PP-8. Locally Advanced and Metastatic Disease (September 13)

ORAL PRESENTATIONS

PP-8-1 Combined Estrogen Suppression and Receptor (ER) Blockade by Buserelin (LHRH-A) and Tamoxifen (TAM) in Premenopausal Metastatic Breast Cancer: Preliminary Results of a 3-Arm Randomized Study (EORTC 10881)

J.G.M. Klijn*, C. Seynaeve, L. Beex, L. Mauriac, J. van Zijl, C. Veyret, J. Wildiers, J. Jassem, J. Burghouts, M. Becquart, M. Namer, M. Piccart, J. Garcia-Conde, F. Mignolet, G. Hoctin-Boes, members of the EORTC Breast Cancer Coop. Group. *Dr. Daniel den Hoed Kliniek, Erasmus University, Rotterdam*

The endocrine and antitumor effects of first-line combined LHRH-A (buserelin implant sc/8 wk) and TAM (40 mg/day) therapy were compared with those of each drug alone. ER/PR-negative pts or pts with unknown ER/PR status with DFS < 2 yr were excluded. From 160 pts randomized between 1988–1995 140 thus far are evaluable. There were no major differences between the 3 treatment groups regarding patient and tumor characteristics. During combined therapy plasma E_2 levels were not differently suppressed than those during LHRH-A alone while pts with TAM showed fluctuating high E_2 levels for years. Combined LHRH-A + TAM therapy appeared to be superior to single LHRH-A or TAM therapy regarding response rate (51 vs 33/29%), duration of response (22 vs 12/19 months), median PFS (9.7 vs 6.5/5.0 m), mean PFS (17 vs 8.2/10.3 m), median overall survival (not reached vs 31.4/37.8 m) and percentage died (40% vs 71/67%). Differences were significant by univariate (p-values 0.02–0.008) and multivariate analysis (p = 0.012). No differences were found between single LHRH-A and TAM therapy. *In conclusion:* combined LHRH-A + TAM therapy is superior to single therapy, probably by combined E_2 suppression and ER blockade.

PP-8-2 First Line Tamoxifen for Invasive Hormonal Sensitive Non Metastatic Breast Carcinomas in Young Postmenopausal Patients

L. Mauriac*, M. Durand, F. Bonichon, A. Floquet. *Institut Bergonié, Regional Cancer Center, 33076 Bordeaux, France*

From 1985 to 1990, 951 postmenopausal women from 50 to 70 years old were treated at Institut Bergonié for an infiltrative non metastatic breast carcinoma with a positive estrogen and/or progesterone receptor positive determination. Treatment was chosen according to tumor (bulk, multicentricity, evolutivity) and patient (choice, general condition) characteristics. So, 707 were treated by initial surgery with or without irradiation, 139 by neoadjuvant chemotherapy and 105 by first line tamoxifen. Forty-five had operable disease (T2 > 30 mm, T3, N0-1) [Group 1] and 60 had T4 tumors [Group 2]. After a mean treatment duration of 5.3 months, 41 (91%) in group 1 and 47 (78%) in group 2 were treated by surgery (conservative or not), with or without irradiation. The other women were treated either with second line chemotherapy or with another hormonotherapy; the remaining patients carried on with tamoxifen regularly. Among patients who received locoregional treatment, 29 have been treated with conservative procedure (64%) in group 1 and 29 (48.3%) in group 2, which is the usual conservative treatment rate for such tumors. With a 57 month median follow-up (min 33, max 106), five-year survival is the same in the two groups (77%). Locoregional and/or metastatic recurrences are more frequent in group 2 than in group 1. This retrospective study does not allow us to use neo-adjuvant hormonotherapy routinely but urges us to initiate a randomised study comparing this strategy to first line surgery followed by adjuvant tamoxifen.

PP-8-3 Double-Blind Trial in Postmenopausal (PMP) Women with Advanced Breast Cancer (ABC) Showing a Dose-Effect and Superiority of 2.5 mg Letrozole Over Megestrol Acetate (MA)

I. Smith*, P. Dombernowsky, G. Falkson, R. Leonard, L. Panasci, J. Bellmunt, W. Bezwoda, G. Gardin, A. Gudgeon, H.A. Chaudri, U. Hornberger, Letrozole International Trial Group (AR/BC2).

Letrozole (L), a highly potent, selective oral non-steroidal aromatase inhibitor, was previously shown to be safe and effective in PMP women with ABC. 551 patients with ABC (measurable/evaluable disease) previously treated with anti-estrogens (adjuvant or therapeutic) were randomized to 0.5 mg L (188 pts), 2.5 mg L (174 pts) or 160 mg MA (189 pts) od in a double-blind trial performed in 10 countries. Tumor response, assessed according to strict UICC criteria, was verified by independent blind peer review. Updated intent-to-treat analyses (mainly for survival) adjusted for prognostic factors were performed 15 months after last patient was enrolled. For 0.5 mg L, 2.5 mg L and MA, respectively, response rate (RR = CR + PR) was 12.8%, 23.6% and 16.4%; median duration of response was 555 d, not reached and 546 d; median time to progression (TTP) was 154 d, 169 d and 168 d; median time to treatment failure (TTF) was 98 d, 155 d and 118 d; and median survival (S) was 633 d, 731 d and 660 d. There was a statistically significant difference in RR (P = 0.043) and TTF (P = 0.038) in favor of 2.5 mg L compared to MA but no significant difference between 0.5 mg L and MA. Furthermore, a statistically significant dose-effect was observed in RR (P = 0.004), TTP (P = 0.023), TTF (P = 0.002) and S (P = 0.05) in favor of 2.5 mg L. Significantly more patients on MA than on either dose of L had severe or life-threatening adverse events, serious adverse events (mainly thrombo-embolic) and those requiring trial discontinuation, or weight gain ≥ 10% compared to baseline. In conclusion, 2.5 mg L is superior to MA and to 0.5 mg L and is demonstrably safer than MA in the treatment of ABC in PMP women.

PP-8-4 An Open, Comparative Randomized Trial Comparing Formestane vs Oral Megestrol Acetate as a Second-Line Therapy in Postmenopausal Advanced Breast Cancer Patients

C. Rose* [1], M. Freue, M. Kjaer, C. Boni, F. Jänicke, C. Coombes, P.H.B. Willemse, S. van Belle, R. Pérez Carrión, J. Jolivet, P. Ibarra de Palacios. [1] *Odense Sygehus, Odense, Denmark*

Formestane (®LENTARON), a synthetic steroid derivative of androstenedione is the first selective aromatize inhibitor to become available. The multicentre study of Formestane (F) (250 mg i.m. fortnightly) vs megestrol acetate (MA) (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 ITT Results are as follows: TTF; Median (days) 169 (F), 169 (MA), 95% CI (days) 105–183 (F), 114–200 (MA), Overall response; CR + PR 16.3% (F), 20.3% (MA), NC 34.4% (F), 32.8% (MA), PD 37.0% (F), 33.6% (MA), Overall survival; Median (days) 561 (F), 597 (MA), 95% CI (days) 508–738 (F), 489–804 (MA).

There was no statistical or clinically relevant difference in TTF, TTP, overall survival, overall response, and duration of response between F and MA; MA was associated with more significant CVS events, increase in weight and vaginal hemorrhage. Formestane was better tolerated than MA.

PP-8-5 A Randomised Study Assessing Oestrogen Suppression with Arimidex™ (Anastrozole) and Formestane in Postmenopausal Advanced Breast Cancer (ABC) Patients

M. Dowsett* [1], D.A. Vorobiof, U.R. Kleeberg, R.P. Carrion, D.J. Dodwell, J.F.R. Robertson, L. Calvo, Arimidex Study Group. [1] *Dept. Academic Biochemistry, Royal Marsden Hospital, England*

Oestrogen suppression with anastrozole (A), a new potent oral once-daily highly selective, non-steroidal aromatize inhibitor (AI), was compared with that of formestane (F), a steroidal selective AI given by i.m injection, in postmenopausal women with ABC. 31 patients were treated with F 250 mg every 2 weeks, whilst 29 patients received A 1 mg oral once-daily, treatment being continued until disease progression or study withdrawal. Plasma oestrogen (oestradiol [E2], oestrone [E1], oestrone sulphate [E1S]) measurements were carried out in all patients at baseline and weeks 1, 2, 3 and 4. Baseline mean E2 concentrations were 32.1 pmol/L and 31.0 pmol/L for A and F respectively. At weeks 1 and 3, mean serum E2 concentrations were 6.5 and 6.2 pmol/L respectively with A and 9.5 and 8.3 pmol/L respectively with F. At weeks 2 and 4, mean E2 concentrations were 5.8 and 6.6 pmol/L respectively with A 1 mg daily. Conversely with F, at weeks 2 and 4 there was a trend toward recovery with mean E2 concentrations being 13.6 and 12.1 pmol/L respectively. Mean E2 concentrations (based on the week 2 and 4 measurements) were reduced by 79% and 58% with A and F respectively, this difference being statistically significant (p = 0.0001).

On average, E2 concentrations relative to entry, were half that with A than with F at 2 and 4 weeks (21% of entry value with A and 42% of entry value with F). E1 and E1S were analysed by a new iodinated radioimmunoassay after column chromatography, and will be reported in detail.

PP-8-6 Paclitaxel (P) Versus Doxorubicin (D) as First Line Chemotherapy (CT) in Advanced Breast Cancer (ABC): A Randomized Trial with Crossover of the EORTC-IDBBC in Collaboration with EORTC-ECSG

P. Bruning*, M.J. Piccart, J. Klijn, T. Gamucci, Z. Kusenda, J.A. Roy, A. Van Vreckem, R. Paridaens, IDBBC.

This trial was designed to investigate the efficacy and safety of P (200 mg/m^2, 3 H infusion, q3w) with crossover to D (75 mg/m^2, q3w) on progression, versus the reverse sequence. Crossover is mandatory if progression occurs within the first seven cycles of first-line CT. Until now, a total of 316 pts have been randomized (expected: 330 pts). Preliminary results on toxicity have been presented (ECCO8). An attempt to correlate some patient/disease characteristics (as possible predictors) with toxicity is ongoing. The following table summarizes the announced best response for pts of first and second line.

Response	Complete (%)	Partial (%)	Stable (%)	Progression (%)
1st line (n = 187)	4	34	27	26
2nd line (n = 49)	2	39	23	18

The intermediate results show a clearcut response rate in 2nd line with both drugs supporting a lack of cross resistance between P and D. An update on toxicity and antitumor activity will be presented.

PP-8-7 Assessment of Response in Bone within an EORTC Randomised Trial of Bisphosphonate Treatment (10924)

J. Vinholes*, R. Coleman, D. Lacombe, F. Mignolet, C. Rose, R. Leonard, J. Nortier, M. Tuibiana-Hulin, EORTC Breast Group.

Assessment of response in bone is currently based on the changes seen on serial plain radiographs. We have prospectively evaluated new biochemical markers of bone resorption including the urinary excretion of peptide-bound N-telopeptide (Ntx) and C-telopeptide (Crosslaps) fragments of type 1 collagen, free deoxypyridinoline (Fdpd), tumour marker levels, the EORTC quality of life QLQ-C30 questionnaire, and a pain score assessing the intensity of pain, analgesic consumption and performance status. 91 patients with newly diagnosed, radiologically confirmed metastatic bone disease were recruited to a placebo-controlled clinical trial designed to evaluate the contribution of oral pamidronate 300 mg daily to standard anticancer treatment. A bone scan and skeletal survey was performed before trial entry and X-rays of involved sites repeated every 3 months and at each change of systemic therapy or skeletal-related event. The biochemical, subjective and quality of life changes are to be correlated with the UICC response in bone to endocrine (n = 51) and chemotherapy (n = 33) both with and without concomitant oral pamidronate.

PP-8-8 Reduction of Skeletal Related Complications in Breast Cancer Patients with Osteolytic Bone Metastases Receiving Hormone Therapy, by Monthly Pamidronate Sodium (AREDIA®) Infusion

R. Theriault, A. Lipton, R. Leff, S. Gluck, J. Stewart, S. Costello, J. Simeone, J. Seaman, R. Knight, M. Heffernan, D. Reitsma*. *Houston, TX; Hershey, PA; Atlanta, GA; Sudbury, Canada; Waratah, Australia; Dunedin, New Zealand; Boston, MA; CIBA-GEIGY, Summit, N.J.*

182 patients receiving endocrine therapy for metastatic breast ca. (with at least one lytic lesion $\geq$ 1 cm) were treated with pamidronate disodium (Aredia) 90 mg infusion over 2 hrs every month $\times$ 12 and 190 patients received placebo. Skeletal related event (SRE) including pathologic fracture, cord compression, surgery and radiation therapy were primary endpoints. The overall skeletal morbidity rate (#SRE/year) was significantly lower for the pamidronate group when compared to the placebo patients (2.4 vs 3.6; p = 0.03). The time to first SRE was 10.9 months in the pamidronate group vs 6.9 months in the placebo arm. Fewer patients treated with pamidronate required radiation to bone (39 vs 63 placebo: p = 0.01). The time to first bone radiation was significantly longer in the pamidronate group (p = 0.005). Fewer pathologic fractures were seen in the patients who received the bisphosphonate (66 v. 83 placebo: p = 0.13). Among the patients with pain at baseline, pain scores decreased for the pamidronate group from baseline while they increased on placebo (p = 0.009). Significantly fewer pamidronate (30%) than placebo patients (43%) had an increase in analgesic use from baseline (p = 0.012). This dosage regimen was well tolerated. In conclusion monthly infusions of 90 mg. pamidronate in addition to hormone therapy are superior to hormone therapy alone in preventing SREs in stage IV breast cancer patients.

PP-8-9 Reduction of Skeletal Related Complications in Breast Cancer Patients with Osteolytic Bone Metastases Receiving Chemotherapy (CT), by Monthly Pamidronate Sodium (PAM) (AREDIA®) Infusion

G.N. Hortobagyi, L. Porter, D. Blayney, R.L. Theriault, A. Lipton, S. Gluck, H. Wheeler, S. Allan, J. Simeone, J. Seaman, R. Knight, M. Heffernan, D. Reitsma*. *Houston, TX; Brentwood, TN; Los Angeles, CA; Hershey, PA; Sudbury, ON; Sydney, Australia; Palmerston North, New Zealand; Boston, MA; Ciba, Summit, NJ*

We report the results of a randomized trial that compared the safety and efficacy of a 2-hour infusion of 90 mg of PAM q 3–4 weeks for 12 months (185 patients) to placebo (PL 197 pts) in preventing skeletal related episodes (SRE: pathologic fracture, cord compression, radiation or surgery to bone, hypercalcemia) in breast cancer patients with $\geq$ 1 osteolytic bone metastases of $\geq$ 1 cm in diameter treated with CT. At 12 months, the proportion of patients having any SRE was statistically significantly lower with PAM (43%) than with PL (56%, p = 0.008). The proportion of patients having any non-vertebral pathologic fracture or radiation to bone was less on PAM, than on PL, as was that of surgery to bone or spinal cord compression. The time to first SRE was longer in the PAM group (median = 13.1 m) than on PL (7.0 m, p = 0.005). Bone lesion response was assessed by X-ray at baseline, 6 and 12 m: CR + PR was 33% on PAM and 18% on PL (p = 0.001). At the last measurement, significantly fewer PAM patients (26%) than PL patients (36%) had an increase in analgesic score from baseline. Pamidronate was well tolerated. We concluded that monthly infusions of 90 mg pamidronate in addition to CT are superior to CT alone in preventing SRE's in Stage IV breast cancer patients.

POSTER PRESENTATIONS

PP-8-10 Breast Cancer in 1980–1995: Meta-Analysis of Dose Intensity (Neoadjuvant Chemotherapy)

J. Shparik. *Dept. Oncology, P.O. Box 2468, Lviv, 290029, Ukraine*

A positive relation between dose intensity (DI) and treatment outcome has been demonstrated not only in advanced breast cancer (BC) but also in adjuvant setting. Only few trials using DI concepts have been performed in neoadjuvant chemotherapy for BC. To determine if chemotherapy DI influences treatment outcome in BC, 41 published trials (some of which were not randomized) from 1984–1995 were retrospectively analyzed. Regimens included such agents as Cyclophosphamide (31 trials), Fluorouracil (26), Doxorubicin (24) or Epidoxorubicin (13), Methotrexate (9), Vincristine (6), Mitoxantrone (3), Cisplatin (2), Mitomycin C (1), and Tiotepa (1) (from single drug therapy to five-drugs combinations). Relative DI (RDI) of each study regimen was calculated against commonly used doses of each drugs in single regimens. Meta-analysis of chemotherapy trials for BC with some various regimens have suggested that higher total RDI correlated strongly with improved response rate (39 trials, r = 0.43, p = 0.0057) and slight but not significantly with complete response (29 trials, r = 0.36, p = 0.0539). It is first retrospective analysis on DI-response relationship in neoadjuvant chemotherapy of BC.

PP-8-11 Half Body (HBI) and Total Body (TBI) Irradiation in Disseminated Breast Cancer Patients (PTS)

V. Vinogradov*, L. Koritova. *Medical Academy for Postgraduated Studies, Central Research Institute of Radiology, St-Petersburg, Russia*

Between 03/1986 and 06/1993 HBI or TBI was performed in 33 breast cancer patients with bone, lung, liver, soft tissues or brain metastases. All pts but one had multiple lesions. The doses of 3 Gy (single-dose TBI), 5–6 Gy (single-dose HBI) or 19.8 Gy in 11 treatments (fractionated HBI) were delivered through opposite anterior-posterior fields, using 15 MeV linear accelerator. Boost accelerated irradiation was given on locally involved sites.