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CLINICAL TRIAL

# Individually tailored treatment with epirubicin and paclitaxel with or without capecitabine as first-line chemotherapy in metastatic breast cancer: a randomized multicenter trial

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**Abstract** Anthracyclines and taxanes are active cytotoxic drugs in the treatment of early metastatic breast cancer. It is yet unclear whether addition of capecitabine to the combination of these drugs improves the treatment outcome. Patients with advanced breast cancer were randomized to first-line chemotherapy with a combination of epirubicin (Farmorubicin®) and paclitaxel (Taxol®) alone (ET) or in combination with capecitabine (Xeloda®, TEX). Starting doses for ET were epirubicin 75 mg/m$^2$ plus paclitaxel 175 mg/m$^2$, and for TEX epirubicin 75 mg/m$^2$, paclitaxel 155 mg/m$^2$, and capecitabine 825 mg/m$^2$ BID for 14 days. Subsequently, doses were tailored related to side effects. Primary endpoint was progression-free survival (PFS); secondary endpoints were overall survival (OS), time to treatment failure (TTF), objective response (OR), safety and quality of life (QoL). 287 patients were randomized, 143 to ET and 144 to TEX. Median PFS was 10.8 months

This study was conducted on behalf of TEX study group.

Participating investigators of the TEX study group are given in Appendix.

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for patients treated with ET, and 12.4 months for those treated with TEX (HR 0.84, 95% CI 0.65–1.07, $P = 0.16$); median OS was 26.0 months for women in the ET versus 29.7 months in the TEX arm (HR 0.84, 95% CI 0.63–1.11, $P = 0.22$). OR was achieved in 44.8% (ET) and 54.2% (TEX), respectively ($\chi^2$ 3.66, $P = 0.16$). TTF was significantly longer for patients treated with TEX, 6.0 months, versus 5.2 months following ET (HR 0.73, 95% CI 0.58–0.93, $P = 0.009$). Severe hematological side effects related to epirubicin and paclitaxel were evenly distributed between the treatment arms, mucositis, diarrhea, and Hand-Foot syndrome were significantly more frequent in the TEX arm. Toxicity-adjusted treatment with ET and TEX showed similar efficacy in terms of PFS, OS, and OR. In this trial with limited power, the addition of capecitabine to epirubicin and paclitaxel as first-line treatment did not translate into clinically relevant improvement of the outcome.

**Keywords** Advanced breast cancer · First-line treatment · Epirubicin · Paclitaxel · Capecitabine

## Introduction

Anthracyclines and taxanes are commonly used cytotoxic drugs in adjuvant therapy and for treatment of early disseminated breast cancer. The combination of an anthracycline with the taxane paclitaxel has been found more efficient in terms of response and time to treatment failure (TTF) than use of either of the drugs alone [1]. For previously untreated patients or for those who have received few cycles of adjuvant treatment with either one or both drugs, anthracycline–taxane combinations may be one reasonable option in the management of metastatic disease. Due to the frequent use of these compounds in the adjuvant setting, there is need for additional drugs in the management of early metastatic disease. Capecitabine is one such option. This compound is, after transformation to the prodrug 5′DFUR, converted into fluorouracil (5-FU) in the presence of the enzyme thymidine phosphorylase (TP). The concentration of fluorouracil is dependent on TP which is enriched in the liver and in tumor tissue [2]. Enhancement of the transformation of capecitabine into fluorouracil in the presence of taxanes has been confirmed by laboratory data. The taxanes, in particular paclitaxel, induce TP, possibly through induction of TNFα [3, 4]. As a result of the combination of a taxane with capecitabine, induction of TP in tumor tissue is expected to increase the local concentration of fluorouracil, resulting in a synergistic rather than additive effect of this combination. This is supported by clinical observations of a significant relationship between response to treatment with the combination of the taxane docetaxel and capecitabine and expression of TP in tumor tissue [5]. Also, anthracyclines have been reported to enhance TP upregulation [6].

A phase II trial on the combination of capecitabine with paclitaxel in patients pretreated with anthracycline showed promising results in terms of objective response (OR) and time to progression [7]. High response rates were also reported from a phase II trial evaluating the combination of epirubicin, capecitabine, and docetaxel [8]. Data from a randomized phase III trial of docetaxel plus epirubicin with or without capecitabine presented at the ASCO meeting 2008 by the same group showed significantly higher response rates for the three-drug combination, but no significant improvement of progression-free survival (PFS) [9].

Despite debate on dose intensity and individual dose adjustment [10–12], chemotherapy is generally dosed in relation to the body surface area (BSA). Dose reductions are performed in relation to the grade of toxicity, but it is not common practice to increase doses above standard as a consequence of no or few side effects. Studies on single nucleotide polymorphisms (SNP) have shown that drug tolerance and efficacy are better explained by genetic host characteristics than BSA [13]. In the present trial, we chose to modify the drugs with increasing or decreasing doses separately in relation to the experienced side effects. This concept was tested in a pilot trial by our group [14].

The rationale of this trial was to investigate, if the proposed conversion of capecitabine to 5-fluorouracil in the presence of higher concentrations of TP induced by the taxane results in higher efficacy of the combination. With the intention to minimize the significance of merely the addition of one further drug, a concept of individual adjustment to equitoxic doses was applied. The study was planned as a composite translational research project. In addition to the comparison between the two different treatment schedules, tumor tissue samples were obtained from patients with metastatic sites accessible for aspiration biopsy. Also, tissue from the primary tumors and blood samples were collected. The results from correlations with the clinical data will be reported separately.

## Patients and methods

The study was designed as an open-labeled randomized multicenter phase III trial with three treatment arms, where one option entailed a combination of epirubicin (Farmorubicin®) and paclitaxel (Taxol®, ET), the second a three-drug combination containing the same drugs but with the addition of capecitabine (Xeloda®, TEX). A third arm contained a combination of fluorouracil, epirubicin, and cyclophosphamide (FEC), and was designed as standard treatment. However, since publications showed superiority

of treatment alternatives containing taxanes [15], the TEX trial group took the decision to discontinue randomization to FEC in May 2004. Therefore, the 17 patients who had been allocated to this option were not included in the present analyses. Likewise, it was decided to terminate enrollment of patients with HER2 amplified tumors in June 2006 after publication of data demonstrating the importance of early onset of treatment with trastuzumab [16, 17]. These patients are, however, included in the analyses.

The study was approved by the Independent Review Boards with jurisdiction for the participating centers and by the Swedish Medical Product Agency. All patients received oral and written information about the study and consented to participate.

## Patients

Study subjects with morphologically confirmed locoregional inoperable or disseminated breast carcinoma were enrolled unless they had received treatment with an anthracycline, a taxane or 5-FU within 1 year before study entry. Previous endocrine treatment for advanced disease in patients with hormone receptor positive breast cancer was allowed. Patients with known brain metastases or other malignancies within the last 5 years were excluded.

## Study treatment and assessments

Patients were randomized to receive either epirubicin 75 mg/m$^2$ and paclitaxel 175 mg/m$^2$ (ET) on day 1 or the combination of epirubicin 75 mg/m$^2$, paclitaxel 155 mg/m$^2$ on day 1 and capecitabine 825 mg/m$^2$ BID on days 1–14 (TEX). After the first course, treatment was individually adjusted in relation to the grade of toxicity (Table 1). Both combinations were administered in a 3-week schedule. All patients received premedication with cetirizine, ranitidine, corticosteroids, and antiemetics. Prophylactic use of G-CSF was used if necessary. Response evaluations based on RECIST version 1.0 [18] were performed after every third course. In patients with metastases confined to bone, WHO classification criteria for evaluation of bone metastases based on bone X-rays were applied [19]. New lesions detected either by CT scan or bone scan were considered as progressive disease regardless of response in previously observed metastases. Treatment was continued until progression, occurrence of unacceptable toxicity or other medical reasons, or on patients' request for termination. In cases with stable disease or OR with no further improvement found at repeated evaluations, study treatment was, on patients' request, replaced by either endocrine treatment in cases with hormone receptor positive tumors, or, in the ET arm, switch to treatment with capecitabine alone using 1,250 mg/m$^2$ × 2 days 1–14 as starting dose. In patients with stable response in whom accumulated epirubicin doses approached levels of increased risk of cardiac toxicity (≥900 mg/m$^2$), or who experienced intolerable symptoms related to any of the cytotoxic drugs despite dose adjustment, treatment continued after removal of these drugs until progression or other medical reasons for terminating the treatment. Patients who progressed after first-line treatment with ET were offered capecitabine as second-line treatment on progression. Toxicity was reported after every course of treatment and was graded according to NCI CTC version 2.0.

**Table 1** Individualized dose schedules

| Drug | Dose steps | |
|---|---|---|
| | ET | TEX |
| Epirubicin [day 1 (mg/m$^2$ IV)] | | |
| 60 | −1 | −1 |
| 75 | 0 | 0 |
| 90 | 1 | 1 |
| Paclitaxel [day 1 (mg/m$^2$ IV)] | | |
| 135 | −2 | −1 |
| 155 | −1 | 0 |
| 175 | 0 | 1 |
| 200 | 1 | 2 |
| Capecitabine [day 1–14 (mg/m$^2$ PO)] | | |
| 425 × 2 (850) | | −2 |
| 625 × 2 (1,250) | | −1 |
| 825 × 2 (1,650) | | 0 |
| 1,000 × 2 (2,000) | | 1 |
| 1,250 × 2 (2,500) | | 2 |

Patients were started on level "0". Doses for each of the drugs was thereafter adjusted individually

## Statistical design

Randomization was performed using a permuted block technique, stratified for the 10 participating centers. The two treatments were compared with regard to PFS as the primary endpoint, defined as the interval from date of randomization to date of disease progression or death. TTF, defined as the time from randomization until termination on progression, death, toxicity or patients wish, overall survival (OS), OR rate, safety and quality of life (QoL) were secondary endpoints. Patients randomized to ET or TEX were included in the analysis (intention to treat). Treatment with the combination ET was regarded as reference treatment in this study. With an expected 6 months median progression-free period for patients in this group, a prolongation by 2.5 months following the TEX regimen was regarded as a clinically relevant benefit. We assumed that the progression-free survival functions were

exponentially distributed giving an expected hazard ratio of TEX versus ET of 0.7059. Using standard formulas [20], we calculated a required number of 258 events plus additional 10% for patients without "events" at the time of the main analysis, totally 284 patients. In the dimensioning, a 3.5-year accrual period followed by a 12 months follow-up period was assumed.

Comparisons of groups were performed using standard Chi-square procedures. For analyses of prognostic variables, the log rank test for univariate and Cox proportional hazard models for multivariate analyses were applied. All analyses were performed using the statistical package JMP version 7.0.1.

**Table 2** Baseline characteristics of the primary tumors

| | ET | % | TEX | % |
|---|---|---|---|---|
| TNM stage at diagnosis | | | | |
| 1 | 20 | *14* | 30 | *21* |
| 2 | 79 | *56* | 74 | *52* |
| 3 | 22 | *16* | 19 | *13* |
| 4 | 20 | *14* | 19 | *13* |
| Unknown | 2 | | 2 | |
| Histologic subtype | | | | |
| Ductal | 110 | *79* | 115 | *83* |
| Lobular | 20 | *14* | 17 | *12* |
| Other | 9 | *6* | 6 | *4* |
| Unknown | 4 | | 6 | |
| Histologic grade | | | | |
| 1 | 7 | *6* | 3 | *3* |
| 2 | 47 | *41* | 60 | *51* |
| 3 | 60 | *53* | 55 | *47* |
| Unknown | 29 | | 26 | |
| Estrogen receptor | | | | |
| Negative | 37 | *28* | 24 | *18* |
| Positive | 97 | *72* | 109 | *82* |
| Unknown | 9 | | 11 | |
| Progesterone receptor | | | | |
| Negative | 57 | *44* | 46 | *39* |
| Positive | 73 | *56* | 73 | *61* |
| Unknown | 13 | | 25 | |
| HER2 status | | | | |
| Negative | 83 | *92* | 76 | *95* |
| Positive | 7 | *8* | 4 | *5* |
| Unknown | 53 | | 64 | |
| Adjuvant systemic treatment | | | | |
| None | 24 | *20* | 19 | *15* |
| Chemotherapy alone | 25 | *20* | 28 | *23* |
| Endocrine treatment alone | 25 | *20* | 37 | *30* |
| Chemotherapy followed by endocrine treatment | 49 | *40* | 40 | *32* |
| Unknown | | | 1 | |

Adjuvant therapy is reported only for patients with limited disease (stages 1–3)

## Results

### Patient population

From December 2002 until June 2007, 291 patients were included. Four patients were randomized but never treated. Two of these were incorrectly randomized, before the involved participating center had been approved by the Swedish Medical Product Agency. A third patient was diagnosed with brain metastases, and the fourth with liver lesions detected by CT scan but, after randomization, identified as benign by cytology. In both of these latter cases, the incorrect inclusion was detected within few days after randomization. Two hundred eighty-seven patients were eligible, 143 in the ET and 144 in the TEX arm. Tumor characteristics at diagnosis of the primary tumor are shown in Table 2. The disease-free interval was 2 years or less in 43 cases (30%) in the ET versus 40 (28%) in the TEX arm. The majority, 204 patients (71%), had received previous adjuvant therapy. Among these, 74 women (52%) in the ET arm and 68 (47%) in the TEX arm had received adjuvant chemotherapy, either alone or followed by endocrine treatment. The adjuvant chemotherapy regimens contained anthracyclines in 57 women in the ET arm and 45 in the TEX arm, fluorouracil in 70 (ET), and 61 cases (TEX), respectively. Use of a taxane was limited to docetaxel in three (ET) and two women (TEX). In none of these cases had chemotherapy been given <12 months before enrollment in the present trial.

Previous local relapse without signs of dissemination was found in 42 cases (15%), 18 (13%) in the ET and 24 (17%) in the TEX arm. Five of these patients underwent surgery followed by a limited series of chemotherapy, one in the TEX arm and four in the ET arm. These patients had not received adjuvant chemotherapy before, and the chemotherapy following local recurrence had been terminated at least 12 months before randomization.

Eighty-six patients, 30%, with hormone receptor positive tumors had received endocrine therapy as first-line treatment of disseminated disease prior to enrollment, 24% (ET), and 35% (TEX), respectively.

Median age at study entry was 57.0 years for patients allocated to ET and 55.7 years for those receiving TEX. Seventy-one (25%) had metastases confined to one site, with bone metastases accounting for 20 cases as the most frequent localization, followed by 19 each for lymph node and liver metastases. The vast majority, 75%, had multiple sites involved. Distribution of all reported metastatic sites is shown in Table 3.

**Table 3** Distribution of metastatic sites

| Metastatic site | ET | % | TEX | % |
|---|---|---|---|---|
| Local recurrence or contralateral breast | 48 | *34* | 24 | *17* |
| Skin, non-local | 19 | *13* | 22 | *15* |
| Lymph nodes | 71 | *50* | 79 | *55* |
| Bone | 74 | *52* | 81 | *56* |
| Lung/pleura | 77 | *54* | 71 | *49* |
| Liver | 64 | *45* | 65 | *45* |

Twenty-five percent had metastases in a single metastatic site, 75%, had multiple sites involved

## Efficacy

The median PFS was 10.8 months for patients treated with ET compared with 12.4 months for those who had received TEX (HR 0.84, 95% CI 0.65–1.07, $P = 0.16$, Fig. 1a). Median OS was 26.0 months for women treated with ET versus 29.7 months for those treated with TEX (HR 0.84, 95% CI 0.63–1.11, $P = 0.22$, Fig. 1b).

TTF was significantly different between the two alternatives (Fig. 2). The median treatment period was 5.2 months for ET and 6.0 months for TEX (HR 0.73, 95% CI 0.58–0.93, $P = 0.009$) with treatment duration up to 19 months with ET and 42 months with TEX.

Median PFS for the subgroup of patients with triple-negative tumors was 6.1 months with ET, and 12.1 months with TEX. Based on only 66 patients in this subgroup, the difference between the two treatments was not significant. Independently from the treatment arm, chemonaïve patients with primarily metastatic disease had a significantly longer time to progression compared with those who had received adjuvant chemotherapy (HR 0.77 HR, 95% CI 0.60–0.99, $P = 0.039$). Only 10 patients with primary histologic grade 1 tumors were enrolled. These tumors were associated with a shorter progression-free survival, 7.9 months, compared with grade 2 (14.0 months) and grade 3 tumors (10.0 months, $P = 0.01$). Although these factors had prognostic impact on the post-recurrence survival, none of them favored any of the two treatment alternatives on a significant level. Previous endocrine treatment had no impact on the efficacy of the chemotherapy regimens used in the trial.

Of the eligible 287 patients, 269 (94%) were evaluable for response according to RECIST (Table 4). OR (CR + PR) was achieved in 53% of the patients. The proportion of OR was higher in women allocated to treatment with TEX, but the difference was not statistically significant ($\chi^2$ 3.66, $P = 0.16$). It should be mentioned that eight of the eleven patients presenting with complete response had not received any previous adjuvant chemotherapy.

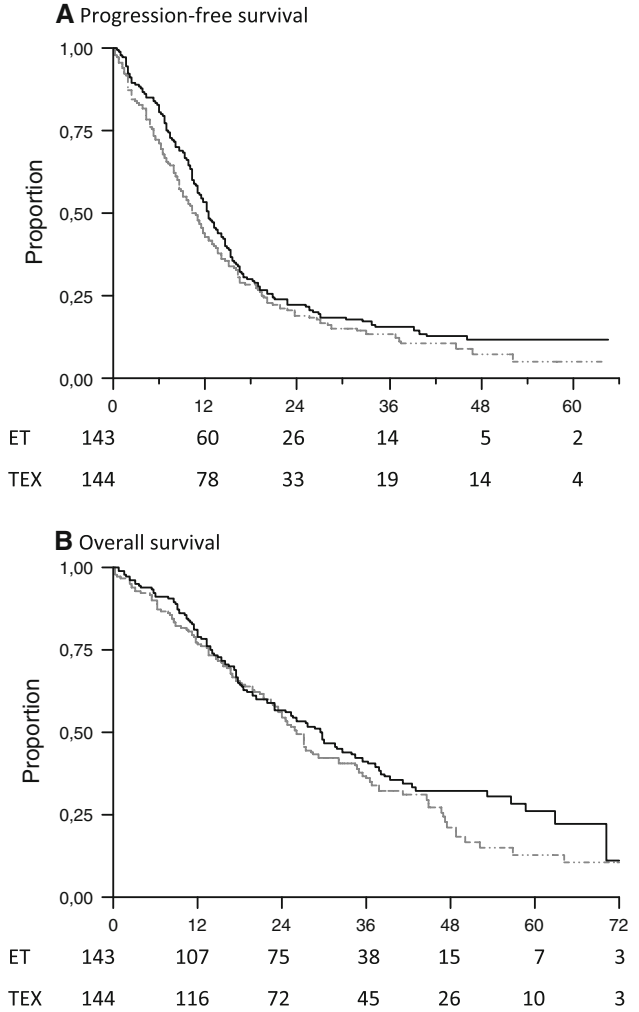


**Fig. 1** **a** progression-free survival (HR 0.84, 95% CI 0.65–1.07, $P = 0.16$) and **b** overall survival (HR 0.84, 95% CI 0.63–1.11, $P = 0.22$) in months since randomization. ET: *dotted line*, TEX: *black line*

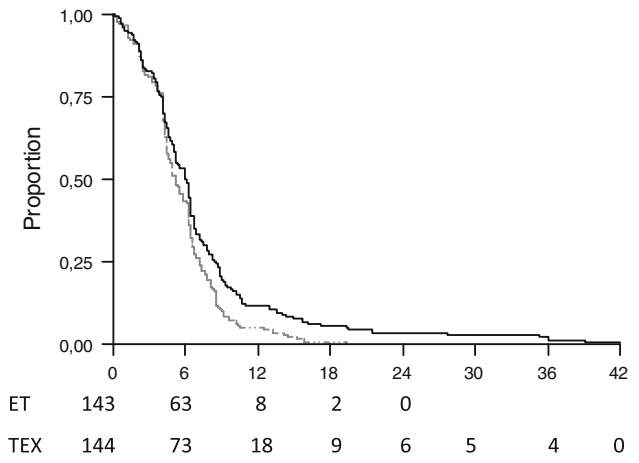


**Fig. 2** Time to treatment failure (TTF) for first-line treatment shows a significant difference in favor of the TEX combination (HR 0.73, 95% 0.58–0.93, $P = 0.009$). ET: *dotted line*, TEX: *black line*

**Table 4** Response according to RECIST 1.0 and WHO (bone) based on 269 evaluable patients ($\chi^2$ 3.66, $df = 2$, $P = 0.16$)

| | ET | % | TEX | % |
|---|---|---|---|---|
| Objective response | 64 | *48* | 78 | *58* |
| Complete response | 5 | *4* | 6 | *4* |
| Partial response | 59 | *44* | 72 | *53* |
| Stable disease | 50 | *37* | 45 | *33* |
| Progressive disease | 20 | *15* | 12 | *9* |
| Unable to determine | 9 | | 9 | |

Treatment was discontinued in 31% of cases due to progressive disease and in 19% due to toxicity (Table 5). In accordance with the protocol, patients with stable disease or OR were, after repeated evaluations without indication of further improvement, offered maintenance treatment with capecitabine (following ET), endocrine treatment in case of hormone receptor positive tumors, local treatment of limited disease, or watchful waiting until progression. The majority, 104 patients (36%), chose to switch to one of these treatment options.

## Safety

Febrile neutropenia was equally frequent in both treatment arms (Table 6). Symptoms related to paclitaxel, such as sensory neuropathy, myalgia/arthralgia, and fatigue were more common among patients treated with ET. Vascular events including deep vein thrombosis (DVT) and pulmonary embolism were more frequently reported due to TEX, assessed as life-threatening in nine of ten cases. These differences between the treatment arms were not statistically significant. In contrast, mucositis, diarrhea, and Hand-Foot syndrome grades 1–3 were significantly more often reported by patients who received capecitabine ($P < 0.0001$).

In total, 135 Serious Adverse Events with probable or certain relationship to the study treatment were reported. Nineteen events of febrile neutropenia were reported for each of the treatment arms, in three cases life-threatening (grade 4). On the recommendation to add G-CSF prophylactic, the frequency of reported cases of febrile neutropenia decreased. Symptoms related to congestive heart failure (CHF) prompted treatment discontinuation in 13 cases, three of these with severe symptoms. All but one of these cases had received cumulative doses of epirubicin exceeding 800 mg/m$^2$, but there was no relationship to accumulated doses of capecitabine or to radiotherapy of the left thoracic wall. Due to the observed cardiotoxicity, the trial group decided to lower the threshold for maximum cumulative doses of epirubicin per individual to 800 mg/m$^2$. Two of the patients who received capecitabine as second-line treatment after previous therapy with ET developed CHF during treatment with this drug. In both arms, acute drug reactions were reported as serious events in three cases. Serious diarrhea (grade 3) was reported in seven cases associated with ET and 14 in cases with TEX treatment.

**Table 5** Reasons for termination of treatment

| | ET | % | TEX | % |
|---|---|---|---|---|
| Progressive disease | 47 | *33* | 42 | *29* |
| Toxicity | 24 | *17* | 30 | *21* |
| Patients' request | 8 | *6* | 15 | *10* |
| Clinical benefit (stable disease ≥6 cycles or confirmed objective response) | | | | |
| Switch to capecitabine until progression* | 15 | *10* | | |
| Endocrine treatment | 38 | *27* | 38 | *26* |
| Local treatment with radiotherapy/surgery | 5 | *3* | 6 | *4* |
| No treatment until progression | 0 | – | 2 | *1* |
| Other reasons, not specified | 6 | *4* | 9 | *6* |
| Ongoing treatment | 0 | – | 2 | *1* |

* ET arm only

Four treatment-related deaths (1.4%) occurred: two patients, one in each arm, succumbed due to septic shock following neutropenia; the other two due to circulatory shock (ET) and severe cardiac heart failure (TEX).

Eight percent of the patients requested change of treatment because they experienced side effects as intolerable.

## Dose intensity

Patients received at median seven cycles in both treatment arms. Mean dose intensity related to the starting dose of epirubicin was 95.6% (71.7 mg/m$^2$/3 weeks), of paclitaxel 92.9% (162.6 mg/m$^2$/3 weeks) in the ET combination versus 88.8% of epirubicin (66.6 mg/m$^2$/3 weeks) and 92.5% of paclitaxel (143.4 mg/m$^2$/3 weeks) of starting doses in the TEX combination. The mean dose intensity of capecitabine was lower than anticipated in the TEX arm, 67.6% (557.8 mg × 2/m$^2$/3 weeks).

## Second-line treatment

Seventy of the 143 patients (49%) randomized to the ET arm received capecitabine as second-line monotherapy, either due to side effects of ET with persistent OR (15 patients) or on progression (55 patients). Partial response following capecitabine was found in eight patients (12%), stable disease in 32 patients (49%). Twenty-five cases (38%) progressed without response. In five cases, response could not be evaluated. Median time to progression was 6.0 months; median TTF was 4.4 months. Reasons for

**Table 6** Proportion of patients with toxicity of all grades and severe (grade 3/4) toxicity according to CTC v. 2.0

| Treatment arm | ET | | | | TEX | | | |
|---|---|---|---|---|---|---|---|---|
| Grades | All | % | 3/4 | % | All | % | 3/4 | % |
| Febrile neutropenia | 28 | *20* | 25 | *17* | 29 | *20* | 25 | *17* |
| Sensory neuropathy | 113 | *79* | 15 | *10* | 110 | *76* | 6 | *4* |
| Mucositis | 71 | *50* | 3 | *2* | 105 | *73* | 4 | *3* |
| Diarrhea | 51 | *36* | 7 | *5* | 86 | *60* | 14 | *10* |
| Fatigue | 112 | *78* | 9 | *6* | 116 | *81* | 8 | *6* |
| Myalgia/Arthralgia | 106 | *74* | 9 | *6* | 92 | *64* | 6 | *4* |
| Cardiac toxicity | 8 | *6* | 4 | *3* | 17 | *12* | 6 | *4* |
| Hand-foot syndrome | 10 | *7* | 1 | *1* | 93 | *65* | 10 | *7* |
| Deep vein thrombosis | 2 | *1* | 2 | *1* | 9 | *6* | 8 | *6* |
| Pulmonary embolism | 4 | *3* | 4 | *3* | 10 | *7* | 10 | *7* |
| Dyspnea | 7 | *5* | 2 | *1* | 10 | *7* | 5 | *3* |
| Hypersensitivity | 40 | *28* | 7 | *5* | 27 | *19* | 6 | *4* |

Mucositis, diarrhea, and hand-foot syndrome grades 1–3 were more frequently reported by patients treated with TEX ($P < 0.0001$)

treatment disruption were disease progression in 45 cases (64.3%), and toxicity in 17 cases (24.3%). Three patients with confirmed partial response requested switch to endocrine therapy. One woman died 1.6 months after start of therapy due to breast cancer, and in four cases, the reason for disruption was not reported.

## Discussion

Addition of a drug to combination chemotherapy improves response rates, particularly if an anthracycline is involved, but has only limited impact on the outcome [21]. Use of taxanes improves the efficacy of treatment significantly [22]. A trial comparing standard treatment with fluorouracil, doxorubicin, and cyclophosphamide (FAC) with a combination of doxorubicin and paclitaxel (AT) showed significant benefit in favor of the regimen containing paclitaxel, 220 mg/m$^2$ [15]. This contrasts with findings from another trial with AT using lower doses of paclitaxel, 175 mg/m$^2$, which failed to show superiority of AT compared with doxorubicin and cyclophosphamide (AC) [23]. Capecitabine is a highly efficient drug in metastatic breast cancer, even in patients previously treated with chemotherapy regimens including taxanes [24]. Presuming a biological synergy between epirubicin and paclitaxel and the prodrug capecitabine, an addition of this drug would be expected to improve the efficacy of the treatment. Previously presented phase II data, either with a similar three-drug combination using docetaxel [8], or paclitaxel with capecitabine in patients pretreated with an anthracycline [7] showed promising results, but a randomized phase III trial comparing a combination of docetaxel and epirubicin alone or together with capecitabine failed to show a significant prolongation of PFS [9]. In this study, the observed PFS exceeded the anticipated time period, which altered the power of the study to reveal a minor difference between the study arms.

Effective cytotoxic treatment is restricted by the accumulation of persistent side effects during long-term treatment. The use of anthracyclines, in the present trial epirubicin, involves a risk of cardiac toxicity unless discontinued at defined maximum cumulative doses. Paclitaxel causes cumulative neurotoxicity and fatigue as major side effects in a large group of patients. Therefore, the use of these drugs is limited despite lasting benefit. In the TEX arm, treatment continued with capecitabine alone after termination of epirubicin and/or paclitaxel. The long-term use probably explains the low-dose intensity compared with the other drugs. Capecitabine is easier administered for a longer period of time since it allows for dose adjustments on a day-to-day basis. The prolonged use of this drug reflects efficacy during a long time period in spite of reduced dosage of the drug.

Use of predefined doses of cytotoxic drugs adjusted to BSA is common practice in the treatment of solid tumors. Combination chemotherapy regimens using more intense dose schedules have better prospects to prolong survival compared with low-dose regimens [25]. Several studies comparing regimens involving anthracyclines and/or taxanes in metastatic breast cancer have shown significantly improved outcome for the group of patients allocated to the drug or drug combination with more toxicity [15, 26]. Conclusions drawn from these trials might have been altered if the competing drug regimens had been tailored in relation to hematological toxicity. This question is relevant for breast cancer trials involving both anthracyclines and taxanes, since both drug

groups cause comparable rates of neutropenia. In the present protocol, the starting dose for paclitaxel was lower in the three-drug combination in order to create equivalent levels of toxicity. Thereafter, separate dose adjustments for each of the drugs in relation to observed side effects were encouraged. The purpose was to reduce the impact of dose intensity as a major factor for differences in efficacy concealing the pure effect of the combination of paclitaxel as inducer of TP and conversion of capecitabine into active 5-fluorouracil in the tumor tissue. This approach allows for dose intensities adapted to individual drug tolerance as an alternative to BSA. Individually tailored treatment schedules have been tested in a few randomized trials on solid tumors based either on the degree of bone-marrow reaction [27] or on pharmacokinetic concentrations of the cytotoxic drug based on data from previous treatment cycles [28]. In these trials, individualized dose adjustment resulted in an improvement of the outcome compared with standard dosing based on BSA. An individualized dose adjustment on a cycle-to-cycle basis for fluorouracil-related drugs is supported by measurements of the activity of dihydropyrimidine dehydrogenase (DPD) in peripheral mononuclear cells related to the metabolism of fluorouracil which may vary in relation to nutritional and other environmental conditions [29]. Data from a small trial also indicates that both TP and DPD have impact on the therapeutic efficacy of capecitabine [30].

In spite of preclinical data suggesting synergism between taxanes and capecitabine and previously published promising phase II data on the addition of capecitabine to paclitaxel or docetaxel, the present trial could not significantly confirm improvement of the outcome associated with the combination of these drugs, despite a favorable hazard ratio for the TEX combination in terms of PFS and OS. Both treatment alternatives exceeded the progression-free period anticipated for use of taxane combinations. A recently published QoL analysis comparing the two treatments in this trial favored the TEX treatment [31]. In trials with equivocal results, QoL might be a useful instrument to decide on the choice of treatment alternative.

Which patients will respond to treatment with anthracycline–taxane–capecitabine combinations? In an era of rapid development of the understanding of biological processes, access to tumor tissue is a prerequisite to study the mechanisms behind treatment response and resistance. As part of the present trial, fine-needle aspirates from metastases and blood samples were collected shortly before start of treatment. These samples are currently analyzed with the intention to relate tumor biological characteristics to treatment response in metastatic disease. We hope that this investigation will reveal new predictive markers for the treatment of patients with advanced breast cancer. These results will be presented separately.

## Conclusion

Toxicity-adjusted tailored treatment with both ET and TEX showed similar efficacy in terms of PFS, OS, and OR. However, the addition of capecitabine to epirubicin and paclitaxel as first-line treatment in metastatic breast cancer did not translate into clinically relevant improvement of the outcome in the present trial.

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## Appendix

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