High-Dose Paclitaxel With Granulocyte Colony-Stimulating Factor in Patients With Advanced Breast Cancer Refractory to Anthracycline Therapy: A European Cancer Center Trial

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Paclitaxel (Taxol; Bristol-Myers Squibb Company, Princeton, NJ) is a novel cytotoxic agent that has shown interesting antitumor activity in patients with advanced breast cancer. Depending on variable patient characteristics and amount and type of prior therapy, as well as the applied dose and schedule of paclitaxel, response rates have varied from 13% to 62%. However, optimal dose and schedule are still unknown. We studied a high-dose (250 to 300 mg/m²) 3-hour paclitaxel infusion schedule in a poor prognostic group of breast cancer patients who progressed or relapsed while taking anthracyclines. This regimen was given every 3 weeks. Twenty-one of the 36 patients studied had increased liver enzymes and 18 had documented liver metastases. The objective response rate was only 6%, but response rate by disease site indicated that soft tissue lesions responded in 30% of cases. For a better comparison with other reported data a uniform definition of "anthracycline refractory" is needed. Neuporpathy, which was found to be dose limiting, and arthralgia/myalgia syndrome were the most frequently occurring toxicities. Both severe myelosuppression (and infections) and severe diarrhea and mucositis were reported more frequently in patients with liver dysfunction. As higher peak levels, increased areas under the concentration time curves, and longer times during which plasma concentrations were above the threshold level of 0.1 μmol/L were found in patients with elevated liver enzymes, a correlation with the observed toxicities is assumed. Further pharmacodynamic studies in such patients receiving a 3-hour infusion seem warranted. Copyright © 1995 by W.B. Saunders Company

DESPITE significant advances in the management of breast cancer, there is still no curative treatment for patients with advanced disease.1 Once therapy with hormonal agents is exhausted, combination chemotherapy is usually introduced. In previously unexposed patients, objective responses may be achieved in approximately two thirds of patients. Complete regression of disease, however, occurs in fewer than 20% of patients. The median duration of response is usually less than 1 year, and median length of survival of responders varies from 14.8 to 33 months.1 The overall probability of a response to second- or third-line chemotherapy varies between 15% and 35%.1 This wide variation in outcome among different phase II studies (range, 0% to 55%) is due to patient selection for these trials, which were performed at different institutions and over different time periods. Any antineoplastic drug demonstrating a level of activity superior to 30% when given as single-agent therapy in patients previously treated for metastatic breast cancer is worth investigating. Paclitaxel (Taxol; Bristol-Myers Squibb Company, Princeton, NJ) is thought to be such a candidate.

BACKGROUND

Paclitaxel is a novel antineoplastic agent extracted from the bark of the Pacific yew (Taxus brevifolia). The drug achieves its cytotoxicity by promoting intracellular tubulin polymerization and stabilizing abnormal microtubule structures.2,3 It was selected in 1977 by the National Cancer Institute for further development as an antitumor agent. In most cases, the dose-limiting toxicity of paclitaxel in phase I evaluation was hematologic, principally neutropenia. Severe hypersensitivity reactions, which occurred in the first phase I studies, were controlled by the introduction of a systemic premedication regimen and, concurrently, by increasing the length of the infusion time. Peripheral neuropathy, myalgia/arthralgia, and mucositis also were noted to be dose related. In leukemia patients in whom myelosuppression did not prevent dose escalation, mucositis was dose limiting with 24-hour paclitaxel doses above 300 mg/m². The recommended phase II dosage in patients with solid tumors was 135 mg/m² to 250 mg/m² given by 24-hour infusion every 3 weeks according to the extent of prior therapy.
Phase II studies with paclitaxel have demonstrated activity in a variety of solid tumor types, including breast cancer. Depending on variable patient characteristics and amount of prior therapy, response rates with paclitaxel in patients with advanced or recurrent breast cancer have ranged from 25% to 62%. Although the optimal dose and schedule of paclitaxel for this indication are still unknown, results with higher doses, and recently reported results of 96-hour infusions, have been promising. At the time we started a trial of paclitaxel as a high-dose, 3-hour infusion, only one phase II study of single-agent paclitaxel in patients with metastatic breast cancer had been completed. In that study, the overall response rate in 25 evaluable patients was 56%. Starting dose of paclitaxel was 250 mg/m², and the drug was given intravenously over 24 hours. Interestingly, two of six patients with primary or secondary resistance to doxorubicin attained partial responses, two had minor responses, and two had progressive disease. Similar positive, although preliminary information was available from ongoing trials at Memorial Sloan-Kettering Cancer Center (New York, NY) and the National Tumor Institute (Milan, Italy).

HIGH-DOSE PACLITAXEL IN ANTHRACYCLINE-RESISTANT BREAST CANCER

There are several theoretic concerns regarding the use of taxanes following anthracycline therapy, largely based on the demonstration of in vitro cross-resistance between paclitaxel and doxorubicin and other agents to which resistance is thought to be at least partly due to P-glycoprotein-mediated pleiotropic drug resistance. Therefore, the above-mentioned observations of response among patients with anthracycline-resistant breast cancer, albeit in small series, were of particular interest. These data and the reported dose-response relationship and comparable antitumor activity of 3- and 24-hour infusions in patients with relapsed ovarian cancer were the major reasons for undertaking this high-dose 3-hour paclitaxel protocol in patients with anthracycline-resistant breast cancer. Our primary objectives were, first, to evaluate the efficacy of such a high-dose paclitaxel regimen in patients with disease progression during adequate anthracycline-containing chemotherapy and, second, to evaluate the safety of this regimen when given in combination with granulocyte colony-stimulating factor support. A tertiary objective was to study the qualitative and quantitative neurotoxic effects of high-dose 3-hour paclitaxel.

PATIENTS AND METHODS

Patients

From May 1992 until November 1993, 36 eligible patients entered this European Cancer Center protocol. The protocol was approved by the Institutional Review Boards and Medical Ethics Committees in both participating institutes. All patients had received a minimum of two courses of chemotherapy containing doxorubicin or epirubicin, and all had disease progression while receiving the anthracycline-containing chemotherapy. Treatment with paclitaxel started as early as possible after assessment of progression but never later than 12 weeks after the patient had received the last dose of the anthracycline. By definition, progression during anthracyline chemotherapy was not due to treatment delay because of toxicity.

Treatment

All patients were to receive paclitaxel (diluted with 1,000 mL of D5W or normal saline) over 3 hours, at a starting dose of 250 mg/m², after standard premedication with dexamethasone, clemastine, and cetomimidine. Doses were modified for subsequent courses based on hematologic and nonhematologic toxic effects observed during the previous course. Dose-escalation steps were 25 mg/m² or 50 mg/m², but doses were not escalated above 300 mg/m². Dose-reduction steps were of the same order, but patients went off study if doses had to be reduced below 100 mg/m² due to toxicity. In the instance of severe hypersensitivity reaction, rechallenge was permitted with a prolonged (24-hour) infusion, which, when tolerated, was repeated in subsequent cycles. All patients who had received at least two courses of paclitaxel were considered evaluable for response. Those patients who developed rapid tumor progression after one course of therapy were also considered evaluable (early progression). Patients with stable disease were to receive six treatment cycles. Patients with partial response continued treatment until relapse, until they had received four treatment cycles after partial response stabilization, or until they experienced unacceptable toxicity. Complete response patients were to continue for four treatment cycles after complete response or until unacceptable toxicity developed. Response and toxicities were evaluated according to World Health Organization criteria. Tumor measurement was done every cycle by physical examination and every other cycle by imaging. Hematologic blood examination was done twice weekly and biochemistry was done on day 1 of each cycle. A detailed neurologic evaluation was carried out prospectively in one of the participating institutions (Free University Hospital) at baseline, after cycle 1, every other cycle thereafter, and following the completion of therapy whenever possible. Because not all patients received multiple cycles, data from only eight patients are available. Use was made of a questionnaire, with emphasis on neuropathic signs and symptoms.
Neurologic examination included bedside measurement of reflexes, muscle strength, Romberg test, tandem walking, and vibratory, position, and pin-prick sense. The vibratory perception threshold on metacarpal 1 and metatarsal 1 and strength of the dominant hand were measured quantitatively. Results, expressed as a score of the different items, were compared with those obtained in two other cohorts of patients treated with standard dosages of paclitaxel in the same hospital, ie, those receiving 135 mg/m² by 3-hour infusion (ovarian cancer patients, all previously treated with cisplatin; group A) and those receiving 175 mg/m² by 3-hour infusion (13 with ovarian cancer, one with breast cancer, and 10 with prior cisplatin; group B).

Pharmacokinetic Studies

Individual patients had blood samples taken at regular time intervals. Use was made of a new sensitive, selective, and validated high-performance liquid chromatography technique combined with a solid-phase extraction as sample pretreatment, as described previously.16

RESULTS

All patients had measurable or evaluable disease, and consent was obtained from all who entered the study. Median patient age was 51 years (age range, 31 to 71 years), and their median Eastern Cooperative Oncology Group performance status was 1 (range, 0 to 2). Hematologic, renal, and hepatic function were adequate; ie, at the start of paclitaxel treatment, patients had an absolute neutrophil count ≥2.0 × 10⁹/L, a platelet count ≥100 × 10⁹/L, a serum creatinine ≤1.25 × the upper limit of normal (ULN), and a total bilirubin count of ≤1.25 × ULN (1.25 to 2.5 × ULN in case of documented liver metastases). Elevated transaminases (n = 15), elevated alkaline phosphatase (n = 15), and elevated bilirubin (n = 1) were found in 21 patients, of whom 18 had documented liver metastases. The median number of prior chemotherapy regimens for patients with metastatic disease was 1 (range, 1 to 3), the median intertreatment interval was 1 month (range, 1 to 3 months), and the median cumulative anthracycline dose (as doxorubicin equivalents) was 300 mg/m² (range, 120 to 590 mg/m²).

Treatment Delivery

All patients started paclitaxel treatment at a dose of 250 mg/m². Seven patients tolerated dose escalation to 275 mg/m², and eight had escalations to 300 mg/m². Dose reduction was required in 10 patients (one protocol violation) without and five patients with initial dose escalation. Six patients received only one treatment cycle, and one patient received treatment by 24-hour instead of 3-hour infusions because of a hypersensitivity reaction at the beginning of the first cycle. As a result, 135 3-hour treatment cycles were administered to the 36 eligible patients in this study, ie, 35 initial 3-hour cycles and 100 consecutive 3-hour cycles in the 29 patients who received more than one course. Forty-seven of these next 100 infusions were given to patients who had increased liver enzymes and 53 to patients with normal liver enzymes. In patients with increased liver enzymes, 12 of 47 (26%) cycles were given at an escalated dose and 13 were given (28%) at a reduced dose. In contrast, in patients with normal liver enzymes, 57% of follow-up cycles were given at escalated dosages and 21% were given at reduced dosages. This resulted in a small difference between patient groups in median dose per patient: 250 mg/m² (range, 187.5 to 275.0 mg/m²) for the patients with increased liver enzymes and 262.5 mg/m² (range, 200 to 300 mg/m²) for patients whose liver enzymes were within the normal range.

Antitumor Activity

In this rather unfavorable patient population, response to high-dose 3-hour paclitaxel was disappointing, with only two of 33 (6%) evaluable patients responding. These responses lasted for 16 and 18 weeks, respectively. More interesting was the response by disease site. Of the 23 patients with evaluable soft tissue lesions (skin, lymph nodes, breast) seven responded (30%). In one patient, a greater than 50% reduction in size of lung metastases was observed. However, this patient (one of 20 with visceral metastases) stopped treatment after two cycles because of severe neuropathy and progression of bone lesions.

Toxicity

Data on hematologic toxicity (worst by patient) are summarized in Tables 1 and 2, and data on nonhematologic toxicity are summarized in Table 3. Hematologic toxicity overall was dose limiting only in a minority of patients. Only four patients developed World Health Organization grade 4 leukopenia, six developed grade 4 neutropenia, and three developed grade 4 thrombocytopenia (Table 1). It was interesting to observe that three of the four instances of grade 4 leukopenia, four of the six instances of grade 4 neutropenia, and all three cases of grade 4 thrombocytopenia oc-
curred in the 18 evaluable patients with liver dysfunction. The difference in myelosuppression observed in patients with differing increases in liver enzyme values was striking (Table 2).

The nonhematologic toxicities observed also are reported in relation to whether patients had increased liver enzymes (Table 3). Neuropathy and arthralgia/myalgia syndrome were the most frequently occurring toxicities. Of the 14 cases of appropriate dose reduction, 10 (71%) were due to neurotoxicity, two (14%) to myelosuppression, one to diarrhea, and one to dizziness and malaise. Severe diarrhea, serious infections, and mucositis were reported more frequently in patients with liver dysfunctions.

**Neurotoxicity**

Details on paclitaxel-induced neuropathy have been reported previously. Sensory symptoms were reported by seven of the eight patients, and interference with activities of daily life was noted by six. In all patients sensory changes, including vibratory perception threshold increases, were observed. Minor extensor hallucis longus paresis and decreasing grip strength occurred in four and three patients, respectively. All patients lost their ankle reflexes after the first cycle. Paclitaxel-induced neuropathy clearly is a dose-related phenomenon (ie, related to dose per cycle and cumulative dose). This is illustrated in Fig 1, which shows the cumulative symptoms score only for those patients in this study (group C) and in the other two cohorts (groups A and B, as described in Patients and Methods), who received a comparable cumulative dose (1,200 to 1,250 mg/m²).

**Pharmacokinetics**

During this study, pharmacokinetic studies were performed in nine patients. One patient was not considered eligible for the study because of a prolonged intertreatment interval. Nevertheless,
she entered the study, was treated according to protocol, and therefore was not excluded from the pharmacokinetic study. One patient had an extremely low serum albumin level and was using diazepam and massive doses of morphine. For obvious reasons this patient was excluded from correlation studies. In Table 4, mean values (±SD) are given for peak concentrations (C_{max}), area under the concentration time curves (AUC), and the time during which plasma concentrations were above the threshold level of 0.1 μmol/L (T > 0.1 μmol/L) in patients with and without increased liver enzymes, respectively. The trend for all parameters was the same; ie, higher peak levels, increased AUCs, and threshold levels persisting for a longer period of time in patients with elevated liver enzymes.

**DISCUSSION**

Treatment results in patients considered refractory to anthracyclines are generally disap-

pointing. On the one hand, this may be due to the fact that a population of patients already exposed to doxorubicin is more likely to include extensively treated patients with exposure to at least two separate combination programs. On the other hand, prior doxorubicin therapy rather than prior therapy with an alkylating agent may be a critical factor in the induction of resistance. Although the positive early reports of the activity of paclitaxel in breast cancer patients refractory to anthracycline therapy were important, the low objective response rate in our study should be examined within the context of what is currently known about this subset of patients. Unfortunately, series still are quite small (Table 5). Moreover, it seems critical to define "resistance to anthracyclines." As evident from Table 5, the definitions vary considerably. The present European Cancer Center study differs from the other studies with respect to this definition. None of the patients in our study had received anthra-

| Table 4. Pharmacokinetic Data in Patients With and Without Increased Liver Enzymes |
|---------------------------------|-------------------------------|----------------|----------------|
|                                 | Liver Enzymes                 | Increased (n = 4) | Not Increased (n = 4) | Probability Value |
| C_{max} (μmol/L; mean ± SD)     | 8.00 ± 1.34                   | 5.25 ± 1.68      | .06             |
| AUC (μmol/L·hr; mean ± SD)      | 30.31 ± 7.41                  | 20.45 ± 3.67     | .04             |
| T > 0.1 μmol/L (mean ± SD)      | 22.62 ± 3.22                  | 14.92 ± 4.71     | .03             |

Abbreviations: C_{max}, peak concentrations; AUC, area under the concentration-time curves; T > 0.1 μmol/L, time during which plasma concentrations were above the threshold level of 0.1 μmol/L.
### Table 5. Response Rates Obtained With Single-Agent Paclitaxel in Anthracycline-Resistant Breast Cancer

<table>
<thead>
<tr>
<th>Dose/Schedule (mg/m²/hr)</th>
<th>No. of Patients</th>
<th>CR + PR (%)</th>
<th>Definition of ANT Resistance</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>140/96*</td>
<td>17</td>
<td>53</td>
<td>Failure to achieve CR; failure to respond</td>
<td>7</td>
</tr>
<tr>
<td>175/3</td>
<td>15</td>
<td>46</td>
<td>PD/relapse on ANT; relapse &lt; 12 mo</td>
<td>8</td>
</tr>
<tr>
<td>200-250/24</td>
<td>6</td>
<td>33</td>
<td>PD/relapse on ANT; relapse &lt; 6 mo</td>
<td>6</td>
</tr>
<tr>
<td>200-250/24*</td>
<td>37</td>
<td>30</td>
<td>PD/relapse on ANT; relapse &lt; 12 mo</td>
<td>9</td>
</tr>
<tr>
<td>175/3</td>
<td>38</td>
<td>29</td>
<td>PD/relapse on ANT; relapse &lt; 6 mo</td>
<td>10</td>
</tr>
<tr>
<td>135/3</td>
<td>30</td>
<td>13</td>
<td>PD/relapse on ANT; relapse &lt; 6 mo</td>
<td>10</td>
</tr>
<tr>
<td>250-300/3*</td>
<td>36</td>
<td>6</td>
<td>PD/relapse during ANT</td>
<td>ECC†</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; PR, partial response; ANT, anthracycline; PD, poorly differentiated; ECC, European Cancer Center.  
* With G-CSF.  
† Present study.

cyclines in the adjuvant setting. All cases of adjuvant chemotherapy (n = 8) had received cyclophosphamide/methotrexate/5-fluorouracil. Only 11 patients (30%) initially had responded to anthracycline-containing regimens prior to relapsing while on treatment. Moreover, the median inter-treatment interval was short (1 month). Our criteria are certainly more strict than those of the Italian study, in which a 3-hour infusion also was used, but at a lower dose. For a better comparison of data in the literature, a uniform definition of anthracycline resistance is urgently needed.

The influences of both dose and schedule of paclitaxel remain undetermined. The European-Canadian study comparing two dose levels (135 mg/m² v 175 mg/m²) but using the same infusion duration (3 hours) showed no difference in the subset of anthracycline-resistant patients either for response rate or for time to progression. The 96-hour infusion schedule, as used by Wilson et al., seems promising, but their definition of anthracycline resistance has been quite liberal. It is hoped that the potential importance of prolonged infusions of paclitaxel in patients with breast cancer will become clear when the results from an ongoing randomized trial comparing 3-hour with 96-hour infusion (M.D. Anderson Cancer Center, Houston, TX) become available. At present, there are no certain data indicating that the 3-hour infusion schedule is inferior to a more prolonged (24-hour) infusion time.

The activity of paclitaxel in the different studies seems to be mainly determined by differences in patient characteristics as well as by differences in definitions of “anthracycline refractory.” Our study showed that the dose-limiting toxicity associated with high-dose 3-hour infusions is not myelosuppression but neurotoxicity. Only a minority of patients exhibited World Health Organization grade 4 hematotoxicity, and this was of short duration. However, most cases of grade 4 myelosuppression were observed in patients with liver enzyme increases ≥2.6 × ULN. It is tempting to assume that the more severe myelosuppression in patients with increased liver enzymes correlates with the observed differences in Cmax, AUC, and duration of threshold level in such patients. Using a 24-hour infusion time, Venook et al reported that there was a relationship between liver dysfunction and paclitaxel-induced toxicity. Patients with liver enzyme increases greater than 2 × ULN (but with normal bilirubin count) could receive paclitaxel safely only at reduced dosages (<135 mg/m²). If indeed AUC plays a crucial role in this, the nonlinear kinetics with shorter infusions might imply that excessive toxicity could be expected when high dosages are given by 3-hour infusions to patients with liver dysfunction. Further pharmacodynamic studies using 3-hour infusions of different dosages of paclitaxel in patients with liver dysfunction are therefore desirable.

**REFERENCES**

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