Paclitaxel and Gemcitabine as Salvage Treatment in Metastatic Breast Cancer

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Both paclitaxel and gemcitabine (Gemzar) have shown activity and manageable toxicity when used as single agents in heavily pretreated patients with metastatic breast cancer. This phase II study evaluated their use in combination for metastatic breast cancer patients whose disease recurred or progressed following treatment with anthracycline-containing regimens.

Treatment of refractory metastatic breast cancer remains a major challenge to the medical oncologist. Second-line treatment after failure of initial chemotherapy is primarily palliative.[1] Although objective responses can be produced with various drug combinations in about 20% to 40% of cases, nearly all patients tend to show rapid tumor progression.[2,3] Therefore, efforts at improving the outcome of patients with this disease are of major interest. Previous Trials

Paclitaxel as Monotherapy
Paclitaxel, a novel antimicrotubule agent derived from the bark of the western yew Taxus brevifolia, is one of the most active anticancer drugs introduced into the clinic during recent years.[4] Unlike other microtubule poisons in use, such as vincristine and vinblastine, paclitaxel promotes the formation of tubulin dimers and stabilizes microtubules against depolymerization, resulting in growth inhibition and loss of cell viability.[5,6] Early phase II trials of paclitaxel revealed significant antitumor activity in various types of solid tumors, including ovarian,[7] non-small-cell lung,[8] and head and neck[9] carcinomas. In previously treated metastatic breast cancer patients, paclitaxel given at doses ranging from 135 to 250 mg/m^2 has produced objective responses in 30% to 60% of cases.[10] In a phase II trial performed at Memorial Sloan-Kettering Cancer Center, where 250 mg/m^2 of paclitaxel was given as initial therapy for advanced disease as a continuous IV infusion every 21 days with hematologic support (recombinant human granulocyte colony-stimulating factor), objective responses were documented in 16 (62%) of 26 evaluable patients, including three (12%) complete responses. Although neutropenia was the doselimiting toxicity, the incidence of life-threatening infectious complications in that study was considered acceptable.[11] These observations were confirmed in other phase II trials, where 175 to 250 mg/m^2 of the drug was given as a 3-hour IV infusion.[12,13] With the confirmation of initial reports of the antitumor activity of single-agent paclitaxel in metastatic breast cancer patients who have undergone prior chemotherapy, interest in this agent has increased substantially.[9-12] Nabholtz et al.[14] in a multicenter randomized trial, compared two different doses of paclitaxel given as a 3-hour infusion in patients with metastatic breast cancer who had failed to respond to previous chemotherapy. A total of 471 patients were randomized to receive intravenous paclitaxel at a dose of 175 or 135 mg/m^2 every 3 weeks. Better treatment results were achieved with high-dose vs low-dose paclitaxel: overall response rate, 29% vs 22% (P = .108); complete response rate, 5% vs 2% (P = .088); median time to disease progression, 4.2 vs 3.0 months (P = .027); and median survival time, 11.7 vs 10.5 months (P = .321). Patients previously exposed or resistant to anthracyclines were as likely to respond as those without such prior exposure. Treatment was well tolerated, as documented by the number of administered treatment courses (median, 6 [range:1-17] vs 5 [range:1-18]), the low frequency of dose reductions (14% vs 7%, P = .024), and the small number of patients (n = 9 [4%] vs n = 5 [2%]) who required treatment discontinuation for adverse reactions. The incidence and severity of neutropenia and peripheral neuropathy were dose-related. After quality-of-life adjusted time-to-progression analysis, the 175 mg/m^2 arm retained its advantage over the 135 mg/m^2 arm.
Follow-up studies have not only confirmed the partial lack of clinical cross-resistance between paclitaxel and anthracyclines, but have also revealed its significant single-agent activity in nonpretreated patients. Indeed, paclitaxel can be considered at least as active as doxorubicin when used as a single agent in phase II trials that have been conducted in patients with metastatic breast cancer. For that reason, it has been progressively incorporated into experimental combination regimens for both first-line and salvage treatment of this disease.

Gemcitabine as Monotherapy
Gemcitabine (Gemzar) is a novel nucleoside analog of deoxycytidine with a broad range of activity against various tumors and an especially favorable toxicity profile, including mild myelosuppression and minimal nonhematologic toxicity. Several important phase II studies of singleagent gemcitabine as first- or secondline chemotherapy have been conducted in patients with metastatic breast cancer. In a US study, gemcitabine at 1,200 mg/m², given on days 1, 8, and 15 as first-line palliative therapy, achieved an overall response rate of 46% (2 complete responses and 10 partial responses among 26 evaluable patients). The same gemcitabine regimen administered to patients who received a prior anthracycline-based regimen resulted in a remission rate of 30% (2 complete and 6 partial responses among 27 evaluable patients). In a study known as the “European” study, gemcitabine was given as first- or second-line therapy at a mean dose of 725 mg/m² once weekly for 3 weeks, followed by a rest period of 4 weeks. Although this dose was relatively low, patients had a remission rate of 25% (3 complete and 7 partial responses among 40 evaluable patients). A study was initiated that used a similar regimen but a higher gemcitabine dose.
(1,000 mg/m\(^2\)) on days 1, 8, and 15 of a 4-week cycle.[24] Of the 40 patients evaluable for response, there were three complete and seven partial responders, for an overall response rate of 25%. Twenty-six of these patients had received prior chemotherapy (including seven in the adjuvant setting). All patients had stage IV disease. Median survival reported in these two studies was 11.5 months. In a recent study that used the same gemcitabine regimen, no complete responses were observed, but there were six partial responses, for an overall response rate of 14.3% among 42 evaluable patients.[25] Median survival for all 42 patients was 15.2 months. Patients received up to one prior chemotherapy regimen in the adjuvant setting. The majority of patients (67%) had visceral disease at study entry. In these phase II studies, hematologic and nonhematologic toxicities with single-agent gemcitabine treatment were mild, with neutropenia being the most clinically relevant untoward event. Treatment delays or withdrawals from treatment were infrequent. Considering the single-agent activity of both paclitaxel and gemcitabine in metastatic breast cancer patients, their different mechanisms of action, and their distinct nonhematologic toxicity profile, we designed this phase II trial in which a combination of the two drugs was evaluated as salvage therapy in patients failing first- or second-line chemotherapy regimens.

### Table 2

**Major Toxicities of Combination Paclitaxel/Gemcitabine Therapy in 137 Cycles (Percentage of Courses Affected)**

<table>
<thead>
<tr>
<th>WHO Severity Grade</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting</td>
<td>0%</td>
<td>71%</td>
<td>23%</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>Absolute neutrophil count</td>
<td>70%</td>
<td>12%</td>
<td>9%</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Platelets</td>
<td>77%</td>
<td>9%</td>
<td>6%</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>35%</td>
<td>38%</td>
<td>21%</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>94%</td>
<td>3%</td>
<td>3%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Mucositis</td>
<td>88%</td>
<td>6%</td>
<td>6%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Neurosensory</td>
<td>0%</td>
<td>85%</td>
<td>12%</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Arthralgia/myalgia</td>
<td>6%</td>
<td>82%</td>
<td>15%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>0%</td>
<td>6%</td>
<td>18%</td>
<td>76%</td>
<td>0%</td>
</tr>
<tr>
<td>Infection</td>
<td>91%</td>
<td>3%</td>
<td>0%</td>
<td>3%</td>
<td>3%</td>
</tr>
</tbody>
</table>

WHO = World Health Organization.

**Patients and Methods Eligibility Criteria**

Eligible patients had histologically confirmed metastatic breast cancer with bidimensionally measurable disease. All had already received first- or second-line therapy with an anthracycline-containing regimen, but had no prior exposure to paclitaxel or gemcitabine. Other eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, age > 70 years with an anticipated life expectancy > 12 weeks, adequate renal and hepatic function, no active infection, no central nervous system involvement or evidence of carcinomatous meningitis, white blood cell count ≥ 4 * 10\(^9\)/L, absolute neutrophil count ≥ 2 * 10\(^9\)/L, hemoglobin level ≥ 10 g/dL, platelet count ≥ 130 * 10\(^9\)/L, and signed written informed consent. Exclusion criteria included a history of prior malignancy other than nonmelanoma skin cancer or cervical carcinoma in situ, significant cardiac disease, and a history of or existing peripheral neuropathy. Prior radiation completed at least 4 weeks from the date of study registration was permitted, as long as it encompassed less than 30% of the total marrow-bearing skeleton. Any hormonal therapy was discontinued at least 3 weeks before study entry. **Treatment Plan**

Twelve hours before administration of paclitaxel, all patients were given oral 8 mg of dexamethasone. This dose was repeated IV 15 minutes before paclitaxel was started. In addition,
dimenhydrinate at 100 mg IV, ranitidine at 50 mg IV, and promethazine at 50 mg intramuscularly were given 30 minutes prior to paclitaxel administration. Treatment on day 1 consisted of paclitaxel at 175 mg/m² IV (diluted in 500 mL of 0.9% normal saline and infused over a period of 3 hours), followed by gemcitabine at 1,000 mg/m² IV (diluted in 250 mL of 0.9% normal saline). On day 8, gemcitabine alone was given at the same dose (schedule G-1,8). Cycles were repeated every 21 days on an outpatient basis for a maximum of eight cycles. In the first five patients, gemcitabine was given at the same dose on days 1, 8, and 15 every 28 days (schedule G-1,8,15). However, this produced an unacceptable level of thrombocytopenia, and the regimen was modified to G-1,8 every 21 days. Cycles were repeated if the neutrophil count exceeded $1 \times 10^9$/L and platelet count exceeded $120 \times 10^9$/L. If either of these hematologic parameters were not within their respective range on the scheduled treatment day, therapy was delayed for a week. If after a delay of 2 weeks these values were still not in the appropriate range, the patient was removed from the study. The doses of paclitaxel and gemcitabine were reduced by 50% in the treatment cycle if febrile neutropenia occurred or if a neutrophil count nadir < $0.5 \times 10^9$/L or platelet count nadir < $50 \times 10^9$/L was documented. Patients with progressive disease after the second cycle and those whose disease stabilized or progressed after the fourth cycle of chemotherapy were also removed from the study.

**Pretreatment Evaluation and Follow-up Studies**

Before protocol enrollment, all patients underwent a complete history and physical examination. Laboratory evaluation included a complete blood count (CBC) with differential and platelet count, a urinalysis and biochemical profile, determination of serum CA 15-3 and lactate dehydrogenase levels, a baseline electrocardiogram, assessment of ECOG performance status, chest x-ray, and ultrasound examination and computed tomography of the abdomen and suspicious areas, including a bone scan. A CBC was repeated on day 8 and day 15, initially, of each cycle. Physical findings, ECOG performance status, CBC with differential and platelets, biochemical profile, and serum CA 15-3 were reevaluated after each cycle. Complete tumor measurements were documented at the end of the second cycle and again at the end of the study. Patients responding to therapy had to repeat the evaluation 4 weeks later using the same methods for response confirmation.

**Table 3**

<table>
<thead>
<tr>
<th>Response</th>
<th>Response Rate</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Objective</td>
<td>16 (55%)</td>
<td>36%–73%</td>
</tr>
<tr>
<td>Complete</td>
<td>5 (17%)</td>
<td>3%–30%</td>
</tr>
<tr>
<td>Partial</td>
<td>11 (38%)</td>
<td>19%–56%</td>
</tr>
<tr>
<td>Stable</td>
<td>6 (20.7%)</td>
<td>5%–40%</td>
</tr>
</tbody>
</table>

**Response Criteria**

All eligible patients were considered for response analysis. Lesions (eg, metastatic pulmonary nodules, lymph nodes, subcutaneous masses, and hepatic metastases) had to be measurable in two dimensions with rulers or calipers, and their surface area was determined by multiplying the longest diameter by the greatest perpendicular diameter. Bone lesions only were not considered measurable disease. For multiple lesions, total tumor size was defined as the sum of the products of the largest perpendicular diameters of each lesion.[26] The definition of response was based on World Health Organization (WHO) recommendations.[27] Complete response meant the complete disappearance of all known disease determined by two observations made no less than 4 weeks apart, without the appearance of a new lesion. Partial response was documented by a decrease of at least 50% (for bidimensionally measurable lesions) of the sum of the products of the two perpendicular diameters of all measured lesions and no new lesion or progression of any lesion, based upon two observations made no less than 4 weeks apart. No change was considered a decrease of > 50%, or < 25% increase in the sum of the products of the two perpendicular diameters of all measured lesions and no new lesions. Progressive disease meant an increase of at least 25% in the size of at least one measurable lesion or the appearance of a new lesion. The occurrence of pleural effusion or ascites was also considered progressive disease if documented by positive cytology. Pathologic fracture was not automatically considered evidence of disease progression. **Evaluation of Adverse Events**
Any patient who had received at least one course of paclitaxel/gemcitabine was evaluable for safety and toxicity. The type and severity of these toxicities was determined using WHO criteria.

**Statistical Considerations**

The two-stage phase II design described by Gehan was applied to this study.[28] The 95% confidence intervals (CI) for response rates were calculated using the binomial theorem. Survival and response duration were calculated using the Kaplan-Meier method, using a microcomputer-assisted program.[29,30]

**Results**

**Patient Characteristics**

Twenty-nine patients with a median age of 46 years (range: 32-68 years) were enrolled. All were considered eligible for evaluation of response and toxicity. Patient characteristics are summarized in Table 1. Previous chemotherapy included (1) fluorouracil (5-FU), doxorubicin (Adriamycin), and cyclophosphamide (Cytoxan, Neosar), known as FAC (14 cases of first-line therapy and four cases of second-line therapy after failure of cyclophosphamide, methotrexate, and 5-FU [CMF]); (2) 5-FU, epirubicin (Ellence), and cyclophosphamide, or FEC (four cases of first-line therapy); (3) mitoxantrone (Novantrone) plus CMF (four cases of first-line therapy); and (4) cisplatin, vinblastine, and mitomycin (Mutamycin) (three cases of second-line therapy after failure of FAC). All but four patients had a tumor response with prior chemotherapy. Seventeen (59%) patients were considered truly anthracycline or anthracenedione refractory (ie, they had progressed during the use of regimens containing these agents). The median follow-up was 22 months.

**Safety and Toxicity**

A total of 137 cycles (median: 4 per patient) were administered. Treatment delays occurred in 13 cycles (9.5%), and dose reductions were needed in 17 (12.4%) cycles. Cycle delays occurred in eight cycles (5.8%) due to thrombocytopenia and in four cycles (2.9%) due to neutropenia. Dose reductions due to myelotoxicity occurred in nine cycles (6.6%). No hypersensitivity reactions were seen. The regimen was well tolerated (Table 2). Nausea/vomiting (grade 1),

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![Figure 1: Combination Paclitaxel/Gemcitabine Treatment as Salvage Therapy of Metastatic Breast Cancer—Kaplan-Meier overall survival curve (N = 29). SV = survival.](image-url)
was well tolerated (Table 2). Nausea/vomiting (grade 1), alopecia (grades 2/3), and neutropenia (grade 1) were seen in most patients. Five patients had grade 1 and two patients had grade 3 neutropenia. Grade 3/4 thrombocytopenia was observed in five (18.5%) of the first 27 cycles (schedule G-1,8,15), although no bleeding was observed, and in six (5.4%) of the 110 subsequent cycles (schedule G-1,8). The difference in frequency of grade 3/4 neutropenia between the two dosing schedules was significant ($P = .04$, Fisher's exact test). Eight patients had grade 3 neutropenia (5 with schedule G-1,8,15). In addition, grade 4 neutropenia was associated with fever in two cases and in four cycles (schedule G-1,8,15). Three patients received blood transfusions due to anemia. Grade 1/2 myalgia and fatigue were also reported in eight patients. One patient developed a reversible bradycardia during paclitaxel infusion. No death due to toxicity occurred.

Responses and Survival
There were 16 (55%) objective responses (95% CI = 36%-73%), including five (17%) complete responses (95% CI = 3%-30%) and 11 (38%) partial responses (95% CI = 19%- 56%). Six (20.7%) patients attained disease stabilization (Table 3). Median response duration was 8 months (range: 4-26 months), and median overall survival was 12 months (range: 4-48+ months). Survival at 1, 2, 3, and 4 years was 45%, 30%, 20%, and 10%, respectively. The overall survival curve is depicted in Figure 1 and the response duration curve in Figure 2. Addition of Trastuzumab
Twenty-two patients were tested for HER2/neu overexpression after tumor progression. In seven, HER2/neu was 3+ positive by immunohistochemistry analysis (HercepTest with monoclonal antibody 4D5). For these patients we added trastuzumab (Herceptin) at 4 mg/kg IV (loading dose), followed by 2 mg/kg IV weekly until progression to the same regimen of paclitaxel and gemcitabine for four additional cycles (postprotocol therapy, at the discretion of the treating oncologist). In three patients (42.9%) we observed a partial response, with a median response duration of 5 months (range: 3-11+ months).

Discussion
Overall objective response rates of metastatic breast cancer to second- or third-line chemotherapy have been very limited, regardless of the choice of drug regimen.[1-3] The modest impact of cytotoxic agents in this setting can be explained, at least in part, by the high percentage of patients exhibiting a poor performance status at the start of treatment, the presence of bulky disease at visceral sites, limited bone marrow reserve, and the presence of highly drug-resistant tumor cells selected by prior exposure to chemotherapy.[1,31] Indeed, various reviews on the effectiveness of combination chemotherapy in this setting revealed objective response rates below 30%, and the responses were usually partial, of short duration, and at the cost of significant toxicity to the patient.[1-3,31] Our results confirm the significant antitumor activity of paclitaxel in combination with gemcitabine as secondor third-line chemotherapy for patients with metastatic breast cancer. Notably, this combination produced objective responses in about half of the 29 patients tested and achieved a complete response in five (17%) of them. Based on current literature, neither agent given alone would have been expected to produce such a substantial response rate. The median overall survival of 12 months, as well as the 1-, 2-, and 3- year survival rates of 45%, 30%, and 20%, respectively, are remarkable and unusual for this subgroup of patients. It is interesting to note that for seven HER2/neu 3+ positive patients, trastuzumab was added to the
same regimen of paclitaxel and gemcitabine for four more cycles, after progression on the protocol. In three (42.9%) of the seven patients we observed a partial response, with a median response duration of 5 months (range: 3-11+ months), which raises the question of whether anti-HER2/neu therapies could restore gemcitabine or paclitaxel tumor cell sensitivity. Despite the theoretical background for possible synergy between gemcitabine and paclitaxel due to their different cellular mechanisms of action, a recent report using in vitro concurrent or sequential treatment of several cell lines with gemcitabine and paclitaxel showed an antagonistic effect.[ 32] Although our study was not designed to test antagonism or in vivo synergy between paclitaxel and gemcitabine, our preliminary results do not suggest antagonism in the clinical setting. Further study of the combination may be necessary to address those specific issues. Importantly, the degree of efficacy observed in this study did not occur at the cost of unacceptable toxicity. On the contrary, toxicity appeared to be predictable and manageable. Omission of day-15 gemcitabine significantly improved the frequency of grade 3/4 thrombocytopenia. In addition, there were no further reports of fever and neutropenia when gemcitabine was administered only on days 1 and 8.[33] This suggests that the best schedule for this combination should be G-1,8; ie, with paclitaxel given on day 1 and gemcitabine given on days 1 and 8 of a 21-day cycle. Our results suggest that the combination of paclitaxel and gemcitabine is very promising and may be an attractive option in the management of patients with metastatic breast cancer. Due to its significant efficacy, as well as manageable toxicity, this regimen deserves further testing in both minimally and heavily pretreated patients with advanced disease. The addition of trastuzumab to this regimen should also be explored.

**Disclosures:** The author(s) have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

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