Proffered papers

Breast cancer—treatment of advanced disease

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A MULTICENTER, RANDOMIZED STUDY OF TWO SCHEDULES OF PACLITAXEL (PTX) IN PATIENTS WITH ADVANCED BREAST CANCER (ABC)

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Bristol-Myers Squibb Taxol Study Group

Five hundred and twenty-one patients with ABC were randomized to receive PTX over 3-hr or 24-hr q 3 wks at an initial dose of 175 mg/m^2 (with escalation when possible). The pre-randomization strata were defined according to prior chemotherapy (CT): none, adjuvant CT only, CT for ABC. Two-thirds of the patients had prior anthracycline exposure; 24% of these were anthracycline resistant, i.e. progressing on or relapsing within 6 months of an anthracycline regimen.

The response rate was 29% in the 3-hr vs 32% in the 24-hr (P = 0.629). It was 28% in both arms among anthracycline pretreated patients. Among all patients, treatment over 24-hr resulted in a longer time to progression (TTP) (median 3.8 mos vs 4.6 mos: P = 0.021) and survival time (median 9.8 mos vs 13.4 mos; P = 0.021). This difference was not apparent after adjustment for prognostic factors, TTP: P = 0.081, survival: P = 0.099. Treatment was well tolerated as documented by the # of crs administered (median 6 (1–22+) vs 7 (1–21); $P < 0.01$). More patients in the 3-hr arm had their PTX dose escalated (65% in the 3-hr vs 33% in the 24-hr. $P < 0.001$), resulting in an increased dose intensity (62 vs 57 mg/m^2/wk; $P < 0.001$). The 2 treatment schedules were not equitoxic even after individual dose adjustments. The 24-hr infusion resulted in more severe hematologic (30% vs 79% grade IV neutropenia, $P < 0.001$; 1% vs 17% febrile neutropenia, $P < 0.001$), and GI toxicity (22% vs 45% mucositis, $P < 0.001$; 25% vs 41% diarrhea, $P < 0.001$). The 3-hr infusion with its higher dose intensity resulted in a higher incidence of peripheral neuropathy (78% vs 65%, P = 0.001). To evaluate the risk-benefit ratio associated with therapy, we retrospectively analyze the time to either progression or to clinically important adverse events (febrile neutropenia, severe hypersensitivity reaction, and severe neuropathy), and found no statistically significant difference between the two arms (median 3.3 mos vs 3.4 mos; P = 0.243).

In the palliative setting, the 24-hr infusion of PTX had some efficacy advantage, but did not result in a significant increase in patient benefit as compared to the 3-hr infusion. This trial confirms the activity of PTX in the treatment of ABC pts, including anthracycline pretreated patients.

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TAXOL OR DOXORUBICIN AS FIRST LINE CHEMOTHERAPY IN ADVANCED BREAST CANCER (ABC). A PROSPECTIVE RANDOMIZED PHASE II STUDY WITH CROSSOVER

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EORTC-Breast Cancer Cooperative Group (IDBBC)

This study investigates the efficacy and safety of Taxol (T) (200 mg/m^2 over 3 h, 3-weekly) or Doxorubicin (D) (75 mg/m^2, 3-weekly) given as first-line chemotherapy (CT) for ABC, with a crossover upon progression. Until now, a total of 185 pts (T:91, D:94) have been randomized and data have been received for 106. Pretreatment characteristics were well balanced between the two groups. The following table summaries the toxicities according to the CTC Toxicity Scale encountered in both arms before crossover.

	Taxol (n = 51)	Doxorubicin (n = 55)
Neutropenia gr 4	35%	78%
Febrile Neutropenia	4%	13%
Vomiting gr 3–4	4%	18%
Stomatitis gr 3–4	0%	13%
Sensory Neurotoxicity gr 2–3	22%	0%
Delays in Drug Administration (% of cycles)	5%	19%

Possible hypersensitivity reactions (Weiss R.B. JCO Vol. 8: 1263–68) were seen in 2 of 236 Taxol cycles. This analysis shows that Taxol 200 mg/m^2 over 3-hours is well tolerated in comparison to Doxorubicin 75 mg/m^2 for the same population of patients. Accrual is planned to be completed by May 1995 (total of 240 pts). At the time of the meeting, further toxicity data will be presented.

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STEROIDS DO REDUCE THE SEVERITY AND DELAY THE ONSET OF DOCETAXEL (DXT) INDUCED FLUID RETENTION: FINAL RESULTS OF A RANDOMIZED TRIAL OF THE EORTC INVESTIGATIONAL DRUG BRANCH FOR BREAST CANCER (IDBBC)

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We have conducted a phase II trial of DXT (Taxotere, RP56976) (50 mg/m^2 day 1 + 8 q3wks) in 83 patients (pts) who had received one prior chemotherapy regimen for metastatic disease. Pts have been randomized between prophylactic oral antihistamines with (arm A) or without (arm B) methylprednisolone (40 mg d −1. 0, + 1, 7, 8, 9 of each course). Among 82 pts considered evaluable for toxicity, the following manifestations of fluid retention were seen:

Toxicity	Arm A (n = 41)	Arm B (n = 41)	p-value (Log-rank test)
Edema - Any	39%	54%	
- Severe	5%	5%	
Median dose to onset (mg/m^2)	550	296	P = 0.003
Pleural effusion - Any	44%	49%	
- Severe	5%	15%	
Median dose to onset (mg/m^2)	571	296	P = 0.006
Overall fluid retention:			
Median dose to onset (mg/m^2)	423	297	P = 0.0017
Median number of cycles (range)	6 (1–12)	5 (1–11)	
Treatment discontinuation	5%	32%	P = 0.0032

Steroids significantly decrease the risk of edema and of pleural effusion, estimated as a function of the cumulative dose of DXT by the Kaplan-Meier method. The overall response rate following external review is 33.7% and the median response duration is 238 days (95% CI: 190–293) with no difference between the 2 arms. We conclude that there is a learning curve in the management of the side effects of this new active agent for breast cancer.

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A PHASE II TRIAL OF DOCETAXEL IN PATIENTS (PTS) WITH ANTHRACYCLINE RESISTANT (AR) METASTATIC BREAST CANCER (MBC)

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51 females pts with AR MBC were treated with docetaxel (Taxotere®) at 100 mg/m^2 as a 1-hour IV infusion every 3 week (wks). Oral steroids