Paclitaxel Plus Epirubicin in Advanced Breast Cancer

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This phase I-II study aimed to determine the maximum tolerated dose (MTD) of paclitaxel (Taxol), infused over 3 hours, when combined with a fixed dose (90 mg/m²) of epirubicin. Other aims were to investigate the combination’s

Paclitaxel (Taxol), an antitubulin agent with a unique mechanism of action, is a highly active drug when used as first- or second-line therapy in the treatment of advanced breast cancer.[1] Moreover, it produces response rates of 20% to 40% in patients who have not responded to prior anthracycline therapy.[2,3] As a result of the high level of activity and incomplete cross-resistance in vivo, several attempts have been made to combine paclitaxel and anthracyclines.[4]

The combination of doxorubicin with paclitaxel, when given as a prolonged infusion, is complicated by schedule- and sequence-dependent toxicities, pharmacokinetic and/or pharmacodynamic interactions, and possible subadditive activity.[5,6] The combination of doxorubicin with a 3-hour infusion of paclitaxel has demonstrated extremely high activity, but initially had a high incidence of cardiotoxic events.[7,8a] It was then showed that by limiting the cumulative dose of doxorubicin to 360 mg/m² or administering the two drugs with a more prolonged interval, the cardiac toxicity of the combination was limited to an incidence of 5%.[8b,8c].

In an attempt to maintain cytotoxic activity and reduce cardiotoxicity, we performed a phase I-II study of paclitaxel, infused over 3 hours, plus epirubicin,[9] an anthracycline analog that is as active as doxorubicin with reduced cardiotoxicity.[10] The objectives of this study were to:

1. Define the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of paclitaxel, given over 3 hours, combined with a fixed dose of epirubicin;
2. Investigate the pharmacokinetics of the combination of paclitaxel and epirubicin;
3. Evaluate the activity and the toxicities of this combination in previously untreated metastatic breast cancer patients; and
4. Investigate the ability of this regimen plus granulocyte colony-stimulating factor (G-CSF, filgrastim) or granulocyte-macrophage colony-stimulating factor (GM-CSF, sargramostim) to mobilize peripheral blood stem cells (PBSCs).

Phase I Study

Patients with histologically confirmed breast cancer and metastatic disease with at least one bidimensionally measurable lesion were eligible for the study. They could have undergone prior adjuvant therapy if it had been stopped at least 6 months before study entry. Patients who had received adjuvant anthracycline-based therapy were included if the total cumulative dose of doxorubicin or epirubicin was less than 180 or 360 mg/m², respectively.

Epirubicin was administered as an IV bolus at a fixed dose of 90 mg/m² before the 3-hour infusion of paclitaxel. The initial dose of paclitaxel was 135 mg/m² and was increased by 20-mg/m² steps in subsequent cohorts of three patients until dose-limiting toxicity occurred. Either a standard or rapid IV premedication schedule for paclitaxel was administered.[11] Courses were repeated every 3 weeks.

Dose-limiting toxicity was defined, according to the World Health Organization (WHO) criteria,[12] by the occurrence of one of the following: absolute neutrophil count (ANC) < 500/µL for more than 7 days; ANC < 100/µL for more than 3 days; febrile neutropenia (ANC < 500/µL and fever > 38°C); grade 4 thrombocytopenia; failure to recover to neutrophils >1,500/µL and/or platelets >100,000/µL by day 28; and/or any grade 3 nonhematologic toxicity (except nausea, vomiting, and alopecia). Maximum tolerated dose was defined as the next lower dose than that causing dose-limiting toxicities during the first two courses in at least two of six patients. Filgrastim was not used
prophylactically.
A total of 32 patients entered this phase of the study. The most frequent toxicity was transient neutropenia. The dose-limiting toxicity of the combination was febrile neutropenia occurring in two of eight patients who received 225 mg/m² of paclitaxel. Therefore, the maximum tolerated dose and recommended dose for phase II of the study was epirubicin, 90 mg/m², plus paclitaxel, 200 mg/m².

**Phase II Study**

An additional 18 patients with metastatic breast cancer received epirubicin, 90 mg/m², plus paclitaxel, 200 mg/m². The most frequent toxicity in this phase was grade 4 neutropenia, which occurred during 49% of the courses; febrile neutropenia was observed in 22% of patients. Nonhematologic toxicity was mild. Grade 3 cardiotoxicity occurred in only 6% of the patients and was reversible with appropriate therapy.

**Phase I-II Study Efficacy Results**

Overall, 50 patients were included in this phase I-II study, 49 of whom were evaluable for response. The overall response rate was 84% (95% confidence interval [CI], 70% to 92%); 9 patients (19%) had a complete response and 32 a partial response (65%). Response rates did not differ between patients who received ≤ 175 mg/m² of paclitaxel and those given > 175 mg/m². The median duration of response in partial responders was 10 months (range, 3 to 27+ months).

At a median follow-up of 14 months (including the nine complete responders), 19 of 49 patients were progression-free and 33 of 50 were alive. [13]

**Pharmacokinetic Study**

Blood samples for measurement of plasma levels of paclitaxel, epirubicin, and its major metabolite epirubicinol were obtained at cycle 1 from at least two patients per dose level of paclitaxel, from 175 to 225 mg/m². Blood samples were obtained from the antecubital vein opposite to the site of drug injection at baseline; 15, 30, and 45 minutes after drug administration; and 1, 2, 3, 4, 6, 8, 12, 18, and 24 hours thereafter. Measurements of plasma epirubicin, epirubicinol, and paclitaxel concentrations were performed using reversed-phase high-performance liquid chromatography. Pharmacokinetic analysis was performed by nonlinear least-square regression modeling. [14,15] The following plasma pharmacokinetic parameters were calculated: maximum concentration (Cmax), time to Cmax (Tmax), elimination half-life (t1/2), area under the concentration-time curve (AUC), volume of distribution (Vd), and systemic clearance (Cl). Plasma concentrations of paclitaxel, epirubicin, and epirubicinol were available in patients treated with 175 mg/m² (N = 2), 200 mg/m² (N = 5), and 225 mg/m² (N = 4) of paclitaxel.

**Results**

Mean peak plasma concentrations of paclitaxel were 5.1, 5.7, and 6.2 µM at doses of 175, 200, and 225 mg/m², respectively. Distribution t1/2 values for the three doses were 0.46, 0.63, and 0.76 hours, respectively, whereas elimination t1/2 values were 2.6, 6.8, and 8.6 hours, respectively. The mean AUC (0-24h) values calculated from the concentration-time data were 20.4 µM/L × h at 175 mg/m² of paclitaxel, 22.2 µM/L × h at 200 mg/m², and 34.2 µM/L × h at 225 mg/m² of paclitaxel. Mean CI values were 13.9, 16.7, and 12.9 L/h for 175, 200, and 225 mg/m² of paclitaxel, respectively, whereas mean V values were 170.3, 133.5, and 122.8 L, respectively.

The Cmax values of epirubicin were 109.7 ± 1.1 ng/mL in patients receiving 175 mg/m² of paclitaxel, 99.1 ± 2.7 ng/mL in patients receiving 200 mg/m², and 114.1 ± 15.5 ng/mL in patients receiving 225 mg/m² of paclitaxel, with no significant differences among subjects. The T of epirubicin was reached at 3.45 ± 0.9 hours in all patients, and the concentration of this metabolite decreased from 47.3 ± 9.4 ng/mL in patients treated with 175 mg/m² of paclitaxel to 44.1 ± 11.2 ng/mL in those given 200 mg/m² and to 37.9 ± 7.5 ng/mL in those given 225 mg/m² of paclitaxel. These differences are not significant. The pharmacokinetic data of paclitaxel, in particular, the time above the threshold level of 0.05 µM, were not significantly related to myelosuppression.

**Induction/Mobilization Phase**

After two to eight courses of cytoreductive chemotherapy, 21 patients received an additional course of chemotherapy followed by recombinant human G-CSF (filgrastim [Neupogen]) or recombinant human granulocyte-macrophage CSF (sargramostim [Leukine, Prokine] to mobilize PBSCs. Filgrastim or sargramostim were given at a dose of 5 mg/kg/day from day +1 until the last leukapheresis or the white blood cell (WBC) count was > 50 × 10/L. The analysis of hematopoietic progenitors was
performed on peripheral blood in all patients and on leukapheresis products in patients who underwent apheresis. From day +6 to day +16, a sample of peripheral blood was collected daily from each patient. A sample of each apheresis product was also collected. Total and differential WBC counts and an analysis for CD34 and CD33 antigen expression were performed on each peripheral blood sample. Cell surface immunophenotyping of PBSCs (by flow cytometry using direct immunofluorescence) was done on the product of leukapheresis.

**Results**

Mobilization of CD34+ cells was assessed by leukapheresis starting from day +6. The median peak of circulating CD34+ cells occurred on day +11 (range, day +9 to day +16) and the median number of CD34+ cells at peak was 69.5 cells/mL (range, 1.4 to 251 cells/mL). The peak of circulating CD34+/CD33 cells occurred on day +11 (range, day +8 to day +16) and their median number was 14.3 cells/mL (range, 1.74 to 195 cells/mL).

In the group of patients who received fewer than six courses of induction chemotherapy before mobilization, the peak of CD34+ cells in peripheral blood occurred on day +11 (range, day +9 to day +13) and the median number of CD34+ cells at peak was 106.7 cells/mL (range, 2.26 to 251 cells/mL). Patients who were more heavily pretreated before mobilization (six or more courses) showed a significantly lower number of CD34+ cells at peak (median, 7.3 cells/mL; range, 1.41 to 64.7 cells/mL), as well as a significantly longer time to reach peak number (median, day +14; range, day +11 to day +16), as compared with those who received fewer courses of induction therapy (both comparisons, \( P = .02 \)).

The mean number of cells collected per apheresis procedure were: \( 2.7 \times 10^8 \) of mononuclear leukocytes/kg (range, 0.15 to 13.5 \( \times \) 10 cells/kg), \( 6.3 \times 10^6 \) of CD34+ cells/kg (range, 0.52 to 20.4 \( \times \) 10 cells/kg), \( 2.0 \times 10^6 \) of CD34+/33 cells/kg (range, 0.8 to 11 \( \times \) 10 cells/kg), and \( 0.18 \times 10^6 \) CD34+/CD38 cells/kg (range, 0 to 44 \( \times \) 10 cells/kg). A target level of \( 2.0 \times 10^6 \) CD34+ cells/kg was achieved with two apheresis procedures in 90% of the patients and with a single apheresis in 70%.[16]

**Discussion**

**Tolerability**

In the dose-finding phase of this study, the maximum tolerated dose of paclitaxel administered over 3 hours with 90 mg/m² of bolus epirubicin was 200 mg/m². At these doses, the combination was administered for a median of six courses to 26 patients, with grade 4 neutropenia occurring during 49% of the courses. However, the incidence of febrile neutropenia was extremely low (6/170; 4% of courses) due to the lack of mucositis and the limited duration of severe neutropenia (median, 4 days). Interestingly, filgrastim was able to shorten neutropenia only in patients treated at the 225-mg/m² dose (median duration of neutropenia, 2 days with filgrastim vs 4 days without; \( P < .009 \)).

Myelotoxicity was not cumulative, and nonhematologic toxicity was usually mild or moderate. Therefore, the drugs were given at the planned doses and scheduled intervals in 89% of the courses. The tolerability of the regimen at these doses is important. A dose-response effect has clearly been demonstrated for epirubicin in three randomized studies[17-19] and has been suggested for paclitaxel in one large randomized trial.[20]

Investigators who have studied the combination of doxorubicin and paclitaxel have reported an 18% to 20% incidence of heart failure, with 50% of patients showing a reduction in left-ventricular ejection fraction below normal levels.[7,8] The dose-dependent cardiomyopathy of epirubicin occurs at higher cumulative doses than that seen after doxorubicin. The incidence of cardiotoxicity is about 3% in patients given 900 mg/m2 of epirubicin, increasing to approximately 10% at 1,000 mg/m2.[10,21]

In our study the incidence of cardiotoxic events was even lower than expected. Only 6% of the patients experienced reversible congestive heart failure, despite the fact that 15 patients had received anthracyclines previously and 22 had undergone prior radiotherapy to the chest.

**Pharmacokinetics**

Pharmacokinetic data from the study suggest that, when epirubicin is administered together with paclitaxel, there is a sudden rebound of plasma levels of epirubicinol soon after the paclitaxel infusion is begun, whereas an increase in paclitaxel dose is associated with a reduction in plasma epirubicinol levels. This opposite behavior of plasma epirubicinol levels[jie, an increase after the start of paclitaxel and a decrease when paclitaxel dose is increasing] may depend on the inhibition of
renal clearance of epirubicinol by paclitaxel and its inhibition of the aldoketo reductase system. The presence of a significant interaction between paclitaxel and anthracyclines has been previously shown by Berg et al,[22] who documented a significant increase in steady-state plasma doxorubicinol concentration in patients treated with paclitaxel and doxorubicin given in combination by continuous 72-hour infusion. In addition, Holmes et al[23] demonstrated a significant reduction in doxorubicin clearance when the anthracycline was preceded by paclitaxel. The mechanism underlying these differences is unclear, although it may be explained by the different schedules and doses of each drug.[24]

The clinical relevance of this finding remains to be elucidated. However, the possible reduction in epirubicinol production by increasing the paclitaxel dose may be a positive finding, as the reduced metabolites of anthracyclines are less active than the parent compounds and, at least in the case of doxorubicin, the hydroxylated metabolite has been shown to cause more cardiotoxicity than doxorubicin.[25]

In this study, we did not observe a clear relationship between the pharmacokinetic data of paclitaxel and myelosuppression. In particular, we found no significant correlation between the time at which plasma levels were above the threshold value of 0.05 µM and the severity of myelosuppression, as was previously reported in a study using the sigmoidal maximum effect analysis.[15] This finding indicates that the presence of epirubicin in the combination treatment produces a substantial change in the pharmacodynamic effect of paclitaxel, which cannot be predicted from the pharmacokinetic data of paclitaxel alone.

Mobilization of PBSCs

Moreover, our data suggest that epirubicin plus paclitaxel in combination with hematopoietic growth factors mobilize circulating hematopoietic progenitors to produce rapid, complete hematopoietic recovery after a myeloablative treatment. The best mobilization is achieved when the procedure is performed early in the induction phase. Eighty percent of the best responses to epirubicin plus paclitaxel were achieved within four courses of treatment. Therefore, the optimal strategy may be induction chemotherapy with four courses of this regimen followed by high-dose chemotherapy plus hematopoietic support.

Antitumor Activity

The overall response rate in this phase I/II study was significant, with 84% of the patients achieving an objective response. This level of activity is superior to that reported with epirubicin at 90 mg/m²[10] or paclitaxel at 135 to 250 mg/m² over 3 hours[26,20] in patients with characteristics similar to our study population. The low cardiotoxicity of the combination has been confirmed by two other studies in which epirubicin was administered at lower doses with reduced antitumor activity.[27,28] Despite the high activity observed in our study, the complete response rate was in the range of rates reported with more conventional regimens.

In studies by Gianni et al[7] and Gehl et al,[8] the combination of doxorubicin and paclitaxel was associated with a complete response rate of 24% to 41%. However, in these two studies, 56 of 65 patients were chemotherapy-naive and only 9 patients had received prior hormonal therapy. In contrast, in the current study population 35 of 50 patients had failed prior adjuvant chemotherapy with anthracyclines in 15 cases) and 27 had progressed after hormonal therapy. These pretreatment characteristics are sufficient to explain the significantly lower complete response rate observed in our study.[2]

Conclusions

The present study shows that epirubicin, 90 mg/m², can be safely given in combination with paclitaxel, 200 mg/m² infused over 3 hours. The dose-limiting toxicity of this regimen is febrile neutropenia, whereas mucositis and typhlitis, which have been reported with doxorubicin-paclitaxel combinations,[17-19] are very rare. The incidence of cardiotoxicity is low, allowing for prolonged treatment even in patients who have proved unresponsive to adjuvant anthracycline.

The pharmacokinetics of paclitaxel are not modified by the administration of epirubicin. On the contrary, the metabolism of epirubicin is affected by paclitaxel; specifically, epirubicinol levels decrease when the dose of paclitaxel is increased. Moreover, the presence of epirubicin is likely to change the pharmacodynamic effects of paclitaxel on bone-marrow progenitors. For these reasons, we believe that further studies are needed to optimize the antitumor cytotoxicity of epirubicin and paclitaxel. We have begun a randomized trial comparing the combination of the two drugs with four courses of epirubicin followed by four courses of paclitaxel.
References:


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