vitro growth kinetics. On the other hand, MX-1 cells were growing much slower than the above cell lines.

Discussion: Our study shows that human breast cancer cell lines exhibit a different expression pattern of the urokinase plasminogen activator system components but a link between this expression and their *in vitro* growth capacity could not be demonstrated. Our findings of higher PAI-1 amount in combination with a higher growth rate by BT-20 cells are in line with the proposed protective mechanism against the proteolytic degradation of tumor cells themselves mediated by PAI-1. Based on our observation that non-PAI-1 producers, MCF-7 cells, also exhibited a high growth capacity we suggest, that disturbance of balance between activator and inhibitor may also result in upregulated *in vitro* tumor growth. Therefore, a direct role of PAI-1 in growth rate of breast carcinoma is, at least *in vitro,* rather unprobable.

P14 Adjuvant tamoxifen treatment in breast cancer induces no activation of blood coagulation

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Based on the incidence of thromboembolic complications (1–14%) during the clinical adjuvant breast cancer trials, tamoxifen is considered as a potentially thrombogenic drug. Studies evaluating changes of hemostasis during tamoxifen treatment report very conflicting results and the cause-and-effect relationship has never been established.

To asses potential effects of antiestrogen treatment on the hemostatic system, we studied blood coagulation and fibrinolysis in 20 postmenopausal women with breast cancer receiving 20 mg tamoxifen daily as an adjuvant therapy. Blood sampling was done before and after the 1st, 3rd and 6th month of treatment. Blood collection was done according to standard protocols.

Pretreatment values of procoagulation [fibrinogen (Fbg), factor VII (FVII)], thrombin-antithrombin-complex (TAT), anticoagulation [antithrombin III (ATIII), protein C (PC), protein S (PS)] or plasminogen and plasminogen activator inhibitor were found within the normal range, whereas tissue-plasminogen activator (t-PA), D-dimer fibrin degradation products (DDIMER) and prothrombin-fragment 1 + 2 (Frag 1 + 2) were elevated. On therapy an initial decrease of all measured parameters was observed during the first month of treatment, followed by consistent plasma levels up to the end of the observation period. This effect was significant for Fbg, FVII, AT III, PC, PS and t-PA. Fibrin degradation products decrease continuously. The analysis of blood coagulation inhibitors revealed decreased AT III (13%), PS (27%) and PC (29%) during the first month of treatment. However, all values remained within the normal range (>70%). No cumulative effects on anticoagulation were seen on therapy.

Our pretreatment data are consistent with an activated hemostatic system (acute-phase-reaction) after major surgery. We can not exclude, that the decrease of hemostatic parameters during the initial phase of tamoxifen treatment refers to the timing of blood collection (<14 days after surgery). The decrease of blood coagulation inhibitors was not associated with a concomittant increase of in vivo coagulation markers (Frag 1 + 2, TAT, DDIMER). Therefore our results are likely to reflect only the resolution of postoperative activation and does not translate into a drug related thrombogenic effect. The epidemiological findings suggesting an increased risk for thromboembolic complications may easily be explained by tumor-induced hypercoagulability, additional anti-tumor therapy or individual predisposing risk factors for thrombosis (inherited or defects of blood coagulation).

P15 Blood coagulation and fibrinolysis after oral or intravenous cyclophosphamide containing adjuvant CMF-chemotherapy

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Epidemiological data suggest an increased incidence of thromboembolic complications (2–17%) during CMF-chemotherapy in breast cancer patients. Several studies report a decrease of blood coagulation inhibitors (protein C and S) induced by adjuvant CMF-chemotherapy containing oral application of cyclophosphamide. Because of an increased alkylating activity after oral administration, the aim of our study was to asses potential different effects of oral (p.o.) and intravenous (i.v.) application of cyclophosphamide during adjuvant CMF-Chemotherapy for breast cancer.

We studied parameters of blood coagulation and fibrinolysis in 20 patients receiving 6 courses of chemotherapy containing of cyclophosphamide (100 mg/m^2 p.o. days 1–14 or 600 mg/m^2 i.v. days 1, 8), methotrexate (40 mg/m^2 days 1, 8) and 5-fluorouracil (600 mg/m^2, days 1, 8). Blood collection was done before the application of the chemotherapy at days 1 and 8 according to standard protocols.

In both treatment groups the pretreatment values of procoagulation [fibrinogen, factor VII (FVII)], anticoagulation (antithrombin III, protein C (PC), protein S (PS), fibrinolysis (plasminogen, tissue-plasminogen activator) and antifibrinolysis (plasminogen-activator-inhibitor) were found within the normal range. Thrombin-antithrombin-complex and D-dimer fibrin split products were elevated. On therapy a decrease of FVII (20–35%), PC activity (20–40%) and antigen (25–38%) was observed from day 1 to 8 in both treatment groups. This effect was only significant ($p < 0.005$) for protein C. Whereas the plasma levels of FVII returned to pretreatment values within the treatment free period, a distinct cumulative effect was demonstrated for protein C with the occurrence of pathological values below 60% of normal range. There was no significant difference within the two treatment groups, but the effect was pronounced with oral cyclophosphamide.

Our data confirm the results of other authors reporting an acquired deficiency of protein C associated with adjuvant CMF-chemotherapy. We observed no significant difference whether cyclophosphamide was given p.o. or i.v.. In absence of any significant cumulative decrease of other vitamin-K-dependent coagulation factors (FVII, PS), the simultaneous decrease of PC activity and antigen, indicates a specific defect of the vitamin-K-dependent synthesis of protein C in the liver. Further analysis is mandatory to evaluate if cyclophosphamide, methotreaxate or 5-fluorouracil cause this effect.

P16 Adjuvant Goserelin depot in premenopausal women with early breast cancer: Ovarian function, bone mineral density and survival. Preliminary data

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Ovary suppression with Goserelin depot is alternative to ovarian ablation: in metastatic breast cancer Goserelin depot yelded objective response in 36% of patients. Ovarian ablation in women aged under 50 was associated with 6% fewer recurrences or deaths after 15 years. Studies are ongoing in order to evaluate the effectiveness of Goserelin depot as adjuvant treatment in the prevention of relapse and reduction in mortality.

We report our experience about 75 premenopausal patients with early breast cancer treated after surgery with Goserelin depot 3.6 mg subcutaneously every 28 days for two years. Median age was 43 years (range 31–50), all patients had regular menses, 36 patients were N+ and 39 were N−. ER status was positive in all patients but one in which was unknown.

One patient had bilateral breast cancer.

Owing to administration of Goserelin depot amenorrhea occurred after the first depot in 11 patients and after the 2nd depot in 64 women.

Spotting was observed in 8 patients and stopped after 10 depots.

At the end of 26 depots regular menses resumed in most patients (73%), on average after 5.3 months.

Weight gain was observed in 61% of patients, in 28.1% of patients weight was unchanged, weight loss occurred in the remaining women. All patients complained of hot flushes, sweating and impairment of libido. Metrorrhagia occurred in 3 patients at the end of therapy: 2 patients underwent hysterectomy. A decline in Bone Mineral Density was observed in patients studied with Dual Energy X-ray Absorptiometry (DEXA). A second primary tumor occurred in four patients: myeloid chronic leukemia, kidney cancer, oat cell carcinoma, second primary breast cancer. At a median follow-up of 51 months overall survival was 90.5% and disease free survival 70.2%.

P17 Weight gain associated with breast cancer adjuvant chemotherapy

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Purpose: Weight gain (WG) is one of the most common, distressful and less appreciated toxicity of adjuvant chemotherapy (CT) of breast cancer (BC). We retrospectively evaluated WG in the adjuvant CT of BC associated with cyclophosphamide, methotrexate, 5-fluorouracil (CMF) or cyclophosphamide, doxorubicin, 5-fluorouracil (CAF).

Methods: The pretreatment and post-treatment weight was determined in all patients and was recorded in the file.

Results: Between 1/94 and 12/95 131 BC pts were treated at our center with adjuvant CMF or CAF. Data were available for 65 CMF and 24 CAF treated pts. WG (range: 1–20, median, 8 kg) was recorded in 62 pts (70%). Weight loss (range: 2–9, median, 4 kg) was recorded in 10 pts (11%) and the remaining 17 pts (19%) maintained their weight during CT. WG was more pronounced in CMF than in CAF (51 pts, 78% vs 11 pts, 46%, $p < 0.004$). WG of >10 kg was noticed in 22 CMF treated pts (34%) vs 2 CAF treated pts (8%). Other factors that significantly affected WG included menopausal status {80% in pre vs 43% in postmenopausal ($p < 0.004$)} and obesity before therapy {100% for pts with pretreatment weight >130% of ideal body weight (IBW) vs 36% for pts with weight <130% IBW ($p < 0.0002$)}. There was no significant influence on WG for the type of surgery (lumpectomy vs mastectomy) or for CT induced amenorrhea.

Conclusion: WG is a common side effect of adjuvant CT for BC and its

degree is influenced by the type of chemotherapy, the menopausal status and pretreatment obesity.

P18 Plasma lipids and lipoproteins in breast cancer women in relation to body mass index (BMI) and fat distribution (WHR)

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Cholesterol or products of its biosynthesis are assumed to play important role in carcinogenesis via influence on DNA synthesis and cell proliferation. Obesity and central body fat distribution are positively related to postmenopausal breast cancer risk. Aim of this study was to assess the lipid/lipoprotein profile of breast cancer women in comparison with healthy controls. Serum levels of total, HDL, LDL cholesterol and triglycerides were evaluated in 150 untreated breast cancer women (mean age 51.0 yrs) and 150 healthy controls (mean age 50.3 yrs), matched by sex, age, BMI and fat distribution (WHR: waist to hip ratio). The mean value of total cholesterol was significantly higher in breast cancer group than in controls (231.6 vs 221.4 mg/dl; $p < 0.03$), as well as LDL cholesterol (155.3 vs 145.4; $p < 0.05$) and triglycerides (132.3 vs 116.4; $p < 0.02$). Obese patients (BMI ≥ 30 kg/m^2) had increased levels of LDL cholesterol in comparison with BMI-matched controls (165.8 vs 138.1 mg/dl; $p < 0.02$). We have not noticed any differences in lipids and lipoproteins plasma concentrations between breast cancer women and controls with central body fat distribution (WHR ≥ 0.8). Association between cholesterol – precursor of sex hormones and lipids disorders observed in breast cancer patients, pronounced in obesity, may constitute "deadly trio" in mammary carcinogenesis.

P19 Value of seric cholesterol in the prognosis and treatment of breast cancer

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Knowing that cholesterol is used in the formation of sterоid hormones including estrogens and that estrogenic receptors are an important prognostic factor, we started a study in 1982 with stage II patients of breast cancer. After operation seric cholesterol was indicated to 123 patients (in 99 of them a complete lipid study was performed). Patients did not receive adjuvant chemotherapy. Afterwards relapse was evaluated.

We found that patients with seric cholesterol lower than 6.46 mmol/l had major percent of relapse before 5 years $p < 0.01$. When we studied total cholesterol/HDLC index (i) we found that patients with i lower than 2 had 100% of relapse before 5 years, from 2–4.9 40.9% of relapse before 10 years, from 5–5.9 14% of relapse before 10 years and higher than 60% of relapse before 10 years ($p < 0.001$). It means that relative increase of HDL cholesterol increased the risk of metastases.

When the patients that relapsed were analyzed, we found that group of total cholesterol lower than 5.17 mmol/l had worse response to chemotherapy (CMF and CAF) $p < 0.05$.

If Hoyer's work is analyzed (Women with higher levels of HDL cholesterol had a significative risk of breast cancer), Cuzick and Reiner (Tamoxifen reduces LDL cholesterol), Potischman (Chemotherapy increases seric cholesterol); we would ask three questions. 1) Would seric cholesterol be a monitor for adjuvant chemotherapy and hormonotherapy?. 2) If we keep in 6 the index would we prevent relapse?. 3) Would cholesterol be controlled by a genetic mechanism?

Thursday, February 26, 1998 9.00–18.00

Diagnostics / Markers

P20 Extensive screening of women with high risk node positive breast cancer: An update

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We have previously reported (J. Clin. Oncol 14: 66, 1966) that extensive staging evaluation detected occult metastases in 23% of women with ≥ 10 positive axillary lymph nodes considered for high dose chemotherapy and autologous marrow support (ABMT). Here we report our expanded experience with this patient population. From 2/93 to 10/97, 129 women with ≥ 10 positive lymph nodes and no evidence of metastases on chest x-ray, bone scan and liver ultrasound were referred to our centre for possible enrollment in a prospective trial of ABMT (CALGB-9082, NCIC-CTG MA13). Forty-two did not undergo protocol staging (CT scan of head, chest, abdomen and pelvis, bilateral bone marrow biopsy): 23 declined participation, 11 had clinical evidence of metastatic disease at referral, 8 were ineligible. Four additional patients were ineligible because of inadequate organ function (low EF, DLCO or bone marrow cellularity). Occult metastatic disease was found by protocol staging evaluation in 14/82 women (17%): Bone marrow 4, liver 2, internal mammary or mediastinal node 4, lung 3, bone 1. This expanded cohort confirms our previous experience with the evaluation of women with high risk breast cancer and emphasizes caution in interpretation of current phase II results of ABMT compared to historical controls, where such extensive evaluation was not performed. Large randomized prospective comparisons of this promising therapy to standard treatment in North America are nearing completion. The final results will not be available for several more years.

P21 High-risk breast cancer patients (>9 involved nodes) M0 at conventional staging procedures: Additional findings suggesting M1-status

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Introduction: Since 6/95 high-risk breast cancer patients younger than 60 years are randomized to dose dense conventional therapy or to tandem high-dose chemotherapy with stem cell support. Beside age and performance status inclusion criteria were R0 resection, N >9, and M0-status as documented by normal clinical examination, negative scintigram, negative chest x-ray and negative abdominal ultrasound. There is growing evidence that tumor load in this subgroup is systematically underestimated (JCO 6/97).

In some patients additional examinations like histological evaluation of resected subscapular lymph nodes, bone-marrow biopsy, supraclavicular ultrasound and bronchoalveolar lavage were performed. Data from these examinations suggesting M0 or M1 status are reported.

Materials and Methods: From 6/95 until 10/97 150 patients were randomized. Operative and histological reports from the first 94 patients were evaluated. Supraclavicular ultrasound and bone-marrow biopsy were performed in 23 and 26 patients respectively.

Results: 70.2% (n = 66) of the patients had modified radical mastectomy. Axillary operative procedure as documented in the operative report consisted in 8.5% of the resection of the lymph nodes of level I–II, in 42.6% of resection of lymph nodes of level I–III. In 46.8% the operative procedure was described as resection of "axillary lymph nodes" without separate histological examination of level I or 2. In 2 cases subscapular lymph node resection and separate histological examination were documented.

None of the bone marrow biopsies (26 histological examinations) revealed bone marrow carcinosis. Supraclavicular ultrasound showed suspicious lymph nodes in 11 of 23 patients despite normal clinical findings in this area.

Conclusion: Our previous data show that about one third of patients with more than 9 involved axillary lymph nodes in breast cancer will have positive subscapular lymph nodes. Therefore the abovementioned operative procedure in the axilla will systematically underestimate the proportion of M1 patients. The same is probably true for supraclavicular ultrasound as documented by the high rate of suspicious findings (11/23) in clinically normal patients. Bone marrow biopsies on the other hand did not reveal histological involvement.

Additional data about CT and immunocytochemical examination of bone marrow will be presented.

P22 Role of single photon emission tomography with ^{99m}Tc-MIBI in diagnosis of metastatic widespread in breast cancer

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Mammascintigraphy (MS) with the ^{99m}Tc-MIBI has been widely used for detection of primary node of breast cancer. In this study we have evaluated the MS advanced with ^{99m}Tc-MIBI single photon emission computed tomography (SPECT) as a tool for diagnosis of the metastatic widespread in breast cancer.

Planar and SPECT MS were performed in 46 ladies with proven breast carcinoma before treatment. SPECT was carried out in 1 h after injection of 740 MBq of ^{99m}Tc-MIBI. In SPECT study axial, frontal and sagittal slices were reconstructed and reported by non-informed radiologist.

The results of mammascintigraphy were correlated with data of pathologic study of the surgically excised specimen. External axillar, sub- and supraclavicular lymph nodes were analysed separately. The results were as following:

The overall sensitivity was 79.6%. No false-positive cases were observed. In 9 ladies also an increased uptake of ^{99m}Tc-MIBI was observed in parasternal regiones. Like axillar lymph nodes, this has been reported as suspective for the parasternal metastatic involvement, although here without morphologic justification. These results were used in all the cases for design of gamma-radiation