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%.

The complete results and possible explanation of these differences will be presented.

PP-6-4 Prognostic Significance of Obvious Peritumoral Emboli in 2692 Primary Operable Breast Carcinoma

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The prognostic significance of obvious peritumoral emboli (OPE) was evaluated in 2692 consecutive operable infiltrating ductal carcinoma of the breast operated and monitored at our institution between 1975 and 1992 (50.2% N− and 49.8% N+). OPE were assessed in routine practice and defined by the presence of neoplastic emboli within unequivocal vascular lumina including both lymphatic spaces and blood capillaries lined by recognizable endothelial cells adjacent to but outside the margins of the carcinoma. The frequency of OPE was 33.8% (19.6% in N−, 49% in N+). In univariate analysis OPE were related to tumour size ($p < 0.0001$), lymph node stage ($p < 0.0001$) and histologic grade ($p < 0.0001$); they were statistically significant with respect to survival (OS): $p < 10^{-29}$, disease-free survival (DFS): $p < 1.7 \times 10^{-13}$ and metastasis-free survival (MFS): $p < 10^{29}$. In multivariate analysis in the N− group, OPE were the most predictive factor for MFS ($p = 7.1 \times 10^{-7}$) before size and grade, and for survival ($p = 1.9 \times 10^{-3}$) after tumor size. In the N+ group OPE were the first predictive factor for local recurrence ($p = 4.1 \times 10^{-7}$).

In conclusion this study confirm with a very simple routine approach the prognostic significance of emboli in breast carcinoma. This is particularly interesting in the N− group to select a subset of patients at high risk, for a possible adjuvant therapy.

PP-6-5 Does Semi-Quantitative Evaluation Improve the Prognostic Value of Histological Grade in Breast Carcinoma: Comparison of Scarff-Bloom-Richardson (SBR) and Elston-Ellis (EE) Grading Systems in a Series of 825 Cases with a Follow-Up of 10 Years

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The respective prognostic value of two grading schemes was compared in a retrospective series of 825 patients treated between 1981 and 1988 for a small invasive carcinoma with conservative surgery and radiation therapy. Histological grade was assessed using the criteria developed by SBR and those recently proposed by EE. In addition, the exact number of mitotic figures per 10 high power field was recorded. Our results showed a strong unbalanced distribution of cases with a majority of Grade I cases (61% according to SBR, 50% according to EE) and a low number of Grade III cases (16% according to SBR, 4% according to EE). However, univariate and multivariate analysis showed that both histological grades were strongly correlated to overall and metastasis free survival. Despite the improvement of EE grading scheme in defining more precisely the morphological features, its prognostic value, in this series, was not better than SBR grading's. The number of mitotic figures was unexpectedly low, which could explain these results. We suggest that the mitotic score threshold are too high considering the small tumor sizes or, that due to the retrospective nature of the study, the technical conditions were less than optimal to properly assess the number of mitotic figures.

PP-6-6 The Prognostic Importance of Tumour Grade in Lymph Node Positive Breast Cancer

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Lymph node status is an important prognostic factor in primary breast cancer. However, considerable prognostic heterogeneity exists such that offering adjuvant systemic therapy to all lymph node positive patients may overtreat a low risk subgroup.

We reviewed the results of 636 patients aged < 70 years treated between 1973 and 1988 with histologically proven lymph node positive breast cancer. No patients received adjuvant systemic therapy.

On univariate analysis histological tumour grade and number of lymph nodes involved were found to be significant prognostic variables ($p < 0.01$). Patient age, menopausal status, oestrogen receptor and tumour size were not significant. In a second representative subgroup of 158 tumours MIB 1, S-phase fraction and erbB-2 were analysed. MIB-1 and S-phase fraction were significant prognostic variables on univariate analysis. On multivariate analysis for survival, tumour grade was the most important factor predicting for survival in the entire group and for the second subgroup.

The 15 year survival and average annual probability of death from breast cancer for lymph node positive grade I patients (n = 87) was 59% and 3.9%/year respectively. This shows that histological grade identifies a group of women who, although lymph node positive, have a 60% chance of surviving 15 years. This is similar to survival in breast cancer patients who are lymph node negative.

PP-6-7 Automated Grading in a Prognostic Index

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The Nottingham prognostic index (NPI) for primary operable breast cancer (NPI = (0.2 × tumour size) + lymph-node stage + histological grade), validated with 15 year survival analysis, remains a powerful clinical tool which defines three subsets of patients with different chances of dying from breast cancer (good, moderate, and poor prognostic groups partitioned by NPI score: < 3.4, 3.4–5.4, > 5.4 respectively). Grade contributes significantly toward NPI scoring but is a semi-objective variable. Quantitative measurement of histological tumour grade derived from automated analysis offers less subjective assessment and potential substitution of conventional techniques. Putative substitutes for grade: MIB1 labelling, cell morphometry (CAS™ image analysis), and proliferative index (PI = % SPF + % G2M) (flow cytometry) were measured on tumour tissue from 102 patients with primary operable breast cancer (median follow-up, 144 months) who received no adjuvant therapy. Multivariate analysis generated a simple (3 level) grade substitute, G^n = 0.02 (MIB1 + standard deviation of nuclear size + PI), weighted by NPI score frequency. A new prognostic index, NPI^n = (0.4 × tumour size) + (0.6 × lymph-node stage) + G^n, defined three subgroups whose survival curves superimposed the corresponding curves generated by the standard NPI. An automated score, G^n, can substitute for histological grade in an established prognostic index.

PP-6-8 Prediction of Tumor Response to Neoadjuvant Chemotherapy in Operable Breast Cancer

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The value of parameters obtained by fine-needle cytopunctures for the prediction of chemosensitivity was evaluated in 105 large operable primary breast carcinoma ((T2 ≥ 30 mm-T3, N0-N1-N2, PEV0-PEV1) treated with AVCMF (3 cycles) or FEC (4 cycles) before surgery. Cytopunctures were studied: before treatment for cytologic nuclear grading (in 2 groups) and S-phase fraction (SPF: 2 groups) by image cytometry; and after one cycle of chemotherapy for cytomorphologic and cell-kinetic changes. 13 patients showed pathologic complete regression (pCR), 26 were scored partial regression (with concordant clinical ≥ 50%, mammographic and histologic findings) and 59 showed no regression. Objective tumor regression and overall pCR were significantly related to high grade, high SPF, and to cytomorphologic and dramatic cell kinetic changes. Univariate analysis showed that high grade and high-SPF remained bad prognostic factors for metastasis free survival (MFS: $p = 0.005$ and $p = 0.003$, respectively; median follow up = 38.5 months). However, the subgroup of patients with pCR experienced a better clinical course (MFS, $p = 0.04$). The Cox model selected 3 variables: node positive, high S-phase and initial tumor size for MFS. At present the subgroup of pCR did not emerge from the Cox model possibly due to its small number of patients.

POSTER PRESENTATIONS

PP-6-9 Prognostic Significance of Epidermal Growth Factor Receptor and Estrogen Receptor in Advanced Breast Cancer

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The Epidermal Growth Factor Receptor EGFR is a specific glycoprotein transmembrane receptor that is believed to be a functional entity constituting