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)

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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

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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)

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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

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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

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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).