Paclitaxel and Epirubicin as First-Line Therapy for Patients With Metastatic Breast Cancer

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Paclitaxel (Taxol) has aroused considerable interest for its high single-agent activity in breast cancer and novel mechanism of action. Epirubicin (Farmorubicin), the 4'epimer of doxorubicin (Adriamycin), also has high activity in

Introduction

Paclitaxel (Taxol) is a taxane known for its high activity in breast and ovarian cancer.[1] Its effectiveness in breast cancer was originally observed by Holmes et al[2] and Reichman et al[3] whose impressive study results indicated that paclitaxel has a high degree of activity compared with other standard chemotherapies for metastatic breast cancer, as well as significant activity in patients who had received multiple prior chemotherapies. In addition, these investigators' studies showed that clinical resistance to doxorubicin (Adriamycin) does not predict resistance to paclitaxel. These results motivated evaluation of a combination of paclitaxel and anthracyclines, which are the other most active drugs available for treatment of metastatic breast cancer. Holmes et al[4] performed a phase I trial using paclitaxel given by 24-hour intravenous infusion, followed by doxorubicin by 48-hour continuous infusion. The dose-limiting toxicity of that trial was mucositis, which occurred with relatively low doses of both substances. Sledge et al[5] repored a phase I study using the same regimen, but the reverse sequence: the doxorubicin infusion was followed after 4 hours by the 24-hour paclitaxel infusion. The rate of severe mucositis developing with this schedule was very low. The maximum tolerated doses identified were doxorubicin 50 mg/m² and paclitaxel 150 mg/m². In other studies, Dombernowsky et al[6] and Gianni et al[7] reported high response rates (94%) in patients with previously untreated metastatic breast cancer treated with paclitaxel combined with doxorubicin. In those studies, paclitaxel was given as a 3-hour infusion. The main toxicities encountered were neutropenia and febrile neutropenia, and both studies described severe cardiac toxicities in 15% to 25% of patients.

Epirubicin (Farmorubicin), the 4'epimer of doxorubicin, is equieffective but less toxic than its parent compound, particularly with respect to cardiac toxicity.[8] Medline search recalled eight trials in which patients with metastatic breast cancer were comparatively treated with doxorubicin vs epirubicin.[9-17] This phase II study was therefore designed to evaluate the safety and feasibility of the combination paclitaxel/epirubicin, with particular emphasis on cardiac side effects.

Patients and Methods

Only patients with histologically proven breast cancer were recruited for this trial. Eligible patients were permitted to have undergone one adjuvant chemotherapy or hormone therapy course or one palliative hormone therapy course. The adjuvant therapy could have included anthracyclines dosed to 300 mg/m². Other eligibility requirements included measurable metastasis and normal hematologic, renal, and hepatic function. Patients also were required to be between 18 and 70 years of age and to have a life expectancy of more than 12 weeks.

The first 57 patients entered (Group A) were treated with epirubicin 60 mg/m² intravenously, given as a 1-hour infusion, followed by paclitaxel 175 mg/m² intravenously over 3 hours. The next 28 patients entered (Group B) received epirubicin 90 mg/m² intravenously over 1 hour, followed by the same starting dose and regimen of paclitaxel as was given to Group A. All patients were premedicated with dexamethasone 20 mg given orally 12 and 6 hours before paclitaxel, and clemastine (Tavist) 2 mg intravenously and ranitidine (Zantac) 50 mg intravenously 30 minutes prior...
to paclitaxel. Patients with congestive heart failure were not eligible for the study.

**Study Design**

Cardiac monitoring involved evaluation of left ventricular ejection fraction after every second cycle. Paclitaxel dose escalation was permitted in 25 mg/m² steps to a maximum of 225 mg/m², assuming a neutrophil nadir of 1 or more x 10⁹/L, a thrombocyte nadir of 100 or more x 10⁹/L, and peripheral neuropathy lower than grade 2, without granulocyte colony-stimulating factor support. In case of higher grades, the paclitaxel dose could be reduced to 100 mg/m², again in 25 mg/m² steps.

**Results**

Of 57 and 28 patients enrolled in Groups A and B, respectively, 43 patients in Group A and 25 patients in Group B were evaluable for response and toxicity. The median age of patients entered in study groups A and B was 51 and 55 years, respectively, and the median Eastern Cooperative Oncology Group performance index for all patients was 0. The majority of entered patients were postmenopausal (Group A, 62%; Group B, 76%), and most had poorly differentiated tumors (Group A, 63%; Group B, 74%). Adjuvant chemotherapy had been administered to 51% of patients in Group A and 36% of patients in Group B. Nearly 20% of patients had primary metastatic breast cancer with a large tumor at the primary site. The localization of metastases is summarized in Table 1. More than 80% of the patients had two or more lesions (Table 2).

**Toxicity**

The main toxicity encountered was neutropenia. No febrile episodes occurred in Group A, but there were two episodes in Group B. World Health Organization grade 3 or 4 neutropenia was reported in 80.9% of the courses overall. Thrombocytopenia and anemia were observed in less than 1% of the courses (Table 3). Alopecia was observed in all patients treated with more than two cycles. No peripheral neuropathy World Health Organization grade greater than 2 was reported and myalgia World Health Organization grade 3 was noted in only 1% of cycles. Severe nausea and emesis were observed in 2% of the cycles (Table 4). No incidence of mucositis was described. To date, no cardiac toxicity has been seen. The left ventricular ejection fraction was checked by echocardiography or cardiac scintigraphy in Group A, but one episode without clinical signs occurred in Group B.

**Dose Escalation**

In 15 patients from Group A we were able to escalate the paclitaxel dose to 200 mg/m² and in seven of these patients further escalation to 225 mg/m² was possible. In Group B, only one patient could be escalated to 200 mg/m² and no patient was escalated to 225 mg/m². In Group A, severe neutropenia necessitated reduction of the paclitaxel dose to 135 mg/m² in 11 patients, and further to 110 mg/m² in four of them. In Group B, three patients required dose reduction to 135 mg/m².

**Response**

Response rate was not a primary concern of this study, but it is one of the checkpoints of oncology treatment. In this poor-prognosis study group we achieved an overall response rate of 68% in Group A and 71% in Group B (Table 5). In 50% of patients who attained a remission, response occurred after the second cycle of treatment, while 25% of the patients had their best response after the fourth cycle, and 25% after the sixth cycle. The median follow-up was 14.1 months in Group A and 8.2 months in Group B. The median progression-free interval was 8.2 months in both groups with a range of 5.3 to 11.3 months in Group A and 7.90 to 8.5 months in Group B. For patients in Group A, the median progression-free interval was 12.5 months (95% confidence interval [CI], 9.7 to 15.3) for those attaining a complete response and 8.1 months (95% CI 6.7 to 10.3) for those with a partial response. In Group B, the median progression-free interval for the patients with a complete response has not been reached, but patients with a partial response had an interval of 8.2 months (95% CI, 7.8 to 8.5). The median overall survival for those in Group A was 15.9 months (95% CI, 12.8 to 19), whereas in Group B the median survival has not been reached.

**Discussion**

The combination of paclitaxel 175 mg/m² and epirubicin 60 or 90 mg/m² showed remarkable efficacy against metastatic breast cancer with an overall response of 68% in the group treated with epirubicin 60 mg/m² and 71% in those treated with epirubicin 90 mg/m². The treatment was generally well tolerated, although the higher epirubicin dose induced more severe neutropenia and one case of cardiotoxicity. The nonhematologic toxicities were mild and no cases of severe mucositis...
or peripheral neuropathy were reported. The higher epirubicin dose did not prolong progression-free survival. The observed remission rates were lower than those reported in the study from Gianni et al,[7] but the progression-free interval was in the same range.

In October 1996, the German AGO Study Group initiated a phase III trial comparing the combination of paclitaxel 175 mg/m² and epirubicin 60 mg/m² with the standard combination of epirubicin 60 mg/m² and cyclophosphamide (Cytoxan) 600 mg/m² as first-line treatment of metastatic breast cancer.

**References:**


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