Treatment of Advanced and Relapsing Breast Cancer With a Combination of Paclitaxel and Mitoxantrone

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A multicenter nonrandomized study was designed to assess the efficacy (response rate and duration of relapse-free survival) and safety of the combination of paclitaxel (Taxol; Bristol-Myers Squibb Company, Princeton, NJ) 200 mg/m² given as a 3-hour intravenous infusion with premedication every 3 weeks, followed by mitoxantrone 12 mg/m², given as an intravenous push every 3 weeks, in patients with metastatic breast carcinoma. So far, 30 patients have entered the study and 27 are evaluable for response. All patients had advanced metastatic breast cancer and have been extensively pretreated with chemotherapy (28 patients), radiotherapy (11 patients), and hormonotherapy (24 patients). Fourteen patients (46.7%) have been previously treated with anthracyclines, and disease progressed in seven (23.3%) during anthracycline treatment. One patient had a complete remission and 14 a partial remission for a total response rate of 55.6%. One of the 15 patients entering remission developed heart failure and was withdrawn from the protocol after 4 months in remission. She then relapsed and died 9 months after entering protocol. The remaining 14 patients continue to respond and their remission durations range from 4- to 12+ months (mean, 9 months; 95% confidence interval [CI] 7.96 to 10.04). Eleven patients (40.7%) developed minor responses or disease stabilization lasting from 1.5 to 11.4+ months (mean, 3.5 months; 95% CI, 1.9 to 6.0) and one of them had disease progression after 3.5 months and is still alive whereas another one who had disease progression died at 1.5 months. Four patients failed to respond and their disease progressed during protocol treatment; two of them died at 6.7 months while the other two are alive at 3.4 and 9.8 months. Overall survival ranged from 1.5 to 12+ months (mean, 6.7 months; 95% CI, 5.5 to 7.9). In the group of 14 anthracycline-pretreated patients, seven showed a partial remission, six a minor response or disease stabilization, and one had disease progression. Response duration ranged from 1.5 to 12+ months (mean, 6.1 months; 95% CI, 4.2 to 8.0); the three patients whose disease progressed died at 1.5, 6.7, and 8.8 months. Bone marrow toxicity was dose-limiting and caused treatment delays as well as dose de-escalation of both drugs in eight patients.  


Paclitaxel (Taxol; Bristol-Myers Squibb Company, Princeton, NJ) has been found to have significant activity against human metastatic breast cancer. Among patients who have received one prior chemotherapy regimen only, a 12% complete remission (CR) rate and a 44% partial remission (PR) rate have been reported, with a median time to progression of 9 months.2 4 When treating patients with advanced disease not previously exposed to chemotherapy, the objective response rate increases to 62%.5 Further, paclitaxel's activity probably is not affected by the development of resistance to doxorubicin.15 The combination of paclitaxel and doxorubicin with granulocyte colony-stimulating factor support increased the proportion of objective responses from 69% to 80% in chemotherapy-naïve patients.6 8

Mitoxantrone has yielded objective response rates of 20% to 32% in phase I and phase II/III trials involving breast cancer patients pretreated with one or two chemotherapy regimens.7 21 When used in earlier stages of the disease, its therapeutic index is improved and, according to our experience and most reported literature, its activity is then nearly comparable with that of anthracyclines.11-15 When mitoxantrone is used in combination with other potent cytotoxic drugs, the proportion of objective responses increases to 58% to 72%.18 19 Its low index of cardiotoxicity permits the drug to be used for longer periods.

This trial was designed to study the effectiveness of combination paclitaxel/mitoxantrone for the treatment of patients with previously treated, advanced metastatic breast cancer.

STUDY DESIGN

In this multicentric and nonrandomized study, patients are stratified according to extent of disease and time elapsed since completion of prior chemotherapy for relapsing or initially extensive disease.

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As no data were available regarding a safe dosage of the two drugs given in combination, we started with a phase I study to identify maximum tolerated doses (MTDs). Three dose levels were planned, starting at paclitaxel 175 mg/m² and mitoxantrone 10 mg/m². If no unacceptable toxicity developed in six consecutive patients at a given dose level, escalation to the next dose level was performed.

The objectives of this study were to determine response (CR and PR rates), response duration, and survival with combination paclitaxel/mitoxantrone; to determine toxicity of the combination; and to correlate response rate, response duration, and survival with the extent of disease, the presence of metastasis to vital organs, the patient's performance status, and previous treatment with anthracyclines.

Patients and Methods

Patients with histologically proven and documented stage III or IV breast cancer were eligible for this study. Prior chemotherapy given in the adjuvant setting and/or as first-line treatment for metastatic disease was allowed. Study criteria included measurable or evaluable disease in a non-radiated field, life expectancy exceeding 2 months, and performance status ≤3 (Eastern Cooperative Oncology Group/World Health Organization scales). Patients whose disease had relapsed after either treatment for initially extensive disease or adjuvant treatment to surgical management with one first-line chemotherapy regimen were allowed, but all previous cytotoxic therapy had to have been completed at least 4 weeks before study entry and patients must have recovered from the effects of prior treatment. Previous radiotherapy was acceptable either as adjuvant treatment after surgery or for metastatic disease as long as less than 40% of the marrow-bearing bone was in the radiation field and the indicator lesions were not previously irradiated.

Patients with central nervous system metastases or spinal cord compression were ineligible for study entry as were patients with active cardiac disease and those taking medications affecting cardiac conduction; patients with renal or hepatic failure or with uncontrolled infection were likewise excluded, as were patients with preexisting motor or sensory neurotoxicity of greater than grade 2 according to World Health Organization criteria (intolerable paresthesia and/or marked motor loss, or worse). Initial laboratory requirements included a leukocyte count greater than 3,500/μL; a platelet count greater than 100,000/μL; a hematocrit value greater than 30%; and blood urea nitrogen, serum creatinine, serum bilirubin, and aspartate amino-transferase levels ≤1.5 × normal values. An electrocardiogram was required to show that there were no conduction abnormalities or arrhythmia worse than a first-degree heart block. All patients reviewed and signed a detailed informed consent according to the Ethics Committee requirements of each participating institution as well as to National Drug Organization (Halogos, Greece) regulations.

Treatment Plan

Patients who fulfilled all the eligibility criteria were enrolled in the protocol. Treatment was administered as a combination of paclitaxel, given as a 3-hour intravenous infusion with premedication, followed by mitoxantrone, given as an intravenous push. The appropriate dose level was determined sequentially, by study entry (Table 1).

Patients were scheduled to receive at least three cycles of therapy, followed by disease re-evaluation. Patients continued in the study if they showed at least stable disease.

A minimum of five patients were planned for treatment at each dose level, and if none experienced any dose-limiting toxicity (Eastern Cooperative Oncology Group/World Health Organization

Table 1. Treatment Administration*  

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Paclitaxel Day 1</th>
<th>Mitoxantrone Day 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>175</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>200</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>200</td>
<td>12</td>
</tr>
</tbody>
</table>

Premedication:
- Dexamethasone 20 mg orally 12 and 6 hr before paclitaxel infusion
- Diphenhydramine 50 mg IV 30 min before paclitaxel infusion
- Ranitidine 50 mg IV 30 min before paclitaxel infusion

NOTE: Cycle duration = 21 days.
Abbreviation: IV, intravenously.
* A minimum of five consecutive patients were planned for study entry at each dose level, if no unacceptable toxicity developed, dosage escalation was permitted for the next group of patients entering.
are shown in Table 2. At entry, 23 patients had undergone surgery for their primary tumor (21 with modified radical mastectomy, two with lumpectomy), followed by adjuvant therapy (chemotherapy, hormone therapy, radiotherapy). The remaining seven patients had widespread metastatic disease at the time of diagnosis. All patients were previously treated, 28 with chemotherapy, 13 with radiotherapy, and 24 with hormone therapy. Fourteen patients were previously exposed to anthracyclines, and in seven (23.3%) of those patients their disease progressed during anthracycline treatment.

One patient with extensive lung metastasis and pleural effusion died of respiratory failure with apparent stable disease 45 days after entering protocol. Another patient was withdrawn from protocol when she was found to have brain metastasis while receiving her second cycle of treatment. For one other patient, it is too early to evaluate response (at 60 days). Of the 27 evaluable patients, 15 (55.6%) responded with either a CR (one patient) or PR (14 patients), and another 11 patients (40.7%) developed minor responses or disease stabilization. Four patients did not respond and their disease progressed during protocol treatment (Table 3).

One of the 15 patients entering remission developed congestive heart failure and was withdrawn from the protocol after 4 months in remission. She was 60 years old and had been diagnosed 1 year ago with adenocarcinoma of the left breast. She had been treated then with local radiation and oral tamoxifen, adjuvantly to mastectomy. When her disease relapsed 6 months later, she received six cycles of cyclophosphamide/doxorubicin/5-fluorouracil (total doxorubicin dose, 380 mg) as well as radiotherapy to her lower lumbar vertebrae, but she developed progressive disease and entered the protocol 2 months after her last doxorubicin treatment. During protocol treatment, she received cumulative doses of mitoxantrone and paclitaxel of 46 and 930 mg, respectively, and achieved a nearly complete remission, with resolution of her measurable disease. After she was withdrawn from the protocol, her disease relapsed and she died 9 months after entering the protocol.

The remaining 14 patients continued to respond, with remission durations ranging from 4+ to 12+ months (mean, 9 months; 95% confidence interval [CI], 7.96 to 10.04). Among the 11 patients who developed minor responses lasting from 1.5 to
Table 3. Treatment Results

<table>
<thead>
<tr>
<th>Result</th>
<th>No. of Patients (%)</th>
<th>Mean Duration, mo (Range)</th>
<th>Mean Survival, mo (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response</td>
<td>15 (55.6)</td>
<td>9 (4-12+)</td>
<td>95 (45-134+)</td>
</tr>
<tr>
<td>Complete remission</td>
<td>1 (3.7)</td>
<td>9+</td>
<td>10+</td>
</tr>
<tr>
<td>Partial remission</td>
<td>14 (51.9)</td>
<td>9 (4-12+)</td>
<td>95 (45-134+)</td>
</tr>
<tr>
<td>Minor response</td>
<td>11 (40.7)</td>
<td>3.5 (1.5-11.4)</td>
<td>37 (15-11.7)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>4 (13.3)</td>
<td>—</td>
<td>6.7 (3.4-9.8+)</td>
</tr>
</tbody>
</table>

11.4+ months (mean, 3.5 months; 95% CI, 1.9 to 6.0), one patient, who is still alive, had disease progression after 3.5 months while another whose disease progressed died at 1.5 months. Two of the four patients who failed to respond died at 6.7 months; the other two are alive at 3.4 and 9.8 months. Overall survival ranged from 1.5 to 13+ months (mean, 6.7; 95% CI, 5.5 to 7.9). In the group of 14 patients who were pretreated with anthracyclines, seven responded with PRs, six with minor responses or disease stabilization, and one had disease progression. Response duration in this group ranged from 1.5 to 12+ months (mean, 6.1; 95% CI, 4.2 to 8.0). Three of these patients (one with PR, one with a minor response, and one with progressive disease) have died at 8.8, 6.7, and 1.5 months, respectively. Disease relapsed in the partial responder after she was withdrawn from the protocol because of congestive heart failure and she died of progressive disease.

This study was planned to identify the MTDs for the combination of paclitaxel and mitoxantrone. Three dose levels were planned, starting with paclitaxel 175 mg/m² and mitoxantrone 10 mg/m². Doses in the next level were paclitaxel 200 mg/m² and mitoxantrone 10 mg/m². These doses were established as the MTDs for the combination because few patients (three of six) tolerated escalation to the next dose level (paclitaxel 200 mg/m² and mitoxantrone 12 mg/m²). The dose of paclitaxel had to be reduced in eight patients to 182 mg/m² after cycle 3 to 5, and the dose of mitoxantrone was reduced to 9.3 mg/m² after two cycles of treatment.

Cardiac toxicity was encountered in one of 30 patients. Bone marrow toxicity was dose-limiting and caused treatment delays as well as dose de-escalation of both drugs in eight patients. Table 4 shows grade ≥2 hematologic toxicity by doses of the combination. Eight patients developed grade 3 and 4 granulocytopenia and three patients developed febrile neutropenia. Neither thrombocytopenia (one case with grade 4 toxicity) nor anemia (three cases with grade 3 toxicity) were major problems. Grade 3 mucositis developed in one patient, and hepatotoxicity and neurotoxicity were rare and mild (three and four cases with grade 1 to 2 toxicity, respectively).

**DISCUSSION**

In this phase I/II study two active agents, paclitaxel and mitoxantrone, have been combined to treat patients with extensively pretreated advanced metastatic breast cancer. This study has documented the toxicity of the combination and we are confident that paclitaxel 200 mg/m² and mitoxantrone 10 mg/m² represent the MTD of this combination. We are, therefore, continuing the study at this dose level. We also have documented the activity of the combination, both in anthracycline-pretreated and anthracycline-naïve patients. Both patient subsets were equally sensitive to the combination of paclitaxel and mitoxantrone. Although 75% of the initially planned number of

<table>
<thead>
<tr>
<th>Dose</th>
<th>Grade</th>
<th>Hemoglobin</th>
<th>WBCs</th>
<th>Platelets</th>
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<tbody>
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<td>1</td>
<td>1</td>
<td>2</td>
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<tr>
<td>12</td>
<td>1</td>
<td>2</td>
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Abbreviation: WBCs, white blood cells.
patients have been enrolled, follow-up time is still too short and no final conclusions have been reached regarding response rate or response duration. As most of the study patients have extensive disease and are heavily pre-treated, the response onset may be delayed, and the time needed to reach maximal response usually exceeds 3 months. We therefore expect that the objective response rate will further improve.

REFERENCES