Paclitaxel Plus Doxorubicin in Metastatic Breast Ca: The Milan Experience

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A pilot study conducted at the National Cancer Institute in Milan, Italy assessed the efficacy of six or eight cycles of paclitaxel (Taxol) 200 mg/m² q3wks plus doxorubicin (Adriamycin) (60 mg/m² q3wks) in 49 women with metastatic breast cancer. Because of the high therapeutic potential of paclitaxel (Taxol) and doxorubicin (Adriamycin) in women with breast cancer, a series of studies evaluating the combination of the two drugs have been undertaken at the National Cancer Institute in Milan, Italy. Investigations aimed at establishing the optimal dosage regimen to maximize the combination’s therapeutic effectiveness and to minimize the cardiotoxicity associated with doxorubicin were particularly important.

**Dose-and Sequence-Finding Study**

The main objective of a dose- and sequence-finding study was to define a paclitaxel/doxorubicin combination that could be used as ambulatory treatment, taking advantage of the feasibility and safety of short-infusion paclitaxel, as indicated by the efficacy of premedication in preventing hypersensitivity reactions.[1] The study showed that tolerability did not depend on sequence, and that the combination was highly effective in women with metastatic breast cancer who had not received prior chemotherapy.[2] However, a high incidence (20%) of clinical cardiac toxicity, manifested by symptomatic but reversible congestive heart failure, raised concerns over potential drug-drug enhancement of toxicity. Although recent trials that prospectively evaluated cardiac function indicated that the adverse cardiac effects associated with doxorubicin occur at lower total doses of the anthracycline[3] than had been estimated from earlier retrospective studies,[4] concerns over toxicity enhancement prompted a reduction in the total dose of doxorubicin to 360 mg/m² for administration in combination with paclitaxel.[5]

**Paclitaxel and Doxorubicin in Anthracycline-Naive Patients**

Overall, we evaluated the effectiveness and tolerability of paclitaxel (200 mg/m² via 3-hour infusion q3wks) plus doxorubicin, 60 mg/m², given for six or eight cycles in 49 patients with metastatic breast cancer who had not received any previous chemotherapy and who were generally in good condition. Table 1 summarizes the baseline characteristics of these patients; Table 2 shows responses in the patients who received six cycles and in those given eight cycles. In this small pilot study, the response rates and numbers of complete responders were high in both groups (Table 2). However, it is important to note that attainment of a complete response requires an extended duration of treatment. All patients who responded began to do so by cycles 6 and 7 (Figure 1).

The level of complete response was increased if treatment was continued with paclitaxel alone after the last administration of doxorubicin in patients who had experienced a partial response. Indeed, the complete response rate increased from approximately 24% at the end of cycle 8 to 38% by cycle 14 in patients maintained on paclitaxel alone at a dose of 200 mg/m² infused over 3 hours. In this study, the reduction in the number of cycles of combination therapy reduced the risk of cardiotoxicity associated with doxorubicin (Figure 2). At a median follow-up of 24 months, the cumulative probability of having congestive heart failure was 24.6% in patients who had received a total of 480 mg/m² of doxorubicin with paclitaxel. However, the probability of cardiac symptoms was reduced to 4.6% in those patients who had received a maximum of 360 mg/m² of the anthracycline. Later analysis in more than 100 patients confirmed that the risk of cardiotoxicity is very low in patients who receive a cumulative dose of doxorubicin of < 360 mg/m².
Conclusions

The experience in Milan has demonstrated that the combination of paclitaxel and doxorubicin is highly effective in patients with previously untreated metastatic breast cancer. In addition, this experience has shown that cardiotoxicity can be minimized by ensuring that the cumulative dose of doxorubicin does not exceed 360 mg/m². This limit does not compromise the effectiveness of the combination. Moreover, by continuing therapy with paclitaxel as a single agent, the complete response rate can be increased.

Finally, analyses suggest that HER2 status is an important factor in defining a subset of patients with a higher probability of responding to the combination.[6] Such findings provide encouraging support for further large-scale, prospective studies to evaluate the benefits of paclitaxel and doxorubicin.

References:


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