Epirubicin and cyclophosphamide versus epirubicin and docetaxel as first-line therapy for women with metastatic breast cancer: final results of a randomised phase III trial

J.-U. Blohmer1,2†, P. Schmid3†, J. Hilfrich4, K. Friese5,6, A. Kleine-Tebbe7, H. Koelbl8, H. Sommer5, G. Morack9, M. B. Wischnewsky10, W. Lichtenegger1,7 & S. Kuemmel1,11

1Department of Gynaecology and Obstetrics, Campus Charité Mitte, Charité University Hospital; 2Department of Gynaecology and Obstetrics, Sankt Gertrauden-Krankenhaus, Berlin, Germany; 3Department of Medical Oncology, Charing Cross Hospital, Imperial College London, London, UK; 4Department of Gynaecology and Obstetrics, Henriettenstift, Hannover; 5Department of Gynaecology and Obstetrics, Ludwig-Maximilians University, München; 6Department of Gynaecology and Obstetrics, University of Rostock, Rostock; 7Department of Gynaecology and Obstetrics, Charité Campus Virchow Klinikum, Charité University Hospital, Berlin; 8Department of Gynaecology and Obstetrics, Martin-Luther University Halle-Wittenberg, Halle; 9Department of Gynaecology and Obstetrics, Helios Klinikum Berlin-Buch, Berlin; 10Department of Biomathematics and Intelligent Systems, University of Bremen, Bremen and 11Breast Unit, Cancer Centre Essen, Kliniken Essen-Mitte, Essen, Germany

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Background: This randomised phase III trial was carried out to compare the efficacy and safety of epirubicin and cyclophosphamide (EC) with epirubicin and docetaxel (Taxotere) (ED) as first-line chemotherapy for metastatic breast cancer.

Patients and methods: Patients (n = 240) were randomly assigned to receive either ED (epirubicin 75 mg/m² and docetaxel 75 mg/m²) or EC (epirubicin 90 mg/m² and cyclophosphamide 600 mg/m²). The primary end point was objective response rate (ORR). Secondary end points were progression-free survival (PFS), overall survival (OS), and safety.

Results: ORR for patients randomly assigned to receive EC and ED were 42% and 47%, respectively (P = 0.63). Median PFS [10.1 versus 10.3 months; hazard ratio (HR) 0.98; log-rank P = 0.38] and OS (19.9 versus 30.0 months; HR 0.663; log-rank P = 0.21) were comparable in both arms. Although grade 3/4 leucopenia occurred more frequently with ED (81% versus 73%; P = 0.01), there were no significant differences in the incidence of febrile neutropenia and grade 3/4 infections. Grade 3/4 non-haematologic toxicity was infrequent in both arms. Congestive heart failure was observed in one patient in each arm.

Conclusion: In this randomised trial, no differences in the efficacy study end points were observed between the two treatment arms.

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

Introduction

Breast cancer is the most common malignancy affecting women in northern Europe and North America, corresponding to an age-corrected annual incidence of 10–12 per 10 000 females. Approximately, 15%–20% of all patients treated with curative intent develop metastatic disease. Currently available treatments are unable to eradicate metastatic breast cancer (MBC). Consequently, treatment goals are to prolong survival, to prolong disease control, and to provide better palliation for patients.

Anthracyclines are among the most active chemotherapeutic agents for the treatment of MBC with response rates ranging from 20%–40% as single-agent therapy [1–5] to 35%–70% when used in combination regimens in untreated populations [6–11]. At the time this study was developed, combinations of anthracyclines and cyclophosphamide were commonly used as first-line chemotherapy, with or without 5-fluorouracil. With the introduction of the taxanes in the 1990s, however, which showed significant activity in first- or second-line MBC and incomplete clinical cross-resistance to anthracyclines, the combination of these two types of agents became a logical next step. Several randomised trials were initiated to evaluate...
patients and methods

study design

This multicentre, open-label, randomised phase III trial was conducted at 49 centres in Germany. The randomisation was centralised with a block design by study centre. There was no stratification for patient characteristics. Enrolment began in February 2000 and ended in November 2003. The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Tripartite Guidelines for Good Clinical Practice, in compliance with local regulations, and with the approval of an independent ethics committee. The primary objective was to compare objective response rates (ORRs) between both treatments. Secondary objectives included comparison of TTP, OS, and safety.

patient eligibility

Eligible patients had to have histologically confirmed MBC and no prior chemotherapy for metastatic disease. Adjuvant chemotherapy with anthracyclines was allowed, but the cumulative doxorubicin and epirubicin doses had to be <300 mg/m² and <420 mg/m², respectively. Patients were required to have measurable disease. All patients had to have adequate haematologic, renal, hepatic, and cardiac function (absolute neutrophil count (ANC) ≥2.0 × 10⁹/l; platelets ≥100 × 10⁹/l; haemoglobin ≥10 g/dl; bilirubin level ≤1.5x upper normal limit (ULN); creatinine level ≤1.5x ULN; left ventricular ejection fraction (LVEF) within normal limits); and a Karnofsky performance status of ≥70%. Written, informed consent was required before enrolment.

Patients were ineligible if they had received high-dose chemotherapy in the adjuvant setting. Further exclusion criteria included brain metastases, bone metastases as the only site of disease, a history of other prior malignancies (except for curatively treated nonmelanoma skin cancer or carcinoma in situ of the cervix), significant cardiac disease, pre-existing peripheral neuropathy of grade 2 or more, or any other serious medical or psychiatric conditions which would impair the ability of the patient to receive protocol treatment. Pregnant or lactating women were ineligible.

treatment plan

Patients received EC or ED on day 1 every 3 weeks. For patients in the EC arm, epirubicin (90 mg/m² body surface area) was given as an i.v. bolus, followed by cyclophosphamide (600 mg/m²) as an i.v. infusion over 30 min. Patients in the ED arm received epirubicin (75 mg/m², i.v. bolus or infusion over 10 min) followed by docetaxel (Taxotere, Sanofi-Aventis, Berlin, Germany) (75 mg/m²) as i.v. infusion over 1 h. Premedications for ED included prophylactic corticosteroid premedication at 12 and 30 min before docetaxel infusion and at 24 and 48 h after docetaxel. Antiemetics were used at the investigator’s discretion. Prophylactic use of haematopoietic growth factors was not allowed.

Treatment was planned for six cycles unless there was evidence of unacceptable toxicity or disease progression. Responding patients could be considered for an additional two cycles for a total of eight cycles if it was felt that the maximum benefit had not been reached. After treatment discontinuation or study completion, no antitumour therapy was permitted until tumour progression was documented or the investigator determined that treatment was necessary.

A new treatment cycle was only started if ANC was ≥2.0 × 10⁹/l, platelet count was ≥100 × 10⁹/l, and non-haematologic toxicity had resolved to grade 2 (alopecia, nausea, and vomiting excepted). If treatment had to be delayed for ≥2 weeks, the patient was withdrawn. Dose reductions were advised in patients who experienced febrile neutropenia or any grade 3/4 non-haematologic toxicity. In case of symptomatic cardiac events or any given grade 4 non-haematologic toxic effects, the patient was discontinued.

assessments

All tumour lesions (measurable and assessable) were evaluated at the end of treatment cycles 2, 4, 6, and 8, or at study treatment discontinuation, and then every 2 months until disease progression of death. Response was classified according to World Health Organization criteria. If response was documented, imaging scans were carried out at least 4 weeks later to confirm the response. Patients with disease progression before or at the end of the third treatment cycle were classified as having progressive disease as best response.

Adverse events and toxic effects were evaluated weekly and recorded for every cycle. They were graded using the National Cancer Institute—Common Toxicity Criteria (version 2.0, dated on 30 April 1999). Cardiac function was monitored by electrocardiogram and echocardiography or multigated radionuclide scan at baseline, after cycles 3 and 6, at the end of the study.

statistical analysis

The primary efficacy end point, ORR, was defined as the percentage of patients with a complete response or a partial response. The trial was initially designed to detect a 15% increase in ORR from 45% with EC to 60% with ED with a power of 80% and an alpha error of 5%. Accordingly, the sample size was estimated at 173 patients per arm. A pre-planned interim analysis was carried out in November 2003 [12]. Although no stopping rules were predefined in the protocol, the steering committee decided after this interim analysis to terminate the trial prematurely. This decision was primarily due to inadequate accrual but also took into consideration the results from the interim analysis, which showed that it would be highly unlikely that the trial could meet its primary end point. Therefore, only exploratory data analyses were applied. With respect to the actual number of patients enrolled, the trial is powered to detect a difference of 18% in ORR assuming a power of 80% and an alpha error of 5%.

TTP was defined as the time from registration until disease progression. Death was regarded as a progression event in those who died before disease progression. Subjects whose disease had not progressed at the time of analysis were censored using the last assessment date. OS was calculated from the date of registration to the date of death for any reason.

All analyses were primarily on the basis of an intention-to-treat basis (ITT). Analyses of ORR was carried out additionally on the per-protocol population. The ITT population included all patients who were randomly assigned to receive at least one course of therapy. The per-protocol population consisted of all patients who did not have a major deviation from the eligibility criteria, did not have an on-study deviation, received at least two cycles of EC or ED, and had at least one complete tumour assessment after the baseline evaluation. Safety analyses were carried out on all patients who received at least one course of therapy.

The χ² test and Fisher’s exact test were used to compare response rates and toxicity. TTP and OS were estimated using the Kaplan–Meier method and compared using a two-sided log-rank test. Cox proportional hazards models were fitted to estimate hazard ratios (HRs) and confidence intervals (CIs). Categorical variables were described by contingency table methods.
and percentages. Continuous variables were described by mean and median values, standard deviations, and minimum and maximum values. All analyses were carried out using the SPSS version 11.0 software package. All P values were two-sided. Differences at P ≤ 0.05 were considered statistically significant.

**results**

**patient characteristics**

A total of 240 patients with MBC were enrolled. Four patients did not receive the allocated study medication and were excluded from ITT and safety analysis. The remaining 236 patients were all assessable for safety and efficacy analysis (Figure 1). There was a slight imbalance between the two arms with more patients being allocated to the ED arm (n = 125) than to the EC arm (n = 111). Nevertheless, baseline characteristics were well balanced, and major negative prognostic factors were similar in both groups (Table 1).

**chemotherapy administration**

A total of 657 courses of EC and 722 courses of ED were administered. Most patients received the full planned therapy, and the median number of cycles was six in both arms. Overall, 83 patients allocated to EC (74.7%) and 93 patients allocated to ED (74.4%) received six or more cycles and 37 (33.3%) and 42 (33.6%) patients, respectively, received the maximum number of eight cycles. Reasons for treatment discontinuation included disease progression (ED 16.0%, EC 22.5%), adverse events (ED 8.8%, EC 5.4%), withdrawn consent (ED 6.4%, EC 6.3%), and other reasons (ED 6.4%, EC 6.4%). Other reasons were primarily investigator decisions to discontinue treatment if maximum benefit had been reached.

Most treatment cycles (EC 85%, ED 89%) were administered in 3-week intervals as planned. Dose modifications were required in 3% of cycles in the EC arm and 8% of cycles in the ED arm. Main reasons for treatment delay or dose modification were logistical reasons or patient request (39%), prolonged neutropenia (34%), or infection (8%). The planned dose intensity (DI) was maintained in the majority of patients with a relative DI of 0.96 on both arms.

**efficacy**

Objective responses were documented in 47 patients (42.4%, 95% CI 33.0% to 52.1%) in the EC arm and in 59 patients (47.2%, 95% CI 38.2% to 56.3%) in the ED arm (Table 2). There were no statistically significant differences in ORRs between the treatment groups both on an ITT (P = 0.63) and per-protocol analysis (P = 0.30).

The median follow-up was 24 months. At the time of this analysis, tumour progression was documented in 171 (71% in the EC arm and 73% in the ED arm) of the 236 patients. The 1-year (2-year) progression-free survival (PFS) was 43.9% (19.3%) for patients receiving EC and 44.6% (19.9%) for patients treated with ED. With an estimated median TTP of 10.1 months for the EC group (95% CI 7.5–11.8 months) and 10.3 months for patients receiving ED (95% CI 8.0–14.0 months), there were no differences between both treatment arms (HR 0.98; log-rank P = 0.38) (Figure 2).

Median OS was also not statistically significantly different between both groups with 19.9 months (95% CI 17.1–24.2 months) in the EC group and 30.0 months (95% CI 16.7–38.3 months) in the ED group (HR 0.663; log-rank P = 0.21). The 1-year (2-year) survival rate was 65.8% (43.3%) for patients in the EC group and 75.8% (57.4%) for patients treated with ED.

**Table 1.** Patient baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>EC (n = 111)</th>
<th>ED (n = 125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>56 (31–73)</td>
<td>57 (35–72)</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td>0</td>
<td>69 (65)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>37 (35)</td>
</tr>
<tr>
<td>Menopausal status, n (%)</td>
<td>Pre</td>
<td>52 (47)</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>59 (53)</td>
</tr>
<tr>
<td>Hormone receptor status, n (%)</td>
<td>ER and PgR positive</td>
<td>53 (48)</td>
</tr>
<tr>
<td></td>
<td>ER and PgR negative</td>
<td>51 (46)</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Number of metastatic sites, n (%)</td>
<td>1</td>
<td>43 (39)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>41 (37)</td>
</tr>
<tr>
<td></td>
<td>≥3</td>
<td>27 (24)</td>
</tr>
<tr>
<td>Neoadjuvant treatment, n (%)</td>
<td>Chemotherapy</td>
<td>40 (36)</td>
</tr>
<tr>
<td></td>
<td>Anthracyclines</td>
<td>15 (14)</td>
</tr>
<tr>
<td></td>
<td>Endocrine therapy</td>
<td>52 (47)</td>
</tr>
</tbody>
</table>

EC, epirubicin and cyclophosphamide; ED, epirubicin and docetaxel; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PgR, progesterone receptor.
safety

Haematologic adverse events were the most frequent toxicity (Table 3). The incidence of grade 3/4 leucopenia was higher with ED than with EC (81% versus 73%; \( P = 0.01 \)) but there were no significant differences in the incidence of febrile neutropenia and grade 3/4 infections between ED and EC. Serious thrombocytopenia and anaemia were infrequent.

Non-haematologic toxic effects were generally reflective of the expected toxicity profiles of each of the regimens. The incidence of grade 3/4 gastrointestinal toxic effects was similar except for diarrhoea [5.6% versus 0%; \( P = \) not significant (ns)] and stomatitis (4.0% versus 0%; \( P = \) ns), which occurred more frequently with ED. No grade 3/4 neurosensory adverse events reported.

Congestive heart failure occurred in one patient in each arm.

discussion

This randomised trial confirmed the tolerability and the expected high antitumour activity of anthracycline-based combination chemotherapy as first-line treatment of MBC. Both treatment regimens were generally well tolerated and
associated with toxic effects that were consistent with the known side-effects of anthracycline–taxane and anthracycline–cytophosphamide combinations [1, 6–11]. As expected, the incidence of cardiac side-effects was low, but only 35 patients (15%) had received prior anthracycline therapy and patients with pre-existing cardiac problems or an abnormal LVEF were excluded from this study. More than 85% of treatment cycles were given at the planned dose and schedule, and the relative DI in both arms was 96%, in spite of the fact that prophylactic use of haematopoetic growth factors was not recommended. Although the efficacy of both treatment groups was broadly in keeping with results reported from other studies, the study failed to demonstrate a significant benefit for ED over EC.

Only one other randomised trial has reported data on the ED combination as first-line chemotherapy for MBC [8]. As this was a phase II study, it was not designed to compare the two treatment arms. Several other randomised trials have compared different combinations and schedules of anthracyclines and taxanes with standard anthracycline–cyto phosphamide regimens (with or without 5-fluorouracil) as first-line chemotherapy, but the results have been inconsistent [6, 7, 9–11]. Whereas some trials demonstrated improved tumour response and/or PFS with taxane-based combinations, other studies failed to show relevant differences.

Thus, a recent meta-analysis of individual data from eight combination studies involving >3000 patients was carried out to assess the benefits of taxanes as first-line therapy of MBC [13]. The selected trials differed markedly with respect to anthracycline type and dose, taxane type and dose, or schedule, and substantial heterogeneity was seen between the results of the various trials. The meta-analysis confirmed a modest benefit for taxane-based combinations in terms of ORR (57% versus 46%; stratified nonresponse odds ratio = 0.63; \( P < 0.001 \)) and PFS (median PFS = 6.9 versus 7.7 months; HR 0.92, 95% CI 0.85–0.99; \( P = 0.031 \)) but failed to show any benefit for OS (median OS = 19.2 versus 19.8 months; HR 0.95, 95% CI 0.88–1.03; \( P = 0.24 \)). The meta-analysis was also unable to define a subset of patients that derived a more pronounced benefit of taxanes. Given these results and the small number of patients in the exploratory analysis, we decided not to carry out subset analyses in the presented study.

There are a few caveats with respect to the design of the presented study, which might have affected the outcome. First, the study was designed to have a high power to detect an increase in response rates with ED of at least 15%. Due to the early termination of the trial, however, only exploratory data analyses were applied. None the less, the reported data indicate that ED is unlikely to be associated with a substantial improvement in terms of response or TTP compared with EC, although smaller differences in outcome are not ruled out by these results.

Secondly, there was an imbalance in the assignment of patients to the study arms with more patients being allocated to ED. There was also no stratification carried out for patient characteristics. Nevertheless, baseline characteristics were well balanced, and major negative prognostic factors were similar in both treatment groups.

Furthermore, it is argued whether ORR is the most appropriate primary end point for this indication. OS is generally viewed as the end point of choice to assess the efficacy of new treatments in MBC but the analysis of OS requires prolonged follow-up, thereby delaying the evaluation of new therapies, and potential effects of first-line therapies on OS may be diluted by the effects of subsequent treatments. Tumour response to first-line chemotherapy has been shown to be an excellent predictor of treatment effects on PFS in a recent meta-analysis (\( P = 0.96, 95\% \) CI 0.73–1.19) but is not a good surrogate for OS [14]. Although the selection of a different primary end point would have affected the statistical design of the study, the actual impact on the outcome of this study would have been limited as the study was terminated prematurely and data analysis is exploratory.

A further caveat is that different doses of epirubicin were given in both treatment groups with 75 mg/m\(^2\) in the ED arm and 90 mg/m\(^2\) in the EC arm. Epirubicin has been extensively used in the treatment of breast cancer but the definition of the optimal dose and the equivalent dose compared with doxorubicin is still controversial. Randomised trials have shown a clear dose response for epirubicin in MBC with doses of ≥90 mg/m\(^2\) every 3 weeks and a DI of ≥30 mg/m\(^2\)/week achieving improved tumour response and PFS compared with lower dose therapy [15–20]. Several studies have tried to establish the optimal doses for anthracycline-taxane combinations. Although docetaxel (at a dose of 75 mg/m\(^2\)) can be safely combined with 90 mg/m\(^2\) epirubicin, phase II or III studies most commonly use an epirubicin dose of 75 mg/m\(^2\), as the rate of myelosuppression and associated infections appears to be lower at this dose level. A formal comparison of the two different doses has, however, not been carried out, and it cannot be excluded that a higher dose of epirubicin could have affected the outcome of this study. Finally, no prospective quality-of-life assessment was undertaken.

### Table 3. Grade 3/4 treatment-related adverse events

<table>
<thead>
<tr>
<th>Body system and adverse event</th>
<th>EC patients</th>
<th>ED patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 111)</td>
<td>(n = 125)</td>
</tr>
<tr>
<td></td>
<td>Number of patients</td>
<td>%</td>
</tr>
<tr>
<td>Haematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>7</td>
<td>6.3</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>82</td>
<td>73.9</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>11</td>
<td>9.9</td>
</tr>
<tr>
<td>Infection (including FN)</td>
<td>7</td>
<td>6.3</td>
</tr>
<tr>
<td>FN</td>
<td>6</td>
<td>5.4</td>
</tr>
<tr>
<td>Nausea</td>
<td>6</td>
<td>5.4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7</td>
<td>6.3</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Skin rash</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nail changes</td>
<td>1</td>
<td>0.9</td>
</tr>
<tr>
<td>CHF</td>
<td>1</td>
<td>0.9</td>
</tr>
</tbody>
</table>

\( *P = 0.01 \), all other differences not significant.

EC, epirubicin and cyclophosphamide; ED, epirubicin and docetaxel; FN, febrile neutropenia; CHF, congestive heart failure.
Despite its limitations, this study confirmed that EC and ED are highly effective combinations for first-line chemotherapy of MBC. The study failed, however, to demonstrate a benefit of the taxane–anthracycline combination over the taxane-free combination.

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**references**