Abstract. Background: Weekly paclitaxel and infusional high-dose 5-fluorouracil/leucovorin (HDFL) are both effective regimens for metastatic breast cancer (MBC) patients. Patients and Methods: A study was designed using weekly paclitaxel 90 mg/m² 1-hour infusion followed by 2,000 mg/m² 5-fluorouracil plus 300 mg/m² leucovorin 24-hour infusion on days 1, 8 and 15, repeated every 28 days, in patients who had previously received a ≥1 regimen for MBC. The dose of paclitaxel was adjusted in each cycle according to toxicity. Results: A total of 182 cycles were given to 28 patients. The doses of paclitaxel needed to be reduced only in 22 (12%) cycles. Forty-five cycles were skipped or delayed more than 7 days, mostly due to neutropenia, infection, or neurotoxicity. Twenty-five patients were evaluable for response. Four had complete response, 13 partial response, seven stable disease, and two progressive disease. The response rate was 60.7% (95% CI: 42.6-78.8). Median survival was 18.1 months (95% CI: 11.4-24.9), and progression-free survival seven months. Conclusion: Weekly paclitaxel plus infusional HDFL is an active and well tolerated regimen for pretreated MBC patients.

Paclitaxel is one of the best available chemotherapeutic agents as a second-line treatment of metastatic breast cancer (MBC) (1). Paclitaxel has been combined with various chemotherapeutic agents in MBC. Most combinations using prolonged infusion of paclitaxel every three weeks resulted in substantial myelosuppression (2, 3).

5-Fluorouracil (5-FU) is widely used in breast cancer treatment. Biochemical modulation of 5-FU by leucovorin has been shown to have a better response than 5-FU alone (5). The side-effects of 5-FU are schedule-dependent. Long infusion with 5-FU is associated with more mucosal toxicity and less myelotoxicity. Ardalan et al. (6) showed that high dose 5-FU (2,600 mg/m²) administered concurrently with leucovorin (500 mg/m²) over 24 hours, known as the HDFL regimen, can be given weekly to patients with colon cancer. There was no myelotoxicity associated with this infusion schedule.

Weekly 1-hour paclitaxel and 24-hour HDFL infusion was therefore planned for MBC patients who were pretreated with anthracycline. Both schedules of administration result in a low probability of myelosuppression. This combination was expected to be easily tolerable. The sequence-dependent drug interaction exists when paclitaxel is combined with other chemotherapeutic agents (7). Based on in vitro observation, paclitaxel should be given before 5-FU to attain synergism (8). The primary objective of this study was to determine the response rate of this combination regimen. The secondary objectives were to investigate the toxicity, progression-free survival, and overall survival of this treatment. The results of this phase II study are reported.
Patients and Methods

Eligibility criteria. Patients older than 18 years of age with pathologically confirmed MBC with a measurable tumor, defined by bi or uni-dimensional lesions on imaging studies or physical examination no less than 1 cm in diameter, were eligible for this study. All patients had at least one regimen of chemotherapy to treat MBC in the past. Further eligibility criteria included performance status 0 to 2 on the Zubrod scale, adequate renal (creatinine <1.5 mg/dl), hepatic (aspartate transaminase and alanine transaminase <5-fold upper limit of normal, bilirubin within normal range), and bone marrow function (hemoglobin >10 mg/dl, absolute neutrophil count (ANC) >1,500/mm³, platelet >100,000/mm³). There should have been more than four weeks between previous systemic therapy and protocol treatment. Patients on hormonal therapy who had progressive disease before entry were included. Palliative radiotherapy was allowed if the irradiated area did not cover all the measurable disease sites. Patients who were not willing to accept an indwelling catheter were excluded from this trial. The institutional ethical committee approved the trial protocol. All patients provided written informed consent to participate in the trial.

Treatment plan. Protocol treatment included paclitaxel (Taxol®: Bristol-Myers Squibb Company, New Jersey, USA) 90 mg/m² 1-hour infusion, followed by 5-FU 2,600 mg/m² plus leucovorin 300 mg/m² 24-hour continuous infusion on days 1, 8, and 15, repeated every 28 days. The first three patients experienced grade 3 or 4 diarrhea by cycle two. However, none of them had hematologic toxicity. The protocol was therefore amended in August 1997, so that the starting dose of 5-FU in the remaining patients was 2,000 mg/m².

The premedications for paclitaxel were oral dexamethasone 20 mg 12 and 6 hours before paclitaxel, ranitidine 50 mg and diphenhydramine 30 mg intravenously 30 minutes before paclitaxel. If there was no hypersensitivity after the first two doses, dexamethasone was reduced to 8 mg per dose.

Dose modification criteria. On days 8 and 15, if the white blood cell count (WBC) was <2,000/mm³ or the ANC <1,000/mm³ or platelets <75,000/mm³ or non-hematologic toxicity was grade 3 or more, T-HDFL on that day was not administered. On day 1, if the ANC was <1,500/mm³ or platelets <100,000/mm³ or non-hematologic toxicity was grade 2 or more, the treatment was delayed up to 14 days until recovery. Granulocyte colony-stimulating factor (G-CSF) was used when the WBC was <1,000/mm³ or the ANC <500/mm³ for more than three days, or febrile neutropenia developed. However, its prophylactic use was not allowed.

The dose modification was as follows: If the WBC was <1,000/mm³, the ANC <500/mm³, or platelets <50,000/mm³ for more than three days, any dose in the previous cycle had been omitted, or there was febrile neutropenia, the dose of paclitaxel was reduced to 70 mg/m² in the next cycle.

Evaluation of tumor response and toxicity. The response was evaluated by computed tomography at the end of every two cycles using standard World Health Organization (WHO) criteria. If there was progressive disease (PD), patients were taken off the protocol treatment. If there was a complete response (CR) or a partial response (PR), treatment continued until two cycles after the maximal response was reached. If there was stable disease (SD) after two cycles, the protocol treatment was continued. If there was SD after four cycles, the protocol treatment was continued or stopped at the discretion of individual physicians. The complete blood cell count with WBC differentiation was checked on days 1, 8 and 15 of each cycle. Blood chemistry and electrolytes were monitored at the beginning of each cycle. Toxicity was evaluated weekly using standard WHO criteria.

Statistical analysis. The study was originally designed to test 39 patients so that the lower 95% confidence limit was higher than the hypothesized null response rate of 30%, provided that the true response rate was ≥50%. This design provided 80% power.

The time to disease progression was defined as the time from the date of starting the protocol treatment to the date of documented disease progression, death due to any cause, or last follow-up. The overall survival was calculated from the date of starting the protocol treatment to the date of patient death or last follow-up using the Kaplan-Meier method.

Results

Patient characteristics. Twenty-eight patients were accrued into the study between June 1997 and May 1999. Because other competing protocols using a taxane plus fluoropyrimidine combination (e.g., docetaxel plus capcitabine) had been introduced at our institution since 1999 and affected patient accrual, we decided to prematurely terminate this trial. Table I summarizes the characteristics of the 28 patients at trial entry. These heavily pretreated patients had received one to six prior regimens (median 2) and two to 29 cycles (median 10). Among them, nine patients had received prior taxane regimens (paclitaxel 175 mg/m² 3-hour intravenous infusion every 3 weeks in two cases, docetaxel 100 mg/m² 1-hour intravenous infusion every 3 weeks in five, both paclitaxel and docetaxel in two). The predominant site of disease was visceral (lung, liver) in 20 patients, whereas bone, lymph node, or soft tissue metastases were present in the remaining patients.

Dose modification. In total, 182 (median 6, range 1-18) cycles were given. The dose of paclitaxel needed to be reduced in 22 (12%) cycles.

Toxicity. The toxicity profile was summarized in Table II. Overall, 45 cycles (25%) were delayed (more than seven days), due to neutropenia (24 cycles), infection (nine cycles), neurotoxicity (six cycles), or others (six cycles). One patient with diabetes mellitus withdrew due to grade 3 neurotoxicity.

Response and survival. Only one cycle of protocol treatment was given in four (16%) patients because of intolerable neurotoxicity (one patient), patient refusal (one patient), and PD (two patients). All other patients completed six cycles of treatment unless they withdrew due to progression...
of disease. Twenty-five patients were evaluable for response. Four had CR, 13 PR, seven SD, and two PD. The intent-to-treat response rate was 60.7% (95% CI: 42.6 to 78.8). Five patients out of nine who previously received taxane therapy responded. With a median duration of follow-up of 17.0 months (range 1.2 - 80.7), median survival was 18.1 months (95% CI: 11.4 to 24.9), 1-year survival was 71%, and 2-year survival was 38% (Figure 1). Median progression-free survival was 7 months (95% CI: 5.0 to 8.9) (Figure 1).

**Discussion**

In this study, weekly paclitaxel plus HDFL was found to be an active and well tolerated regimen for patients with pretreated MBC.

The present study is one of the reported series of combination chemotherapy treatments with taxane and fluoropyrimidine for anthracycline-pretreated MBC (Table III) (9-13). The objective response rates of these reported studies (42-59%) have varied widely and are difficult to compare because of possible bias in patient selection.

At the time this trial was designed, the most common administration of paclitaxel in MBC was 135-175 mg/m² over 3- or 24-hour infusion, repeated every three weeks. Subsequently, paclitaxel administered on a weekly schedule at doses of 80 - 100 mg/m² was shown to be active and well tolerated (14, 15). Preliminary results of a direct comparison showed superiority of paclitaxel 80 mg/m² 1-hour infusion weekly compared with paclitaxel 175 mg/m² 3-hour infusion every three weeks in terms of response rate and time to progression (16).

The better therapeutic index of HDFL, as compared with a 5-FU/leucovorin bolus regimen, has been demonstrated in phase III randomized trials of advanced colorectal cancers.
Table III: Taxane and fluoropyrimidine combination chemotherapy for anthracycline-pretreated MBC.

<table>
<thead>
<tr>
<th>Series</th>
<th>Regimen (mg/m²)</th>
<th>No. Response of pts</th>
<th>Complete response rate</th>
<th>Median survival rate (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klaassen et al.</td>
<td>P 175 3hr d1, 22</td>
<td>54</td>
<td>59%</td>
<td>4%</td>
</tr>
<tr>
<td>phase II (9)</td>
<td>F 2000 24hr &amp; L 500 d1, 8, 15, 22, 29, 36 Every 49 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicholson et al.</td>
<td>P 175 3hr d1</td>
<td>47</td>
<td>49%</td>
<td>4%</td>
</tr>
<tr>
<td>phase II (10)</td>
<td>F 350 &amp; L 300 bolus d1-3 Every 28 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Batista et al.</td>
<td>P 175 3hr d1</td>
<td>73</td>
<td>52%</td>
<td>11%</td>
</tr>
<tr>
<td>phase II (11)</td>
<td>C 1000 BID d1-14</td>
<td>Every 21 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lothorlary et al.</td>
<td>D 85 1hr d1</td>
<td>41</td>
<td>54%</td>
<td>2%</td>
</tr>
<tr>
<td>phase II (12)</td>
<td>F 750 24 hr d1-5</td>
<td>Every 21 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O'Shaughnessy et al. Phase III (13)</td>
<td>D 75 1hr d1 C 1250 BID d1-14 Every 21 days</td>
<td>255</td>
<td>42%</td>
<td>5%</td>
</tr>
<tr>
<td>This study</td>
<td>P 90 1hr d1, 8, 15</td>
<td>Every 28 days</td>
<td>28</td>
<td>61%</td>
</tr>
<tr>
<td></td>
<td>F 2000 &amp; L 300 24 hr d1, 8, 15</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BID, two times a day; C, capecitabine; D, docetaxel; F, 5-fluorouracil; L, leucovorin; P, paclitaxel.

BID, two times a day; C, capecitabine; D, docetaxel; F, 5-fluorouracil; L, leucovorin; P, paclitaxel.

(17, 18). In addition, we have clarified the mechanisms responsible for the low bone marrow toxicities of the HDFL regimen (19). Moreover, in an in vitro experiment mimicking the pharmacokinetics of HDFL, prolonged exposure of gastric cancer cells to 2.5-5 μM of 5-FU resulted in a more durable suppression of thymidylate synthase and enhanced cytotoxicity compared to brief exposure (20). Further studies are warranted to explore the optimal dosage and schedule of 5-FU/leucovorin in MBC.

The generally low toxicity of the current paclitaxel-HDFL protocol was well tolerated. Although paclitaxel-related neurotoxicity did occur in this study, it was usually mild under this weekly schedule. Grade 3 neuropathy occurred in 11% of patients only. Only one patient with diabetes mellitus discontinued the protocol treatment due to paclitaxel-related neuropathy. Because grade 3 or 4 diarrhea occurred in the first three accrued patients, the protocol was amended and the 5-FU dose was reduced from 2,600 to 2,000 mg/m² in the subsequent 25 patients. Thereafter, the rate of grade 3 or 4 diarrhea declined substantially (only in 4% of patients) and was probably of lesser severity than that of other taxane-fluoropyrimidine regimens (7-19%) (9-13). Although oral capecitabine might provide some convenience as compared to the HDFL used in this study, the present paclitaxel-HDFL regimen did not result in the severe hand-foot syndrome commonly seen in taxane-capecitabine combination (0% vs. 11-29% (11, 13)). The neutropenia and leukopenia of this study were comparable to those of other taxane plus fluoropyrimidine regimens (9-13) and less prevalent than the most common combination of an anthracycline and a taxane (7, 21, 22). Although grade 3 or 4 neutropenia (25%) and leukopenia (25%) were still common, the rarity of both grade 3 or 4 mucositis and diarrhea in the latter 25 patients may have contributed to the acceptable rate of grade 3 or 4 infections (11%), given that prophylactic G-CSF support was not used in this study. Besides, this combination did not result in any cardiac toxicity, which is a common problem in the anthracycline / taxane combination (7, 21, 22). The combination of weekly paclitaxel and HDFL has also been shown to be well tolerated in patients with other cancer types, such as metastatic gastric cancer (23) and hormone-refractory prostate cancer (24).

We conclude that the combination of weekly paclitaxel and 24-h infusion of high-dose 5-FU plus leucovorin is an effective regimen with a well-tolerated toxicity profile for a second-line treatment of advanced breast cancer.

References


Lin et al: Paclitaxel-HDFL for Chemotherapy-pretreated MBC

Received August 22, 2006
Revised November 1, 2006
Accepted November 16, 2006

645