Paclitaxel and Carboplatin as First-Line Chemotherapy for Advanced Breast Cancer

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In a phase II study, 66 patients with advanced breast cancer (median age 56 years; range, 28 to 75 years) were treated with paclitaxel (Taxol), 175 mg/m² infused over 3 hours, and carboplatin (Paraplatin), dosed to attain an

Paclitaxel (Taxol) is one of the most exciting new anticancer drugs, with impressive clinical activity in several tumor types, such as ovarian, breast, lung, and head and neck cancers.[1] Furthermore, a number of clinical trials have established the activity of this drug in patients with advanced breast cancer, even in those previously treated with anthracyclines.[2-4]

Two studies have reported the combination of paclitaxel and cisplatin (Platinol) to be highly effective in advanced breast cancer.[5,6] Substitution of carboplatin (Paraplatin) for cisplatin allows the treatment to be given on an outpatient basis, even in patients with compromised cardiac or renal function. Carboplatin has also demonstrated significant activity in untreated patients with advanced breast cancer.[7]

Our group recently published the results of a phase II study of the combination of paclitaxel and carboplatin in anthracycline-resistant advanced breast cancer.[8] The excellent tolerability and definite activity of this combination prompted us to conduct the present phase II study evaluating its use as first-line chemotherapy in patients with advanced breast cancer.

Patients and Methods

Inclusion and Exclusion Criteria [1] To be eligible for the present study, all patients had to fulfill all of the following criteria: (1) histologic proof of inoperable, locally advanced (stage IIIB) or metastatic breast cancer; (2) measurable or evaluable disease outside of previously irradiated areas, unless subsequent progression was documented; (3) performance status ≤ 2 on the Eastern Cooperative Oncology Group (ECOG) scale; (4) age ≥ 18 years; (5) adequate bone marrow, hepatic, and renal function; (5) a life expectancy of ≥ 3 months; and (6) a witnessed informed consent according to our institutional policies. Prior palliative radiotherapy or hormonal therapy was allowed, but this had to have been discontinued at least four weeks before entry into the study.

Patients were excluded from the study if they had any of the following characteristics: (1) symptomatic brain metastases; (2) past or current history of neoplasm, except for nonmelanoma skin cancer or carcinoma in situ of the cervix treated with curative intent; (3) history of atrial or ventricular arrhythmias and/or congestive heart failure, even if medically controlled; (4) preexisting motor or sensory neurotoxicity grade 2, according to the World Health Organization (WHO) criteria; (5) active infection or other serious underlying medical condition that would impair the patient’s ability to receive protocol treatment; or (6) pregnancy.

Pretreatment Evaluation included a complete medical history, physical examination, complete blood cell (CBC) count, complete biochemistry panel, electrocardiogram, chest x-ray, bone scan, liver ultrasound, and computed tomographic (CT) scan, as indicated. The CBC count and biochemistries were repeated prior to each course of chemotherapy.

Treatment Regimen [1] The chemotherapy regimen consisted of paclitaxel, at a dose of 175 mg/m² infused over three hours, followed immediately by carboplatin, dosed to attain an area under the concentration-time curve (AUC) of 6 mg × min/mL (according to the Calvert formula). The carboplatin was diluted in 500 mL of normal saline and administered as a 30-minute infusion. Treatment was repeated every three weeks at an outpatient clinic. All patients were pretreated with dexamethasone, 20 mg intramuscularly 12 and 6 hours before paclitaxel administration; and dimethidene maleate, 4 mg, and cimetidine, 150 mg intravenously,
both given 30 minutes before paclitaxel. All patients received ondansetron (Zofran) as antiemetic treatment.

**Assessment of Tumor Response** Tumor response was assessed every three cycles if a CT scan was required to document measurable or evaluable disease, or after every cycle if clinical examination was adequate for response evaluation.

**Dose Modifications/Treatments for Toxicity** Drug doses were reduced if granulocytopenia or thrombocytopenia was present for ≥ 7 days or if febrile neutropenia occurred. The following dosing levels were used to modify the dose of paclitaxel: level 0, 175 mg/m²; level 1, 150 mg/m²; level 2, 120 mg/m²; and level 3, 100 mg/m². Any patient who could not tolerate the 100-mg/m² dose level was taken off the study. Dose escalation was not allowed.

Granulocyte colony-stimulating factor (G-CSF, filgrastim [Neupogen]), 5 mg/kg/day, was administered in patients who developed febrile neutropenia or whose absolute neutrophil count (ANC) decreased to less than 1,000/mL. In such patients, G-CSF was given prophylactically during all subsequent cycles.

If grade 2 neutropenia and/or thrombocytopenia were present for ≥ 7 days (for two consecutive counts 1 week apart) despite the use of G-CSF, the paclitaxel dose was reduced by one dose level. Similarly, in cases of grade 3 neutropenia and/or thrombocytopenia, the paclitaxel dose was decreased by two dose levels. In patients who developed febrile neutropenia with or without documented infection and/or severe bleeding, the paclitaxel dose was reduced by three dose levels. The ANC had to be ≥ 1,500/mL and the platelet count ≥ 100,000/mL prior to the beginning of the next treatment cycle.

In patients who developed grade 2 or 3 thrombocytopenia or granulocytopenia, carboplatin dose was reduced so as to yield an AUC of 5 or 4 mg × min/mL, respectively, in all subsequent cycles. If hematologic recovery did not occur after 2 weeks, the patient was taken off the study.

In cases of grade 3 mucositis, the dose of paclitaxel was reduced by one dose level and that of carboplatin was lowered to achieve an AUC of 5 mg × min/mL. In patients who experienced grade 4 neurotoxicity, severe hypersensitivity reactions, symptomatic arrhythmias, second- or third-degree atrioventricular block, treatment was discontinued and the patient was taken off the study. Toxicity criteria were those adopted by the WHO.[9]

**Efficacy End Points** Time to progression was calculated from the initiation of treatment with paclitaxel and carboplatin to the date on which progression of the disease was first documented, and survival was calculated from the initiation of paclitaxel-carboplatin to the date of last contact or the date of death. Patients who were progression-free or were alive on the day of last update were censored. Patients who died of causes probably related to the treatment were considered as if they had tumor progression at the time of death. Time to progression and survival were calculated by the Kaplan-Meier method.[10]

**Results**

From January 1996 to March 1997, 66 patients entered the study. Selected patient and tumor characteristics are shown in Table 1. Most of the patients were symptomatic at presentation and had two or more metastatic sites. A total of 38 (58%) patients had received previous adjuvant chemotherapy, 21 of whom had been treated with a regimen containing an anthracycline or mitoxantrone (Novantrone). The median relapse-free interval of these 21 patients was 28 months (range, 8 to 80 months). The relapse-free interval was ≤ 1 year in 4 patients and > 1 year in 17 patients.

As of May 1, 1997, 34 patients have completed all six cycles of paclitaxel-carboplatin treatment while 10 patients are still continuing their treatment. Reasons for treatment discontinuation were tumor progression (17 patients), early death (2 patients), voluntary withdrawal (1 patients), and toxicity (2 patients). A total of 295 cycles have been administered, 248 (84%) at full dose. The median interval between cycles is 21 days (range, 19 to 38 days). The relative dose intensity of paclitaxel is 0.9 (range, 0.5 to 1.2).

So far, 8 patients (12%; 95% confidence interval [CI], 4% to 20%) have achieved a complete response and 27 (41%; 95% CI, 29% to 53%) a partial response, for a total response rate of 53% (95% CI, 41% to 65%). Among the 21 patients who previously received an anthracyline- or mitoxantrone-containing adjuvant chemotherapeutic regimen, four have achieved a complete response and nine a partial response to the combination of paclitaxel and carboplatin. Complete responses have been observed in soft-tissue, osseous, hepatic, and pulmonary metastases.

Grade 3-4 toxicities have included anemia (occurring in 5% of patients), leukopenia (25%),
thrombocytopenia (5%), nausea/vomiting (7%), myalgias/arthritis (4%), allergic reaction, neurotoxicity, and infection (2% each). Alopecia has been universal.

As of May 1997, 29 (44%) patients have demonstrated tumor progression and 8 (12%) have died. Median time to tumor progression is 8.9 months (range, 0.5 to 14.6+ months), while median survival has not yet been reached.

Discussion

In this article, we describe the preliminary results of a phase II study evaluating the combination of paclitaxel (administered by a 3-hour infusion) and carboplatin in patients with advanced breast cancer. To our knowledge, this is the first study reporting on the activity of this regimen as first-line chemotherapy in advanced breast cancer.

Paclitaxel has been tested in combination with several other drugs in advanced breast cancer. Recently, there has been increasing interest in combining paclitaxel with cisplatin. The activity of this combination in ovarian cancer[11] makes it an attractive regimen for the treatment of other epithelial malignancies, including breast cancer. Substitution of carboplatin for cisplatin allows treatment to be given on an outpatient basis, even in patients with serious comorbid diseases that preclude prehydration or the administration of anthracyclines.

The overall response rate of 53% produced by the combination of paclitaxel and carboplatin observed in the present study appears to be higher than that achieved with a similar dose and schedule of single-agent paclitaxel in advanced breast cancer. However, definite conclusions about the superiority of the combination over paclitaxel monotherapy cannot be drawn, since randomized trials comparing the two regimens have not been conducted.

An interesting finding of our study was the excellent tolerability of the combination. Serious toxicities were seen infrequently, with the exception of leukopenia, which was noted in one-quarter of the patient population. However, the subsequent use of G-CSF ameliorated this side effect in most of the patients.

Conclusions

The present study has demonstrated that the combination of paclitaxel (delivered by a 3-hour infusion) and carboplatin has significant activity in advanced breast cancer and can be easily administered in an outpatient setting with manageable toxicity, especially in patients to whom anthracyclines or cisplatin administration is precluded because of other comorbid diseases. Randomized studies comparing this combination with other active regimens in advanced breast cancer are warranted.

References:
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