Proferred Paper Sessions

PP-7. New Drugs — Phases I–II (September 13)

ORAL PRESENTATIONS

PP-7-1 Phase II Study of Liarozole in Advanced Breast Cancer Patients

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Liarozole is an imidazole compound that, in vitro, inhibits the intracellular catabolism of retinoic acid. Liarozole has also some aromatase inhibitory effect. A multicenter phase II study of Liarozole is presently ongoing in postmenopausal women with advanced breast carcinoma prospectively stratified into 4 groups: 1) ER+, tumor growing on tamoxifen = tamoxifen refractory disease, 2) ER+, unknown or ER– tumor and chemotherapy resistant disease, 3) ER+ or unknown tumor and potentially hormone sensitive disease and 4) ER– tumor never treated for metastatic disease. The starting dose of Liarozole is 150 mg p.o. bid to be increased after two weeks to 300 mg p.o. bid as long as toxicity is minimal. Until now, 75 women have been included in the study and toxicity data are available for 54 patients.

Type of toxicity	No. of patients with CTC grade (drug related toxicity)			
	1	2	3	4
Skin	10	30	6	
Fatigue	11	9	1	1
Anorexia	6	8	5	
Alopecia	14	1		
Nausea	7	4	2	1

The most frequently reported signs and/or symptoms of skin toxicity were retinoid-like such as itching, dryness, rash, erythema and desquamation. Partial responses have already been observed in groups 2, 3 and 4 where the accrual has been more active. Planned accrual of the full study is a maximum of 29 patients per group (total 116) and group 2 has already been closed.

PP-7-2 Neoadjuvant Chemotherapy by VEC Regimen in Breast Cancer. Preliminary Results of a Phase II Trial

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In order to increase conservative surgery for breast cancer with tumor size > 30 mm, we started a neoadjuvant chemotherapy (VEC) consisting in 3 courses of Vinorelbine (VNR) 40 mg/m^2 + Cyclophosphamide 500 mg/m^2 (D1) followed by 3 courses of VNR 40 mg/m^2 + Epuribicine 75 mg/m^2 (D1). Day 1 = Day 21.

From 07-95 to 01-96, 29 patients (pts) of median age 48 years (26–66) were enrolled. Seventeen pts were menopaused and 12 pts were not. Clinical TNM staging was: T2: 17 (58%); T3: 8 (28%); T4: 4 (14%); N0: 10 (34%); N1: 19 (66%). All pts were M0.

Pathological proof by biopsy showed: Ductal carcinoma: 17 (no SBR I), lobular carcinoma: 4, undifferenciated carcinoma: 8.

Actually, 16 pts are evaluable for toxicity and efficacy. Haematological toxicity reached Gr 3 for 4 pts, but no patient needed hospitalization for febrile neutropenia and/or transfusion. Other toxicities were nausea Gr 3 (3 pts), constipation Gr 3 (5 pts), neurotoxicity Gr 2 (7 pts), veinitis Gr 2 (3 pts) and alopecia Gr 2 or 3 (16 pts). Due to neurotoxicity and constipation, VNR dose was reduced to 35 mg/m^2 beyond the 16th pt. An objective clinical response was observed for 9 pts: 6 CR received exclusive radiotherapy, 3 PR were treated by conservative surgery + radiotherapy; 5 pts had SD treated by mastectomy. One pt progressed on treatment and for the last pt, VEC was discontinued for Gr 3 constipation and depression after 4 courses and had mastectomy. The study is on going and definitive results for all pts will be presented in next September.

PP-7-3 Epirubicin (E) Plus Paclitaxel (P) in Advanced Breast Cancer: A Regimen with High Activity and Low Cardiac Toxicity which Mobilizes Peripheral Blood Stem Cells

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We have performed a dose escalation study of P over 3 hours plus bolus E 90 mg/sqm every 3 weeks. The starting dose of P was 135 mg/sqm and was escalated by 20 mg/sqm in cohorts of 3 to 6 patients. 32 patients have been treated; 27/32 (84%) had failed adjuvant chemotherapy with anthracyclines in 14 cases. A grade 4 neutropenia was observed in 63% of 192 courses with 14 episodes of febrile neutropenia that represented the DLT at P225 mg/sqm. The cardiac effects were surprisingly low: the median L-VEF was 58% at study entry and 56% after a cumulative E dose > 930 mg/sqm; 18 (56%) patients had a decline of L-VEF of less than 20%; only 1 patient experienced a mild CHF responsive to therapy. Supraventricular and ventricular arrhytmias were unchanged before and after therapy. So far 30 patients are evaluable for response after at least 3 courses; 4 complete responses and 19 partial responses (RR 77%, 95% CI 58–90%) have been reported. In 18 patients we have evaluated the mobilization of PBSC after E + P + G-CSF; the median number of CD34+ cells was 61.7/ul (range 6.8–201) and was inversely related to the number of prior courses. A median of 6.3 × 10^6/kg CD34+ cells have been harvested; these patients entered a programme of high dose consolidation therapy. In conclusion: 1) E + P is an active and safe regimen 2) the suggested dose for phase II trials are E 90 mg/sqm + P 200 mg/sqm, 3) this combination + G-CSF mobilizes CD34+ cells.

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PP-7-4 Phase I/II Study of Taxol® (paclitaxel) in Combination with Epirubicin and Cyclophosphamide without G-CSF as a First Line Treatment of Metastatic Breast Carcinoma (MBC)

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The objective of this trial was to determine the Maximum Tolerated Dose (MTD) of Taxol® (T) administered in escalated doses (150, 175, 200 and 225 mg/m^2) as a 3-h infusion on D1 of a 21 days cycle. In combination with Epirubicin (E) 50 mg/m^2 and Cyclophosphamide (Cy) 500 mg/m^2, as a first-line CT in MBC.

Dose Limiting Toxicities (DLT) were determined on the 1st cycle: Gr. 4 neutropenia > 7 d; febrile neutropenia requiring IV antibiotics; Gr. 4 thrombocytopenia; Gr. ≥ 3 mucositis for 5 days or more; no hematological recovery at day 21; neurotoxicity > Gr. 2. If any of the preceding events occurred during the first cycle (cy) in 2 or more out of 6 pts, the MTD would be considered as reached.

Twenty-one pts have been accrued until now. All pts and 106 cy are evaluable for toxicity. On the first 3 dose levels 2 DLT have been observed during the 1st cy, both consisting on febrile neutropenia: 1 pt on dose level 1 (T 150 mg/m^2) and 1 pt on dose level 2 (T 175 mg/m^2). The MTD has been reached at the 4th dose level: T 225 mg/m^2 (1 febrile neutropenia followed by septicemia and death, and 1 grade II persistent neuropathy after the 1st cycle). No clinical cardiac toxicity has been observed and objective responses have been obtained in all dose levels.

In order to increase the anthracycline dose-intensity, we have amended the protocol to allow progressive dose escalation of E to 60, 75 and 90 mg/m^2, keeping T doses fixed at 200 mg/m^2 and Cy doses at 500 mg/m^2.