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

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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

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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

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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)

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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)

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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.

In 3 pts TBI was repeated during the follow-up period. Radiation therapy was well tolerated. Partial or minor responses were obtained in 29 cases, even after failed chemotherapy. Disease stabilization occurred in 3, and progression in 1 pts. Median 2-years survival was 36%. This data confirms the value of HBI and TBI in the management of metastatic breast cancer.

PP-8-12 Unclear Value of Salvage Chemotherapy After Failure to First-Line 5-Fluorouracil, Epirubicin, Cyclophosphamide (FEC) Regimen for Metastatic Breast Cancer

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The clinical benefit of salvage chemotherapy following failure of a first-line regimen was retrospectively analyzed in 140 metastatic breast cancer patients all homogeneously treated with first-line FEC and followed until death by a single institution. Pt characteristics: median age 54.5 yr. (range, 29–71 yr.); median ECOG PS 0 (0–3); median DFI 22 mos. (0–164); dominant site: soft tissue 13 (9%), bone 43 (31%), viscera 84 (60%). After disease progression, 72/140 (51%) pts received at least 1 line of salvage CT. Overall response (CR + PR), response rate (RR) and time to treatment failure (TTF) of FEC and all subsequent salvage regimens was:

Treatment	Total	CR + PR	RR (%)	Median TTF in months
I CT (FEC)	140	57	40.7	7.5
II CT line	72	7	9.7	2.6
III CT line	24	1	4.2	1.7
IV CT line	10	1	10.0	0.9
V CT line	3	0	0.0	1.9
VI CT line	1	0	0.0	–

Only a very small fraction of pts receiving first-line FEC can objectively respond to subsequent CT regimens. The advantages of salvage CT are unclear and must be weighed against the inconvenience, cost, and morbidity of treatment.

PP-8-13 Chemoradiotherapy in Complex Treatment of Locally Advanced Breast Cancer

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On purpose to compare the efficacy of two chemotherapy regimens, the complex treatment method was applied to 121 patients with locally advanced breast cancer (LABC). Radiotherapy was given before operation with CMF to 61 patients or VAM to 60 patients. All women were operated on with mastectomy. Chemotherapy was continued after operation. Whole course of treatment consisted of 6 cycles of CMF or VAM respectively. Hormonotherapy was administered in patients with ER+ tumours. Androgens or prednisone were given in premenopausal patients after ovariectomy. Postmenopausal women were treated with tamoxifen for two years. While comparing results we couldn't find any difference in survival rate in patients treated with CMF or VAM. 5-year overall survival was 62.79% in VAM group and 66.26% in CMF group. Disease-free survival was 48.08 and 50.67% respectively. Our finding suggest that CMF regimen is of the same efficacy as VAM in treatment of patients with LABC and can be successfully used in treatment of patients with LABC.

PP-8-14 Five-Year Results of a Multimodal Management of Stage III B Breast Cancer

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Stage III B breast cancer carries a high incidence of local and/or distant metastases reaching even 70% and with a 5-year overall survival of 20%. The present study was initiated to verify the effectiveness of a combined modality approach which includes primary chemotherapy, surgery, radiation and adjuvant therapy, in improving prognosis. Forty-four pts in age from 36 to 71 years (median 51), PS 0–1, 21 premenopausal, with T_4 N_{1-3} M_0 breast carcinoma, following the tru-cut biopsy for the histology and prognostic factors, were treated by 3–5 cycles of q 21 or q 14 FEC 50 or 120-100 mg/m^2 Epirubicin or MMM. 13 pts were ER$^+$, 9 PgR$^+$, 9 Ki-67 L.I.$^+$, 24 G_2, 20 G_3, 32 infiltrating ductal, 8 lobular, 4 mixed. *Clinical response:* of 42 evaluable pts 1 (2.4%) reached a CR, 25 (59.5%) a PR > 50%, 14 (33.3%) a PR < 50% and 2 (4.8%) a NC. *Surgery* was performed in 40 pts (95.2%), radical in 37 pts (92.5%) and conservative in 3 pts (7.5%). Moreover all pts received radiation and adjuvant chemotherapy. *Pathological response* (40 pts) was pT_0 in 2 pts (5%), pT_1 in 5 (12.5%), pT_2 in 17 (42.5%), pT_3 in 6 (15%) and pT_4 in 10 (25%). Lymph nodes were involved in 40/40 pts, 1–3 in 11 pts (27.5%), 4–10 in 16 pts (40%), > 10 in 13 (32.5%). Response (CR + PR > 50%) not significantly correlate with ER status (50% ER$^+$, 66.6% ER$^-$). Of 42 pts, 23 relapsed (54.8%) (3 local, 9 distant, 11 mixed) and 12 of these (28.6%) died. None of the pts who achieved a CR relapsed while no significant difference in relapsing was found between those with PR > 50% and with less than PR. Kaplan-Meier 60 months overall and disease-specific-survival were 38.26% and 31.74% respectively. Since our study demonstrates the efficacy of the primary chemotherapy in making technically resectable the 95.2% of pts, the combined modality approach, even if could improve the outlook of many pts, it do not significantly betters the poor prognosis of these patients suggesting that more effective systemic therapies, including high-dose chemotherapy with PBPC need to be evaluated.

PP-8-15 Phase II Studies with Rivizor® (Vorozole) in Advanced Breast Cancer

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Rivizor® (vorozole) is an orally active, potent and selective, non-steroidal aromatase inhibitor. In DMBA-induced rat mammary tumors the reduction in tumor growth with vorozole was equal to oophorectomy. *In vivo* peripheral aromatization in postmenopausal women was inhibited by at least 93%.

Four phase II trials were performed with vorozole in a total of 114 patients. Patients had ER +ve or ER-unknown tumours, measurable disease, and failed prior tamoxifen as adjuvant or as first-line therapy for advanced disease. Previous adjuvant chemotherapy was allowed. Performance status had to be 0–2. Vorozole was given at a dose of 2.5 mg OD p.o. until progression. Response was assessed by UICC criteria every 2 months. 114 patients were evaluable for toxicity and 107 patients were evaluable for response. 29 patients responded to vorozole (26%, 5 CR, 24 PR), for a median duration of 11.7 months (min 8.6–max. 15). Responses occurred more frequently in soft tissue disease. Serum oestradiol was suppressed significantly (90%). Vorozole did not affect adrenal function as assessed by ACTH stimulation test; there were no effects on androgens, progesterone or TSH. Vorozole was very well tolerated; toxicities were mild and consisted mainly of hot flushes, nausea and anorexia.

A phase III programme comparing vorozole to aminoglutethimide and megestrol acetate is ongoing.

PP-8-16 Detection of Liver Metastases in Advanced Breast Cancer

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The routine use of imaging tests to identify liver metastases is disputed and in some centres imaging is only performed in those patients with abnormal liver function tests (LFTs) — AST, ALT and GGT. We have reviewed 65 consecutive patients with advanced breast cancer who had both liver ultrasound scans and LFTs performed. In 43 patients the scan was performed as part of routine restaging and in 22 because of a suspicion of liver involvement due to either clinical features (n = 15) or abnormal LFTs (n = 7). 29 scans (45%) were diagnostic of liver metastases, with 25 showing multiple lesions and 4 a single metastasis. LFTs were abnormal in 21 (positive predictive value = 0.72) but 8 patients (31%) with liver metastases had normal LFTs. Conversely in 36 patients with a normal scan, LFTs were normal in only 18 (negative predictive value = 0.5). The median survival from detection of liver metastases was 5 (range 0.1–34) months. We believe ultrasound scans should be part of routine restaging of patients with advanced breast cancer prior to any change in systemic therapy and that imaging of the liver should not be restricted to patients with abnormal LFTs or clinical features of liver involvement.

PP-8-17 Biochemical Markers of Bone Resorption Predict Response to Bisphosphonate Treatment

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Around one half of patients experience symptomatic response with pain relief following intravenous pamidronate but the mechanisms which underly a lack of response are unknown. In a randomised placebo-controlled