Feasibility and Tolerability of Sequential Doxorubicin/Paclitaxel Followed by Cyclophosphamide, Methotrexate, and Fluorouracil and Its Effects on Tumor Response as Preoperative Therapy

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Abstract

**Purpose:** The European Cooperative Trial in Operable breast cancer (ECTO) randomly tested whether efficacy of adjuvant doxorubicin followed by i.v. cyclophosphamide, methotrexate, and fluorouracil (CMF; doxorubicin → CMF, arm A) could be improved by adding paclitaxel (doxorubicin/paclitaxel → CMF) as adjuvant (arm B) or primary systemic therapy (PST, arm C). We report here feasibility, tolerability, locoregional antitumor activity, and breast conservation rate.

**Methods:** A total of 1,355 women entered the study. Feasibility and safety were compared in arm A versus arms B plus C. Surgical findings were compared in arms A plus B versus arm C.

**Results:** Grade 3 or 4 National Cancer Institute toxicities were low (<5%) in all arms. Neuropathy was more frequent in the paclitaxel-containing arms (grade 2, 20.5% versus 5.0%; grade 3, 1.3% versus 0.2%). At 31 months of follow-up, asymptomatic drop of left ventricular ejection fraction was similar in all arms, whereas symptomatic cardiotoxicity was recorded in three patients (0.5%) in A and in three patients (0.3%) in B plus C. PST induced clinical complete plus partial remission in 78%, with an in-breast pathologic complete response rate of 23% and an in-breast plus axilla pathologic complete response rate of 20%. In the multivariate analysis, only estrogen receptor (ER) status was significantly associated with pathologic complete response (odds ratio for ER negative, 5.77; 95% confidence interval, 3.49-9.52; *P* < 0.0001). PTS induced a significant axillary downstaging (*P* < 0.001), and breast sparing surgery was feasible in 65% versus 34% (*P* < 0.001).

**Conclusions:** Doxorubicin/paclitaxel → CMF is feasible, safe, and well tolerated. Given as PST, it is markedly active, allowing for breast-sparing surgery in a large fraction of patients.
Operable breast cancer (ECTO); Fig. 1] addressing the potential role of introducing paclitaxel within a sequential regimen of non–cross-resistant chemotherapies. The ECTO study randomized patients with breast cancer > 2 cm to adjuvant doxorubicin → CMF or doxorubicin/paclitaxel → CMF (Fig. 1, arms A and B, respectively). In the ECTO study, the planned delivery of maximum of four cycles of doxorubicin/paclitaxel (240 mg/m² of total doxorubicin) before CMF seemed therefore consistent with the goal of exploiting the potential benefits of doxorubicin/paclitaxel without exposing the patients to excessive cardiac risk.

Based on kinetic considerations (12) and on animal experiments indicating that systemic therapy before surgery inhibited the tumor growth stimulatory response triggered by surgery (13, 14), the ECTO study is also addressing the effectiveness of doxorubicin/paclitaxel → CMF before surgery (Fig. 1, arm B versus C). The pivotal NSABP-B18 study showed that the doxorubicin and cyclophosphamide combination afforded equivalent efficacy when given either as primary or adjuvant systemic therapy (15, 16). The same investigation and other studies also showed that eradication of the invasive tumor in the breast assessed at surgery (pathologic complete response) is an independent predictor of long term outcome (15–18). In the ECTO trial, we reasoned that a prolonged administration of a sequential non–cross-resistant chemotherapy containing paclitaxel could yield a large increment of the rate of pathologic complete response that may increase the likelihood of observing a difference of benefit. Analysis of the main efficacy outcomes of the ECTO study awaits for the appropriate period of observation. However, at median 31 months of follow-up, data on toxicity of the delivered regimens and on locoregional antitumor activity of primary systemic therapy, a secondary aim of the ECTO trial, are available and reported here.

**Patients and Methods**

*Patient eligibility and study procedures.* Women at participating ECTO centers who had primary operable breast tumor > 2.0 cm at diagnosis (T2–T3, N0–N1, M0) were eligible for this study. Patients with locally advanced or bilateral breast carcinoma, prior anticancer treatment, inadequate bone marrow reserve, abnormal renal and liver function tests, and history of relevant cardiac disease were not eligible for the study. Also excluded were patients pregnant or lactating or with active infection or with a history of other invasive malignancy.

The study and the informed consent form had to be approved by each local ethic committee. Patients were to undersign the written informed consent to enter the study.

Between November 6, 1996 and May 29, 2002, a total of 1,355 patients were enrolled. Breast cancers were diagnosed by core biopsy (82%) or fine-needle aspiration cytology (18%). Either method of diagnosis was evenly distributed among the three treatment arm. Approximately 50% of the tumor diagnosed by fine-needle aspiration had clinical involvement of axillary nodes, and after major surgical intervention, all tumors were classified as invasive carcinomas. Assessment of hormonal receptor status and tumor grade was required.

Treatment allocation was done centrally at the ECTO Operations Office using a minimization algorithm (19) to balance assignments according to primary tumor size (<4.0 cm versus ≥4.0 cm), tumor grade (low versus intermediate versus high), and hormonal receptor status (estrogen and/or progesterone positive versus both negative). Geographic area of the participating center was also taken into account before randomization.

**Treatment.** Patients in arm A first received surgery followed by sequential single-agent doxorubicin and CMF; patients in arm B first underwent surgery followed by sequential doxorubicin/paclitaxel and CMF; patients in arm C received sequential doxorubicin/paclitaxel and CMF followed by surgery.

Breast irradiation (50 Gy through two opposing tangential fields to be started after completion of chemotherapy or within 4 weeks from surgery in arm C) was required after breast sparing surgery. In the presence of pT4 lesion after mastectomy, chest wall irradiation was recommended.

In arm A (Fig. 1), doxorubicin was given at the dose of 75 mg/m² by i.v. bolus every 3 weeks. In arms B and C, doxorubicin was given as a 60 mg/m² i.v. bolus followed by paclitaxel at 200 mg/m² infused over 3 hours, and each course was repeated every 3 weeks. CMF consisted in i.v. cyclophosphamide (600 mg/m²), methotrexate (40 mg/m²), and fluorouracil (600 mg/m²) on days 1 and 8 every 4 weeks. No dose reduction was allowed except following febrile neutropenia (as defined by absolute neutrophil count < 500/μL and fever > 38°C), grade 2+ neuropathy due to paclitaxel, and grade 2+ gastrointestinal toxicity on doxorubicin/paclitaxel regimen, when a 25% temporary reduction was required. In the presence of hematologic toxicity on the planned day of treatment, drug administration was delayed until marrow recovery. Before paclitaxel, premedication consisted of prednisone (25 mg orally the evening before therapy), hydrocortisone (250 mg i.v.) plus chlorphenamnine (10 mg i.v. or i.m.), and cimetidine (300 mg i.v.), all given 30 minutes before the taxane. Antiemetic therapy was administered according to the policy of the participating center.

At the end of the surgery-chemotherapy approach, all patients, regardless of age and receptor status, were originally offered tamoxifen (20 mg/d) for five consecutive years. The protocol was amended, and after June 30, 2000, tamoxifen was offered only to women whose tumors were either estrogen or progesterone positive.

**Primary tumor size determination and evaluation of primary systemic therapy response.** Clinical size of primary breast cancers was determined at diagnosis and before administration of each cycle of chemotherapy. Mammogram or breast ultrasound were planned at the end of each chemotherapy regimen. In the absence of clinical evidence of tumor in the breast and in the absence of any new lesions, treatment response was categorized as clinically complete. When the reduction in size of the breast tumor was >50% in the product of the two greatest perpendicular diameters, the response was judged to be partial; when the reduction was <50% but >25%, the response was categorized as minor. When there was an increase of >50% compared with a previous measurement or when a new lesion appeared, the patient was considered to have progressive disease. Patients whose tumor response did not meet any of the above definitions were considered nonresponders.

Surgical breast and axillary node resection specimens were carefully evaluated for pathologic tumor response according to the guidelines provided by an ad hoc committee before starting the trial. Patients who had no residual invasive cancer in the breast were considered to have had a pathologic complete response. Because this definition did
not take histologic nodal status into account, patients with noninvasive or no residual cancer could have had positive axial lymph nodes.

Side effects from chemotherapy. Side effects were assessed at each treatment cycle and graded according to the National Cancer Institute Common Toxicity Criteria (20). Electrocardiogram, physical examination, and measurement of left ventricular ejection fraction (LVEF) were required at diagnosis, at the end of each chemotherapy regimen and every 6 months during at least the first 2 years of follow-up.

Statistical methods. The primary objective of the ECTO study was to assess the freedom from breast cancer progression or relapse as measured from the date of randomization. Based on the prior experience of the doxorubicin → CMF regimen at the Milan Cancer Institute, it was planned to accrue 450 patients in each study arm, with an 80% power of the log-rank test to detect a 30% between-group relative difference in the hazard of occurrence of end point events, at the 5% significance level (two-sided test).

The second objective of the study, which is the aim of this report, was to compare the rate of breast-saving procedures and of pathologic nodal status after primary chemotherapy (arm C) versus primary surgery (arms A and B grouped together). Simple proportions were examined by use of the χ2 test. A second aim was attempting to identify pretreatment variables likely to predict clinical and pathologic response to primary chemotherapy with doxorubicin/paclitaxel → CMF. Assessment was done by analyzing both simple proportions on univariate analyses and by performing logistic regression analyses using a backward procedure (21). All analyses are based on data received as of July 31, 2003.

Results

Patient population and tumor characteristics. A total of 1,355 patients were enrolled into study (Table 1). Eight patients (0.6%) failed to meet the eligibility criteria because of locally advanced disease (n = 2), distant metastases (n = 2), no invasive breast cancer on biopsy (n = 2), bilateral breast cancer (n = 1), and chronic hepatitis (n = 1). In addition, 23 women (1.7%) refused to be treated according to their allocated program. Main patient characteristics at randomization (Table 1) remained evenly distributed in the study arms. Approximately 20% of patients had tumors > 4.0 cm, and more than half were ages ≥50 years. Approximately one third of tumors were both estrogen receptor (ER) and progesterone receptor negative, and more than half were categorized as intermediate grade.

Therapy, compliance, and adverse events. The planned eight cycles of therapy were completed in 89% of all patients irrespective of the allocated arm of treatment (Table 1). Of note, ~97% of patients completed the first four courses of either doxorubicin or doxorubicin/paclitaxel. Toxic events were reported as reason for treatment discontinuation in 2% of all patients. Repeated episodes of nonfebrile neutropenia (0.8%) were the most frequent cause. One patient had a drop in LVEF to 33% after the second cycle of CMF, and another woman developed a myocardial infarction (see below for cardiac events). Other causes of treatment discontinuation include intervening nonneoplastic medical conditions (six patients) and discontinuation of CMF after the third cycle because of poor patient tolerance (10 women).

In view of the even distribution of main patient characteristics and treatment delivery in the three arms of the study (Table 1), further analysis of toxicity can be presented pooling together observations and events in arms B and C, in which patients received the same regimen consisting of doxorubicin/paclitaxel → CMF. Data in Table 2 show that almost all major toxic events were similar whether or not paclitaxel was part of the chemotherapy regimen. As expected, reversible peripheral neuropathy was significantly more frequent with the paclitaxel-containing regimen (Table 2). Signs and symptoms of peripheral neuropathy were documented after the second cycle of doxorubicin/paclitaxel, lasted in median 3 months, and completely recovered before the end of CMF. In only one woman did neuropathy last 8 months before complete recovery.

Serial measures of LVEF in 91% of all patients allowed for grading of cardiac effects for a median observation time of 31 months from randomization (Table 2). A total of 11.8% of patients developed grade 2 toxicity, that included either LVEF values of <50% (6.2%) or a decrease of >20% from basal values (5.6%). The incidence of either type of event was similar with doxorubicin → CMF and doxorubicin/paclitaxel → CMF (Table 2). Six patients (arm A, 3% or 0.5%; arms B plus C, 3% or 0.3%) developed grade 3 toxicity. All of these patients were alive after a minimum of 8 months to >5 years from occurrence of the cardiac event.

Comparison of surgical procedures and pathologic findings after primary surgery or primary systemic therapy. A total of 296 women (34%) in the primary surgery arms underwent breast conservative surgery, with no differences between arm A and B. After primary chemotherapy, the rate of breast conservative surgery increased to 65% (284 of 438), showing a statistically
significant reduction \((P < 0.001)\) in the requirement for mastectomy. Figure 2 shows the effects of primary systemic therapy on locoregional disease. Breast-sparing surgical procedures were significantly more frequent after primary systemic therapy in all categories of initial tumor size. This is especially marked for tumors \(> 4\) cm at diagnosis (Fig. 2A). The low rate of breast conservative surgery in patients presenting with tumors measuring up to \(3.0\) cm in arms A and B can in part be explained by the fact that many centers in Europe still perform mastectomy in women with tumors \(> 2.5\) cm, especially if axillary nodes are clinically palpable.

The ability of primary systemic therapy in increasing the feasibility rate of breast-saving procedures was not counterbalanced by an increased risk of in-breast recurrence. In fact, 31 months after randomization, the total risk of recurrence was even lower, albeit nonstatistically significant because of the low number of events, after PTS and conservative surgery [total risk: 1.4%, 95% confidence interval (95% CI), 0-3.4; tumor size \(\leq 4.0\) cm, 0.7%; 95% CI, 0-2.2; tumor size \(> 4.0\) cm, 2.4%; 95% CI, 0-7.0] compared with the risk observed after conservative surgery followed by adjuvant systemic therapy (total risk, 3.6%; 95% CI, 0.8-6.3; tumor size \(\leq 4.0\) cm, 2.8%; 95% CI, 0.8-3.6; tumor size \(> 4.0\) cm, 3.1%; 95% CI, 0.3-5.9).

The administration of primary chemotherapy also contributed to a significant downstaging of pathologic nodal status: 263 (60%) patients were pathologically node negative compared with 39% in the primary surgery group \((P < 0.001)\). Of note, fewer positive nodes were found in patients who received primary chemotherapy, as shown in Fig. 2B.

Clinical response after primary systemic therapy. Major shrinkage of the primary tumor was measured in 78% of the patients (clinically complete response, 49%; partial response, 29%) after primary doxorubicin/paclitaxel \(\rightarrow\) CMF. An analysis of the degree of response after doxorubicin/paclitaxel and after CMF was feasible in 373 patients and is reported in Table 3. Overall, 100 patients (27%) achieved a clinically complete response after the first four cycles of doxorubicin/paclitaxel. Of note, 151 of 273 patients (55%) having a residual clinically palpable tumor mass after doxorubicin/paclitaxel had an improvement of the response with CMF. Three women (1%) had progressive disease while on therapy.

Pathologic findings after primary systemic therapy. After primary doxorubicin/paclitaxel \(\rightarrow\) CMF, six patients refused surgery (two after achieving a clinically complete response), two were not operated because of progressive disease; in two cases, no reasons for missing surgery were provided. Pathologic findings are available for overall 438 patients (98%). Complete absence of cancer cells was reported in breast specimens of 75 patients (17%). In 27 additional cases (6%) residual in situ carcinoma only was described, so that 23% of patients had no residual invasive cancer in the breast. Considering also the pathologic findings in the axillary lymph nodes, overall 89 of 438 patients (20%) had no evidence of invasive cancer after primary doxorubicin/paclitaxel \(\rightarrow\) CMF.

Univariate and multivariate analysis of clinical and pathologic response. The likelihood of achieving a response to primary doxorubicin/paclitaxel \(\rightarrow\) CMF was assessed as a function of main pretreatment variables (age, clinical tumor size, clinical

<table>
<thead>
<tr>
<th>Table 2. Main toxicities</th>
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</thead>
<tbody>
<tr>
<td><strong>Events</strong></td>
</tr>
<tr>
<td><strong>Neutropenia (&lt;500 ANC/µL)</strong></td>
</tr>
<tr>
<td><strong>Febrile neutropenia</strong></td>
</tr>
<tr>
<td><strong>Infection G2-G3</strong></td>
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<tr>
<td><strong>Allergic reaction</strong></td>
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<tr>
<td><strong>G2</strong></td>
</tr>
<tr>
<td><strong>G4</strong></td>
</tr>
<tr>
<td><strong>Neuropathy</strong></td>
</tr>
<tr>
<td><strong>G2</strong></td>
</tr>
<tr>
<td><strong>G3</strong></td>
</tr>
<tr>
<td><strong>Stomatitis</strong></td>
</tr>
<tr>
<td><strong>G3</strong></td>
</tr>
<tr>
<td><strong>G4</strong></td>
</tr>
<tr>
<td><strong>Cardiac events</strong></td>
</tr>
<tr>
<td><strong>CTC 0</strong></td>
</tr>
<tr>
<td><strong>CTC 1</strong></td>
</tr>
<tr>
<td><strong>CTC 2</strong></td>
</tr>
<tr>
<td><strong>LVEF (&lt;50%)</strong></td>
</tr>
<tr>
<td><strong>&gt;20% decrease from basal values</strong></td>
</tr>
</tbody>
</table>

Abbreviations: A, doxorubicin; AT, doxorubicin/paclitaxel; ANC, absolute neutrophil count; CTC, Common Toxicity Criteria.

* ANC (<500/µL and fever > 38°C).

*Unrelated to febrile neutropenia or surgical reasons.
Discussion

The present first report on the ECTO trial shows that inclusion of paclitaxel in the doxorubicin/paclitaxel → CMF is feasible, well tolerated, and endowed of marked antitumor activity. The tolerability of doxorubicin → CMF was of the same type and incidence already reported in the single-institution experience (2), and the toxicity of doxorubicin/paclitaxel → CMF was similar, except for the significantly higher incidence of peripheral neuropathy induced by paclitaxel (7). Peripheral neuropathy was reversible in all patients and lasted in median 3 months. Severe neutropenia and febrile neutropenia were infrequent with and without paclitaxel. The ECTO study called for administration of full doses of all drugs based on counts on the day of treatment. This approach allowed for delivery of full doses to the vast majority of patients without compromising on planned dose intensity and requiring administration of granulocyte colony-stimulating factor to a very small proportion of women. The approach was different from that in other investigations of doxorubicin/paclitaxel, in which dose reductions were based on nadir counts and led to a marked decrease of dose intensity (22). The good hematologic tolerability of doxorubicin/paclitaxel → CMF is in contrast with that reported in other trials of sequential regimens inclusive of docetaxel, in which high rates of severe neutropenia and febrile neutropenia were reported in spite of prophylactic granulocyte colony-stimulating factor administration to all patients, and toxic deaths did occur (23, 24).

In the ECTO trial, the most careful monitoring was applied to the cardiac function because of the higher-than-expected cardiac toxicity reported in early studies of doxorubicin/paclitaxel (7, 8). LVEF was similarly affected in patients receiving single-agent doxorubicin in arm A for a total dose of 300 mg/m² and in those treated with doxorubicin/paclitaxel in arms B and C for a total dose of 240 mg/m² of doxorubicin. The decrease was almost always non symptomatic and was reversible in the vast majority of patients after delivery of chemotherapy. Symptomatic cardiac events (grade 3) were rare, had similar incidence with both regimens (0.5% in arm A versus 0.3% in arms B and C), were responsive to cardiac medications, and were all observed during or soon after chemotherapy. At median 31 months after randomization, the incidence of grade 3 events is lower than the one reported with other anthracycline-containing regimens for early breast cancer (5, 25, 26). Although longer follow-up only will rule out that the regimen does not entail increased cardiac risk at later times, the early findings reported here are reassuring.

The proportion of women achieving eradication of invasive carcinoma in the breast after four cycles of chemotherapy has been in the low range of 3% to 14% in spite of the much higher proportion of them having major clinical response (15–18).

Table 3. Clinical response of primary breast cancer after both AT and CMF

<table>
<thead>
<tr>
<th>Response after AT</th>
<th>CCR</th>
<th>PR</th>
<th>MR</th>
<th>NR</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>184</td>
<td>107</td>
<td>54</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td>PR</td>
<td>120</td>
<td>57</td>
<td>62</td>
<td>12</td>
<td>22</td>
</tr>
<tr>
<td>MR</td>
<td>84</td>
<td>18</td>
<td>33</td>
<td>32</td>
<td>3</td>
</tr>
<tr>
<td>NR</td>
<td>68</td>
<td>9</td>
<td>12</td>
<td>22</td>
<td>25</td>
</tr>
<tr>
<td>PD</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Abbreviations: AT, doxorubicin and paclitaxel; CCR, clinical complete response; PR, partial response; MR, minor response; NR, no response; PD, progressive disease.
Many trials of primary chemotherapy in the 1990s attempted at improving the rate of pathologic complete response by designing new regimens that included taxanes and/or new modalities of drug administration (23, 24, 27), while also prolonging the total duration of treatment. This report shows that doxorubicin/paclitaxel prolonging the total duration of treatment. This report shows that doxorubicin/paclitaxel contributes to increasing complete responses from 23% to the remarkable rate of 42% (7, 32). However, the ECTO trial also suggests a role of the sequential application of non–cross-resistant regimens. Indeed, clinical response to CMF leads to major clinical response; PR, progesterone receptor.

<table>
<thead>
<tr>
<th>Category</th>
<th>% CCR</th>
<th>P</th>
<th>% PCR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>42</td>
<td>0.005</td>
<td>12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Negative</td>
<td>60</td>
<td></td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>PR status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>43</td>
<td>0.02</td>
<td>13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Negative</td>
<td>55</td>
<td></td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Tumor grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low + intermediate</td>
<td>43</td>
<td>0.006</td>
<td>19</td>
<td>0.006</td>
</tr>
<tr>
<td>High</td>
<td>58</td>
<td></td>
<td>30</td>
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</tbody>
</table>

NOTE: Univariate analysis. Abbreviations: CCR, clinical complete response; PCR, pathologic complete response; PR, progesterone receptor.

The ECTO study also provides a relevant qualification of the tumor response after doxorubicin/paclitaxel → CMF. Of note, 42% of patients with ER negative tumors had pathologic complete response versus 12% in the ER-positive group and in multivariate analysis ER status emerged as the only independent variable significantly associated with likelihood of achieving a clinically complete response (odds ratio, 2.1), and most importantly a pathologic complete response (odds ratio, 5.77; P < 0.0001). The association between ER status and likelihood of pathologic complete response is in agreement with other reports, indicating that ER-negative tumors are more sensitive to chemotherapy than ER-positive ones (23, 24). In the ECTO trial, different sensitivity according to ER status was remarkably high, but it should be pointed out that pathologic complete response rate in ER-positive tumors should not be discounted as negligible. On the contrary, the different pathologic complete response rate in the two subsets of patients justifies the design of different drug approaches according to hormonal receptor status.

The present report points out to an immediate advantage of the preoperative regimen when comparing surgical findings after doxorubicin/paclitaxel → CMF to those in patients undergoing surgery first (arms A and B). Tumor size was decreased enough to allow for breast sparing procedures in 65% of patients versus 34% in the adjuvant arms. Importantly, at a median follow-up in excess of 24 months from surgery, such an improvement in breast conservation was not at the cost of an increased risk of local relapses (35).
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References

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