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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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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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

and antihistamines were given prior to docetaxel. AR was represented as follows: 5 pts has a metastatic relapse while on adjuvant, 25 pts had a progression as their best response in advance disease and 19 pts had stable disease after 4 cycles first line CT (16 pts had PD during anthracycline, 3 pts progressed off treatment); 2 pts were not AR. Median (med) age = 47 years (27–72), WHO PS: 0–1 = 88%, 41% of pts had >2 organs involved, 67% had visceral involvement (liver: 43%). 38 pts were eligible and evaluable. The response rate (RR) in intent-to-treat analysis was 29.4%, 15 PRs (31.6% in evaluable pts). RR in pts with >2 organs involved = 44% with visceral involvement = 26%. Med duration of response = 24 wks (12+–33), med survival time = 10 months (0.2–11+). 258 cycles were given (med = 5, range = 1–12); relative dose intensity = 0.95 (0.66–1.02). Main toxicities (NCI grade): AGC gr 4 = 49 pts (81% of cycles) (med duration = 7 days); febrile neutropenia = 7% of cycles; neurosensory in 33 pts (only 3 pts gr 3, no gr 4), skin reaction in 19 pts (gr 3 = 2 pts: gr 4 = 1 pt), fluid retention (FR) in 30 pts (no severe cases; med cumulative dose to onset of FR = 400 mg/m^2 (100–1200+). Docetaxel is active in pts with AR MBC. Oral premeditation with steroids appears to reduce both the incidence and severity of FR and skin toxicities.

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HIGH DOSE CHEMOTHERAPY WITH HEMATOPOETIC RESCUE AS PRIMARY TREATMENT FOR METASTATIC BREAST CANCER: A RANDOMISED TRIAL

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Ninety patients were entered into a study comparing 2 cycles of high dose CNV (cyclophosphamide 2.4 g/m^2 + mitoxantrone 35–45 mg/m^2 + VP16 2.5 g/m^2) to 6–8 cycles of conventional dose CNV (cyclophosphamide 600 mg/m^2 + Mitoxantrone 12 mg/m^2 + vincristine 1.4 g/m^2) as first line treatment for metastatic breast cancer. The high dose regimen included either autologous bone marrow or peripheral stem cell rescue. All 90 patients are evaluable. The response rates were significantly different. Overall response for high dose CNV was 43/45 (95%) with 23/45 (51%) achieving CR. 24/45 (53%) patients receiving conventional dose CNV have responded with only 2 patients achieving CR. Both duration of response as well as duration of survival was significantly longer for the patients receiving HD-CNV. Toxicity of the high dose therapy was moderate in most patients. Grade 2–3 mucositis and hematologic suppression requiring supportive treatment was universal, but hematologic recovery to neutrophils >500 and Platelets >40,000 occurred at day 18 (median) after therapy.

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EFFICACY OF PAMIDRONATE ON SKELETAL COMPLICATIONS FROM BREAST CANCER METASTASES. A PROSPECTIVE RANDOMIZED DOUBLE BLIND PLACEBO CONTROLLED TRIAL

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Women with skeletal metastases from breast cancer were treated by pamidronate 60 mg iv. q 4 w or saline at the same interval in a double blind placebo controlled randomized study.

Patients were recruited at 27 institutions in Sweden and Norway from November 90 to September 93. Specific antitumor treatment, endocrine and/or cytotoxic, was individually chosen at the discretion of the physician.

Endpoints of the study were the incidence of skeletal-related symptoms i.e. increased pain, hypercalcemia, fractures and paresis due to vertebral metastases as well as the incidence of palliative measures indicated by the skeletal complications, i.e. osteosynthesis, radiotherapy and laminectomy. Changes in antitumor therapy were recorded as well as analgetic medication. Quality of life related to pain parameters as recorded by the patients were analysed.

Recordings of these parameters were made every third month up to 24 months, when the patients left the study without uncoding the study medication. At present the code is not broken and treatment will be referred to as arm A and B.

Results: Four hundred and one patients were recruited with a mean age of 59 and 60 years in the A and B groups respectively. Other pretreatment parameters were well balanced.

The number of patients in file study over time was not significantly different between the two arms. The cumulated incidence of symptoms of skeletal progression as well as survival without symptoms of skeletal progression was significantly different between the two treatment groups. The median time for symptoms of skeletal progression was 9 and 14 months respectively. No difference was found in the incidence of fractures nor need of palliative radiotherapy. The incidence of changed baseline antitumor therapy was not different.

Conclusion: In a large randomized double blind placebo controlled trial on the efficacy of pamidronate 60 mg iv. q 4 weeks differences were found in the progression of skeletal symptoms, though not in the need for palliative radio therapy nor for changes in base-line antitumor treatment. The two treatment arms, still blinded, will be uncoded at the time of presentation of the study.

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TWO RANDOMISED TRIALS ESTABLISHING EFFICACY AND TOLERABILITY OF ARIMIDEX (ZD1033) IN THE TREATMENT OF POSTMENOPAUSAL WOMEN WITH ADVANCED BREAST CANCER (PABC)

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'ARIMIDEX' (A) is a new potent and highly selective aromatase inhibitor with a pharmacokinetic profile allowing once daily oral administration. Two randomised trials compared (A) to megestrol acetate (MA) as first-line or second-line treatment of PABC after relapse on prior adjuvant or advanced disease treatment. Between 3/93 and 6/94, pts were randomised to (A) 1 mg (263 pts), (A) 10 mg (248 pts) or (MA) 160 mg (253 pts). The 3 groups were comparable in regards to their main baseline characteristics. The response rate for the two trials (CR + PR + SD ≥6 months) was 35% for (A) 1 mg, 32% for (A) 10 mg and 33% for (MA), with no differences in time to progression. Patients on (MA) had significantly higher incidence of adverse events (AE) of weight gain (12%).

Withdrawal rate due to (AE) was 3% for (A) 1 and 10 mg and 4% for (MA). 'ARIMIDEX' is a new effective and well tolerated treatment for PABC.

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AN OPEN, COMPARATIVE RANDOMIZED TRIAL COMPARING FORMESTANE VS ORAL MEGESTROL ACETATE AS A SECOND-LINE THERAPY IN POSTMENOPAUSAL ADVANCED BREAST CANCER PATIENTS

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Formestane (®LENTARON), a synthetic steroid derivative of androstenedione is the first selective aromatase inhibitor to become available. The multicentre study of ®LENTARON (250 mg i.m. fortnightly) vs megestrol acetate (160 mg oral once daily) enrolled 547 patients. All patients had histologically proven advanced breast cancer, had documented relapse of disease while under adjuvant therapy with tamoxifen administered for at least 12 months or had experienced progression of advanced breast cancer after an initial response for at least 3 months while under first-line therapy with tamoxifen and had ER and/or PgR positive or unknown. The primary end-point was time to treatment failure. Secondary endpoints were objective tumour response (in accordance with UICC criteria), time to progression, and overall survival time. Efficacy analysis was performed for the intent to treat patients and for the eligible patients who were evaluable for tumour response and will be presented. Preliminary analysis of safety data indicate a trend of more serious adverse events in the Megace group (pulmonary embolism and vaginal bleeding) in comparison with the ®LENTARON group.