Combined doxorubicin and paclitaxel in advanced breast cancer: Effective and cardiotoxic

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Summary

Background: Paclitaxel has shown activity in metastatic breast cancer, including anthracycline-resistant breast cancer. The efficacy, toxicity and optimal scheduling of the combination of the two drugs needs to be defined.

Patients and methods: Thirty women with advanced breast cancer who had undergone at most one prior adjuvant chemotherapy regimen, were treated at three different dose levels with doxorubicin (50, 60 and 60 mg/m²) followed 30 minutes later by paclitaxel (155, 175 and 200 mg/m², respectively) every 3 weeks.

Results: The overall response rate was 83% (95% CI: 64–94), with 24% of patients achieving CR. The median response duration for complete responders was 11 months (range 4–14+) and median survival 18 months (range 3–28+). Two hundred sixty-five treatment courses were given (median 9, range 3–13) and the median cumulative dose of doxorubicin was 369 mg/m² (range 114–550). The main toxicities were neutropenia, paresthesia, nausea/vomiting, alopecia, myalgia and cardiotoxicity. Fifteen patients (50%) had reductions of left ventricular ejection fraction to below normal levels and 6 of these patients (20%) developed congestive heart failure.

Conclusion: The combination of doxorubicin and paclitaxel is highly active, but is accompanied by the dose-limiting toxic effects of neutropenia, neuropathy and cardiotoxicity.

Key words: advanced breast cancer, cardiotoxicity, doxorubicin, paclitaxel

Introduction

The anthracyclines are the most active class of drugs for the treatment of metastatic breast cancer [1–3]. However, with a less than 20% 5-year survival rate in stage IV breast cancer [4], new active drugs and drug combinations must be explored. Paclitaxel has demonstrated high activity in advanced breast cancer, including anthracycline-resistant breast cancer [5, 6]. Several studies aiming to define the optimal dose, schedule and sequence of paclitaxel and doxorubicin have now been completed or are ongoing [7]. Phase I–II studies [8–11] have yielded encouraging response rates but quite variable toxicity profiles, depending on the schedule employed. As one study [9] indicated better tolerability when doxorubicin preceded paclitaxel, this sequence was chosen.

The purpose of this phase I–II study was to investigate the efficacy and toxicity of short-infusion doxorubicin followed by paclitaxel in a 3-hour infusion as first-line chemotherapy in patients with advanced breast cancer.

Patients and methods

The protocol was in accordance with the Declaration of Helsinki and was approved by the local Ethics Committee and the Danish National Board of Health. The informed, written consent of the patients was required.

Eligibility criteria

Patients with histologically-proven, locally advanced or metastatic breast cancer and uni- or bi-dimensionally measurable disease were eligible, as were those who had received one prior adjuvant chemotherapy regimen not containing anthracyclines; prior endocrine therapy and radiotherapy, either adjuvant or for metastatic disease, up to 4 weeks prior to their inclusion, were also permitted. Further eligibility criteria were: Eastern Cooperative Oncology Group (ECOG) performance status <2, life expectancy exceeding 12 weeks, bilirubin and creatinine levels less than 1.25 times upper normal limit, absolute neutrophil count above 1.5 x 10⁹/l (liter) and blood platelets above 100 x 10⁷/l. The left ventricular ejection fraction (LVEF) as evaluated by multigated isotope cardiography (MUGA) [12] had to be within normal limits (46% or more).

Treatment and response evaluation

Doxorubicin (Farmitalia Carlo Erba, Nerviano, Milan, Italy) was dissolved in 250 ml of isotone glucose and administered as a short infusion (approx. 30 minutes) followed 30 minutes later by paclitaxel (Bristol-Myers Squibb, Wallingford, CT, USA) infused over 3 hours. Paclitaxel, dissolved in 5 ml vials containing 30 mg of paclitaxel in 50% polyoxyethylated castor oil and 50% dehydrated alcohol, was diluted in 1000 ml of isotone glucose and infused through filter and PVC-free infusion lines. Standard premedication for paclitaxel consisted of oral prednisolone 125 mg 6 and 12 hours, and cimetidine 300 mg i.v., clemastine 2 mg i.v. 30 min., prior
to paclitaxel infusion. Pulse and blood pressure were monitored every 15 minutes for the first hour during the infusion and again at its conclusion. Courses were administered at 3-week intervals, most of them on an out-patient basis. Hematopoietic growth factors were not used.

The patients were seen weekly. Full blood counts were performed weekly, and blood chemistry prior to each course.

Electrocardiography (ECG) and MUGA-scans were done before treatment and initially after a cumulative doxorubicin dose of 400 mg/m² and 500 mg/m². During the study it was decided to increase the frequency of MUGA scans to every other course for the first 6 courses of the combination and after that before every course. When paclitaxel was continued as single drug, MUGA scans were performed after every other course. Patients were also monitored at termination of therapy and then every 3 months for the first year. Initially, the maximum cumulative dose of doxorubicin was set at 550 mg/m², but as cardiac toxicity was encountered, a decision was taken to stop doxorubicin administration at 480 mg/m², and subsequently at 360 mg/m². After the maximum cumulative dose of doxorubicin was reached, treatment continued with paclitaxel alone at the same dosage as during the combination therapy.

The duration of therapy was dependent on clinical response. In instances of complete response, treatment was continued for 4 further courses. In case of partial response, treatment could continue for 10 or more courses, depending on the amount of benefit to the patient. Patients with stable disease continued for a maximum of 10 courses and those with progressive disease were taken off study.

The doses of both drugs were reduced in the succeeding courses in patients with febrile neutropenia, grade IV neutropenia lasting longer than 7 days, documented infection or serious hemorrhage. In later courses the dose was either maintained at the reduced level or the starting level was resumed, depending on the individual case. Patients with unacceptable toxic effects were taken off study.

Evaluation was performed by clinical examination, CT scan, X-ray or ultrasound, depending on the location of lesions. Response (including response in bone lesions) and toxicity were evaluated according to WHO criteria [13] except for myalgia, which was reported according to NCIC (National Cancer Institute of Canada) criteria.

Statistics

The study is based on one protocol and a subsequent amendment. In the original protocol, dose levels 1 and 2 (50 and 60 mg/m² of doxorubicin combined with 155 and 175 mg/m² of paclitaxel, respectively) were investigated. Determining a response rate (CR + PR) of >40% as the criteria for considering the drug combination effective and a response rate of <20% for considering it ineffective, 16-32 patients per dose level were expected to be included in the first protocol. Since more than half of the first 24 patients responded to treatment, but the maximally tolerable dose was not reached, a third dose level was added for dose levels 1, 2 and 3 patients receiving <360 mg/m², 8 patients receiving <480 mg/m² and 8 patients receiving <550 mg/m². Twenty-four courses were given at dose level 1, 179 courses at dose level 2 and 62 courses at dose level 3. Patient characteristics (age, performance status and previous treatment) are summarized in Table 1 and disease extent in the patient population is shown in Table 2. All patients had bidimensionally measurable disease. There was one protocol violation among the 30 patients who entered the study: a premenopausal patient received radiotherapy of the ovaries simultaneously with start of chemotherapy. This patient is included in the analysis for toxicity but not for response. One patient was included in the study despite an LVEF of 45%. A total of 7 patients were censored from time to progression analysis and from response duration analysis due to going off study because of toxicity and receiving other treatment for advanced disease.


### Results

**Patient inclusion**

Thirty patients were included from November 1993 to November 1994. As of April 1996 the median observation time was 23 months (range 17-29 months).

Three patients were treated at dose level 1 (50 mg/m² of doxorubicin, 155 mg/m² of paclitaxel), 21 patients at dose level 2 (60 mg/m² of doxorubicin and 175 mg/m² of paclitaxel) and 6 patients at dose level 3 (60 mg/m² of doxorubicin and 200 mg/m² of paclitaxel). A total of 265 courses were administered with a median of 9 courses per patient (range 3-13). The median cumulative dose of doxorubicin was 369 mg/m² (range 114-550), with 14 patients receiving <360 mg/m², 8 patients receiving <480 mg/m² and 8 patients receiving <550 mg/m². Twenty-four courses were given at dose level 1, 179 courses at dose level 2 and 62 courses at dose level 3. Patient characteristics (age, performance status and previous treatment) are summarized in Table 1 and disease extent in the patient population is shown in Table 2. All patients had bidimensionally measurable disease. There was one protocol violation among the 30 patients who entered the study: a premenopausal patient received radiotherapy of the ovaries simultaneously with start of chemotherapy. This patient is included in the analysis for toxicity but not for response. One patient was included in the study despite an LVEF of 45%. A total of 7 patients were censored from time to progression analysis and from response duration analysis due to going off study because of toxicity and receiving other treatment for advanced disease.

**Prior adjuvant therapy**

Chemotherapy (CMF)

- Median disease free interval 25 months (range 10-100)
- Endocrine therapy

**Disease free interval 10 months**

Radiotherapy of ovaries

- Disease free interval 17 and 47 months
- Radiotherapy of thorax right (1/left) (7)

**Prior therapy for advanced disease**

- Surgery
- Endocrine therapy
- Radiotherapy of thorax right (1/left) (3)
- Radiotherapy for bone metastases

**No previous therapy**

- Six patients received both systemic and local adjuvant treatment and 5 pts. received more than one type of treatment for advanced disease. Seven patients received both adjuvant therapy and therapy for advanced disease.
- Cyclophosphamide, methotrexate, 5-fluorouracil.
- Tamoxifen and/or megestrol acetate.
residual disease (5 patients), death unrelated to breast cancer (1 patient), and the protocol violation cited above of radiation of the ovaries simultaneously with chemotherapy (1 patient).

**Therapeutic results**

The response rates are shown in Table 3. The overall response rate in 29 patients was 83%, with 7 patients (24%) achieving complete response and 17 patients (59%) achieving partial response. For the lowest dose level, the response rate was 33% in 3 patients, but 1 patient went off study after 3 courses due to neurotoxicity. For the second dose level, a response rate of 86% was observed in 21 patients and at the highest dose level all 5 of the evaluable patients responded (100%). Response by disease site is shown in Figure 1. For the patients achieving complete response, the median time to CR was 6 courses (median 4 months, range 3–5). The median response duration of CR was 11 months (range 4–17+) and the median duration of overall response 9 months (range 4–22+). The median time to progression was 9 months (range 2–22+). Nine patients progressed during treatment (7 of these after initially responding), and 4 of the 9 progressed with CNS metastases. The median survival was 18 months (range 3–28+).

**Toxicity**

Table 4 summarizes the main non-cardiac toxicities at the three dose levels. There appeared to be no major differences in toxicity among the three dose levels. All patients experienced grade III alopecia. Grades III–IV neutropenia was experienced in 77% of all courses over all the dose levels, but only 8 courses (3%) led to febrile neutropenia, which resulted in dose reductions in a total of 34 of the succeeding courses (13%).

In 12 patients (40%) dose reductions of 45 subsequent courses (17% of all courses), were necessary because of: febrile neutropenia (8 patients and 34 courses), neutropenia grade IV for more than 7 days (1 patient and 7 courses), paresthesia (1 patient and 1 course), mucositis (1 patient and 2 courses), and patient refusal of full-dose chemotherapy (1 patient and 1 course).
In addition, protocol violations occurred in 5 patients and 9 courses, as doses were reduced because of neutropenia lasting less than 7 days. Altogether, 20% of courses were administered at a reduced level. No patients received hemopoietic growth factors at any point.

The average number of days of hospitalization per patient due to toxicity during the entire treatment period was four.

In two cases hypersensitivity occurred in the form of angioedema which resolved after treatment with steroids and clemastine, when the patients resumed treatment at full dose.

One black woman developed hyperpigmentation on the palms and soles of her feet and in the oral mucosa, a condition previously reported to be associated with doxorubicin [14, 15].

One HIV-positive patient completed 8 courses of treatment and achieved a partial response. During and after treatment the patient received prophylaxis against pneumocystis carinii infection (oral sulfamethoxazole and trimethoprim). Three months after completion of treatment the level of her CD 4-positive lymphocytes dropped substantially and she subsequently died of pneumonia and CHF. AIDS was suspected but not confirmed.

Changes in LVEF are summarized in Figures 2 and 3, and Table 5 summarizes the characteristics of the patients who developed CHF. A total of 180 MUGA-scans were performed, 91 during treatment with combined doxorubicin and paclitaxel, 89 during the follow-up period (Figure 3, bottom panel), i.e., after combination therapy, regardless of whether the patients continued on single-drug paclitaxel (36 scans) or not (53 scans). Fifteen of 30 patients (50%, 95% CI: 31–69) developed below-normal LVEF values (<46%) at some point during treatment, with 11 of the 15 later achieving LVEF values within the normal range. Of the 15 patients, 6 had received ≤360 mg/m² of doxorubicin and 5 of these 6 later achieved LVEF values within the normal range. There was a significant drop in LVEF from an initial median value of 60% (range, 45–72) to a median of 52% (range, 41–61) after 360 mg/m² of doxorubicin (P < 0.006, Mann–Whitney test).
Sixteen patients continued with paclitaxel as single-drug therapy following cessation of doxorubicin, and LVEF was monitored in 13 of these (Figure 3, top panel). Two of these patients had pronounced drops in LVEF at the first measurement, but this was ascribable to the cardiotoxic effects of the last dose of the combination treatment. LVEF was still stable after treatment with paclitaxel alone 2 and 3 months post-combination treatment. On the basis of LVEF measurements, we conclude that paclitaxel as single-drug continued after combination treatment with doxorubicin is not cardiotoxic. The first measurement 1 month post-treatment during follow-up for the patient group as a whole after cessation of combination treatment (Figure 3, bottom panel) revealed LVEF decreases in a few patients, probably as a result of the immediately preceding dose of combination therapy. At 3, 6, 9 and 12 months post-treatment, the median LVEF value remains stable, but at a lower level (46%–51%) than the baseline 60%.

Six patients developed congestive heart failure (CHF) (Table 5) with New York Heart Association (NYHA) [16] grades II–III symptoms and objective signs of CHF. Of the 6 patients, 2 were considered at risk as 1 was HIV-positive and 1 had received electron field radiotherapy toward the left side of the thorax 6 years earlier. However, in this study a total of 10 patients had previously received radiotherapy toward the left side of the thorax (8 with electron field and 2 with tangential photon-field) and 9 of these did not develop CHF. Of note is the fact that after the initial drop in LVEF, 3 patients have achieved normal LVEF, indicating a certain degree of reversibility in CHF.

A total of 8 patients went off study because of toxic effects, 5 patients, who had received median doxorubicin doses of 392 mg/m² (range 114–506), due to cardiotoxicity after a median of 8 courses (range 6–13), and 3, who had received cumulative paclitaxel doses of 467, 1204 and 1619 mg/m², due to neurotoxicity after 3, 7 and 9 courses, respectively.

**Discussion**

In this study, there was an overall response rate of 83% in 29 women with metastatic breast cancer who had not previously received chemotherapy for advanced disease. This is of particular interest, as the patients had quite extensive disease, with bone and/or visceral involvement in 83% of them. The high response rate achieved in our study corresponds to results seen by Gianni et al. from Milan [11] who administered doxorubicin 60 mg/m² as a short infusion and paclitaxel 125–200 mg/m² as a 3-hour continuous infusion as first-line chemotherapy for metastatic breast cancer. The overall response rate in 32 patients was 94%, with dose-limiting toxic effects of neutropenia, mucositis and CHF. In the Italian study [11], the overall response rate was higher (41%) than in this study, probably because their patient population had a better perfor-

<p>| Table 5. Patients with congestive heart failure. |
|---|---|---|---|---|---|---|---|---|</p>
<table>
<thead>
<tr>
<th>Age</th>
<th>Possible risk factors</th>
<th>Cumulated dose doxorubicin/m² (dose level)</th>
<th>Max. drop in LVEF (%)</th>
<th>Highest LVEF (%) post treatment</th>
<th>NYHA* grade</th>
<th>Enlargement of cardiac silhouette b at X-ray</th>
<th>Signs of pulmonary congestion c at X-ray</th>
<th>Signs of cardiomyopathy at echocardiography d</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>HIV-pos.</td>
<td>370 mg/m² (2)</td>
<td>62/21</td>
<td>25</td>
<td>III</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>63</td>
<td>None</td>
<td>392 mg/m² (2)</td>
<td>53/25</td>
<td>44</td>
<td>III</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>50</td>
<td>Previous radiation electronfield left thorax</td>
<td>550 mg/m² (2)</td>
<td>68/34</td>
<td>50</td>
<td>III</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>43</td>
<td>None e</td>
<td>503 mg/m² (1)</td>
<td>57/43</td>
<td>52</td>
<td>III</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>50</td>
<td>None</td>
<td>329 mg/m² (2)</td>
<td>60/39</td>
<td>50</td>
<td>II</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>57</td>
<td>None</td>
<td>400 mg/m² (2)</td>
<td>52/34</td>
<td>42</td>
<td>II</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

* New York Heart Association [16].

b ++ = slight enlargement; ++ = significant enlargement.

c Lung stasis and/or pleural effusion.

d Hypokinesia of the left ventricle, dilation of left ventricle, reduced fractional shortening and increase in mitral-septal separation.

e This patient only received 3 courses of combined doxorubicin and paclitaxel, after that she continued on doxorubicin alone due to paclitaxel-induced neurotoxicity.
mance status and none of them had received adjuvant chemotherapy.

In our study, 9 patients (31%) progressed during treatment and of these, 4 progressed with CNS metastases. This is in accord with pharmacokinetic data showing poor penetration into the CNS by paclitaxel [17] and doxorubicin [1].

The median time to progression of 9 months and median survival of 18 months do not appear to indicate an advantage for other anthracycline-based regimens [3, 18], but these findings do accord with the conclusion of a number of reviews on metastatic breast cancer that response rates, but not time to progression and survival, have significantly improved over recent decades [3, 5, 19, 20]. A possible explanation could be that although there is clinical partial non-cross-resistance between doxorubicin and paclitaxel [5, 6], there may also in fact be clinical cross-resistance in parts of the tumors, allowing a multi-resistant clone to survive amidst very efficient reduction of the tumor mass.

Several preclinical studies report an individual effect of cremophor, the solvent used for paclitaxel, on reversing multidrug resistance [21–23]. This could indicate that there is not only a synergistic effect between doxorubicin and paclitaxel but also between cremophor and doxorubicin and possibly even paclitaxel. However, the clinical significance of these findings are not known.

The toxicity data do not indicate major differences among the 3 different dose levels, but the data on response rate seem to indicate a possible advantage for the higher dose levels. Even though the number of patients is too small for firm conclusions to be drawn, we suggest that the lowest dose levels not be chosen.

We found a high incidence of cardiotoxicity, with 50% of the patients developing LVEF below the norm for our institution and 20% of patients developing clinical signs of CHF. All of the patients were monitored closely and doxorubicin was discontinued in case of clinical signs of cardiomyopathy or a drop in LVEF to below normal levels. It is likely that the incidence of cardiomyopathy would have been even higher had the patients been monitored less closely. It is, however, also worth noting that a number of patients later had increased LVEF values, even in the group with CHF, indicating a certain degree of reversibility.

The median cumulative dose of doxorubicin with which CHF occurred was 392 mg/m² (range 329–550 mg/m²). In the Milan study [11], 21% of patients developed CHF after a median 480 mg/m². Two intergroup analyses of the risk of CHF caused by doxorubicin [24, 25] report an approximately 5% risk of developing CHF after 500 mg/m² of doxorubicin. Thus, it is logical to assume that the high incidence of cardiomyopathy found in this study is due to this particular combination regimen and schedule. Interestingly, we did not observe adverse effects from continuing paclitaxel as single agent following combination therapy, which is in accordance with data from the Milan group [11] and a study of 35 patients receiving paclitaxel within 12 months of doxorubicin exposure, which reported no decrease in LVEF during paclitaxel treatment [26]. This indicates that the cardiotoxicity could be due to a synergistic effect above a certain threshold when the peak values of the two drugs occur within a short period of time. This synergy could, at least in part, be due to a pharmacokinetic interaction resulting in decreased clearance of doxorubicin, as found by Holmes et al. [27], or the doxorubicin metabolite doxorubicinol, as indicated by Berg et al. [28] using both single-drug and concomitant 72-hour infusion of the two drugs [8]. A recent study by Gianni et al. [29] also indicates this.

In conclusion, this study shows that the combination of paclitaxel and doxorubicin is a highly effective, but also toxic, particularly cardiotoxic, regimen. Further research should investigate various doses and schedules of the two drugs, with the aim of lessening cardiotoxicity while maintaining the activity of the combination. This regimen can, however, be continued in the present form if doxorubicin administration is stopped at 360 mg/m²; in this regard it is noteworthy that the response rates observed in this study were obtained with a median cumulative doxorubicin dose of 369 mg/m². At the highest dose level, all 5 of the 5 patients who responded received a maximum of 360 mg/m² of doxorubicin.

Results from randomised studies of anthracycline-taxane regimens and the best-known other anthracycline-based therapy investigating in particular time to progression and survival, but also toxicity, efficacy, quality of life and cost, are awaited with great interest.

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