mg/m^2 and methotrexate 30 mg/m^2 both IV 3 weekly plus tamoxifen 20 mg/day (2MT).

59 patients have received 3MT and 66 have received 2MT as primary medical treatment. The 3MT and 2MT regimens resulted in no palpable abnormality in 10 (17%) and 16 (24%) of patients respectively and in only minimal residual nodularity in 23 (39%) and 17 (26%) of patients respectively. (No significant difference). Both regimens resulted in an overall response rate of 85%. We have observed no evidence of haemolytic uraemic syndrome with 2MT.

Therefore 2M is an effective, easy to give chemotherapeutic regimen which in the treatment of primary breast cancer can be safely combined with tamoxifen.

58 POSTER

OPERABLE BREAST CANCER IN WOMEN UNDER FORTY YEARS

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The aim of this study was to determine whether breast cancer in women under forty has a poorer prognosis as compared to cancers occurring in older premenopausal women.

From January 74 to December 90, 658 premenopausal women underwent surgery as first treatment for operable breast cancer (invasive ca., first single breast primary cancer, no personal history of invasive cancer, no inflammatory sign, tumor size under 7 cm). One hundred and thirty-nine patients were under 40 years old.

Adjuvant treatment was determined according to nodal status: axillary node positive patients received chemotherapy and/or hormonotherapy (ovarian suppression).

Patients' characteristics (T, N, histologic grade, hormone receptors) are equal in both groups under and above 40 years. Median follow-up is 10 years.

Overall survival is not significantly different between women under and above 40 years of age. On the other hand, disease free survival is shorter for women under 40 ($P = 0.01$). This difference is not explained by a more intensive follow-up after treatment for younger patients and prompted us to intensify or to respect dose intensity.

59 POSTER

TAMOXIFEN (TAM) IN BREAST CANCER (BC): TOXICITY OF LONG TERM ADJUVANT TREATMENT

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To evaluate collateral effects of a TAM prolonged treatment, we analyzed, in a retrospective study, 243 pts, whose mean age was 59.2 years (27–85), all BC treated with radical surgery and adjuvant TAM for more than 2 years, 61/243 in premenopausal (25.1%) and 182/243 in postmenopausal age (74.9%). Twenty-nine out of 243 pts (11.9%) had a precedent hysterectomy for other benign gynaecological diseases. Forty-three pts (17.7%) received TAM 20 mg/die and 200 (82.3%) 30 mg/die; median treatment duration was 50.5 months (24–120 m) (front 2 to 3 years: 58 pts, from 3 to 4 years: 39 pts, from 4 to 5 years: 97 pts, >5 years: 49 pts, in which TAM was readministrated as first line too). The median follow-up was 70.3 m (2–15 years). For intolerance, 22 (9.1%) pts reduced TAM from 30 to 20 mg/die while 12 (4.9%) pts stopped for the same problem. We reported these side effects: thrombophlebitis in 13 pts (5.3%), epigastralgia of mild entity in 18 pts (7.4%), leucopaenia grade I WHO in 5 pts (2.1%), thrombocytopenia grade II in 2 pts (0.8%), mild hyperglycemia in 15 pts (6.2%), mild nausea in 8 pts (3.3%), leukorrea in 5 pts (2.1%), flashing in 12 pts (4.9%), spotting from endometrial hyperplasia in 22/214 pts (10.3%). Only 3 pts had a controlateral BC (1.2%). We reported 4 gynaecological cancers (1.9%): 2 endometrial adenocarcinomas after 22 and 60 months of TAM treatment, 1 ovarian granulosa-cells tumor after 30 months and 1 ovarian tumor-not style typized-after 60 months. Two pts (0.8%) had gallbladder cancer (1 pt after 52 months; 1 pt after 67), 1 pt (0.4%) had a stomach cancer after 6 months interruption of therapy with TAM for 96 months, 1 pt (0.4%) had a pancreas cancer after 51 months. In conclusion, our results reflect the literature about the risk of a secondary endometrial cancers in long term treated pts (*Lancet* 1989, **i**, 117); the correlation between TAM and endometrial cancer is sure; there is no evidence of correlation with other tumors. We suggest periodic gynaecological control in patients treated with TAM for more than two years.

60 POSTER

TAMOXIFEN AND TOREMIFENE: THE BENEFICIAL HYPOLIPEMIC EFFECT IN WOMEN IS MEDIATED BY CHOLESTEROL BIOSYNTHESIS INHIBITION

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Tamoxifen (TAM) is an effective antiestrogenic anticancer drug. In long-term therapy it decreases serum cholesterol and LDL-cholesterol levels and decreases the risk of coronary artery disease. The mechanism of the hypolipemic effect has not been fully elucidated. Toremifene (TOR) is a new antiestrogenic anticancer drug that has clinical efficacy equal to that of TAM. The structure of TOR is closely related to that of TAM and animal experiments suggest that also TOR can have hypolipemic effects. The effect of TAM and TOR therapy on serum lipid levels were studied in postmenopausal advanced breast cancer patients. The effect on cholesterol biosynthesis was evaluated by measuring cholesterol precursor levels by gas-liquid chromatography at pre-dose and after 2, 6 or 12 months therapy. Both drugs decreased cholesterol and LDL-cholesterol levels almost equally. This suggests that also TOR can be expected to have TAM-like beneficial antiatherogenic effect during long-term therapy. Of the cholesterol precursors Δ^8-cholestenol level was increased up to about 50-fold with both drugs; in other precursor levels only minor changes were seen. This indicates that these antiestrogens inhibit Δ^8-cholestenol conversion to lathosterol and as a result the cholesterol biosynthesis is downregulated. This inhibition is suggested to be the main method for the hypolipemic effect of these drugs.

61 POSTER

ENDOMETRIAL CANCER INDUCTION BY TAMOXIFEN IN THE RAT

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Tamoxifen (TAM) is an antiestrogenic breast cancer drug. Medication with TAM increases the risk of secondary cancers in the endometrium. In the rat TAM is a strong hepatocarcinogen. Toremifene (TOR), a new antiestrogen clinically as effective as TAM, has not shown any hepatic or endometrial adverse effects. We studied the effects of TAM and TOR on rat endometrium. Three separate studies were put together. Female SD-rats were daily treated with vehiche or with the drugs at equimolar doses (20 or 80 μmol/kg) p.o. for 13–52 weeks. Both drugs produced comparable uterine atrophy and weight reduction at both dose levels indicating an equal hormonal effect. No preneoplastic or neoplastic changes were observed in control or TOR groups or in the low-dose TAM group. The incidence of squamous cell metaplasia with prominent keratinization was 10% in the high-dose TAM group. In 3 of the metaplasias there was a focal dysplastic change and two of these animals beared also a focal invasive squamous cell carcinoma. The carcinomas were found after 20 or 26 weeks of dosing, in both cases after a recovery period. The histopathological outlook of these lesions argued against a mere hormonal etiology. TOR produced no lesions although the estrogen antagonist/agonist activities and the endometrial proliferative potentials of these two drugs at the dose levels used are closely comparable. In conclusion, a nonhormonal (possibly genotoxic) mechanism in the TAM-induced endometrial carcinogenesis is probable. TOR might be more safe clinically, especially when healthy women are treated with antiestrogens in breast cancer preventive indication.

62 POSTER

NEOADJUVANT CHEMOTHERAPY FOR STAGE III PRIMARY BREAST CANCER

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Neoadjuvant chemotherapy is showing promising results in the primary treatment of breast cancer. We have analysed the data on 91 patients (age 30–78 years) representing 15 years of experience firm 1980–1995 in our unit. All patients had advanced tumours, 69% being T4 (46% of these inflammatory), with 76% of tumours more than 5 cm in size and 68% clinically node positive at diagnosis. Four chemotherapy regimens have been used: (1) Ariamycin 40 mg/m^2 + Vincristine 1 mg/m^3 × 3 cycles. (2) Mitozanstrone 14 mg/m^2 × 3 cycles. (3) Cyclophosphemide

500–600 mg/m^2, Methotrexate 40–50 mg/m^2, 5 Fluorouracil 500–600 mg/m^2 (CMF) × 3–6 cycles. (4) Cyclophosphamide 500–600 mg/m^2, Adriamycin/Epirubicin 40–50 mg/m^2, 5 Fluorcuracil 500–600 mg/m^2 (CAF/CEF) × 3–6 cycles. The breast and glandular areas were irradiated with 40–50 Gy in 15–25 fractions ± 5–10 Gy boost in 2–5 fractions. The overall 2, 5 and 10 year actuarial survival rates are 54%, 28% and 11% respectively. Overall response rates to chemotherapy were 61% (14% CR). Response rates were highest [92% (50% CR)] with CAF/CEF based regimens. The addition of radiotherapy increased the response rate to 93% overall, and with CAF/CEF there was a 75% CR rate. The median time to maximum clinical response was 5 months and 9 months on radiological criteria. Sixty-one patients have relapsed, 54% due to metastases, 15% synchronous local and metastatic disease, 31% local failure only. Thirty-one percent of patients had mastectomy, with only 10% of patients having uncontrolled inoperable local disease after therapy.

63 POSTER

INCIDENCE AND CAUSES OF LEUCOCYTOPENIA IN POST-OPERATIVELY IRRADIATED BREAST CANCER PATIENTS

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Purpose: Leucocytopenia (LCP) (<4000/μl) in breast cancer patients treated by adjuvant chemotherapy (CT) is an excepted side effect. In contrast radiation (RT) induced LCP in postoperatively irradiated breast carcinoma is unusual. We analysed the incidence of RT induced LCP and possible reasons of its occurrence.

Patients: From 1989–93 185 patients with primary breast carcinoma (T1–4N0–2 M0) were treated by surgery alone (n = 87), by additional CT with CMF (n = 10), by postoperative RT only (chest wall/breast and/or regional lymph nodes) (n = 54) or by all three modalities (n = 36). All groups were comparable with regard to age. Blood examinations were performed once weekly.

Results: LCP was observed in women treated by surgery alone in 4.6%, by surgery and CT in 60%, by postoperative RT in 31.5% and by combined procedure in 88.9%. In all irradiated women (n = 90) leucocytes counts were lower than in those without RT ($P = 0.001$). In contrast to chest wall/breast irradiation alone, all patients treated by CT and RT of the chest wall/breast including regional lymph nodes revealed decreasing leucocytes counts (<4000 n = 14, <2000 n = 5). LCP depended on doses given to the supraclavicular and parasternal region ($P = 0.003$).

Conclusions: Our data suggest that the size of irradiated volume can significantly enhance the risk of LCP in primary breast cancer patients treated by CT. Our results enable to define criteria necessary for selection of patients with recommended frequent blood examinations.

64 POSTER

CORRELATION BETWEEN DOSE INTENSITY, HEMATOLOGICAL TOXICITY AND OUTCOME OF ADJUVANT CHEMOTHERAPY IN BREAST CANCER

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The purpose of the study was to determine significance of total dose (TD), dose intensity of all given cycles (TDI), dose intensity of the two first cycles (DI2) and hematological toxicity on efficacy of doxorubicin (adriamycin) containing adjuvant chemotherapy for stage II and III breast cancer.

Patients and Methods: 211 patients with stage II and III breast cancer were treated with 8 cycles of adjuvant chemotherapy (cyclophosphamide, adriamycin and oral ftorafur). TDI, DI2, TD and the impact of hematological toxicity were compared with values for distant disease-free (DDFS) and overall survival (OS).

Results: A preliminary analysis indicated that adriamycin DI2 correlated to DDFS. Patients with a lower leukocyte nadir during the chemotherapy had significantly better DDFS. The same trend was established for OS.

Conclusion: The initial dose intensity is important to assure the optimal effect from adjuvant chemotherapy. The correlation between lower leukocyte nadir and improved treatment outcome indicates that the better results associated with patients who received the higher dose intensity resulted neither from selection for better tolerance to chemotherapy nor for better performance status.

65 POSTER

THE EFFECTS OF TAMOXIFEN AND TOREMIFENE ON PLASMA LIPID LEVELS IN POSTMENOPAUSAL EARLY BREAST CANCER PATIENTS

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Tamoxifen as adjuvant therapy for women with breast cancer decreases serum lipids and lipoproteins by its estrogenic agonist effects. We evaluated whether a novel antiestrogen, toremifene, has similar effects.

Patients and Methods: 49 postmenopausal early breast cancer patients were randomized to adjuvant tamoxifen or toremifene treatment groups. Total, LDL and HDL cholesterol, apolipoprotein A-I, A-II and B and Lp(a) were measured before treatment and after 12 months.

Results: Both antiestrogens reduced significantly serum total and LDL cholesterol and apo B levels. The response of HDL cholesterol to treatment was clearly different between the groups. Toremifene increased the HDL-level 14% whereas tamoxifen decreased it 5% ($P = 0.001$). Both Chol/HDL and LDL/HDL ratios fell more in the toremifene than tamoxifen group ($P = 0.008$; $P = 0.03$, respectively). Toremifene also increased apo A-I level ($P = 0.00007$) and apo A-I/A-II ratio ($P = 0.018$). In both tamoxifen and toremifene treatment groups Lp(a) concentration fell significantly (change: 34% vs 41%).

Conclusion: These results provide positive evidence that toremifene has highly antiatherogenic properties with an exceptional potency to improve all lipoproteins which are associated with increased coronary heart disease risk.

66 POSTER

ADJUVANT ANTIESTROGENS (TAM) VS ESTROGENS (EST) IN POSTMENOPAUSAL NODE POSITIVE (N+) BREAST CANCER PATIENTS

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In 1985–1989 in phase III randomized trial for evaluation of efficacy of adjuvant TAM (20 mg/day for 12 months) and EST (synoestroli 20 mg/day, i.m. for 6 months) were enrolled 172 (87 and 85 respectively) postmenopausal N+ breast cancer patients (pT1–3N1–2M0). The 5-year overall survival were 65.5% in TAM group and 71.7% in EST group ($P > 0.05$).

Toxicity of EST (30.5%) were much higher than TAM (3.4%) ($P < 0.05$). The main side effects of therapy with EST were methrorrhagia and arterial hypertension (grade III). In 19 cases (22.3%) they were the main reasons of early treatment termination. In TAM group the study treatment were well tolerated.

67 POSTER

SURGICAL THERAPY OF CYSTOSARCOMA PHYLLOIDES (CSP)

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CSP is a rare fibroepithelial tumour. The incidence comes to 1% of all breast neoplasms. Morphological differentiation between benign and malign lesions can be difficult. We examined 21 female patients who underwent surgical treatment on our department from 1/80 to 12/94. The age range was 24 to 82 (mean 54) years.

Median tumour diameter in first treatment was 1.5–10 cm (mean 4 cm). Modified radical mastectomy was performed in 5, simple mastectomy in 3 cases. Thirteen patients were treated by tumourectomy with tumour free resection margins of 2 cm. Median follow up was 6.7 years (8 m–15 y). Six patients (28.5%) showed at least once local recurrence following first treatment (mean 26 month). In one case we saw 5 relapses. From 5 malignant CSP (23.8%) 4 patients died during follow up.

In our examination we observed no correlation between tumour size and recurrence rate. A sufficient wide histologically verified tumour free resection margin seems to be unalterable. According to literature and to our experience axillary dissection is useless even in cases of malignancy.