A Phase II Trial of Neoadjuvant Docetaxel and Capecitabine for Locally Advanced Breast Cancer

Peter F. Lebowitz, Jennifer Eng-Wong, Sandra M. Swain, Arlene Berman, Maria J. Merino, Catherine K. Chow, David Venzon, Farah Zia, David Danforth, Edison Liu, and JoAnne Zujewski

1Medical Oncology Clinical Research Unit, 2Cancer Therapeutics Branch, 3Laboratory of Pathology, 4Biostatistics and Data Management, and 5Surgery Branch, National Cancer Institute, Bethesda, Maryland; and 6Diagnostic Radiology Department, National Institutes of Health, Bethesda, Maryland

ABSTRACT

Purpose: This study evaluated the toxicity and efficacy of docetaxel/capecitabine as neoadjuvant treatment for stage 2/3 breast cancer.

Experimental Design: Subjects with newly diagnosed invasive stage 2 and 3 breast cancer were eligible. The first cohort of patients was treated at dose A with neoadjuvant docetaxel (75 mg/m² i.v. day 1) and capecitabine (1000 mg/m² orally twice daily days 2–15) for four cycles. A second cohort of subjects was treated with a reduced dose, dose B, of docetaxel (60 mg/m² i.v. day 1) and capecitabine (937.5 mg/m² orally twice daily days 2–15).

Results: Thirty patients were enrolled. Eight of 10 patients treated at dose A required dose reductions of either docetaxel or capecitabine secondary to grade 3 or 4 toxicities: mucositis (1), hand-foot syndrome (3), diarrhea (2), perirectal abscess (1), and neutropenia (2). Because of a high rate of dose reductions, the next 20 patients were treated at dose B. The mean cumulative administered dose of docetaxel was 285 and 231 mg/m² at dose A and dose B, respectively. For capecitabine, the mean cumulative dose at dose A and B were similar at 1585 and 1627 mg/m²/day, respectively. The overall clinical response rate was 90% with 71% having a complete response and 59% having a partial response. A pathological complete response in the breast was achieved in 10% of patients after four cycles of docetaxel/capecitabine.

Conclusions: Docetaxel/capecitabine is a highly active regimen in the neoadjuvant setting. Neoadjuvant therapy with 75 mg/m² docetaxel and 1600 mg/m²/day days 2–15 is recommended.

INTRODUCTION

Primary (or neoadjuvant) chemotherapy for the treatment of locally advanced breast cancer has become a standard therapy (1). Randomized trials comparing this approach to adjuvant chemotherapy have demonstrated that neoadjuvant chemotherapy is as efficacious as adjuvant chemotherapy and allows for a higher rate of breast conservation (2, 3). In addition to its clinical benefits, neoadjuvant therapy also provides advantages when used in the research setting. Although adjuvant trials require years to allow efficacy comparisons of different regimens, a neoadjuvant trial allows assessment of the clinical response and biological activity of different regimens in months. Results from early neoadjuvant trials have shown that pathological complete response is an independent predictor of disease-free and overall survival (2, 4, 5). Although we still await more mature data from trials comparing neoadjuvant taxane-based regimens, preliminary data suggest that these regimens, which have superior pathological complete response rates, will also provide an improvement in survival (6).

In an attempt to define chemotherapy regimens with maximal activity, randomized trials have compared neoadjuvant regimens using the pathological complete response rate as an intermediate end point (6–10). These trials have demonstrated an advantage to using sequential, non–cross-resistant regimens such as doxorubicin/cyclophosphamide followed by docetaxel. Sequential addition of taxanes to anthracycline regimens appears to provide a higher rate of pathological complete response (34 versus 16%) and perhaps improved survival, although survival data are preliminary (6, 9). If this survival advantage is confirmed, the testing of more potent, synergistic regimens in the neoadjuvant setting becomes even more compelling.

One synergistic regimen of interest is docetaxel and capecitabine (11). Capecitabine is an oral fluoropyrimidine prodrug that is converted to 5-fluorouracil through the action of thymidine phosphorylase (12). Because many human tumors have a higher activity of thymidine phosphorylase than normal tissue, there is preferential conversion of the prodrug to its active form in tumors. In preclinical and clinical studies, docetaxel has been found to additionally up-regulate thymidine phosphorylase in tumor tissues, suggesting a potential mechanism for synergy between docetaxel and capecitabine (13, 14). In xenograft models, the combination of these two drugs resulted in synergistic antitumor activity, whereas administration of 5-fluorouracil with docetaxel provided only additive activity. Taxane administration should precede administration of the capecitabine for optimal effect (15).

On the basis of these promising findings, a phase III trial was done comparing single agent docetaxel (100 mg/m²) to the
combination of docetaxel (75 mg/m²) and capecitabine (1250 mg/m²) twice daily on days 1–14 (11). The combined regimen resulted in superior tumor response (42 versus 30%), time-to-progression (6.1 versus 4.2 months), and overall survival (14.5 versus 11.5 months) with comparable overall toxicity. Additional analysis of this trial revealed that frequent dose reduction of capecitabine was required; however, dose reduction did not affect efficacy (16).

We designed a phase II trial with neoadjuvant docetaxel/capecitabine in stage 2 and 3 breast cancer to determine toxicities and efficacy of this regimen as preoperative therapy. We report the results of this study which shows a high response rate with manageable toxicity.

PATIENTS AND METHODS

Patient Eligibility. Patients referred to the National Cancer Institute with newly diagnosed stage 2 or 3 breast cancer (American Joint Commission on Cancer, fifth version) with a tumor size of >2 cm were eligible (17). Eligibility criteria included an absolute neutrophil count > 1200/mm², platelet count > 100,000, creatinine < 1.5 mg/dL, calculated creatinine clearance > 50 mL/min, total bilirubin < 1.4, aspartate aminotransferase/alanine aminotransferase < 1.5× upper limit of normal, alkaline phosphatase < 2.5 upper limit of normal, and Zubrod performance status 0 to 2.

Patients were excluded if they had a bleeding disorder, a cardiac ejection fraction below normal limits, serious cardiac events within the past 12 months, or prior treatment of breast cancer. Pregnant or lactating women were excluded.

The protocol was approved by the Institutional Review Board of the National Cancer Institute and written informed consent was obtained.

Study Design. Initial assessment of patients included medical history, physical examination, complete blood count with differential, metabolic panel, chest X-ray, electrocardiogram, ejection fraction measurement, bilateral mammogram, pregnancy test, and pathological review of tissue. Immunohistochemistry was used to assess the following tumor markers: estrogen receptor, progesterone receptor, p53, and HER2. Estrogen receptor and/or progesterone receptor were considered positive if >1% of any sample stained positive. For p53, any degree of positive staining was considered p53 positive. Tumor grade was assessed by Bloom-Richardson score.

Stage 3 patients had a baseline bone scan and a computed tomography scan of the abdomen. Additional studies were performed as clinically indicated. Women without menstrual bleeding within the last 12 months were considered to be postmenopausal.

All patients started treatment with docetaxel and capecitabine. Chemotherapy with doxorubicin and cyclophosphamide was given either before or after surgery. (Fig. 1) Recommendations regarding timing of further chemotherapy, surgery, and radiation were made on a case-by-case basis.

Treatment Regimen. Patients received four cycles of docetaxel/capecitabine every 21 days. The initial dose (dose A) was docetaxel (75 mg/m² i.v.) on day 1 and capecitabine (1000 mg/m² p.o.) twice daily on days 2–15 every 21 days for four cycles. This dose is similar to the dose used in the metastatic trial, although the dose of capecitabine was lowered by 25% (16).

Because of excessive toxicity at dose A, both agents were reduced to docetaxel (60 mg/m²) and capecitabine (937.5 mg/m²) twice daily. Premedication with dexamethasone (8 mg orally twice daily × 3 days) was given starting the day before docetaxel administration. Complete blood count with differential was obtained twice weekly.

Dose reductions during docetaxel/capecitabine treatments were performed as described below. For hematologic toxicities, patients who started at docetaxel (75 mg/m²) and docetaxel (60 mg/m²) had their dose reduced to 60 and 45 mg/m², respectively, for absolute neutrophil count < 500 per mm³ for >5 days or a single platelet count < 20,000 mm³ and capecitabine was reduced by 25%. Patients with absolute neutrophil count < 1200 mm³ or platelets < 20,000 mm³ on the scheduled day of treatment had treatment held until recovery. Patients who required delay for over a week had the doses reduced as above. For nonhematologic toxicity of grade 2 or greater, capecitabine treatment was interrupted without dose reduction until resolution to grade 1 or less. For the second and third occurrences of grade 2 toxicity, capecitabine was reduced to 75 and 50% of the previous dose, respectively. For the first and second occurrences of grade 3 toxicity, the dose of capecitabine was reduced to 75 and 50% of the previous dose, respectively. The first occurrence of grade 4 toxicity resulted in a 50% reduction of capecitabine, and if toxicity recurred after the 50% dose reduction, capecitabine treatment was discontinued.

Patients received four cycles of doxorubicin (60 mg/m²) and cyclophosphamide (600 mg/m²) on day 1 every 21 days.
(doxorubicin/cyclophosphamide) either before or after surgery (see Fig. 1). Patients developing neutropenia with an absolute neutrophil count < 500 mm$^3$ for >5 days were treated with either filgrastim or pegfilgrastim.

**Locoregional Therapy.** Modified radical mastectomy or lumpectomy with axillary lymph node dissection was performed ~4 weeks after completion of chemotherapy. Criteria used for determining if patients were breast conservation candidates included tumor to breast ratio, involvement of the nipple, involvement of skin, tumor size, multicentric disease, suspicious microcalcifications, and contraindications to radiation therapy (1). Radiation therapy was performed with an individualized treatment plan.

**Hormonal Therapy.** Patients with hormone receptor-positive tumors were treated with hormonal therapy. With the release of data supporting the use of adjuvant anastrozole, the protocol was amended after the first 23 patients were enrolled to include the option of using either tamoxifen (20 mg daily) or anastrozole (1 mg daily) in postmenopausal women (18). Premenopausal women were treated with tamoxifen and goserelin (3.6 mg s.c. implant every 28 days).

**Patient Assessment and Outcome Measurement.** History with toxicity assessment using Common Toxicity Criteria, version 2.0, and a physical exam with tumor measurement were done at the start of each cycle. A mammogram and a breast magnetic resonance image were done at the completion of four cycles of chemotherapy or earlier if clinically indicated. Partial response was defined as a decrease in unidimensional measurement of at least 30%. Complete response was defined as the absence of palpable tumor on clinical exam. Pathological complete response was defined, as per the Chevallier classification, as disappearance of all invasive tumor pathologically at the time of definitive surgery (19).

**Statistical Analysis.** The initial study design planned an enrollment of up to 36 patients. The null hypothesis was that the response rate of this regimen was equivalent to the 79% figure obtained by National Surgical Adjuvant Breast and Bowel Project, using doxorubicin/cyclophosphamide, and tested against the alternative of a response rate of 60%. If no more than 25 responses were obtained in the full sample of 36 patients, the null hypothesis was to be rejected. This provided 91% power, with a 12% probability of erroneously rejecting the null hypothesis when the true response rate is 79%. An interim analysis was performed after the first 18 patients were evaluated for response. If 9 or fewer responses had been obtained in those 18, the null hypothesis would have been rejected at the $P < 0.01$ level.

The actual accrual of 30 was based on the high response rate in these patients. It was observed that there were 26 responses in the first 29 evaluable patients (90%), which provides 95% confidence interval that the true response rate is >75% with this regimen.

**RESULTS**

**Study Profile.** From January 2001 to August 2003, 30 patients were enrolled and treated with 116 total courses of docetaxel and capecitabine (Fig. 2). One patient voluntarily withdrew from the trial after one cycle of therapy; the remainder of the patients completed the treatment phase of the trial.

Because 8 of the first 10 patients required dose reductions of either docetaxel or capecitabine at dose A [docetaxel (75 mg/m²) and capecitabine (1000 mg/m²/day orally twice daily)], the protocol was amended with a dose reduction. Toxicities requiring dose reduction included mucositis (1), hand-foot syndrome (3), diarrhea (2), perirectal abscess (1), and neutropenia (2). The next 20 patients were treated at dose B [docetaxel (60 mg/m²) and capecitabine (937.5 mg/m²/day orally twice daily)].

Of 29 evaluable patients, 10 received doxorubicin/cyclophosphamide immediately after docetaxel/capecitabine to further reduce tumor size. All other patients, received doxorubicin/cyclophosphamide after surgery.

Twelve patients underwent modified radical mastectomy,
and 17 patients underwent lumpectomy. Axillary lymph node dissection was performed on 26 patients. The median number of lymph nodes evaluated was 20 (range, 7 to 41). Three patients refused axillary lymph node dissection. One patient refused radiation therapy.

**Patient Demographics and Tumor Characteristics.**
Patient demographics are listed in Table 1. Only 4 of 30 (13%) patients were candidates for breast conservation therapy before chemotherapy.

Tumor characteristics are shown in Table 2. One patient had two distinct masses, which were determined to be two different primary tumors with different histology and receptor staining.

**Chemotherapy Administration.**
At dose A, 10 patients received 37 cycles of chemotherapy. No patient received both drugs at the full dose for all four cycles. Capecitabine was administered at a reduced dose in 54% of cycles delivered. Docetaxel was dose reduced in 24% of cycles.

At dose B, 20 patients received 79 cycles of chemotherapy. Full doses of both drugs were given to 20% of patients. Capecitabine was given at reduced dose in 43% of cycles. Docetaxel was dose reduced in only 8% of cycles and was held due to total bilirubin elevation in three patients for a total of four cycles. Fig. 3 shows the average dose administered as a percentage of planned dose per cycle. The results with dose A are similar to those previously reported in the metastatic setting (11, 20).

The mean total dose of docetaxel administered to each patient for dose A and dose B was 285 mg/m² (95% of planned) and 231 mg/m² (96% of planned), respectively. For capecitabine, the mean dose administered was similar at dose A and dose B at 1585 mg/m²/day (79% of planned) versus 1627 mg/m²/day (87% of planned), respectively.

Thus, with the lower dose of docetaxel/capecitabine, less docetaxel was administered, but a similar amount of capecitabine was given due to decreased interruptions of therapy.

**Toxicities.** Treatment-related adverse events for both dose levels are shown in Table 3. The most notable toxicities were grade 3 to 4 neutropenia (83%), grade 2 to 3 hand-foot syndrome (60%), infection (27%), myalgias (20%), fatigue (17%), and diarrhea (13%). The only notable difference between dose A and dose B was an increased incidence of myalgias (50% versus 17%), and diarrhea (13% versus 20%). The incidence and severity of hand-foot syndrome was not diminished with the lower starting doses of capecitabine. Despite the high incidence of neutropenia at both doses, there were no episodes of febrile neutropenia or sepsis, and there was only one episode of neutropenia with infection.

**Clinical Efficacy.** The response rate after docetaxel/capecitabine was determined by clinical measurement (20). Combined data from two dose levels of docetaxel/capecitabine in 29 evaluable patients demonstrated an overall response rate of 90% with a complete response rate of 31% and a partial response rate of 59% after treatment with the docetaxel/capecitabine. Ten percent of patients did not respond. A pathological complete response in breast and lymph nodes was seen in two patients (7%). An additional patient had a pathological complete response in the breast with one positive lymph node for a pathological complete response in the breast of 10% (Table 4).
Of 29 evaluable patients, 83% were not candidates for breast conserving therapy before treatment. Of these patients, treatment with docetaxel/capecitabine alone for four cycles allowed 40% to undergo breast conserving therapy. At dose A, 75% of the pretreatment, non-breast conserving therapy patients received breast conserving therapy after four cycles of docetaxel/capecitabine versus 24% at dose B.

Patients were treated with doxorubicin and cyclophosphamide before surgery if further decrease in tumor size would improve the surgical results. Ten patients were treated with doxorubicin and cyclophosphamide before surgery. The additional chemotherapy resulted in an additional reduction in tumor size in 70% of patients however none of these patients had a clinical or pathological complete response.

**DISCUSSION**

This study provides the first reported experience using docetaxel and capecitabine in the neoadjuvant setting. The regimen is notable for its preclinical synergy and a demonstrated survival advantage in metastatic breast cancer. Trials are ongoing and being planned using this regimen in the adjuvant setting. Our experience in the neoadjuvant setting, therefore, provides important observations in determining the efficacy, toxicities, and dosing of this regimen.

Overall, the response rate for the docetaxel/capecitabine regimen was comparable with that seen with other highly active chemotherapy regimens in the neoadjuvant setting (8). In large neoadjuvant trials such as National Surgical Adjuvant Breast and Bowel Project B-18 and B-27, four cycles of doxorubicin/cyclophosphamide alone yielded a clinical complete response rate between 36 and 40% and a pathological complete response (in breast) rate of ~13% (10, 21). In comparison to the current trial, these studies accrued patients with less advanced tumors and a lower incidence of clinically positive lymph nodes. Smaller studies using other highly active regimens have achieved similar results. Doxorubicin and docetaxel given for six cycles achieved a pathological complete response rate of 8% as did docetaxel, doxorubicin, and cyclophosphamide (22, 23). This compares favorably with the 31% (clinical complete response), 10% (pathological complete response in breast), and 7% (pathological complete response in breast and nodes) rates seen in our study with four cycles of docetaxel and capecitabine. These result argue that further testing of this regimen in the adjuvant and neoadjuvant setting is a high priority.

The toxicities were quite similar at dose A and dose B, although the higher dose did require more frequent dose reductions because of diarrhea and infection. The high rate of neutropenia in this trial as compared with a prior metastatic trial may be due to reporting differences between the two studies (11).

The cumulative dose of capecitabine delivered was similar at the lower and higher doses due to a decrease in treatment interruptions at the 1875 mg/m²/day dose. At dose B, the mean dose delivered was 1627 mg/m²/day arguing that this is a reasonable starting dose. As would be expected, however, the cumulative delivered dose of docetaxel was decreased at 60 mg/m² as compared with 75 mg/m². Although the study was not powered to determine efficacy differences between the dose levels, the response rates for both were high and comparable with other highly active regimens. However, the question of

**Table 3** Toxicities

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>2 (7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4 (13)</td>
<td>11 (37)</td>
<td>14 (47)</td>
</tr>
<tr>
<td>Infection with neutropenia</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Infection without neutropenia</td>
<td>6 (20)</td>
<td>1 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>30 (100)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>2 (7)</td>
<td>2 (7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2 (7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (10)</td>
<td>1 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (10)</td>
<td>1 (3)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>4 (13)</td>
<td>14 (47)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Mucositis/Stomatits</td>
<td>3 (10)</td>
<td>1 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Myalgia/Muscle weakness</td>
<td>4 (13)</td>
<td>2 (7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>2 (7)</td>
<td>1 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Transaminosis/ Hyperbilirubinemia</td>
<td>5 (17)</td>
<td>1 (3)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

**NOTE.** Thirty patients treated over 116 cycles. Toxicity reported as worst grade over treatment course.
relative efficacy of the two doses of docetaxel remains unanswered. Although there was somewhat greater toxicity at the higher docetaxel dose, there were no episodes of febrile neutropenia, sepsis, or more than grade 2 neuropathy. This suggests that docetaxel at 75 mg/m² is manageable in the neoadjuvant setting, albeit with some dose reductions in the latter cycles.

In conclusion, this phase II study shows that docetaxel/capecitabine is a highly active regimen in the neoadjuvant setting and deserves further study particularly in comparison to other regimens. A docetaxel dose of 75 mg/m² on day 1 with a capecitabine dose of 1600 mg/m² days 2–15 is recommended for the neoadjuvant setting.

ACKNOWLEDGMENTS

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REFERENCES


Table 4 Clinical end points with docetaxel/capecitabine

<table>
<thead>
<tr>
<th>Clinical parameter</th>
<th>Dose A (n = 9)</th>
<th>Dose B (n = 20)</th>
<th>Combined (n = 29)</th>
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</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>2 (22.2)</td>
<td>7 (35.0)</td>
<td>9 (31.0)</td>
</tr>
<tr>
<td>Partial response</td>
<td>7 (77.8)</td>
<td>10 (50.0)</td>
<td>17 (59.0)</td>
</tr>
<tr>
<td>Overall response</td>
<td>9 (100.0)</td>
<td>17 (85.0)</td>
<td>26 (89.7)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>0 (0)</td>
<td>2 (10.0)</td>
<td>2 (6.9)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>0 (0)</td>
<td>1 (5.0)</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>Pathologic complete response (in breast)</td>
<td>1 (11.1)</td>
<td>2 (10.0)</td>
<td>3 (10.3)</td>
</tr>
<tr>
<td>Pathologic complete response (in breast and nodes)</td>
<td>0 (0)</td>
<td>2 (10.0)</td>
<td>2 (6.9)</td>
</tr>
<tr>
<td>Conversion to breast conserving therapy*</td>
<td>75% (6/8)</td>
<td>24% (4/17)</td>
<td>40% (10/25)</td>
</tr>
</tbody>
</table>

* In patients who were not candidates for breast conserving therapy before chemotherapy.
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