A randomized phase II study of sequential docetaxel and doxorubicin/cyclophosphamide in patients with metastatic breast cancer

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Background: Docetaxel has yielded promising response rates as a component of doxorubicin-based combination schedules in patients with metastatic breast cancer, including docetaxel/doxorubicin and docetaxel/doxorubicin/cyclophosphamide (AC). This randomized two-stage phase II study was conducted to evaluate sequential treatment with docetaxel and AC as first-line treatment in patients with recurrent or metastatic breast cancer previously untreated with chemotherapy for metastatic disease.

Patients and methods: Thirty-three patients were randomized to either docetaxel (100 mg/m2) on day 1 of a 21-day cycle for three cycles followed by AC (60/600 mg/m2) on day 1 of a 21-day cycle for three cycles (n = 17) or vice-versa (n = 16), without prophylactic granulocyte colony-stimulating factor support. In addition, we compared pre-treatment serum sErbB1 and sErbB2 protein concentrations with that of an age- and menopausal status-matched group of healthy women, and examined changes in serum sErbB1 and sErbB2 protein concentrations in these two treatment schedules. Data from each one of the two arms of the trial (docetaxel then AC, or AC and then docetaxel) were analyzed separately.

Results: Enrollment was suspended after the first-stage of accrual, based on statistical design. Confirmed objective response rates after six cycles of treatment were 35% [95% confidence interval (CI) 14% to 62%] with docetaxel then AC and 38% (95% CI 15% to 65%) with AC then docetaxel. Dose reductions were frequent and mostly due to grade 4 neutropenia. Median survival time was 2.5 years in the docetaxel then AC group, and 1.1 years in the AC then docetaxel group. Serum sErbB1 concentrations were not significantly different between the study patients and healthy women, and did not change significantly after three and six cycles of treatment. In contrast, serum sErbB2 concentrations were significantly higher in the study patients compared with healthy women and tended to decrease after three and six cycles of treatment.

Conclusions: Response rates at the end of six cycles of treatment, which led to termination of accrual after the first stage using either the sequence of docetaxel first or docetaxel after AC chemotherapy, were lower than anticipated. However, median survival times and median progression-free survival times are similar to those reported in other studies. These data further suggest that additional studies to assess whether serum sErbB2 concentrations are useful predictors of responsiveness to chemotherapy are warranted.

Key words: breast cancer, chemotherapy, docetaxel

Introduction

Breast cancer is still a leading cause of cancer death in women in the United States and Europe [1, 2]. Randomized clinical trials have demonstrated that the extent of surgical resection is not the sole determinant of clinical outcome [3], and that systemic therapy following surgery improves both disease-free survival and overall survival [4]. However, a recent meta-analysis of adjuvant chemotherapy trials for patients with breast cancer showed that ~40% of patients experience recurrence [5]. Among current polychemotherapies used in the adjuvant setting, anthracycline-containing schedules have a modest but real impact on breast cancer survival rates.

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Although many chemotherapeutic modalities have been investigated to optimize antitumor efficacy in patients with metastatic breast cancer, how best to integrate different modalities remains an important clinical question. Specifically, it has not been resolved whether patients should receive effective agents sequentially in response to tumor progression (use one and reserve others until after tumor progression to the first therapy), or whether clinical activity can be improved by alternating or sequencing chemotherapy agents before tumor progression. An anthracycline, doxorubicin, has been shown to be an active agent in the first- and second-line treatment of advanced breast cancer. Doxorubicin as a single agent demonstrated overall response rates of 29–41% in phase II and III trials of patients with metastatic breast cancer [6]. Combination chemotherapy with doxorubicin/cyclophosphamide (AC) produced response rates of 45–65% in the metastatic setting [7].

In the 1990s, docetaxel, a semi-synthetic compound derived from the needles of the yew tree Taxus baccata, emerged as an active new agent in the treatment of breast cancer [8]. Overall response rates of up to 68% were achieved in phase II trials of docetaxel at a dose of 100 mg/m² as a first-line treatment for metastatic disease [9–12]. Randomized phase III trials in patients treated previously with anthracycline-containing schedules showed a significant increase in both the response rate and median time to progression with docetaxel over non-taxane, non-anthracycline combination schedules [13–15]. Notably, second-line treatment with docetaxel has yielded significant antitumor activity in patients with strictly defined anthracycline-resistant metastatic breast cancer, thus suggesting a relative lack of complete cross-resistance between the drugs [16, 17].

Given the well-established role of doxorubicin and the high activity of docetaxel in the treatment of metastatic breast cancer, it seemed logical to study the two drugs in combination [18–23]. The differences in activity and mechanisms of action between AC combination chemotherapy and the single agent docetaxel made these modalities an attractive set of therapies to study in combination.

Deregulation of cell growth by the ErbB family of receptor tyrosine kinases is most often associated with breast cancer [24, 25]. This family of receptors comprises four structurally related transmembrane receptors: the epidermal growth factor receptors (EGFR, ErbB1, HER1), ErbB2 (HER2, neu), ErbB3 (HER3) and ErbB4 (HER4) [26]. Amplification and over-expression of the c-erbB1 and c-erbB2 proto-oncogenes and their protein products have been found in breast carcinomas, and have been associated with disease recurrence and poorer prognosis [27–33]. In addition to the transmembrane forms of ErbB receptors, secreted or soluble isoforms (sErbB), which contain only the extracellular domain (ECD), are produced by normal and malignant cells [34]. These soluble isoforms of ErbB receptors are currently being examined as possible cancer biomarkers [35–36]. Immunoassays have shown that sErbB1 concentrations are decreased in the urine of patients with bladder cancer and in the serum of females with advanced-stage epithelial ovarian cancer [37–39]. In contrast, serum sErbB2 concentrations are elevated in women with breast and ovarian cancer in comparison with healthy women [40–47]. In addition, elevated pre-treatment sErbB2 concentrations have been correlated with poor clinical responsiveness to hormone therapy and chemotherapy in metastatic breast cancer patients [48–51]. Together, these studies suggest that alterations in serum sErbB concentrations may be useful in diagnosing cancer, in monitoring disease recurrence, and in predicting therapeutic responsiveness and disease outcome in cancer patients.

Against this background, we conducted a randomized study to assess the antitumor activity and toxicity profiles of two sequential schedules of docetaxel and AC in women with recurrent or metastatic breast cancer. We also compared pre-treatment serum sErbB1 and sErbB2 protein concentrations with those of an age- and menopausal status-matched group of healthy women, and examined changes in serum sErbB1 and sErbB2 protein concentrations in these two treatment schedules.

Patients and methods

Patients

This was a randomized, multicenter study conducted by the North Central Cancer Treatment Group between October 1997 and June 1998, with the approval of the institutional review boards of each participating institution and the informed, written consent of all participants. The study population consisted of women (aged ≥18 years) with recurrent or metastatic breast cancer. The eligibility criteria were measurable or assessable disease, Eastern Cooperative Oncology Group performance status ≤2, life expectancy ≥6 months, adequate hematological values (absolute neutrophil count (ANC) ≥1500/µl and platelet count ≥100000/µl) and adequate renal and hepatic function [creatinine ≤1.5 x the upper limit of normal (ULN), total bilirubin within normal limits and aspartate transaminases <2.5 ULN].

Patients were excluded if they had received prior systemic chemotherapies for metastatic breast cancer. Prior adjuvant anthracycline-containing adjuvant therapy was allowed only if the cumulative dose was <240 mg/m² and the patient had a normal cardiac ejection fraction. Prior radiation to >25% of the bone marrow was not permitted. Other exclusion criteria included prior malignancy (except adequately treated basal cell or squamous cell skin carcinoma, adequately treated non-invasive carcinoma, and other carcinomas from which the patient had been disease-free for ≥5 years), uncontrolled infection, congestive heart failure requiring medication, central nervous system metastases, pre-existing effusion, ascites or peripheral edema, and poorly controlled diabetes mellitus. Pregnant or lactating women were not eligible for this study.

Treatment plan

Drug treatment. Patients were randomized to two multicenter phase II trials (conducted independently of each other) examining two different schedules of docetaxel and AC (Figure 1). Randomization was by a dynamic allocation procedure designed to balance the distribution of the type of indicator lesion (measurable versus assessable) between the two
• Patients were randomized to two multicenter phase II trials (conducted independently of each other).

• **Schedule A (T → AC)**
  - Cycles 1-3: Docetaxel (100 mg/m², 1-hour IV infusion) on day 1, q 3 weeks and
dexamethasone 8 mg po BID x 3 days starting the day before each Docetaxel infusion
  - Cycles 4-6: Doxorubicin (60 mg/m², IV push) and Cyclophosphamide (600 mg/m², 20-30
  minute IV infusion) on day 1, q 3 weeks
  - Cycle 7 – progression: Docetaxel (100 mg/m²) q 3 weeks

• **Schedule B (AC → T)**
  - Cycles 1-3: Doxorubicin (60 mg/m², IV push) and Cyclophosphamide (600 mg/m², 20-30
  minute IV infusion) on day 1, q 3 weeks
  - Cycles 4-6: Progression: Docetaxel (100 mg/m², 1-hour IV infusion) on day 1, q 3 weeks

**Figure 1.** Schema. T, Taxotere (docetaxel); AC, doxorubicin/cyclophosphamide.

Schedules. In the first trial, patients received docetaxel [100 mg/m², 1-h intravenous (i.v.) infusion in 250 ml 5% dextrose water or normal saline (NS)] on day 1 of a 21-day cycle for three cycles, then doxorubicin (60 mg/m², i.v. push in 250 ml NS) and cyclophosphamide (600 mg/m², 20-30 min i.v. infusion in 250 ml NS) on day 1 of a 21-day cycle for the next three cycles, then docetaxel (100 mg/m², 1-h i.v. infusion) on day 1 of subsequent cycles; this schedule would be referred to as ‘docetaxel then AC’. In the second trial, patients received doxorubicin (60 mg/m², i.v. push) and cyclophosphamide (600 mg/m², 20-30 min i.v. infusion) on day 1 of a 21-day cycle for three cycles, then docetaxel (100 mg/m², 1-h i.v. infusion) on day 1 of subsequent cycles; this schedule will be referred to as ‘AC then docetaxel’. To minimize docetaxel-related hypersensitivity reactions and fluid retention, all patients received prophylactic oral dexamethasone (8 mg b.i.d.) for 3 days starting the day before each docetaxel infusion.

**Dose adjustments.** Dose modifications were performed based on toxicity grading with the National Cancer Institute common toxicity criteria (NCI-CTC). The docetaxel dose was to be reduced by 20% if a patient developed grade 4 neutropenia or thrombocytopenia, grade 3 non-hematological toxicity, or grade 2 edema; a 25% reduction for 2.5 day 1 of a 21-day cycle for three cycles, then docetaxel (100 mg/m², 1-h i.v. infusion) on day 1 of a 21-day cycle for the next three cycles, then docetaxel (100 mg/m², 1-h i.v. infusion) on day 1 of a subsequent cycle; this schedule will be referred to as ‘docetaxel then AC’. In the second trial, patients received doxorubicin (60 mg/m², i.v. push) and cyclophosphamide (600 mg/m², 20-30 min. i.v. infusion) on day 1 of a 21-day cycle for three cycles, then docetaxel (100 mg/m², 1-h i.v. infusion) on day 1 of subsequent cycles; this schedule will be referred to as ‘AC then docetaxel’. To minimize docetaxel-related hypersensitivity reactions and fluid retention, all patients received prophylactic oral dexamethasone (8 mg b.i.d.) for 3 days starting the day before each docetaxel infusion.

**Supportive care.** Anti-emetic medication was given as clinically indicated. Granulocyte colony-stimulating factor or granulocyte–macrophage colony-stimulating factor was not to be administered prophylactically or substituted for protocol-stipulated dose reductions due to toxicity, but therapeutic use was permitted in patients with serious neutropenic complications.

**Statistical analysis**

The primary end point was the objective response rate after five cycles of treatment; this was defined as the proportion of eligible patients who achieved a CR, PR or REGR after cycle 5 that was maintained after cycle 6. The smallest objective response rate of interest for further study was 75%. The study was designed to test the null hypothesis that true response rate was at most 55% against the alternative that it was at least 75%. In the first stage, 15 eligible patients were randomized to each treatment schedule. If nine or fewer eligible patients on a given treatment schedule achieved a response after five cycles that was maintained after six cycles, then accrual to that treatment schedule would be terminated. The decision to terminate accrual to a particular treatment schedule was made independently of the antitumor activity of the other treatment schedule. If accrual were re-opened to one (both) of the treatment schedules, then 28 additional eligible patients would be accrued (randomized) to that (each) treatment schedule. If 29 or more of the 43 eligible patients accrued to a treatment schedule achieved a response after cycle 5 that was maintained after cycle 6, and excessive toxicity was not observed, then that treatment
schedule would be recommended for further testing in subsequent clinical trials. For each treatment schedule, there was an 80% chance of detecting whether the objective response rate after five cycles of treatment was at least 75% at a significance level of 0.05.

Secondary end points were the response rate after three cycles of treatment, progression-free and overall survival, toxicity and dose intensity. The response rate after three cycles of treatment was defined as the percentage of eligible patients who achieve a CR, PR or REGR after the third cycle of treatment (not necessarily maintained at the end of a fourth cycle of treatment). Confidence intervals for the response rates were constructed using the properties of the binomial distribution. Progression-free survival was defined as the time from registration on study until documented disease progression. Patients who died without documentation of progression were considered to have progressive disease at the time of death. Overall survival time was defined as the time from registration on study until death due to any cause. The distributions of overall survival times and progression-free survival times were estimated using the Kaplan–Meier method. The delivered dose intensity was determined for each patient for whom the agents were administered. Dose intensity was defined as the dose of that agent/m² received during its first three cycles of administration divided by the number of weeks. For each level of toxicity, the proportion of patients who reported that toxicity (NCI-CTC grade 3 or higher) was determined.

Results

Patient accrual

Thirty-four patients with previously untreated recurrent or metastatic breast cancer were randomized to receive docetaxel then AC or AC then docetaxel (each n = 17). One patient in the AC then docetaxel group was declared ineligible due to pre-existing pleural effusion. The characteristics of the 33 eligible patients are presented in Table 1. The two treatment groups were similar with respect to age, type of indicator lesion and number of metastatic sites. A suspension of accrual notice was sent out after 15 eligible patients were randomized to each treatment group, but three additional patients were allowed to start on trial as they had already begun eligibility evaluation. Accrual was terminated to each treatment group as fewer than 10 of the first 15 patients accrued into each group achieved an objective response.

Treatment course

The median number of cycles administered was seven (range 1–35) in the docetaxel then AC group, and 9.5 (range 1–23) in the AC then docetaxel group. Six patients (three from each treatment group) discontinued treatment after one cycle because of progression (three patients), death due to a myocardial infarction (MI) (one patient), refusal due to multiple toxicities including a reaction to the docetaxel infusion (one patient), and failure to rechallenge after a reaction to the docetaxel infusion (one patient). Twelve of the remaining 13 patients in the AC then docetaxel group had at least one dose reduction during the first six cycles of treatment. These dose reductions were because of severe neutropenia (nine patients), grade 4 vomiting and diarrhea (one), grade 4 stomatitis (one) and physician discretion (one). Twelve of the remaining 14 patients in the docetaxel then AC group had at least one dose reduction during the first six cycles of treatment. These dose reductions were because of severe neutropenia (eight patients), anaphylactic reaction to docetaxel/not rechallenged (two), grade 3 neurosensory toxicity (one), poor venous access (one), and grade 2 edema (one). Table 2 shows the dose intensity of each drug during the first six cycles of treatment.

Toxicity

Fifteen patients in the docetaxel then AC group and 16 in the AC then docetaxel group were evaluable for hematological toxicity. On docetaxel then AC, grade 4 neutropenia occurred in 12 patients (80%) during the first cycle and in 15 patients (100%) during the course of the study. On AC then docetaxel, grade 4 neutropenia occurred in 10 patients (63%) during the first cycle and 14 (88%) during the course of the study. Febrile
neutropenia was observed in 6 of 15 patients (40%) on docetaxel then AC, and in 4 of 16 patients (25%) on AC then docetaxel (Table 3).

Four patients, all in the docetaxel then AC group, had an allergic reaction to the docetaxel. Three of these patients were withdrawn from treatment because of the severity of the reaction without being rechallenged. The fourth patient refused to continue treatment having been rechallenged with i.v. premedication. Her dyspnea persisted and she experienced chills, arthralgia and myalgia.

Table 1. Patient and disease characteristics at baseline

<table>
<thead>
<tr>
<th></th>
<th>Docetaxel then AC</th>
<th>AC then docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>54 (38–68)</td>
<td>64 (43–72)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>53%</td>
<td>25%</td>
</tr>
<tr>
<td>1</td>
<td>47%</td>
<td>75%</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infiltrating ductal</td>
<td>88%</td>
<td>100%</td>
</tr>
<tr>
<td>Infiltrating lobular</td>
<td>12%</td>
<td>0%</td>
</tr>
<tr>
<td>Indicator lesion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measurable</td>
<td>65%</td>
<td>65%</td>
</tr>
<tr>
<td>Assessable</td>
<td>35%</td>
<td>35%</td>
</tr>
<tr>
<td>Number of metastatic sites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>35%</td>
<td>38%</td>
</tr>
<tr>
<td>2</td>
<td>35%</td>
<td>38%</td>
</tr>
<tr>
<td>3</td>
<td>24%</td>
<td>13%</td>
</tr>
<tr>
<td>4</td>
<td>6%</td>
<td>13%</td>
</tr>
<tr>
<td>Type of dominant tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soft tissue</td>
<td>18%</td>
<td>13%</td>
</tr>
<tr>
<td>Osseous</td>
<td>18%</td>
<td>31%</td>
</tr>
<tr>
<td>Visceral</td>
<td>65%</td>
<td>56%</td>
</tr>
<tr>
<td>Prior therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiation</td>
<td>35%</td>
<td>44%</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>41%\textsuperscript{a}</td>
<td>56%\textsuperscript{b}</td>
</tr>
<tr>
<td>Hormonal therapy</td>
<td>47%</td>
<td>75%</td>
</tr>
</tbody>
</table>

\textsuperscript{a}One patient received 170 mg/m\textsuperscript{2} of doxorubicin 3 years before study entry.
\textsuperscript{b}Two patients received doxorubicin: one 181 mg/m\textsuperscript{2} 1.2 years before study entry, the other 240 mg/m\textsuperscript{2} 1.7 years before study entry.

AC, doxorubicin/cyclophosphamide; ECOG, Eastern Cooperative Oncology Group.

Table 2. Patients receiving at least 95% of starting dose

<table>
<thead>
<tr>
<th></th>
<th>Docetaxel then AC</th>
<th>AC then docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Docetaxel</td>
<td>Doxorubicin</td>
</tr>
<tr>
<td>Cycle 1</td>
<td>16/17</td>
<td>–</td>
</tr>
<tr>
<td>Cycle 2</td>
<td>4/14</td>
<td>–</td>
</tr>
<tr>
<td>Cycle 3</td>
<td>3/12</td>
<td>–</td>
</tr>
<tr>
<td>Cycle 4</td>
<td>–</td>
<td>8/11</td>
</tr>
<tr>
<td>Cycle 5</td>
<td>–</td>
<td>3/10</td>
</tr>
<tr>
<td>Cycle 6</td>
<td>–</td>
<td>3/10</td>
</tr>
<tr>
<td>Intensity (mg/m\textsuperscript{2}/week), median (range)</td>
<td>28 (0–88)</td>
<td>16 (9–20)</td>
</tr>
</tbody>
</table>

AC, doxorubicin/cyclophosphamide.
In addition to the three patients who were withdrawn from treatment because of severe reactions to docetaxel, there were five patients who withdrew from treatment because of other severe non-hematological toxicities. These toxicities were: grade 4 cardiac dysrhythmia after 12 cycles of docetaxel then AC, grade 3 neurosensory and grade 2 neuromotor toxicities after 13 cycles on docetaxel then AC, febrile neutropenia and grade 4 vomiting after four cycles of AC then docetaxel, grade 4 edema and grade 3 dyspnea after nine cycles on AC then docetaxel, and grade 3 infected port resulting in treatment being delayed > 6 weeks after 10 cycles of AC then docetaxel.

Three patients experienced severe dyspnea, musculoskeletal pain, and thrombotic events in addition to the allergic reactions to docetaxel. All the remaining severe non-hematological toxicities observed occurred in no more than two patients.

Response

The primary efficacy end point was an objective response after five cycles of treatment that was maintained after the sixth cycle of treatment. There were one CR, four PRs and one REGR among the 17 patients in the docetaxel then AC group, and four PRs and two REGRs among the 16 patients in the AC then docetaxel group. Thus, the confirmed response rate after five cycles was 35% [95% confidence interval (CI) 14% to 62%] in the docetaxel then AC group and 38% (95% CI 15% to 65%) in the AC then docetaxel group. At the third cycle evaluation, there were one CR, three PRs and one REGR among the 17 patients in the docetaxel then AC group, and three PRs and two REGRs among the 16 patients in the AC then docetaxel group. Thus, the response rate after three cycles was 29% (95% CI 10% to 56%) in the docetaxel then AC and 25% (95% CI 11% to 59%) in the AC then docetaxel group. These data are presented in Table 4.

**Progression and survival**

In the docetaxel then AC group, there is one patient alive who has not progressed, one patient who died at day 11 of an MI not having progressed, seven patients alive who progressed, and eight patients who progressed and died. In the AC then docetaxel group, there are three patients alive who have not progressed, three patients alive who progressed, and 10 patients who progressed and died. The median length of follow-up for those still alive is 2.5 years (range 2.1–3.0 years).

In the docetaxel then AC group, the median progression-free survival time is 12 months and the median survival time is 2.5 years (Figure 2). In the AC to docetaxel group, the median progression-free survival time is 10.2 months and the median survival time is 1.1 years (Figure 3).

**sErbB1 and sErbB-2 serum concentrations**

Serum sErbB1 and sErbB2 concentrations were determined for 29 of the 33 eligible patients. Serum sErbB1 and sErbB2...
concentrations also were determined for a cohort of healthy women who were age- and menopausal status-matched to the clinical trial patients. The median pre-treatment sErbB1 level was 4700 fmol/ml (range 68–109954 fmol/ml) in the trial patients and 3156 fmol/ml (range 146–24068 fmol/ml) in the healthy women (Figure 4). No significant difference was found between the pre-treatment sErbB1 concentrations of the study patients and those of the healthy women ($P = 0.15$). The

Figure 2. Progression-free survival (PFS) (solid line) and survival times (dashed lines) of patients treated with docetaxel then doxorubicin/cyclophosphamide.

Figure 3. Progression-free survival (PFS) (solid line) and survival times (dashed lines) of patients treated with doxorubicin/cyclophosphamide then docetaxel.
The median pre-treatment sErB2 level was 7.05 ng/ml (range 1.24–433.38 ng/ml) in the trial patients and 2.08 ng/ml (range 0.90–19.72 ng/ml) in the healthy women (Figure 5). The pre-treatment sErB2 concentrations of the trial patients were significantly higher than those of the healthy women ($P = 0.0003$).

Serum samples were available from 23 of the 25 patients who had three cycles of treatment (10 of 12 in the docetaxel then AC group; 13 of 13 in the AC then docetaxel group). Serum samples also were available from 15 of the 21 patients who received six cycles of treatment (8 of 10 in the docetaxel then AC group; seven of 11 in the AC then docetaxel group). The percentage change between pre-treatment sErB1 concentrations and sErB1 concentrations before the fourth or seventh treatment cycles was not significantly different from zero with either treatment schedule (all $P$ values >0.35). In the docetaxel then AC group, the percentage change between pre-treatment sErB2 concentrations and sErB2 concentrations before the fourth treatment cycle (after docetaxel) was not significantly different from zero ($P = 0.432$). Interestingly, the percentage change between the pre-treatment sErB2 concentrations and sErB2 concentrations before the seventh cycle (after AC) tended to be negative ($P = 0.078$). In the AC then docetaxel group, the percentage change between pre-treatment sErB2 concentrations and sErB2 concentrations before the fourth treatment cycle (after AC) was also negative ($P = 0.021$); however, the percentage change between pre-treatment sErB2 concentrations and sErB2 concentrations before the seventh cycle (after docetaxel) did not differ from zero ($P = 0.297$).

**Discussion**

This randomized study was designed to investigate the efficacy and toxicity of two alternating, sequential schedules of docetaxel and AC. The population randomized to receive the two schedules was representative of patients with metastatic breast cancer commonly referred for treatment. Objective response rates of 35% and 38% were achieved after five cycles for docetaxel then AC and vice versa, respectively. These response rates were unexpectedly low, and, in accordance with the protocol, led to termination of the trial after the first stage of accrual.

The response rates observed in our study are similar to those achieved with doxorubicin alone in patients with metastatic breast cancer [6]. However, they were considerably lower than those obtained for docetaxel monotherapy in patients with metastatic disease [8, 17].

Our response rates are also considerably lower than those obtained in studies of docetaxel- and doxorubicin-based combination therapy. For example, in a phase II randomized study, patients given doxorubicin/docetaxel had a 60% response rate, compared with 40% in patients given AC [22]. The three drug combination of docetaxel, doxorubicin and cyclophosphamide has yielded a response rate of 77% [23]. One of the potential explanations for our lower response rates may be that we defined response after five cycles of treatment, instead of the more commonly used two or three cycles of therapy.

Previous studies evaluating sequential schedules, including docetaxel and doxorubicin, yielded promising results. A response rate of 67% was reported for patients with metastatic breast cancer treated with docetaxel followed by doxorubicin...
ErbB3 or ErbB4. One, therefore, might predict that serum levels of soluble ErbB receptors might be coordinately regulated. We have recently demonstrated that a soluble form of the EGFR, i.e. p110 sErbB1, is present in human serum [39]. In this study, we compared pre- and post-treatment sErbB1 and sErbB2 concentrations in advanced breast cancer patients. Our results demonstrate that there are no significant differences between sErbB1 concentrations in breast cancer patients previously untreated with systemic chemotherapy and those of healthy women. In addition, sErbB2 concentrations in breast cancer patients previously untreated with systemic chemotherapy were significantly higher than in healthy women, and serum sErbB2 concentrations tended to decrease over the course of treatment. A larger study in metastatic breast cancer patients will be needed to confirm these observations, and to determine whether these effects on sErbB2 concentrations can be used to predict and/or monitor clinical responsiveness to chemotherapy.

In conclusion, the sequential docetaxel/AC schedules as administered in the present study led to lower response rates than anticipated at the end of six cycles of treatment but led to median survival times to similar those of some other trials in metastatic breast cancer. Further studies to assess whether sErbB2 concentrations are useful predictors of responsiveness to chemotherapy are warranted.

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