Phase I/II Trial of Biweekly Paclitaxel and Cisplatin in the Treatment of Metastatic Breast Cancer


Purpose: To determine the maximum-tolerated dose of escalating doses of paclitaxel (Taxol; Bristol-Myers Squibb, Princeton, NJ) administered biweekly with a fixed dose of cisplatin, to assess the toxicity, and to evaluate the activity of this combination in a phase I/II trial in metastatic breast cancer.

Patients and Methods: Twenty-nine women with metastatic breast cancer were enrolled; 27 are assessable for response and 29 for toxicity. All but two of the women had received prior adjuvant chemotherapy, with 23 receiving anthracyclines and six previous cisplatin.

Results: The initial starting dose of paclitaxel 90 mg/m² and cisplatin 60 mg/m² became the phase II dose due to dose-limiting neutropenia. Responses were seen in 85% of assessable patients, with three patients (11%) achieving a complete response (CR) and 20 patients (14%) a partial response (PR), for an overall response rate of 85% (95% confidence interval [CI], 66% to 96%). The time to disease progression for patients who achieved a CR was 110 to 200 days, and for those with a PR, it was 96 to 377+ days, with a median time to progression of 7.1 months and a median response duration of 7.9 months. Sites of CR were skin, soft tissue, and lung, and all occurred in women with previous exposure to anthracyclines. Septic events were rare, with two grade 3 infections (7%), only one of which required hospital admission. There was no grade 4 nonhematologic toxicity and minimal grade 3 toxicity. A total of 251 chemotherapy cycles were given—16 with paclitaxel alone in five patients. Forty-five percent of patients required dose reductions, while 32% had delays due to neutropenia.

Conclusion: Biweekly paclitaxel and cisplatin is an active combination in the treatment of metastatic breast cancer, including for patients with previous exposure to anthracyclines.


Breast cancer is the single most common malignancy encountered in North American women. Although some patients diagnosed with breast cancer are cured with surgery or adjuvant chemotherapy and radiotherapy, 75% of women with axillary-positive nodes and 30% of those with axillary-negative nodes will relapse with metastatic or recurrent disease and require further therapy.1 There are a number of drugs with activity in metastatic breast cancer, but the duration of response to the currently available agents tends to be short.2 Also, many cases are either refractory to the most effective agents or become resistant after an initial response.

Paclitaxel (Taxol; Bristol-Myers Squibb, Princeton, NJ) is a diterpenoid plant product that interferes with microtubular polymerization by promoting abnormal assembly of microtubules and inhibiting their subsequent disassembly and normal function.3 Phase II studies have shown paclitaxel to be an active single agent in metastatic breast cancer, with reported response rates of 17% to 62%; the variability generally reflects the number of previous chemotherapy regimens the patients have received.4-7 Promising results have also been reported with combinations of paclitaxel with other active agents such as doxorubicin, cyclophosphamide, and etodextrate.8-13 Taxol is now approved for the treatment of breast cancer that has progressed after combination chemotherapy for metastatic disease or relapsed within 6 months of adjuvant chemotherapy in both the original and semisynthetic formulations.

During the early experience at our institution, administering paclitaxel in a 3-week dosing schedule, we observed that many patients had an abrupt WBC nadir at 8 days, with recovery of counts by day 15.14 A biweekly schedule was proposed with the possibility of increasing exposure to paclitaxel. The initial phase I study was planned to attempt also to increase the dose-intensity of paclitaxel.

We were also interested in combining the new agent with a non-cross-resistant drug with a different spectrum of toxicity. Cisplatin seemed to be an appropriate choice. First, although it is not an agent used widely in breast cancer, its activity in metastatic disease has been documented in several studies, with response rates of 47% to 54%.15-18 Second, it is usually not used in the adjuvant setting and, therefore, most patients should not have developed resistance to it when they develop metastatic disease. The mechanisms of resistance for cisplatin and paclitaxel differ, with multiple drug resistance (MDR) and tubulin mutations considered the culprits in paclitaxel...
resistance, but not in cisplatin. Third, except for neurotoxicity, the toxicities associated with cisplatin do not overlap those of paclitaxel. Finally, synergism between paclitaxel/cisplatin has been established in preclinical models and this has been translated as clear clinical benefits. In fact, in ovarian cancer, the association of paclitaxel/cisplatin has improved survival when administered as first-line therapy. 19 Cisplatin has demonstrated synergism with a variety of other cytotoxic drugs, such as fluorouracil (5FU) 20 and etoposide. 21,22 Pharmacokinetic interactions and sequence analysis of this combination of agents have been previously defined with both delayed clearance of paclitaxel and more hematologic toxicity associated with the sequence of cisplatin preceding rather than following a 24-hour paclitaxel infusion. 23

With these theoretic considerations, we designed a nonrandomized phase II dose-escalating study of biweekly paclitaxel and cisplatin as first-line chemotherapy treatment in metastatic breast cancer. The objectives of the study were (1) to determine the toxicity of paclitaxel and cisplatin in a biweekly schedule, (2) to establish the maximum-tolerated dose of paclitaxel in combination with a fixed dose of cisplatin (60 mg/m²) for patients with metastatic breast cancer, (3) to determine the feasibility of repeated biweekly administrations, and (4) to evaluate the activity of this combination in this disease setting.

PATIENTS AND METHODS

 Patients with histologically proven metastatic breast cancer (estrogen receptor—positive or —negative) who had received either no previous chemotherapy or one adjuvant chemotherapy regimen were eligible for study entry. Previous radiotherapy or hormonal therapy was also allowed; radiotherapy had to have involved less than 50% of the bone marrow and had to have been terminated at least 4 weeks before study entry. Patients were nonpregnant, nonlactating women 18 years of age or older with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and a life expectancy of ≥12 weeks. Adequate hematologic, renal, and hepatic functions were required, defined as a granulocyte count greater than 1.5 × 10⁹/L, platelet count greater than 100 × 10⁹/L, bilirubin level less than 1.5 times upper normal limit, and creatinine concentration less than 1.5 times upper normal limit. Patients with a total bilirubin level at baseline between 1.5 and 2.5 times the normal limit due to liver metastases were eligible provided liver function was regularly monitored. All patients had to be accessible for follow-up evaluation and management of complications.

For the phase II portion of the study, patients were required to have clinically or radiologically bidimensional measurable disease, defined as a proven malignant manifestation capable of a twofold improvement. Initially, a tumor marker (carcinoembryonic antigen [CEA] or CA15-3) greater than twice normal was considered as measurable disease; however, this was not used in the analysis. Patients were excluded if any of the following conditions were present: history of malignancy other than the entry diagnosis (except for nonmelanomatous skin cancer or curatively treated cervical carcinoma-in-situ), previous anthracycline treatment to a cumulative dose greater than 450 mg/m² with an abnormal serial gated cardioigraphy (MUGA) scan, prior chemotherapy regimens for the treatment of metastatic breast cancer, history of atrial or ventricular arrhythmias or congestive heart failure, and preexisting motor sensory neurotoxicity (World Health Organization [WHO] ≥ grade II). Patients who were receiving concurrent treatment with other experimental drugs were also ineligible for the study.

All of the patients who entered the trial gave written informed consent. The protocol was approved by the British Columbia Cancer Agency (BCCA) and the University of British Columbia ethics committee. Paclitaxel was provided by Bristol-Myers Squibb and cisplatin was provided from the commercial supply by the BCCA pharmacy.

All patients underwent a pretreatment evaluation that consisted of a history and physical examination; determination of hematology, chemistry, and tumor marker levels (CEA and CA15-3); ECG; and radiologic evaluation of all measurable and assessable disease within 14 days of enrollment.

TREATMENT

The planned dose-escalation scheme was cisplatin at a fixed dose of 60 mg/m² with a paclitaxel starting dose of 90 mg/m² increasing by increments of 10 mg/m² (eg, 100 mg/m², 110 mg/m², 120 mg/m², etc). Escalations were planned in cohorts of three or more patients to a maximum of 130 mg/m². The dose could also be adjusted down in an individual patient depending on tolerance to a minimum dose of 70 mg/m².

Paclitaxel and cisplatin were administered sequentially, each by 3-hour infusion, with paclitaxel preceding cisplatin. This sequence was based on previous reports of severe neutropenia in patients who received cisplatin before paclitaxel. 23 To avoid hypersensitivity reactions, the following standard premedication package was administered: dexamethasone 20 mg orally 12 and 6 hours before paclitaxel infusion, dexamethasone 10 mg intravenously 30 minutes before infusion followed by diphenhydramine 50 mg intravenously, and cimetidine 300 mg intravenously over 10 minutes. Treatment cycles were given every 2 weeks; treatment delays and dose modifications were based on complete blood cell counts taken the day before the next planned treatment (day 14) (Table 1).

Concomitant supportive therapy, including analgesics and antiemetics, was allowed and recorded on the case report forms. Patients all received ondansetron 8 mg orally before cisplatin, and most continued to take oral ondansetron 8 mg and dexamethasone 4 to 8 mg every 8 to 12 hours for 48 to 72 hours after treatment. Cytokine support was not given.

Toxicity was assessed at the biweekly visits and recorded according to WHO toxicity criteria. 24 Complete blood cell counts were performed three times per week for the first 4 weeks and then weekly.

Table 1. Dose Modifications by Day 14 Counts (day before treatment)

<table>
<thead>
<tr>
<th>Granulocytes (× 10⁹/L)</th>
<th>Platelets (× 10⁹/L)</th>
<th>Delay</th>
<th>Dose Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 0.75 and &lt; 0.75</td>
<td>No</td>
<td>Same</td>
<td></td>
</tr>
<tr>
<td>&lt; 0.75</td>
<td>Yes*</td>
<td>-1</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>platelet transfusions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile or Severe bleeding or &gt; 2</td>
<td>Yes*</td>
<td>-2</td>
<td></td>
</tr>
</tbody>
</table>

*Delay until hematologic recovery, defined as granulocytes > 0.75 and platelets > 75. Complete blood cell count to be performed 3 times per week.
for the remaining treatments. Dose escalation was stopped if two of six patients experienced grade 3 nonhematologic toxicity, or if the same number of patients could not receive the first three treatments on time due to hematologic toxicity as defined in Table 1. All patients who received one cycle of chemotherapy were considered assessable for toxicity. Patients were assessed every 2 weeks by physical examination for response and every 4 weeks with radiologic evaluation. All patients in the phase II portion of the study who received at least two courses of chemotherapy were considered assessable for response. Responses were confirmed by monitors, with a complete response (CR) defined as the complete disappearance of all measurable and assessable disease and a partial response (PR) as a greater than 50% reduction in the sums of the product of two perpendicular diameters of the tumor. Stable disease (SD) was considered for all patients who had less than a PR but no evidence of progressive disease (PD). All responses had to be confirmed at least 4 weeks after the initial assessment. PD was defined as an unequivocal increase of ≥ 25% in the sums of the product of measured lesions and/or the appearance of significant new lesions.

It was planned that patients would be treated for four cycles past a CR, two to four cycles after a PR, or until SD with an initial assumption of eight cycles. This was later modified to allow patients to continue treatment until progression or toxicity.

**Statistical Analysis**

Statistical analysis was performed by Bristol-Myers Squibb using the SAS software package (Statistical Analysis System; SAS Institute, Cary, NC). All 29 patients who received at least one cycle of chemotherapy were considered assessable for toxicity. All 27 patients who met the phase II criteria and received at least two courses of therapy were included in the efficacy analysis.

Duration of overall response was calculated from the first day of treatment to the date of first observation of PD for all responding patients (PRs and CRs). Time to progression was calculated for all patients from the day of first treatment until PD was first noted. Three patients had not progressed at the time of the analysis and were censored at their last follow-up evaluation.

No formal statistical tests were performed on the data from this phase I/II trial. For time-to-event data (ie, duration of response, time to progression, and survival), the cumulative proportion of patients who had not yet experienced the event was plotted as a function of time by means of the Kaplan-Meier product-limit approach.

**RESULTS**

**Patient Characteristics**

Twenty-nine patients were enrolled onto the study and all are assessable for toxicity. Twenty-seven patients had bidimensionally measurable disease and are assessable for response.

Characteristics of the 29 patients entered are listed in Table 2. Twenty-seven patients had received prior adjuvant chemotherapy. Four patients had been treated with cyclophosphamide, methotrexate, and 5FU (CMF), and the remaining 23 patients had received an anthracycline-based chemotherapy in the form of doxorubicin/cyclophosphamide (AC) for eight patients, doxorubicin/cyclophosphamide/5FU (CAF) for seven patients, doxorubicin/cyclophosphamide/methotrexate/5FU (ACMF) for two patients, and a dose-intensive doxorubicin-based protocol of cyclophosphamide, doxorubicin, methotrexate, 5FU, cisplatin, etoposide, and prednisone (Quartet) for six patients with extreme risk or locally advanced disease. Despite a previous exposure to cisplatin in the adjuvant setting with a total cisplatin dose of 150 mg/m², these patients are included in the analysis and are mentioned specifically in the response and toxicity sections. Only two patients had not received any prior chemotherapy.

**Drug Delivery**

A total of 251 cycles of chemotherapy were given during this study, with 236 consisting of paclitaxel/cisplatin. Five patients in 15 cycles were treated with single-agent paclitaxel starting at cycles 7, 8, 10, 11, and 17. Cisplatin was eliminated in these patients for neuropathy in three, diarrhea in one, and fatigue in one. A median
of eight cycles were administered, with a range of three to 20.

Patients were not treated to progression but rather treatments were stopped at best response, toxicity, or many at eight cycles due to the original study design. Table 3 lists cycle delays and dose reductions. Overall, 13 patients (45%) required dose reductions (six required one reduction and seven, two reductions.) for hematologic toxicities. Figure 1 shows the timing and number of dose reductions for the first eight cycles.

Only five patients received all of their treatments every 2 weeks. Nine other patients had delays for reasons other than neutropenia, and these included fatigue in six patients, bone fracture in one, and infections not associated with neutropenia in three, including pneumonia, recurrent otitis media, and a wound infection. Twelve of 22 patients who had eight or more treatments had no delays for neutropenia. All treatment delays were for ≤1 week.

Toxicity

The biweekly schedule of paclitaxel and cisplatin was well tolerated. Neutropenia was dose-limiting and precluded escalation of the paclitaxel from the initial dose of 90 mg/m²; thus, all of the reported results are at that dose level. Hematologic toxicity is listed in Table 4 and ranked according to WHO toxicity using the worst toxicity on study for individual patients. Hemoglobin counts ranged from 76 to 120 g/dL (median, 99). WBC nadirs ranged from 700 to 4,000/μL (median, 1,900). Absolute neutrophil counts ranged from 100 to 1,800/μL (median, 500), with the median day of nadir being day 14 (range, 8 to 15). There was only one episode of significant sepsis, which occurred in a woman with a large open axillary recurrence who required a brief hospital admission for intravenous antibiotics. During the febrile period, this patient also experienced grade IV thrombocytopenia, which resolved within 2 days following treatment of the infection.

Nonhematologic toxicity data for the 29 assessable patients are listed in Table 4. There was limited grade III and no grade IV nonhematologic toxicity. The major nonhematologic toxicity was nausea and vomiting, which is frequently reported with cisplatin administration. No severe hypersensitivity reactions occurred with the 3-hour paclitaxel infusion, although 16 patients (55%) experienced mild reactions in 38 courses (15%). The most frequently occurring reaction was flushing in 12 patients. Hypertension, agitation, and somnolence were reported in three patients, respectively. General fatigue was reported in 29 patients and was grade 3 in six (21%). Alopecia was common but not universal. Arthralgias and myalgias were seen in 13 and 12 patients, with one patient reporting grade 3 arthralgias. Parathesias were reported

### Table 3. Dose Reductions and Delays

<table>
<thead>
<tr>
<th>Variable</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Any delays, any cause</td>
<td>5</td>
</tr>
<tr>
<td>Delays due to neutropenia</td>
<td>14</td>
</tr>
<tr>
<td>Delays due to fatigue</td>
<td>22</td>
</tr>
<tr>
<td>Dose reductions</td>
<td>16</td>
</tr>
</tbody>
</table>

NOTE: Total number of treatments is 251, with a median of 8 treatments per patient (range, 3 to 20)

### Table 4. Toxicity by Worst Grade on Study (N = 29)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>WHO Grade</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>% Grade 3 or 4</th>
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<tbody>
<tr>
<td>Asthenia</td>
<td></td>
<td>8</td>
<td>14</td>
<td>7</td>
<td>0</td>
<td>24</td>
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<tr>
<td>Alopecia</td>
<td></td>
<td>2</td>
<td>2</td>
<td>19</td>
<td>0</td>
<td>66</td>
</tr>
<tr>
<td>Infection (any)</td>
<td></td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td>7</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td></td>
<td>14</td>
<td>6</td>
<td>5</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>Anorexia</td>
<td></td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Arthralgia</td>
<td></td>
<td>8</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Myalgia</td>
<td></td>
<td>10</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td></td>
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<tr>
<td>Parasthesia</td>
<td></td>
<td>18</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>3</td>
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<td>Bone pain</td>
<td></td>
<td>9</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Chest pain</td>
<td></td>
<td>7</td>
<td>4</td>
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<td>0</td>
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<tr>
<td>Respiratory discomfort</td>
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<td>7</td>
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<td>7</td>
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<tr>
<td>Hemoglobin</td>
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<td>14</td>
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<td>WBC</td>
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<tr>
<td>ANC</td>
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<td>3</td>
<td>10</td>
<td>12</td>
<td>76</td>
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<tr>
<td>Platelets</td>
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<td>0</td>
<td>1</td>
<td>1</td>
<td>7</td>
</tr>
</tbody>
</table>

NOTE: Signs and symptoms reported in at least 24% of patients regardless of relationship to study drug

Abbreviation: ANC, absolute neutrophil count.
in 23 patients (79%), but only one patient experienced dose-limiting symptoms.

Cumulative toxicity was not common, with only three patients withdrawing from the trial for cumulative paraesthesias, two for progressive fatigue, and one with an increasing creatinine concentration. These withdrawals occurred at cycles 9, 9, and 14 for patients with neuropathy, 7 and 8 for fatigue, and 8 with the increased creatinine level. Two of the patients with cumulative peripheral neuropathy had been previously treated with cisplatin adjuvantly. This was the only toxicity that was more common in this group of patients.

Overall, there were two hospital admissions for toxicity, one episode of febrile neutropenic episode described earlier, and one upper gastrointestinal hemorrhage associated with a small Mallory-Weiss tear diagnosed endoscopically, which resolved on the day of admission.

Responses

Twenty-seven patients were assessable for response; three (11%) had a CR and 20 (74%) a PR, for an overall response rate of 85% (95% confidence interval [CI], 66% to 96%) Sites of CR included skin, soft tissue, and lung. All three patients with a CR were previously treated with anthracycline-containing adjuvant regimens. Of the seven patients with previous exposure to cisplatin in the Quartet regimen, one had a CR, four had PRs, and one had PD. Omitting those patients from the analysis, the response rate remained high at 90%, with responses in 19 of 21 assessable patients. All completely responding patients have relapsed with a time to disease progression of 110 to 200 days (median, 5.8 months [176.9 days]). Figure 2 depicts time to progression for the 27 patients who were assessable for response (median, 7.1 months). The median duration of overall response for the 24 responding patients was 7.9 months (range, 96 to 377+ days).

DISCUSSION

After observing a brief WBC nadir when paclitaxel was delivered on the 3-week schedule, we initiated a trial of biweekly paclitaxel and cisplatin to try to take advantage of the 14-day recovery period of the WBCs and to try to increase the dose-intensity of the drugs. This study confirms that paclitaxel lends itself to this type of frequent scheduling, as the majority of patients were able to be treated with this type of dose-intense regimen.

Due to hematologic dose-limiting toxicity, we were unable to escalate the paclitaxel dose and treatment continued at a dose of 90 mg/m². The level of hematologic toxicity in this study was greater than expected for the dose of paclitaxel administered and not typical of cisplatin alone. Studies of the pharmacokinetics of paclitaxel and cisplatin have suggested a sequence dependence, with more significant neutropenia occurring when cisplatin preceded paclitaxel, but these studies used a 24-hour infusion of paclitaxel. The observed neutropenia in this study may be explained by the decreased clearance of paclitaxel caused by the cisplatin increasing drug exposure. This may also enhance the cytotoxic effect and explain the provocative response rate. To investigate this, we plan to perform pharmacokinetic studies of patients receiving a 3-hour infusion of paclitaxel and cisplatin in both sequence alternatives and compare these results with the published data on the 24-hour infusion. In addition to dose-limiting neutropenia, we observed fatigue, nausea, and peripheral neuropathy. The majority of these side effects were mild, reversible, and tolerable.

The dose of paclitaxel used in this study translates into a dose-intensity per week of 45 mg/m² or equivalent to the 3-week dose of 135 mg/m². With this rather modest dose, we observed a response rate of 85%, whereas a previous study that used 135 mg/m² every 3 weeks over 3 hours in a more heavily pretreated group reported a 21% response rate. This response rate suggests that the paclitaxel/cisplatin biweekly schedule is an active combination in the treatment of metastatic breast cancer. This is significant, as our patient population differs from many of the other current studies of paclitaxel couplets, which are enrolling previously untreated patients or patients not previously exposed to anthracyclines. All but two of the women in our trial had been treated with previous adjuvant chemotherapy, and 23 of 29 patients had previous exposure to anthracyclines. Few agents have been reported to give significant responses after exposure to anthracyclines. Also, although we were unable to deliver
consistently the full planned dose on schedule in all the patients, the activity of this combination was maintained. The response rates seen in this trial are particularly intriguing when they are compared with other trials of paclitaxel and cisplatin. One study from New York University (NYU) used a 3-week schedule of paclitaxel 200 mg/m² over 24 hours and cisplatin 75 mg/m² with granulocyte colony-stimulating factor (G-CSF) 5 μg/kg subcutaneously from day 3. Although 16 of 40 patients had not received prior chemotherapy, the overall response rate was 44% and significant neuropathy was observed (J.L. Speyer, personal communication, January 1995). The differences in the two trials include the duration of the infusion (3 hours in our study and 24 hours at NYU) and the biweekly schedule, which may contribute to the response rates if repetitive exposure is important. Schedule is less likely implicated, as neuropathy is more commonly observed with a 3-hour than a 24-hour infusion of paclitaxel (BMS 071 preliminary data; personal communication). The higher dose in the NYU study may explain the increase in the incidence and severity of neuropathy, which resulted in 17 patients discontinuing the study due to progressive neuropathy. This may partially account for the differences in response rate, as our study, with less peripheral neuropathy, was able to achieve a greater dose rate of cisplatin combined with paclitaxel. In the biweekly study, only three patients discontinued treatment due to neuropathy.

In an attempt to decrease further the toxicity and to ascertain the contribution of cisplatin to the response rates of this couplet, we are currently nearing completion of a phase I/II study of single-agent biweekly paclitaxel in metastatic breast cancer. This will help us to differentiate which toxicities were due to each of the drugs used in the combination and to define the response rate of biweekly paclitaxel as a single agent. Questions of the optimal schedule for delivering paclitaxel are being pursued by studies comparing various infusion durations, but the frequency of dosing may also be important.

Another strategy is to define a less neurotoxic combination. Although phase II studies of carboplatin in advanced breast cancer have suggested a lower response rate than with cisplatin, we are initiating a study of this couplet to attempt to decrease the neurotoxicity. The combination of paclitaxel and carboplatin is active and well tolerated in patients with non–small-cell lung cancer and ovarian cancer, and may be an option in patients with advanced breast cancer.

Initial studies with paclitaxel were limited in the number of cycles due to the short supply of the drug. Many centers now treat patients with paclitaxel until disease progression. The excellent tolerance of the drug as a single agent without severe cumulative organ toxicity allows this long duration of cytotoxic therapy. This study was initially designed to give only eight cycles of therapy (ie, 4 months) and many patients were discontinued at that point. Whether the response duration would have been longer with continuous treatment and whether the duration reported here can be compared with that of trials with different end points is speculative. The observed response duration of 7.9 months is within the expected range for an active combination. However, it may be relevant that the smaller dose per cycle and the relatively small number of cycles in an outpatient setting may contribute to the patient’s quality of life.

Although CRs were seen with the combination of paclitaxel and cisplatin, these were not durable. This reflects the disappointing fact that a clinical CR in a trial only represents a further log kill of cells and, although it is associated with a longer survival time, it is not a cure. However, the fact that we did have a high response rate and did observe CRs suggests that this active couplet may have a role in adjuvant treatment. The combination of paclitaxel/cisplatin alternating or sequentially with doxorubicin and cyclophosphamide may provide a non–cross-resistant combination and may translate into improved survival in the adjuvant setting.

Paclitaxel and cisplatin on a biweekly schedule appears to be an active combination in the treatment of metastatic breast cancer in this single-institution phase I/II trial. Further confirmatory trials of this combination and other novel schedules of paclitaxel are necessary to further our understanding of how to best use this novel agent.

REFERENCES


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