8), with DE and DC, respectively. Severe toxicity included grade 3–4 neutropenia (57% versus 46%; P = 0.07), febrile neutropenia (11% versus 8%; P = 0.4), hand–foot syndrome (0% versus 4%; P = 0.02), grade 2–3 anemia (20% versus 7%; P = 0.001) and asthenia (12% versus 6%; P = 0.09) with DE and DC, respectively.

Conclusions: The DE and DC regimens have similar efficacy but different toxicity. Either regimen can be used as front-line treatment of ABC.

Key words: capecitabine, chemotherapy, docetaxel, epirubicin, metastatic breast cancer

introduction

The optimal regimen for front-line treatment of metastatic breast cancer (MBC) remains unknown. For the individual patient with breast cancer, this may depend on the specific disease characteristics as well as the history of prior therapy. The use of serial single agents is an appropriate alternative to combination regimens for most patients. However, combination therapy may be preferred in some situations where the higher response rates that can be achieved with combination therapy are clinically relevant (e.g. rapidly progressive or symptomatic metastatic disease).

Nowadays more patients presenting with metastatic disease have relapsed following adjuvant or neoadjuvant chemotherapy, which often includes combinations of anthracyclines and taxanes [1]. Moreover, the readministration of anthracycline may be associated with reduced efficacy and significant cardiotoxicity [2]. Therefore, there is a need for development of non-anthracycline-containing regimens for the treatment of patients with advanced disease.

The anthracyclines and the taxanes are considered among the most active drugs for breast cancer, while other agents such as capecitabine, gemcitabine and vinorelbine are increasingly used. The combination of docetaxel and epirubicin (DE) has been evaluated in many studies and was found to be very active and with manageable toxicity [3–7]. As first-line treatment of MBC, it results in 50%–70% overall response rate (ORR).
including 5%–23% complete responses, a median time to
disease progression (TTP) of 8–12 months and median overall
survival (OS) of 18–34 months [4–7]. Moreover, investigations
on cardiac safety of the DE combination raised no serious
concerns [8]. The high efficacy and manageable toxicity reported
for the DE combination from phase II and III clinical trials have
also been reproduced in everyday clinical practice in one open
access study of 470 patients [9]. Therefore, the DE combination
is considered by many as a ‘standard’ regimen especially for
women with rapidly progressive visceral disease [10].

The combination of docetaxel plus capcitabine (DC) was
evaluated based on in vitro and in vivo synergy [11] and proved
to be very active in anthracycline-pretreated MBC [12]. In
a large phase III study, the DC combination therapy was superior
to docetaxel monotherapy in terms of objective response rate,
TTP and OS [12]. Moreover, dose reduction of capcitabine
and/or docetaxel for the management of adverse events did not
affect the efficacy of the regimen [13]. The DC combination
offers a 3-month median survival advantage over docetaxel
monotherapy and was judged to be highly cost-effective [14].

Based on these results, the DC combination is widely used in
some countries in patients with anthracycline-pretreated MBC.

In this multicenter randomized study, we compared the DE
and DC regimens as first-line treatment for women with locally
advanced or MBC.

patients and methods

eligibility criteria

Women 18–75 years old with histologically- or cytologically confirmed and
previously untreated locally advanced or metastatic breast adenocarcinoma
were eligible for the study. Prior adjuvant or neoadjuvant chemotherapy
with an anthracycline-based regimen was allowed if it had been completed
>1 year before enrollment. Other eligibility criteria included the presence of measurable disease (RECIST criteria), performance status of zero to two
(World Health Organization criteria), adequate hematological (absolute
granulocyte count >1.5 x 10^9/l and platelet count >100 x 10^9/l), renal
(creatinine level <1.5 mg/dl) and hepatic (transaminases <1.5x the upper
normal limit (UNL), alkaline phosphatases <2.5 UNL and bilirubin <UNL)
function and normal left ventricular ejection fraction (LVEF >50%). Prior
hormonal therapy or radiation therapy was allowed if they had been
completed at least 1 month before enrollment and if <25% of the active
cancer mass had been irradiated.

Exclusion criteria included active central nervous system metastases,
history of serious cardiac disease contraindicating the use of anthracyclines,
history of previous cancer (except treated basal cell and squamous cell
carcinoma of the skin or cancer of the uterine cervix) and other serious
concomitant illness. The concurrent administration of other antineoplastic
treatment was not allowed. Patients with HER2-positive disease were
excluded from the study. Written informed consent was obtained from each
patient before enrollment. The protocol was approved by the Ethics and
Scientific Committees of all participating centers. The study was conducted
in accordance with the Declaration of Helsinki and the applicable guidelines
on good clinical practice.

study design and treatment plan

Treatment allocation was carried out centrally with stratification for age,
menopausal status, prior anthracycline treatment and presence of hepatic
metastases. Patients were randomly assigned to receive either epirubicin
(Farmorubicin, Pfizer, New York, NY) 75 mg/m² i.v. combined with
docetaxel (Taxotere, Aventis, Bridgewater, NJ) 75 mg/m² i.v. both given on
day 1 cycles every 3 weeks (DE regimen) or docetaxel 75 mg/m² i.v. on day
1 combined with capcitabine (Xeloda, Roche, Basel, Switzerland) 950 mg/
m² given orally twice daily on days 1–14 every 3 weeks (DC regimen).
Docetaxel was infused over a 1-h period with routine steroid premedication
over a 3-day period starting the day before treatment. Epirubicin was
administered as a 15-min bolus i.v. infusion following standard antiemetic
premedication. Six cycles of treatment were scheduled for patients without
serious toxicity or disease progression; continuation of treatment was
allowed in responding patients.

dose modifications

Treatment cycles were administered as scheduled every 21 days provided
that the absolute granulocyte count was >1.5 x 10^9/l and the platelet count
>100 x 10^9/l and all other toxic effects (except alopecia) had resolved to
grade 51 [National Cancer Institute—Common Toxicity Criteria (NCI-
CTC)]. In patients with grade 4 neutropenia lasting >3 days, febrile
neutropenia, grade 3–4 thrombocytopenia or grade 3–4 non-hematological
toxicity (except nausea and vomiting), the doses of all drugs were reduced
by 20% in subsequent cycles. If toxicity recurred, a second dose reduction
by 20% in the doses of all drugs was allowed. If toxicity recurred despite
two previous dose reductions, the treatment was discontinued. The use of
granulocyte colony-stimulating factor (G-CSF) was allowed at the
discretion of the treating physician for the treatment of patients with febrile
neutropenia, grade 3–4 neutropenia or a treatment delay of >7 days because
of neutropenia.

For patients developing LVEF <50% or a 15% decrease of LVEF over
pretreatment values or congestive heart failure, the treatment was
discontinued and patients were required to undergo repeat LVEF
measurement 3 months later. Discontinuation of treatment was required
for disease progression, unacceptable toxicity and grade 3 or 4 cardiac
events. Treatment could also be discontinued at the discretion of the patient
(consent withdrawal).

baseline and follow-up evaluations

Baseline evaluation included patient history, physical examination, chest X-
rays, complete blood count (CBC) with differential, blood chemistry with
CA 15-3 and carcinoembryonic antigen (CEA) measurement,
electrocardiogram (ECG), echocardiography or multiple gated acquisition
scan (MUGA) with LVEF measurement, computed tomography (CT) scan
of chest and abdomen and a bone scan. CBCs were repeated weekly for all
patients throughout the treatment or daily in case of grade 3–4 neutropenia,
thrombocytopenia or febrile neutropenia and until hematological recovery
occurred.

Before each cycle, evaluation included patient history, physical
examination, CBC, blood chemistry with CEA and CA 15-3 determination
and an ECG. Other tests were carried out when clinically indicated. Cardiac
monitoring consisted of physical examination and ECG carried out every 3
weeks and LVEF measurement every three cycles of treatment (DE regimen).
Evaluation of response was carried out after each cycle if measurable disease
was assessable by physical examination or after every three cycles of
treatment by repeating the CT scans. All objective responses, assessed by two
independent radiologists, had to be maintained for at least 4 weeks.

Long-term follow-up included patient history, physical examination,
CBC, blood chemistry and radiological assessments every 3 months until
disease progression occurred and every 6 months thereafter until death.
Response to treatment was assessed by using RECIST. Toxicity was
graded according to NCI-CTC version 2.0.

statistical considerations

This was a prospective, multicenter, randomized phase III study. The
primary objective of the trial was to compare TTP between DE and DC
arms. Secondary end points of the study were to compare OS, response rates, duration of response, toxicity and safety between the two arms. This was designed as a superiority study based on a presumed median TTP difference between the two arms of 9 months for DE [3, 4] versus 14 months for DC (no TTP data available for DC in first-line setting), a randomization ratio 1 : 1, and an accrual period of 36 months; 136 assessable patients were required in each arm to provide 80% power with a two-sided type I error of 5%.

Duration of response was calculated from the day of the first documentation of response to disease progression; TTP was calculated from study entry until the day of the first evidence of disease progression. OS was measured from study entry to death. Follow-up time was measured from study entry to last contact or death.

The efficacy and safety analysis was carried out on all patients who received at least one dose of study medication. The actuarial survival was estimated using Kaplan–Meier curves, and the associated 95% confidence intervals (CIs) were calculated using Greenwood’s formula [15]. The comparison of OS and TTP was assessed using the log-rank test. Quantitative factors were compared by Pearson’s χ² contingency table analysis (or Fisher’s exact test whenever appropriate); relative risks were estimated by the odds ratios [15, 16]. The independent effect of treatment and other prognostic factors on the primary and secondary binary end points was analyzed by logistic regression [16, 17] and on survival and TTP by Cox proportional hazards model [15].

All clinical data were held centrally (Clinical Trial Office, Department of Medical Oncology, University General Hospital of Heraklion, Crete, Greece) and analyzed using the SPSS (version 13.0) program.

results

patient enrollment and baseline characteristics

Between May 2002 and November 2007, 307 previously untreated patients with advanced breast cancer (ABC) were assessed for enrollment in the study. Twenty-one patients were excluded because they did not meet the eligibility criteria and 286 were registered and randomly assigned to DE (n = 141) and DC (n = 145). Five patients assigned to DE and nine to DC withdrew their consent before initiation of therapy and did not receive study treatment. One hundred and thirty-six patients received DE and 136 DC. Figure 1 shows the CONSORT diagram of the study. Table 1 presents the baseline patient characteristics. There was a trend toward higher previous chemotherapy exposure in the DC arm.

![CONSORT diagram of the study](https://academic.oup.com/annonc/article-abstract/21/1/48/146142/fig1.png)
The ORR was 51.5% (95% CI 43.07% to 59.87%) with DE versus 52.9% (95% CI 44.55% to 61.33%) with DC ($P = 0.808$; Table 2). The median duration of response was 10.4 months on DE versus 13.7 months on DC ($P = 0.602$; Table 2). After a median follow-up of 39.8 months (range 1.5–75.8) in the DE arm versus 43.8 months (range 1.1–75.6) in the DC arm ($P = 0.692$), disease had progressed in 109 (80%) versus 107 (79%) patients, respectively, and 63 (46%) versus 65 (48%) patients had died. The median TTP was 10.6 versus 11.0 months ($P = 0.735$; Figure 2A) and the Kaplan–Meier estimated median OS was 37.6 versus 35.7 months ($P = 0.744$; Figure 2B), respectively. The probability of 1-year survival was 84.9% for DE and 87.3% for DC patients.

For patients who had previously received anthracyclines as neoadjuvant and/or adjuvant treatment, the ORR was 46% in both arms ($P = 0.996$); the median duration of response was 5.6 versus 8.7 months ($P = 0.664$); the median TTP was 8.1 versus 9.1 months ($P = 0.598$) and the median OS was 35.9 versus 26.6 months ($P = 0.750$), respectively.

Eighty-two (60.3%) patients in the DE arm and 80 (58.8%) in the DC arm received second or subsequent lines of chemotherapy, which included capecitabine in 25 (30.5%) patients in the DE arm and an anthracycline in 42 (52.5%) patients in the DC arm. Similar proportions of patients on DE and DC received gemcitabine (34% versus 26%, respectively) or vinorelbine (28% versus 30%, respectively) as a subsequent line of therapy.

### treatment administration

A total of 803 and 796 cycles of DE and DC regimens were administered, with a median of six (range 1–11) versus six (range 1–14) cycles per patient, respectively. The median duration of cycles were 21 (range 21–27) versus 21 (range 21–29.5) days for DE and DC regimens, respectively. Treatment delays occurred in 78 (9.7%) DE versus 85 (10.7%) DC cycles ($P = 0.524$) due to hematological (14 versus 10 cycles, respectively), non-hematological toxicity (two versus zero cycles, respectively) or both (zero versus three cycles, respectively). The remaining delays [62 (7.7%) DE cycles versus 72 (9.1%) DC cycles] were due to reasons unrelated to toxicity.
such as pending imaging studies, and patients’ personal reasons.

Dose reduction occurred in 40 (5.0%) cycles of DE versus 84 (10.6%) of DC \( (P = 0.0001) \) due to hematological (30 versus 55 cycles, respectively), non-hematological (three versus 15 cycles, respectively) or both (seven versus 14 cycles, respectively). G-CSF was administered in 499 (62%) cycles of DE versus 211 (26%) with DC \( (P = 0.0001) \). Table 3 presents the delivered dose intensities which were >90% of the protocol-planned doses for all drugs.

Treatment was completed as scheduled (six cycles) in 109 patients (80%) in the DE arm versus 107 (79%) in the DC arm. Seventeen (12.5%) versus 23 (16.9%) patients, respectively, discontinued treatment due to disease progression while four versus three, respectively, discontinued due to toxicity [febrile neutropenia \( (n = 2) \) and cardiotoxicity \( (n = 2) \) in the DE arm and ashenia \( (n = 1) \), hand–foot syndrome \( (n = 1) \) and allergic reaction \( (n = 1) \) in the DC arm. Moreover, six patients on DE and three on DC arms refused to complete the study treatment. Sixty three (46.3%) patients on DE and 65 (50.8%) on DC died of disease progression (59 versus 62 patients, respectively), toxic death (one patient on DE) or other unrelated reasons (three patients on DE arm); in addition, three patients on the DC arm were lost to follow-up.

toxicity

Table 4 presents the hematological and non-hematological toxic effects of the two regimens. Grade 3–4 neutropenia was observed in 77 patients (57%) with DE versus 62 (46%) with DC \( (P = 0.069) \), whereas febrile neutropenia was reported in 15 (11%) versus 11 (8%) patients \( (P = 0.409) \), respectively. Grade 2–3 anemia occurred in 27 (20%) patients receiving DE versus nine (7%) on DC \( (P = 0.001) \). The most common non-hematological toxicity was ashenia, which occurred at grade 2–3 in 17 (12%) patients with DE versus nine (6%) with DC \( (P = 0.099) \). Hand–foot syndrome grade 3 was observed in none with DE versus five patients (4%) with DC \( (P = 0.024) \). Nausea and vomiting grade 2–3 occurred in seven (4.7%) patients with DE versus 12 (8%) with DC \( (P = 0.067) \). Eight (6%) and four (3%) patients on DE arm developed grade 1 and 2 cardiac toxicity, respectively, consisting of decreased LVEF; no patient developed congestive heart failure. Hospitalization for the treatment of chemotherapy-related toxicity occurred in 18 (13%) patients with DE versus seven (5%) with DC \( (P = 0.021) \).

There was one toxic death in a patient on DE arm due to grade 4 neutropenia with sepsis versus none with DC arm \( (P = 0.316) \).

discussion

The primary objective of this study, which was to show a large superiority in TTP for the DC regimen compared with DE, was not met; however, the study lacks power to rule out smaller differences. Nevertheless, our results indicate that the activity and efficacy of the two regimens as first-line therapy are similar in terms of ORR, duration of response, TTP and OS. This is
especially important since almost half of our patients had previously received neoadjuvant and/or adjuvant chemotherapy which included an anthracycline in two-thirds of cases. Although the patient numbers are relatively small, the efficacy of the two regimens was similar even in the anthracycline-pretreated subgroup. Moreover, subgroup analyses based on menopausal status, performance status, ductal histology, stage i.e. disease, visceral disease and hormone receptor expression also revealed similar efficacy for the two regimens (data not shown). An effect of subsequent chemotherapy on survival cannot be excluded although only 18% of DE patients received subsequent capecitabine and 31% of DC patients an anthracycline.

The two regimens were different in terms of toxicity. DE regimen was relatively more toxic resulting in more neutropenia, anemia, asthenia and toxicity-related hospitalizations versus more hand–foot syndrome and nausea–vomiting with the DC regimen. Febrile neutropenia was similarly infrequent in the two arms, presumably because of the liberal use of G-CSF. A higher proportion of patients in the DE than the DC arm received G-CSF. This difference in G-CSF use should be attributed not only to the higher rate of severe neutropenia with DE but also to the more frequent implementation of dose reduction with the DC regimen. The observed high level of efficacy and reduced toxicity with this lower dose of DC is in accordance with previous reports indicating that dosing flexibility with the DC regimen allows management of side-effects without compromising efficacy [13].

Our study has certain limitations which should be mentioned. Based on the statistical hypothesis, the study was designed as a superiority trial to detect a large difference in TTP in favor of the DC regimen over DE, and therefore, it was not powered to detect smaller differences which may in fact exist between the two arms. Furthermore, the study population was very heterogeneous, and although major differences in patient characteristics were not observed, a differential effect in the efficacy of the two regimens for a specific subgroup of patients cannot be excluded. The observed increased toxicity with the DE regimen could be related to the more frequent dose reductions implemented with the DC regimen. Although severe cardiac toxicity was not observed with the DE regimen, the omission of routine LVEF measurements on the DC arm introduced a potential bias in cardiotoxicity assessment. Also, since quality-of-life data were not recorded, the difference in toxicity between the two regimens could not be determined from the patients’ perspective.

Another yet unpublished study has compared the paclitaxel–epirubicin combination with the paclitaxel–capecitabine regimen as first-line treatment of MBC [18]; in the final report, the two regimens were found to have similar efficacy but different toxicity similar to the results of the present study. In another study, the DC regimen has been directly compared with the docetaxel–gemcitabine (DG) regimen in anthracycline-pretreated patients with MBC [19]. The results indicate that the DC and DG regimens have similar efficacy but the DG regimen is favored because of less non-hematological toxicity. However, the capcitabine dose used in that study (1250 mg/m²) was higher than that used in the present trial (950 mg/m²). Finally, recent data have shown that the toxicity and efficacy of the DC regimen could be further optimized by changing the treatment schedule [20] or selecting patients based on thymidine phosphorylase expression in the primary tumor [21].

In conclusion, this multicenter randomized study indicates that the DE and DC regimens have similar efficacy but different toxicity as first-line treatment of ABC. Until individualized therapy becomes a reality in everyday clinical practice, either regimen can be used for the treatment of women with HER2-negative ABC who due to aggressive disease might benefit from combination chemotherapy.

disclosure

The authors indicated no potential conflicts of interest.

Table 4. Hematological and non-hematological toxicity

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>DE (n = 136)</th>
<th>DC (n = 136)</th>
<th>P value</th>
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<tr>
<td></td>
<td>1 n (%)</td>
<td>2 n (%)</td>
<td>3 n (%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>89 (65)</td>
<td>26 (19)</td>
<td>1 (0.7)</td>
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<tr>
<td>Neutropenia</td>
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<td>15 (11)</td>
<td>30 (22)</td>
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<td>1 (0.7)</td>
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<td>Thrombocytopenia</td>
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<td>1 (0.7)</td>
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<td>Nausea/vomiting</td>
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<td>6 (4)</td>
<td>1 (0.7)</td>
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<tr>
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<td>9 (7)</td>
<td>8 (6)</td>
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<tr>
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<td>8 (6)</td>
<td>4 (3)</td>
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<td>4 (3)</td>
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</tr>
<tr>
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<td>29 (21)</td>
<td>15 (11)</td>
<td>2 (1)</td>
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<td>Hypersensitivity reactions</td>
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<td>Nail changes</td>
<td>4 (2.9)</td>
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*aComparison of grade 2–3.
*bComparison of grade 3–4.
References