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LOW DOSE, SHORT-TERM ADJUVANT CHEMOTHERAPY IN STAGE I , HORMONE RECEPTOR NEGATIVE BREAST CANCER

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Adjuvant therapy is able to improve the disease free survival and the overall survival of patients with breast cancer. Currently there is no information about the necessary dose-intensity in patients with stage I disease available. Thus, a randomized clinical trial was performed to test the hypothesis whether or not low dose chemotherapy lasting only 35 days improves the outcome of breast cancer patients with stage I disease and negative estrogen and progesterone receptors. Between 1984 and 1990 277 stage I breast cancer patients were randomized between an untreated control and a low dose, short-term chemotherapy. Chemotherapy consisted of one cycle doxorubicin and vincristin on day 1 followed by one cycle of cyclophosphamide, methotrexat, and 5-fluorouracil on days 28 and 35. Patients were stratified for tumor stage, type of operation, menopausal status, and participating center. Results were analyzed both by univariate and multivariate statistics. After a median follow-up of 78 months disease free survival and overall survival do not differ significantly between patients receiving adjuvant therapy and the control arm. Univariate and multivariate statistics do not show any significant prognostic or therapy related factor. The major conclusion from this mature study is the observation that a low dose, short-term adjuvant chemotherapy is insufficient to improve the prognosis of patients with stage I breast cancer and negative hormone receptors.

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TAMOXIFEN +/- SHORT-TERM CHEMOTHERAPY IN THE TREATMENT OF NODE POSITIVE, HORMONE RECEPTOR POSITIVE BREAST CANCER: 7-YEAR RESULTS OF A RANDOMIZED TRIAL INCLUDING 517 PATIENTS

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Tamoxifen has a strong impact upon the disease free survival and the overall survival of patients with breast cancer and hormone receptor positive tumors. Cytostatic treatment improves the prognosis of node positive patients. Whether the combination of both treatment modalities is beneficial for node positive, hormone receptor positive patients has been discussed controversially. Since patients with hormone depending tumors have a relatively favorable prognosis, it has been suggested to use low dose short-term cytotoxic treatment in order to minimize side effects. We designed a prospective randomized multicenter trial to investigate the effects of one cycle of doxorubicin 20 mg/m² and vincristin 1 mg/m² on day 1 followed by one cycle of cyclophosphamide (300 mg/m²), methotrexat (25 mg/m²), and 5-fluorouracil (600 mg/m²) on days 28 and 35 in addition to tamoxifen 20 mg/d for at least two years. The results were analyzed both by univariate and multivariate statistics. After a median follow-up of 7 years no beneficial effect of the chemotherapy regimen used upon disease free survival and overall survival was detected. Subgroup analyses according to various prognostic factors such as grading, quantitative receptor measurement, and number of involved nodes have been performed and the sults will be presented in detail. In conclusion our data show that chemotherapy with low dose-intensity lacks any efficacy in the treatment of patients with stage II, hormone receptor positive breast cancer when added to tamoxifen. Thus, patients with hormone responsive tumors should be treated with tamoxifen alone or - especially when additional adverse risk factors for

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TREATMENT OF ADVANCED BREAST CANCER WITH VINORELBINE (VLB), FLUOROURACIL (FU), L-LEUCOVORIN (LLV), AND HUMAN GRANULOCYTE COLONY-STIMULATING FACTOR (GCSF)

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29 women with advanced breast cancer were treated with an iv combination regimen consisting of vinorelbine (40 mg/m2 iv on days 1 and 14), FU (400mg/m2, days 1-5), LLV (100mg/m2, days 1-5) and GCSF (5mcg/kg/d sc on days 6-12). Treatment cycles were repeated every 4 weeks. 27 patients (pts) are evaluable for response and toxicitiy assessment. 9 pts were refractory to first-line chemotherapy, all others were chemotherapeutically naive. 11 pts were pre- and 18 pts postmenopausal. The median age was 56 (29 to 75) yrs, and the median WHO performance status 1 (0-2). Predominant tumour sites were visceral in 23, soft-tissue and bone in 3 pts each. After a median of 5 (2-6) treatment cycles, 11/18 (61%) previously untreated pts with metastatic disease, and 2/9 (22%) chemotherapeutically pretreated pts had objective tumour response, including 3 CR. The median time to response was only 1.8 (1.5 - 4.2) months, median duration of both response and survival have not been reached yet. WHO grade III and IV hematologic side effects occurred in 9 and 3 pts, including 2 cases with septicaemia. Severe nonhematologic side effects (WHO III/IV) requiring dose attenuations occurred in 4 pts, and included stomatitis in 2, emesis and neuropathy in 1 pt each. Other commonly encountered, though generally mild adverse reactions were nausea/vomiting (55%), constipation (31%) and local reactions at the injection site (27%). We conclude, that VLB/FU/LLV+GCSF is an effective regimen for treatment of advanced breast cancer, particularly if used for first-line therapy.

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Cell Proliferation of Breast Cancer as a Marker of Radio- and Chemoendocrine Sensibility.

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The present investigation included 69 breast cancer patients (I group-T3N0-38; II group-T4N0-31). The tumor proliferation was studied by radiochemistry using H3-timidine and by immunocytochemistry using the KBI antibody to Ki67 and the antibody to PCNA supplied by ZYMED. Samples of the breast tissue were obtained by minimal open biopsy, surgical excision or FNA. Oestrogen receptor (ER) status was determined by radioassay using H3-oestradiol. In I group patients (T3N0-38) we have studied the proliferation of the breast cancer tissue before and after preoperative radiotherapy (RT-4Gr-5 days); in II group (T4N0-31) - before and after 14 days of the chemoendocrine therapy (CEF 5-Fluorouracil, Cyclophosphan, Tamoxifen).

The changes of the proliferation activity during preoperative RT were: for H3-timidine from 10.4+0.09 to 7.8+0.04 depart.in min/mc DNA, for Ki67 the med.I from 12.1 to 5.7II, for PCNA the med.I from 4.1 to 3.3II. The proliferation activity changes during CEF in ER positive cancer tissue (18 patients) were: for H3-timidine from 13.7+1.18 to 9.5+1.01 depart.in min/mc DNA, for Ki67 the med.I from 8.1 to 5.1II, for PCNA the med.I from 2.9 to 2.0II. These data suggest that H3-timidine and Ki67 tests as markers of cell proliferation may be used for the confirmation of radiosensibility and chemoendocrine sensibility of ER positive breast cancer.

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Plasminogen activator inhibitor type 1 as a prognostic factor in breast cancer

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Urokinase plasminogen activator (uPA) and its inhibitor, plasminogen activator inhibitor type 1 (PAI-1) have been reported to be correlated with prognosis in breast cancer.

Aim: To investigate the prognostic importance of PAI-1.

Patients and Methods: PAI-1 was measured with ELISA in cytosol routinely used for estrogen - (ER) and progesteron receptor (PgR) analysis in patients not treated with any systemic adjuvant therapy (n=100). Information on uPA was available for all cases.

Results: The estimated relapse free survival, median follow up 38 months, was better (p = 0.014) for those with low PAI-1 compared to those with high. The corresponding test for uPA showed similar results (p=0.012). Multivariate analysis: When analysed separately, uPA and PAI-1 seem to give approximately the same prognostic information in addition to that of lymph node status, tumor size and PgR (p=0.060 and p=0.024, respectively).

Conclusion: PAI-1 is a promising prognostic factor in breast cancer, which should be further investigated.

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CEF±G-CSF AS PRIMARY CHEMOTHERAPY (PCT) IN ≥ 3 CM BREAST CANCER (BC) PATIENTS (PTS).

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Ninetynine pts with ≥ 3 cm BC, 56 considered having a resectable tumor (group A, T2 > 3 cm or T3, N0-1, M0) and 43 a locally advanced tumor (group B, T4 and/or N2, M0), were treated with PCT consisting of 3 cycles of CEF (CTX 400 mg/m², EPI 50 mg/m², 5-FU 500 mg/m²) iv on days 1 and 8, ± G-CSF 300 μg/day sc every other day from day 5 to 17. The aims of the study were 1) to substitute conservative for mutilating surgery (group A) or to make resectable unresectable tumors (group B); 2) to improve disease free survival and overall survival (group A and B). Fiftysix pts in the group A and 41 in the group B are evaluable. There were 2 pCR and 46 pPR in group A (85.7%) and 1 pCR and 33 pPR in group B (82.9%). Only 1 pt in group A progressed during treatment. Myelosoppression was the most important side effect, with G3-G4 neutropenia in 42/58 pts (72.41%) treated with CEF plus G-CSF, and in 41/51 pts (80%) treated with CEF alone; the planned dose-intensity of CEF was mantained in 79.31% of the G-CSF pts, and in 31% of the no-G-CSF pts ($p < 0.0001$). For this reason the study is continuing with G-CSF in all of the pts. Breast conserving surgery was carried out in 20/54 pts in group A (37%) and in 8/41 pts in group B (19.5%). The relative low percentage of quandrantectomy in group A was related to a particulary, unfavourable patient population with bifocal or multifocal residual malignancy, or with an extensive intraductal component, and central or retroareolar tumors. After surgery, responsive pts received 3 adjuvant cycles of the same CT; non responsive pts received 3 cycles of an alternative non-cross resistant adjuvant CT (Vinorelbine + Mitomycin C). Adjuvant CT was followed by RT in pts treated with quadrantectomy or with T4 and/or N2 tumors, and TAM in those with ER+ tumors. With a median follow-up of 25 months (range 1-64), we have documented a new disease manifestation in 18 pts in group A (33%) and 16 pts in group B (37.2%). Among the 18 pts who relapsed in group A and the 16 who had a recurrence in group B, 16 and 15, respectively, had had a response to PCT (88.8% and 93.7%). The majority of relapsed pts had axillary positive lymphnodes at surgery (66.6 pts group A and 75% group B), notwithstanding the good response to PCT of primary tumor. Therefore, the response to induction chemotherapy of primary tumor may be not sufficient to select the appropriate adjuvant treatment, which should be based on both the response of primary tumor and axillary lymphnodes. In this regard, new biologic parameters (gp 170, p53, bcl-2) will be analyzed.