administrated and a group not administrated tamoxifen. The two groups showed no differences in back ground factors. In the observation period of 34 weeks, localized recurrences were not found in the tamoxifen group but appeared in two patients in the untreated group. The premenopausal ER (+) patients were all comedo type and EIC (+). Concomitant use of tamoxifen appears to be useful as postoperative treatment in premenopausal patients undergoing breast preservation therapy.

PP-5-14 FEC-75 Plus G-CSF in Locally Advanced Breast Carcinoma

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Aim. – To assess efficacy and tolerability of chemotherapy (CT) given every 14 days to increase dose-intensity (DI) and reduce time to surgery in patients with T3/T4 and/or N2 breast carcinoma.

CT scheme. – FEC-75 (5-FU 600 mg/m^2, epirubicin 75 mg/m^2, ciclophosphamide 600 mg/m^2) day 1st plus filgrastim 30 mU SC, days 3 to 12. Courses were repeated every 14 d up to 4 courses (c).

Patients. – From April/94 40 patients (p) have been included in 4 hospitals: median age 54 y (32–65); ECOG 0 40 p; post-menopausal 21 p; T1–2 6 p, T3 19 p, T4b 6 p, T4d 6 p; N0 13 p, N1 9 p, N2 15 p; G2 22 p, G3 8 p. Stages IIb 9 p, IIIa 15 p, IIIb 13 p.

Results. – Courses given: 119. Actual dose: 100% in every c. without delay (DI 150%). Non-hematological toxicity: N&V G2 35 c (29%), mucositis G1 6 c, flu-like synd G1 6 c, G2 1 c, alopecia 40 p. No cardiotoxicity (LVEF measured in 18 p). Hematological toxicity: On day 1 of the course, only 1 p had thrombopenia G1. anemia G1 12 p.

Responses (OR) en 22/35 p (63%): RC 5 p, RP 17 p, EE 13. No progressive disease. Surgery already performed in 33 p (mastectomy 25 p, conservative 8 p).

Conclusions. – FEC-75/14d × 3–4c + G-CSF showed high response rate without severe toxicity. Pathologic CR rate remains low. DI was significatively increased and time to surgery reduced. Radical surgical procedures were performed in all patients in our experience.

PP-5-15 Postoperative Adjuvant Randomized Trial Comparing Chemoendocrine Therapy, Chemotherapy and Immunotherapy for Patients with Stage II Breast Cancer

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The effects of using ftorafur (FT) or PSK (an immunotherapy agent) in combination with adjuvant therapy using mitomycin (MMC) + tamoxifen (TAM) were assessed in stage II, ER+ breast cancer patients. In stage II, ER– breast cancer patients the effects of adjuvant therapy using MMC + FT were compared with those using MMC + PSK. On the day of surgery, MMC (13 mg/m^2) was administered. ER+ patients received one of three regimens, starting 2 weeks after surgery: regimen A (30 mg/day of TAM), regimen B (30 mg/day of TAM and 600 mg/day of FT) or regimen C (30 mg/day of TAM and 3 g/day of PSK). ER– patients received either regimen D (600 mg/day of FT) or regimen E (3 g/day of PSK). Of the 540 ER+ patients, 525 were evaluated. The 5-year survival (OS) was higher for patients who received regimen B than for those who received other regimens (P = 0.063). The 5-year relapse-free rate (RFS) was higher for regimen B than for other regimens (P = 0.010). Stratified analysis revealed better results with regimen B in premenopausal patients and patients positive for lymph node metastasis. Of the 376 ER– patients, 364 were evaluated. There was no significant difference in OS or RFS between the D and E regimens.

PP-5-16 A Study of Postoperative Adjuvant Chemotherapy of 5′-DFUR in Breast Cancer Patients (1st Report) — On Compliance and Safety — "The 5′-BC Study Group" (5′-DFUR Adjuvant Chemotherapy for Breast Cancer Study Group)

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Introduction 5′-deoxy-fluorouridine (5′-DFUR), an analogue of 5-fluorouracil synthesized by Cook et al. in 1976, is used orally to treat stomach, colorectal, cervical, bladder, and breast cancers in Japan. To assess the usefulness of postoperative adjuvant 5′-DFUR chemotherapy in breast cancer, we conducted a controlled comparative study at 153 institutions; control groups received only surgical resection. Subjects were of T < 3 cm, N0 or N1a, M0 and Brt + Ax or over after gross curative resection. From June 1990 to December 1992 (2 years and 7 months), 1217 patients were registered in the study. The report rate of cumulative follow up data was 97%.

Methods Patients were randomly assigned to a repetitive or intermittent dosage group. Repetitive dosage: Method Y (5′-DFUR from 2 wks. after operation at 1200 mg/day × 4 wks., discontinuance for 2 wks. followed by 600 mg/day × 20 wks.) and method X (surgery only). Intermittent dosage: Method B (5′-DFUR from 2 wks. after operation at 1200 mg/day × 4 wks., discontinuance for 2 wks., 1200 mg/day × 2 wks. alternated with 2 wks. discontinuance until 28 wks. after operation) and Method A (surgery only).

Results Compliance was favorable: 91.1% of Method Y and 88.0% of Method B patients achieved 80% or more of the drug administration rate (Actual total dose/scheduled total dose) in our protocol. While incidence of adverse reactions was 24.8% (Method Y) and 27.2% (Method B), most adverse reactions were mild (grade 1 or 2) gastrointestinal symptoms, e.g., diarrhea, etc. Although follow-up results continue to be compiled (median observation time, 4.3 years), interim findings are available on request.

PP-5-17 High-Dose Cyclophosphamide (CTX), Mitoxantrone (MXT), and Paclitaxel (Taxol®, TXL) for the Treatment of Metastatic Breast Cancer (MBC) with Blood Cell Support

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A Phase I study using CTX 6 g/m^2, MXT 70 mg/m^2, in combination with TXL at a starting dose of 250 mg/m^2 in dose escalation for the purpose of determining dose limiting toxicity (DLT), maximum tolerated dose, and efficacy of this drug combination in a transplantation setting with pharmacokinetic analysis of TXL is being performed. Patients between the age of 18–55 with MBC not previously treated with cytotoxic drugs for metastatic disease are eligible. So far, 45 patients were enrolled and 31 patients have completed the treatment. The blood cell transplantation and recovery time was delivered completely in an out-patient setting. Recovery for ANC ≥ 0.5/nl was 10–16, median 12 days. Recovery for platelets ≥ 20/nl was 18–20, median 12 days. 15 patients developed neutropenic fever that required IV antibiotics. Up to the 3rd dose level of TXL, few patients have experienced grade II and III toxicity other than, hematotoxicity. In the 4th dose level, 6 patients were treated; 3 of them experienced DLT; therefore, an extended infusion schedule delivering the 400 mg/m^2 TXL over 6 rather than 3 hours is used. This study is ongoing.

PP-5-18 Adjuvant Epirubicin and CMF +/– Hormonotherapy in More than 3 Nodes Positive Breast Cancer Patients: Preliminary Data

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206 patients with early breast cancer were treated with Epirubicin 110 mg/sqm iv d 1 q 3 weeks × 4 cycles followed by CMF (CTX 500 mg/sqm iv d 1–8, MTX 40 mg/sqm iv d 1–8.5-FU 600 mg/sqm i.v. d 1–8 q 4 weeks) × 4 cycles +/– Hormonotherapy: Goserelin depot sc every 28 days × 2 years in premenopausal patients and Tamoxifen 20 mg/os/day × 5 years in postmenopausal patients. Radiotherapy was given after conservative surgery.

Median age was 42 years in premenopausal patients and 59 in postmenopausal patients.

We have observed 24 relapses (11.6%) equally balanced between pre and postmenopausal patients.

Toxicity was generally acceptable, no particular cardiac toxicity was observed.

PP-5-19 Intensification Chemotherapy (IQ) with Autologous Peripheral Blood Progenitor Cell (PBPC) Support in Patients with Breast Cancer: Results of the Transplantation Procedure

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From Dec. 93 to February 96, 25 p. with breast cancer were included in our program of I.Q. with autologous PBPC support. *Methods:* On day 14, after a course of CAF chemotherapy, priming was given with G-CSF 10 μg/kg/day × 7 for mobilization, with planned apheresis on days 5. (& 6–7 if needed), following the surgical implantation of a double lumen CVC, performed with the use of one of two cont. flow blood cell separators (Baxter CS 3000 & Cobe Spectra), until a number of 7 × 10^8/kg MNC were reached. The product was reconstituted with DMSO & autologous plasma, and cryopreserved (controlled rate freezing to −197°C). I.Q. was given as an outpatient procedure with Carboplatin 800 mg/m^2, Mitoxantrone 25 mg/m^2 and Thiotepa 600 mg/m^2 on days −5 to −3.; P. were admitted to individual rooms with double barrier nursing on day −1 and each bag of PBPC infused in less than 15 min. under cardiovascular control. Antiemetic was given with Granisetron & Dexamethasone. Infection prophylaxis was made by Cotrimoxazole, Acyclovir, Fluconazole, and after day +2, GCSF 5 μg/kg until ANC > 1.0 × 10^9 × 2 days. Pentoxiphylline was added for 2 months. *Transplantation Results:* Age (median): 44 (26–53); Stages: IIB: 12; IIIA: 1; IIIB: 7; IV: 5; Apheresis: (median): 2; Hospitalization days: 12 (10–16). *Product of cells infused/kg* (1 p. was excluded for this analysis because CD34 pos. selection was used) (median): M. nucleated Cells (MNC) 7.46 × 10^8, CFU-GM: 34.1 × 10^4 (in 12 p.), CD34+: 7.05 × 10^6. Viability (Trypan blue): 90%. *Hematologic recovery:* days with ANC < 0.5 × 10^9/l: 7 (5–9); platelets < 20 × 10^9/l: 4 (1–7). *Toxicities:* Hypertension (post-infusion) > 30 mmHg: 11 p; Mucositis GII: 4 p. GIII: 1 p; Vomiting: GIII: 5 GII: 10 p; Diarrhea: GIII: 3 p, GII: 3 p.; Hepatotoxicity: GII 1 p; Flebitis > 5 days: 2 p; Low Back pain during G-CSF priming: 21 p, *Complications:* Fever > 38.5°C: 11 p; Days with empiric antibiotics: 3.8 (0–9); *Blood support:* Single-donor platelets products: 3 (1–5); Packed red cells: 1.6 (0–2). Peritransplantation mortality: 0; *Outcome (N:25):* With a median follow up of 14 m. (2–26) 4 of the 5 p. in stage IV have recurred at m. 12, 1, 1, & 6 months of transplantation and one is in RC after 22 m. For the 20 p. in the adjuvant setting, 1 recurred at 11 m. *Conclusions:* Autologous PBPC support of this I.Q. therapy was associated with low morbidity and the phases of mobilization, apheresis and intensification could be given in an outpatient setting, reducing thus the cost of the procedure. The outcome for the first 5 patients in stage IV appears to be negative. Further studies with longer follow-up & more patients are needed.

PP-6. Prognosis 1: Clinico-Pathological Factors (September 12)

ORAL PRESENTATIONS

PP-6-1 Time Since Birth is a Prognostic Factor in Primary Breast Cancer

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The Danish Breast Cancer Cooperative Group has since 1977 collected population-based information on primary clinical data, treatment regimes, and follow-up status on Danish women with breast cancer. Detailed information on pregnancy history was added from the Danish Civil Registration System and the National Birth Registry. Included in the study were 5,954 patients who at the time of breast cancer diagnosis were 45 years of age or less. Women classified with low-risk breast cancer, i. e. lymph node negative cancers, less than 2 years after having given birth had a crude survival of 75.0 percent (5-year) and 55.6 percent (10-year), respectively, compared with 88.5 percent (5-year) and 77.8 percent (10-year) for women whose last child birth were more than 2 years prior to their diagnosis. After adjusting for age, reproductive factors, and stage of disease (tumor size, axillary nodal status, and histologic grading), a diagnosis less than 2 years since birth remained significantly associated with a poor survival (RR = 1.64, 95% CI: 1.28–2.09). Stratified analyses showed that the effect was independent of age at diagnosis, tumor size, and nodal status.

These data illustrate a growth-enhancing effect of pregnancy on breast cancer. A diagnosis of breast cancer less than 2 years after having given birth is associated with a particularly poor survival irrespective of the stage of disease at presentation. It should be considered to offer the subset of patients, who are otherwise classified as having low risk disease, systemic adjuvant treatment.

PP-6-2 Incidence and Prognostic Value of Routine Clinical Parameters in 2273 Patients with Primary Breast Cancer Treated between 1978–1990

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The clinical data of 2273 pts with primary breast cancer and known ER status were collected: mean age 56 yr (22–89 yr); premenopausal 41%; T_1 = 43%, T_2 = 45%, T_3/T_4 = 11%; N^0 = 46%, N^{1-3} = 27%, N^{4-9} = 17%, $N \geq^{10}$ = 10%; ER^+ = 78%, PgR^+ = 72%; median follow-up 6 yr; adj. syst. ther. 24%; recurrence rate 47%. The percentage of T_1 tumors increased from ± 30% before 1985 to 40–54% after 1985 while N^0 tumors increased from ± 40% to 50% in the same period. Within the group of 962 patients with T_1 tumors 36% were node-positive (N^{1-3} = 24%, N ≥ 4 = 12%). By multivariate analysis tumor size ($p < 0.0001$), nodal status ($p < 0.0001$), age ($p < 0.0001$), menopausal status ($p < 0.03$) and ER/PR status ($p < 0.001$) were independent prognostic factors, while high grade predicted poor survival. Although in the pT_1-category there was no difference in survival between N^0 pts and pts with only one positive node, relapse-free survival (RFS) decreased by increasing number of positive nodes. Pts treated with adjuvant chemotherapy showed better survival curves than not adjuvantly treated pts within all N^+ subcategories. The small discriminatory effect of ER and PgR status was most significant after 3 yrs of follow-up, but disappeared after 7 yrs. The duration of RFS, ER and PgR status and site of metastasis were predictive factors for duration of postrelapse (progression-free) survival.

In conclusion: although new cell biological factors independently add, classic clinical parameters are still of important value for prognosis of pts with breast cancer (supported by Dutch Cancer Society, DDHK 92–04).

PP-6-3 The Selection of Patients with DCIS for a Clinical Randomised Trial: Differences between Large Participating Centres

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In multicentre randomised trials the interpretation of selection criteria may differ between participating centres, which will result in different entry rates. This "institutional" selection bias may also explain differences in outcome of a trial when evaluated per centre.

We analysed the possible influence of institutional selection in four institutes participating in the EORTC 10853 trial. This trial compares radiation therapy versus no additional treatment after local excision for ductal carcinoma in situ of the breast. The trial was started in 1986. Eligibility criteria for the trial are: age < 70 years, no previous malignancy including contralateral breast cancer, complete excision of the lesion, DCIS < 5 cm and absence of microinvasion and of Paget's disease of the nipple. The four institutes have the disposal of a complete registration of all patients with breast cancer treated at the centre. Medical histories of all cases of DCIS diagnosed during the period the centres participated in the trial were reviewed. The following parameters were analysed: the total number of patients with DCIS treated, the number of patients entered and the number of patients eligible for the trial. Main reasons for non-entry were contralateral breast cancer, size of DCIS, and patient's refusal. This, however, does not explain sufficiently the different entry rates, which varied from 7 to 66%.