A Phase II Study of Doxorubicin/Paclitaxel Plus G-CSF for Metastatic Breast Cancer

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This phase II trial was conducted to evaluate the percentage of objective responses and the toxicity profile of combination doxorubicin (Adriamycin) and paclitaxel (Taxol) with granulocyte colony-stimulating factor as first-line therapy.

Introduction

Metastatic breast cancer remains incurable with currently available therapeutic strategies. Doxorubicin (Adriamycin), a DNA intercalator that inhibits topoisomerase II, is considered one of the most active drugs for single-agent treatment of this disease, producing objective responses in about 30% to 40% of patients. Combination regimens including doxorubicin may induce objective responses in 40% to 70% of patients with metastatic breast cancer, although the percentage of complete remissions is only about 5% to 15%, and metastatic breast cancer relapses in virtually all cases within a median follow-up time of 6 to 24 months.

Paclitaxel (Taxol), a novel tubulin-interacting agent that promotes the formation and stabilization of microtubules, has been shown to produce objective tumor responses in about 20% to 60% of patients with metastatic breast cancer. Notably, a response rate of about 20% to 30% has been observed in heavily pretreated patients. This level of objective response compares favorably with that observed with most cytotoxic agents previously tested in phase II trials against this disease.

The combination of doxorubicin and paclitaxel exhibits at least partial synergism against human breast cancer cell lines in vitro. That observation, added to the comparable levels of antitumor effects of the two agents in patients with metastatic breast cancer, and the fact that the agents act through separate and distinct intracellular mechanisms, prompted the design of a study to evaluate the combined effect of doxorubicin/paclitaxel in women with metastatic breast cancer.

STUDY RATIONALE

Over the last few years, various investigators have studied the single-agent activity of paclitaxel at different doses and infusion times. In a pilot evaluation conducted at our institution, we administered paclitaxel 250 mg/m², given as a 3-hour intravenous (IV) infusion every 3 weeks, to a group of 20 heavily pretreated patients with visceral metastatic breast cancer that had progressed after therapy with a doxorubicin-containing regimen. An objective response rate of 16% was observed and short-lasting reversible neutropenia was the main dose-limiting toxicity encountered. Considering the tolerability of the study regimen in this group of patients, we decided to evaluate the merits of bolus doxorubicin combined with a 3-hour IV infusion of paclitaxel as first-line therapy in patients with metastatic breast cancer. Granulocyte colony-stimulating factor (G-CSF) was added to prevent life-threatening neutropenia, and only women with visceral-dominant disease were included.

PATIENTS AND METHODS

This open-label, nonrandomized phase II study was conducted by the South-American Office for Anticancer Drug Development in Porto Alegre, Brazil. The trial was conducted according to guidelines of the local ethics committee and good clinical research practice. The study was designed to accrue 25 consecutive and evaluable patients from different institutions. The trial was divided into two stages to allow its early discontinuation in the event of severe life-threatening toxicity or lack of...
efficacy; at least three objective responses among the first 10 patients were required to continue the study.[10]

**Patient Selection**

Patients with histologically proven metastatic breast cancer, a life expectancy of at least 3 months, and a World Health Organization performance status of 0 to 2 were eligible for study entry. Prior adjuvant chemotherapy (excluding anthracyclines) and/or hormonal therapy were allowed, but no cytotoxic therapy for the management of advanced disease was permitted. Radiotherapy for locoregional management of disease and/or palliation of bone metastases was allowed, as long as patients who had received radiotherapy had completed treatment at least 3 weeks prior to study entry and all acute toxic effects of therapy had resolved.

Study subjects had bidimensionally measurable lesions in areas that had not been irradiated previously. Only patients with predominantly visceral disease were included in the trial. Patients who had only skin, soft tissue, or lymph node (including supraclavicular) involvement were not eligible for the study; patients with brain metastases also were excluded.

Additional eligibility requirements included adequate bone marrow (white blood cell count 3,500/mm³ or greater, absolute granulocyte count 2,000/mm³ or greater, and a platelet count 100,000/mm³ or greater). Patients also were required to have adequate hepatic (serum bilirubin level 1.5 mg/dL or greater) and kidney (serum creatinine level 2.0 mg/dL or greater) function. Patients with active infections or severe concurrent medical conditions were excluded.

**Pretreatment and Follow-Up Evaluation**

All patients gave a complete history and underwent physical examination, complete blood cell count, biochemistry analysis (including renal and liver tests, and serum electrolytes), urinalysis, chest x-ray, and an electrocardiogram. During drug treatment, patients were re-examined and laboratory tests were repeated on a weekly basis. Tumor measurements were taken and toxicity assessed before each course of therapy. Additional imaging studies, such as computed tomography scan or magnetic resonance imaging were repeated every two courses to evaluate marker lesions. Whenever possible, the left ventricular ejection fraction was measured by ultrasound or radioisotopic techniques at baseline and after every treatment course.

**Treatment Plan**

Doxorubicin was supplied by Pharmacia Laboratories, Rio de Janeiro, Brazil; paclitaxel was provided by Bristol-Myers Squibb Laboratories, São Paulo, Brazil; and G-CSF was supplied by Roche Laboratories, São Paulo, Brazil. Doxorubicin 60 mg/m² was administered by IV bolus on day 1, followed immediately by paclitaxel 250 mg/m², administered as a 3-hour IV infusion. Premedication to avoid allergic reactions to paclitaxel consisted of dexamethasone 20 mg IV, ranitidine 50 mg IV or cimetidine 200 mg IV, and diphenhydramine 100 mg IV, and promethazine 50 mg intramuscularly, 30 minutes prior to paclitaxel administration. As part of the antiemetic regimen, dexamethasone was repeated at 10 mg IV after 4 and 8 hours, and then daily at 4 mg orally every 8 hours for an additional 3 days. Cimetidine 200 mg IV was given after 8 hours on day 1 and maintained for 3 days at 300 mg orally every 8 hours to prevent gastrointestinal complications of dexamethasone. Diphenhydramine 100 mg IV was repeated once after 8 hours on day 1.

Prophylactic G-CSF 5 µg/kg was administered daily as a subcutaneous injection, starting on day 2 and continuing until the granulocyte count reached 1,500/mm³. Treatment was repeated every 3 weeks for a maximum of six cycles, after which patient management was decided by the individual's physician. In the case of a granulocyte count lower than 1,500/mm³ and/or a platelet count less than 100,000/mm³ on day 21, treatment was postponed for 1 week. If counts had returned at least to lower normal limits by day 28, treatment was repeated at the same dose level. If recovery was documented only after a 2-week delay (ie, by day 35), or if the patient developed severe mucositis and/or neutropenic fever necessitating antibiotics and hospitalization, treatment was repeated at a reduced dose, arbitrarily set at doxorubicin 50 mg/m² and paclitaxel 175 mg/m². The paclitaxel dose was based on preliminary information obtained from other concomitant trials.[5,6,14] Given that complete information on the safety of this dose level was not yet completed during the treatment period for the current study, G-CSF was also maintained according to the study protocol. Patients whose treatment was interrupted for more than 2 weeks were not re-treated in the protocol but were managed on the basis of clinical judgment.

**Response and Toxicity Evaluation**

Identification of objective response was based on the response definitions established by the World Health Organization. Progression-free survival was calculated as the time from first documentation of objective response (complete [CR] or partial [PR]) to first documentation of disease progression. Toxicity evaluation was based on the National Cancer Institute Common Toxicity Criteria.
Patient Characteristics
Between September 1992 and May 1995, 25 patients were accrued to this study. The trial was temporarily interrupted twice due to a shortage in the paclitaxel supply that resulted in a total of 11 months without patient accrual. However, this fact did not seem to influence patient selection or introduce any detectable bias into the protocol study.

The main characteristics of this group of patients are listed in Table 1. All 25 women had visceral-dominant disease; World Health Organization median performance status of 1 (range, 1 to 2), and a median age of 49 years (range, 29 to 65 years), with only three patients older than 60 years. All patients were initially treated by radical modified mastectomy or conservative surgery, followed by axillary lymph node dissection plus radiotherapy. No patient had undergone prior hormonal, immunologic, or cytotoxic therapy for advanced disease. Adjuvant cyclophosphamide-methotrexate-5-fluorouracil therapy had been given to 19 of the 25 patients.

Toxicity Profile and Dose Administrations
The main toxic effects observed in the trial were neutropenia, thrombocytopenia, mucositis, and total alopecia. Less common mild to moderate side effects were myalgia/arthritis, nausea and vomiting, peripheral neuropathy, isolated cases of reversible mild hypotension, and short-lasting and reversible skin papuloerythematous reaction during paclitaxel infusion. These findings are summarized in Table 2.

In spite of prophylactic G-CSF administration, and with the exception of one patient whose disease progressed after the first course of therapy, all patients required dose reduction after the second or third treatment course. In six patients, severe mucositis plus neutropenic fever necessitated supportive care and/or hospitalization. In all other patients, dose reductions were based on the duration of neutropenia with or without fever, clinical signs of septicemia, and/or severe mucositis.

No toxic deaths were documented in the study. Dose reduction was needed for one of three patients receiving two courses of therapy, and for all patients who received more than two courses of therapy.

Thus, of 102 courses studied, 27 were delivered at the initial planned dose (doxorubicin 60 mg/m², paclitaxel 250 mg/m²), and 75 were administered at the reduced dose (doxorubicin 50 mg/m², paclitaxel 175 mg/m²). At the higher dose level, grade 3/4 neutropenia occurred in all courses (grade 4, 93%), and grade 3/4 thrombocytopenia occurred in 67% of courses (grade 3, 63%). Grade 3 mucositis was observed in 37% of courses. In contrast, grade 3/4 neutropenia was documented in 65% of courses at the reduced dose level (grade 4, 35%), and thrombocytopenia was seen in only 16% (grade 4, 4%). Grade 3 mucositis was observed in 3% of courses.

In general, repeated courses of the reduced-dose regimen given with G-CSF were well tolerated, with 17 of 25 patients receiving four or more treatment courses. It is worth noting that no case of life-threatening neutropenia-related infection or severe mucositis requiring hospitalization for IV hydration was observed in this group of patients.

As part of the initial locoregional treatment, 20 of the 25 patients received radiation to the left anterior chest wall, internal mammary nodes, and axilla, but no other detectable risk factor for heart disease was present in the study population. The median cumulative dose of doxorubicin was 220 mg/m² (range, 60 to 320 mg/m²).

Unfortunately, follow-up cardiac toxicity evaluation by echocardiogram and/or multiple gated image acquisition analysis was not performed systematically in all patients. In 16 patients, however, at least one left ventricular ejection fraction measurement was taken prior to entry into the trial and was repeated after two to six courses either by multiple gated image acquisition analysis scan or echocardiogram. In two cases, reductions of 12% and 14% were observed in relation to baseline values. However, no clinical signs of cardiotoxicity, such as the development of congestive heart failure, cardiac arrhythmia, or angina were seen. Both patients had received prior chest radiation and their cumulative doxorubicin doses were 270 and 320 mg/m². The two patients were removed from the study and continued treatment with paclitaxel alone, one for an additional three courses and the other for two courses.

Efficacy and Progression-Free Survival
Objective responses (CR-PR) were documented in 80% of patients, with 28% (seven cases) achieving a complete response (Table 3). Of the seven patients who achieved a CR, four were referred to experimental high-dose chemotherapy programs for consolidation after the fourth course.

Unfortunately, disease relapsed in all four patients at 3, 7, 11, and 16 months, following the latter procedure. Responding patients (both CR and PR) who were not referred to high-dose chemotherapy programs were treated with paclitaxel alone for additional courses, switched to a different chemotherapy regimen, or maintained on tamoxifen 20 mg/d or megestrol acetate 160 mg/d. 
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Progression-free survival for the whole group of patients, as well as for responders and nonresponders, is depicted in Figure 1. Relapses occurred most commonly in visceral sites, while central nervous system metastasis was the site of initial failure in three cases. After a 24-month follow-up, only one patient (from the PR group) remained progression free. This patient received four courses of therapy and then decided to withdraw from the study for treatment with mitoxantrone for three courses, after which she was maintained on tamoxifen therapy. The median progression-free survival time was 11 months (range, 3 to 24 months) for patients who achieved a CR, 7+ months (range, 2 to 14+ months) for those with a PR, and 5 months (range, 3 to 9 months) for nonresponding patients.

DISCUSSION

Paclitaxel as first- or second-line chemotherapy has been associated with high objective response rates in women with metastatic breast cancer.[5] Paclitaxel also has been shown to produce objective responses in 20% to 40% of patients who fail to respond to doxorubicin-containing regimens,[6] suggesting a lack of complete clinical cross-resistance between the two agents. Although preliminary data on the combined use of doxorubicin and paclitaxel have revealed a high percentage of objective responses in patients with metastatic breast cancer, the potential toxicity of the combination is disturbing.[11-13] Of particular concern are possible pharmacokinetic interactions between the agents, superimposable dose-limiting toxicities to the bone marrow, and, more specifically, potential risks of cardiotoxicity.[14-16]

Recently, Gianni and colleagues, from the National Tumor Institute in Milan, Italy, reported on the high efficacy of combination paclitaxel by 3-hour infusion plus bolus doxorubicin in women with previously untreated metastatic breast cancer.[14] The authors observed a 41% complete response rate and a 94% overall response rate. After a median follow-up of 12 months (range, 3 to 18 months), the median response duration was 11 months (range, 2+ to 18+ months) for patients who achieved a complete response and 8 months (range 1+ to 15+ months) for those with a partial response. These results are in accordance with our report, considering our overall objective response rate of 80% and our complete response rate of 28%. Further, the median progression-free survival in our study was 11 months for those attaining a complete response and 7+ months for those with a partial response.

Our study confirms the high level of antitumor activity of the doxorubicin/paclitaxel combination in patients with metastatic breast cancer, particularly meaningful in that our study population consisted totally of patients with visceral disease. Only about 20% of patients receiving paclitaxel/doxorubicin in the Milan trial had soft tissue involvement. The limited number of patients and large confidence intervals, as well as distinct patient characteristics, probably account for the observed differences in CR rate (28% vs 41% in the Italian study) between these two studies.

Toxicities of the Regimen

In addition to severe neutropenia and mucositis (World Health Organization grade 3/4), which occurred in all except one patient, grade 2 peripheral neuropathy was observed in one third of the cases in the Milan trial. Further, clinically reversible congestive heart failure (New York Heart Association grades II to III) developed in six patients (18%), five of whom received a cumulative doxorubicin dose of 480 mg/m². A history of high blood pressure was documented in four cases, a family history of heart failure and irradiation of the left breast in one patient each. Although it has been shown previously that paclitaxel can modify the pharmacokinetics of doxorubicin and its main metabolite, doxorubicinol, thereby enhancing the adverse effects of the drug,[15,16] the authors did not see any influence of drug sequence on the antitumor or toxic effects of the study regimen.[14]

Despite concomitant G-CSF administration, severe neutropenia and, less often, mucositis necessitated dose reductions (to doxorubicin 50 mg/m² and paclitaxel 175 mg/m²) in all patients who received two or more treatment courses. With this modified regimen, patients could be re-treated at 21-day intervals, without further compromising the dose intensity of the two drugs. As G-CSF was given to all patients according to the study protocol, its value for preventing life-threatening infections in the specific context of dose reduction cannot be evaluated. Based on the experience of Gianni and colleagues,[14] however, G-CSF might not be necessary for patients treated at the reduced dose level. This aspect of the study deserves further evaluation.

Likewise, the median cumulative dose of doxorubicin given to patients in our trial was 220 mg/m² (range, 60 to 320 mg/m²), which could explain the lack of clinical cardiotoxicity. In fact, our strategy was to administer a maximum of six cycles of therapy even to responding women. Patients younger than 50 years with good performance status were referred for high-dose therapy after completing
four courses of therapy; other responding patients (CR and PR) switched to other chemotherapy regimens or maintenance therapy with tamoxifen or megestrol acetate after they completed their sixth course. Notably, most patients, including those who exhibited a slight decrease in the left ventricular ejection fraction, had irradiation of the left chest wall as part of their primary management, but had no other detectable risk factor for the development of heart disease. Interestingly, no major allergic reactions developed in our patient population. This observation is notable because the premedication regimen we used was slightly different from that used routinely with paclitaxel, consisting of antiallergic agents given only 30 minutes before starting the infusion. In addition, peripheral neuropathy was not a significant problem in our study, probably due primarily to the small number of paclitaxel courses administered. Also, however, these patients had no prior exposure to neurotoxic agents and no known predisposing medical condition, like chronic alcohol abuse, diabetes, or other metabolic disorders. Alopecia was universal, as would be expected for this drug combination. Other toxicities were easily managed and of no clinical importance.

CONCLUSION

Our trial of combination doxorubicin/paclitaxel given as first-line treatment for patients with visceral-dominant metastatic breast cancer produced high objective response rates, with manageable toxicity following dose reduction. The need for G-CSF support in the reduced-dose regimen remains unclear. Unfortunately, progression-free survival was short, even in the subgroup of patients who had achieved a complete response. This observation implies that, although the two-drug combination achieved marked tumor cell kill, a significant number of resistant tumor cells remained viable to produce disease progression. Thus, other active agents, with different mechanisms of action, are still needed to achieve long-lasting responses in patients with this disease.

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