A pilot phase II study examined the feasibility of 75 mg/m² of docetaxel (Taxotere) in combination with 50 mg/m² of doxorubicin and 500 mg/m² of cyclophosphamide (Cytoxan, Neosar) in the first-line treatment of metastatic breast cancer. This study was designed to evaluate the efficacy and toxicity of the docetaxel/doxorubicin/cyclophosphamide combination both alone and as induction before high-dose chemotherapy, supplemented by autologous peripheral blood stem-cell transplantation.

**Introduction**

To be useful in the clinical setting, the taxanes must be integrated into multi-agent chemotherapy. The combination of paclitaxel (Taxol) and doxorubicin has proven highly effective, but its utility is limited by the incidence of cardiotoxicity.[1,2] Docetaxel (Taxotere) has also shown promising results in combination with doxorubicin.[3] Phase II studies suggest that with doses of 75 mg/m² of docetaxel and 50 mg/m² of doxorubicin, there is no clinically significant cardiotoxicity.[4] These observations led to a feasibility study using docetaxel, doxorubicin, and cyclophosphamide (Cytoxan, Neosar) in combination. The efficacy and safety of this combination alone and as induction before high-dose chemotherapy, supplemented by autologous peripheral blood stem-cell transplantation (APBSCT), were evaluated in a pilot phase II trial. This study will serve as the basis for an imminent international program of randomized trials.

**Objectives**

The primary objective of this study was to determine the feasibility of a docetaxel/doxorubicin/cyclophosphamide regimen in two subgroups of patients. The first group received eight courses of the regimen alone. The second group received 4 to 6 courses of the regimen in a nonrandomized fashion as induction chemotherapy before high-dose mitoxantrone (Novantrone), cyclophosphamide, and vinorelbine (Navelbine), supplemented by autologous peripheral blood stem-cell transplantation. The toxicity profile of the combination regimen and the role of prophylactic oral ciprofloxacin (Cipro) were evaluated.

The second objective was to assess the efficacy in terms of response rate and progression-free survival. The third objective was to evaluate the capacity of the docetaxel/doxorubicin/cyclophosphamide regimen to prime peripheral stem cells before harvesting them for potential autologous peripheral blood stem-cell transplantation. The effect of the regimen alone and in combination with granulocyte colony-stimulating factor (G-CSF, filgrastim [Neupogen]) support was evaluated.

**Patient Profiles**

Female patients between the ages of 18 and 75 years with measurable metastatic breast cancer were eligible for inclusion into the study. Prior treatment using adjuvant and/or neoadjuvant chemotherapy without anthracyclines and hormonal therapy at the adjuvant and/or metastatic stage were permitted. Patients had to have normal cardiac function on multiple gated acquisition scan, normal visceral status (as determined by liver status), and Karnofsky index performance status over 60%.

**Treatment Regimen**

**Group 1**

In the first group, patients received 75 mg/m² of docetaxel, 50 mg/m² of doxorubicin, and 500 mg/m² of cyclophosphamide as 1 course every 3 weeks (Figure 1). Cyclophosphamide was administered...
first, followed by doxorubicin, and then docetaxel as a 1-hour infusion beginning 1 hour after doxorubicin. All patients received steroid premedication for 3 days before chemotherapy. Patients received a total of 8 courses of the regimen.

**Group 2**

In the second group, patients received 4 to 6 courses of docetaxel/doxorubicin/cyclophosphamide as induction chemotherapy, followed by a course of high-dose chemotherapy and autologous peripheral blood stem-cell transplantation.

Patients were administered 2 to 4 courses of the docetaxel/doxorubicin/cyclophosphamide regimen initially to obtain a major response and were then split into 2 subgroups. Each subgroup received an additional 2 courses of the regimen with cell sampling 3 times a week; ie, harvest of peripheral blood stem cells and determination of stem-cell kinetics (granulocyte-macrophage colony-forming units [GM-CFU] and CD34+ cells). One subgroup received additional G-CSF after high-dose chemotherapy, and the other subgroup did not (Figure 1). High-dose chemotherapy consisted of 64 mg/m² of mitoxantrone, 6 g/m² of cyclophosphamide, and 85 to 105 mg/m² of vinorelbine, administered over 4 days. The phase I program for this regimen increased the vinorelbine dosage from 45 to 95 mg/m², infused over 96 hours, and found a maximum tolerated dose of 85 mg/m².[5]

**Results**

**Patient Characteristics**

Over a 6-month period, 42 patients were enrolled. Their mean age was 52 years (range, 43 to 70 years). Seven patients (25%) had received prior adjuvant chemotherapy with cyclophosphamide, methotrexate, and fluorouracil (5-FU). None had received anthracycline chemotherapy. The sites of metastases were mostly visceral: 18 patients (64%) had visceral metastases, 15 (54%) had bone metastases, and 11 patients (39%) had more than three metastatic sites. The majority of the patients were functioning well: 26 (92%) had a Karnofsky index over 80% before treatment.

Of the patients receiving docetaxel/doxorubicin/cyclophosphamide, 28 were evaluable for toxicity and response. These patients had received a total of 165 courses, 149 of which were evaluable, for an average of 5.3 courses per patient. Some of the patients had not had the full regimen of courses, and the results presented here are preliminary.

**Efficacy**

The major response rate was 82%, with five (18%) complete responses and 18 (64.0%) partial responses. Another five patients (18%) had stable disease, and no patient had disease progression.

**Toxicity**

The most frequent hematologic toxicity was neutropenia. No anemia or thrombocytopenia was observed. Grades 1 and 2 neutropenia occurred in two patients (7.1%), and grade 3 occurred in 26 patients (92.8%). In 24 patients (85.7%), neutropenia progressed to grade 4. Neutropenia occurred early, generally lasting less than 7 days, with a low incidence of fever. Nine patients (32%) had febrile neutropenia, but none developed an infection. Oral ciprofloxacin (500 mg twice daily) was administered from days 5 to 15 in 137 of the 149 evaluable courses. Table 1 describes the cumulative incidence of neutropenia in the evaluable courses.

Nonhematologic adverse events were not severe, with no grade 4 toxicity and only 9 courses with grade 3 toxicity, none clinically significant. The most common events were fatigue, pain, and vomiting (Table 2). There were no significant problems with fluid retention at this dosage of docetaxel.

Multiple-gated acquisition scans were performed every other course. In only 1 of the 28 patients (3.6%), left-ventricular ejection fraction fell more than 10%. There was no clinically significant cardiotoxicity and no cardiac failure.

**Discussion**

These results, although preliminary, demonstrate a lack of clinically significant cardiotoxicity compared with that seen with the combination of paclitaxel and an anthracycline.[1] The high response rate and low incidence of toxicity justify additional trials of the docetaxel/doxorubicin/cyclophosphamide regimen as adjuvant therapy. Historical comparison of this regimen with 5-FU/doxorubicin/cyclophosphamide and 5 mg/kg of G-CSF shows that the former provides better priming.[5]

**References:**

1. Gianni L, Capri G, Tarenzi E, et al: Efficacy and cardiac effects of 3-h paclitaxel (P) plus bolus...


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