793 POSTER

Dose-intensive adjuvant Chemotherapy with Epirubicin/Paclitaxel vs. Epirubicin/Cyclophosphamide in breast cancer patients with 4–9/over 9 (second group) positive nodes: Preliminary data of this phase II/III trial

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Taxanes and anthracyclines represent the two most active groups of agents for the treatment of breast cancer. The purpose is to evaluate this combination in patients with more than 3 positive lymph nodes in an adjuvant, dose-intensive, sequentially therapy in comparison with the standard chemotherapy regimen epirubicin/cyclophosphamide.

Methods: Since 9/96 191 patients with 4–9/over 9 positive lymph nodes have been recruited from 23 participating centers in an ongoing trial. 99 patients were prospectively randomised for first-line chemotherapy to treatment group A (epirubicin 90 mg/m"-paclitaxel 175 mg/m"; 4 cycles biweekly, supported by G-CSF 5 μg/kg/bw day 5–13 and 3 sequential cycles CMF 600/40/600 mg/m" at 2-weeks interval) and 92 patients to treatment group B (epirubicin 90 mg/m"-cyclophosphamide 600 mg/m"; 4 cycles triweekly, and 3 sequential cycles CMF 600/40/600 mg/m" at 3-weeks interval).

Results: Preliminary safety and toxicity data are evaluable for 929 cycles. Data about response rate and Disease-Free-Interval and and Overall Survival will be delivered later. For the hematological toxicity the main grade 3 and 4 (WHO) adverse events for A vs. B were: leucopenia 18.2% vs 11.1%, febrile neutropenia 1.2% vs 0.5% -anemia (<5.9 mmol/L) 0.7% vs 0.5%-thrombopenia 0.1% vs 0%. Non-hematological toxicity occurred more frequently in group A (WHO grade 2, 3, 4):-neuropathy 4.3% vs 0%,-nausea/emesis 31.2% vs 24.2%,-fatique 10,1.6% vs 3.4% and stomatitis 3.1% vs 0.5%.

Conclusion: The schedule of the dose-intensive application form with G-CSF-support (Epirubicin/paclitaxel) was well tolerated. After completion of this trial (12/1999), its role in relation to the standard chemotherapy with epirubicin/cyclophoshamide, accordingly to an higher efficacy and a significantly shorter treatment duration, will be possible. The study was grant supported by Bristol-Myers Squibb Oncology, Pharmacia Upjohn and Amgen Gmbh.

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Clinicopathological evaluation of MR imaging of nonpalpable breast cancer with bloody nipple discharge

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Purpose: MR mammography is a sensitive diagnostic method for the detection of breast cancer. We evaluated the utility of contrasted material enhanced and fat suppressed MR images (FFE and SPIR method) of the nonpalpable breast cancer cases with bloody nipple discharge comparing with surgical indication and pathological results.

Materials and Methods: From 1995 to 1999, 195 women underwent MR imaging in our hospital. There were 10 nonpalpable breast cancer cases with bloody nipple discharge. These cases were reviewed regarding to conventional diagnostic images, ductscopic findings, surgical approach and pathological results.

Results: MR mammography revealed high signal intensity in the early phase of a dynamic scan, which means malignant changes in all the cases. Cytological examination showed Class V in 3, Class III in 3 and Class II in 4 cases. MR images coincided with malignant area in 8 cases pathologically. Extensive intraductal component was identified in 9 cases on pathological examination.

Conclusion: MR mammography can be extremely useful in addition to conventional diagnostic modality in determining the surgical line.

795 POSTER

Role of increased arterial inflow in arm edema after modified radical mastectomy

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Purpose: Chronic arm edema is a common finding after modified radical mastectomy and its pathophysiology is not clear. In a prospective randomized study the value of increased arterial inflow and venous abnormalities after mastectomy was evaluated.

Methods: Arterial and venous blood flow in axillary vessels of 39 patients with arm swelling and 16 patients without swelling were investigated by Doppler ultrasound.

Results: In patients with arm edema the arterial flow on surgical treated side was 689.73 $\pm$ 44.6 (mean $\pm$ sem) ml/min and 427.73 $\pm$ 30.8 ml/min on contralateral side ($p < 0.05$). In those without swelling the flow was 447.75 $\pm$ 37.8 ml/min on treated side and 354.95 $\pm$ 28.7 ml/min on contralateral side ($p > 0.05$). The difference between arterial flow measurements on treated sides of the patients with and without arm swelling was statistically significant. There was no significant difference between the measurements on contralateral sides of both groups. Venous abnormalities were not detected in both groups of patients.

Conclusion: Modified radical mastectomy causes increased inflow in ipsilateral arm and it may play an important role in the etiology of arm swelling in breast cancer patients.

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Measuring radiation fibrosis: The inter-observer reliability of two methods of determining the degree of radiation fibrosis

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Purpose: To compare the inter-observer reliability of the palpation method with the quantitative method of measuring tissue compliance with a "tissue compliance meter" (TCM) on women who had had breast conserving surgery and radiotherapy for breast cancer.

Method: 38 patients and 30 controls were measured with the palpation method by 2 radiotherapists and with the TCM by two physiotherapists. Measurements were taken on 4 locations of the breasts of all 68 women. Reliability coefficients were computed for both methods. A weighted kappa score was computed for the palpation method and this was compared with the intraclass correlation coefficient (ICC), which was computed for the TCM-method. The difference in compliance between both breasts in the patient group was compared with that of the control group.

Results: A weighted kappa of 0.65 was computed for the palpation method and an ICC of 0.91 was computed for the TCM-method. The difference in compliance between both breasts is significantly larger in the patient group then in the control group.

Conclusion: The inter-observer reliability of the TCM-method is superior to that of the palpation method, although both methods have a good reliability. Another advantage of the TCM-method is its greater sensitivity to change ('responsiveness'), since measurements are made on a continuous scale. At locations were the TCM is not applicable, palpation is a good alternative.

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Initial doxorubicinol 7-deoxyaglycone (Dol 7-d) levels and persisting cardiotoxicity after adjuvant doxorubicin in women with early breast cancer

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Anthracycline containing adjuvant therapy improves outcome but long term cardiotoxicity remains a concern despite limiting the cumulative dose.

Anthracyclines are extensively metabolised. Quinone ring reduction leads to 7-deoxyaglycones with concommitant free radical superoxide formation. Differing Dol 7-d levels may reflect the variability seen in cardiotoxicity for the same cumulative dose.

We prospectively studied 36 women (age range 25 to 58) with breast cancer receiving single agent doxorubicin (75 mg/m^2) as part of their adjuvant therapy. They had normal baseline ECG, liver biochemistry and 2-D echocardiography. Blood was taken 30 minutes after the first bolus injection for metabolite analysis. Echocardiograms were repeated at 3 and 9 weeks, prior to further doxorubicin doses and at 1 year.

57% of patients had Dol 7-d levels, ranging from 2 to 90 ng/ml. No patient developed cardiac failure (mean drop in LVEF of 3.5% after 1 year). Significant differences in diastolic function (Peak E) were found by 9 weeks (paired t-test, $p < 0.01$) which persisted at 1 year (paired t-test, $p < 0.05$) but not linked with LVEF changes. Dol 7-d levels at 30 minutes correlate with Peak E changes at 9 weeks (Kendal's rank correlation coefficient, $p < 0.01$) but not at 1 year ($p < 0.1$) and not with other variables such as age or smoking history. These results support the hypothesis that Dol 7-d levels are associated with early free radical damage to the heart but not with long term cardiotoxicity.

798 POSTER

GEPARDO – A German trial of preop. chemotherapy with ADoc in breast cancer: First promising results

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Purpose: To assess the tolerability and efficacy of preoperative chemotherapy with adriamycin and docetaxel (ADoc) in patients with primary op. breast cancer.

Patients and Methods: In a prospective phase II-trial 195 patients with hi-stologically confirmed primary breast cancer (tumor > 3 cm, not T4) received dose-intensified adriamycin (50 mg/m^2) and docetaxel (75 mg/m^2) every 14 days and surgery after 4 cycles. Patients also were randomized to simultane-ous tamoxifen vs no tamoxifen. We report about an intermediate evaluation on 45 patients (T > 5 cm, N+ 58%)

Results: Response using best imaging was: CR 5%, PR 69%, NC 23%, PD 3%. Breast conserving surgery was performed in 74% of the patients. Hi-stol. CR was achieved in 6 patients (14.3%). Therapy was interrupted in 2 patients. Hemat. tox. III/IV 32/12%, gastroint.tox was mild as well as muco-sa and cutane tox..

Comclusion: 8 weeks of preop.Adocñtam efficiently reduce tumor size, achievehigh rate of PCR and breast concerving. Toxicity was well acceptable and tolerable in 95% of the patients.

799 POSTER

Endometrial changes caused by tamoxifen

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Purpose: Prolonged therapy with tamoxifen gives rise to endometrial abnormalities and has been reported to increase the subsequent development of endometrial cancer six fold. This prospective study was designed to examine the time course over which endometrial abnormlities occur in an adjuvant setting.

Methods: Patients requiring adjuvant tamoxifen as part of their normal treatment for breast cancer underwent baseline pelvic examination, transvaginal ultrasound scanning (TVUS) to measure endometrial thickness (ET) and biopsy for histology and insulin growth factor-1 levels if ET was >7 mm. Subsequent TVUS (and biopsy if ET > 7 mm) was performed at 1, 2, 3, 6, 12, 24 and 36 months.

Results: Twenty seven patients have been studied for a mean of 15.8 months. The mean endometrial thickness has increased from 3.45 mm before tamoxifen (0 months) to 4.99, 5.7, 5.3, 4.98, 4.85, 5.55 and 6.6 mm at 1, 2, 3, 6, 12, 24 and 36 months. After 6 months therapy with tamoxifen, 41% of women had an increase in endometrial thickness of >100% and this had risen to 50% of women after 12 months therapy but had decreased to 40% after 24 months therapy.

Conclusion: Tamoxifen causes a rapid initial rise in endometrial thickness, perhaps due to oedema, but then continues to increase endometrial thickness progressively with increased duration of use.

800 POSTER

Systemic therapy and acute reactions during adjuvant RT after conservative surgery in early breast cancer

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Purpose: To evaluate the influence of different adjuvant chemotherapy (CT) or hormone therapy (HT) regimens, on acute reactions during post-operative RT, in pts with stage I–II breast cancer treated in 12 Institutions of Northern Italy (Lombardy), in 1997.

Methods: The analysis concerns local toxicity (EORTC-RTOG scale) in 1610 pts (mean age 57 yrs, 69% post-menopausal, 31% N+). The whole breast was irradiated with 60Co or 4–6 MV photons at the mean ICRU dose of 50 Gy, plus a booster of 10 Gy in 1070 cases: 38% of pts had CT, 33.4% HT, 28.6% only RT.

Results: The incidence of acute skin reactions in pts treated with only RT was: grade (G)0 = 19.6%, G1 = 61.4%, G2 = 17%, G3 = 2%; in pts treated with HT: G0 = 14.3%, G1 = 66.2%, G2 = 17.3%, G3 = 2.2%; and in pts treated with CT: G0 = 12.4%, G1 = 62.2%, G2 = 21.1%, G3 = 4.3%. No acute toxicity involving lung or heart was detected. RT had to be interrupted in 35 cases owing to the toxicity of the combined treatment (RT + CT). There are no significant differences in acute cutaneous toxicity due to the types of chemotherapy (ADR based CT, CMF or others).

Conclusion: Post-operative RT was well tollerated, also with concomitant CT. The conclusive data including follow-up for cosmesis and survival will allow us to evaluate results and cost-effectivness according to different treatments and RT modalities.

801 POSTER

Concurrent sequencing of full dose CMF chemotherapy and radiation therapy in early breast cancer

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Purpose: The aim of this study was to evaluate whether the concurrent sequencing of CMF chemotherapy and adjuvant tangent breast irradiation effects the ability to deliver optimum doses of both treatment modalities.

Methods: Between the years 1986–1998, 105 patients were treated with CMF chemotherapy and radiation therapy. 67 were treated with concurrently (group 1) and 38 sequentially (group 2). Patients were well balanced with respect to age (48 vs 49 p = 0.9), no. positive nodes (0.3 vs 1), comorbid conditions (12.5% vs 10%) and breast seperation (18 vs 19.2). Mean follow up was 2.8 yrs. in group 1 and 3 yrs. in group 2.

Results: There was no significant difference in the % of prescribed chemotherapy actually delivered in the two groups (95% vs 95%), chemotherapy delay (7.4 days vs 6.6 p = 0.22), or nadir platelet and granulocyte counts (179 vs 187 p = 0.09, 1272 vs 1473 p = 0.06). There was a small but significant delay in radiotherapy delivery (1.85 days vs 0.4 p = 0.006). Of the patients followed for >2 yrs. 66%, 27% and 5% had excellent, good or satisfactory cosmesis in group 1 compared with 75%, 25% and 0% in group 2. There has been no local failures in group 1 compared with one (2.4%) in group 2 and 1 (1.4%) distant failure in group 1 compared with 4 (11%) in group 2 to date.

Conclusion: It is possible to safely deliver optimum doses of CMF chemotherapy and radiation therapy concurrently.

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Her 2 and topoisomerase (TOPO)IIα as predictive markers for node-positive (N+) breast cancer (BC) patients (PTS) randomised to adjuvant CMF or epirubicin (E) – cyclophosphamide (C)

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At ASCO '99 we reported the results of a clinical study where 777 pre- and post-menopausal N+ BC pts were randomised to: a) CMF (oral C) × 6; b) EC (E 60 mg/m^2, C 500 mg/m^2) d 1 i.v. q 3 wks × 8; c) high dose EC (HEC) (E 100 mg/m^2, C 830 mg/m^2) d1 i.v. q 3 wks × 8. The median follow-up is 50