P79 Three new highly active cisplatin-containing combinations in locally-advanced (stage III) and locally-recurrent breast carcinoma. A phase II randomized study

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We designed three new four-drug cisplatin-containing combinations to be tested in breast carcinoma. All schedules included methotrexate (M) on day 1 and cisplatin (P) on day 2, as in the classical MVAC combination, and differed from one to another in the addition of other two drugs among epirubicin (Epi), vincristine (V), etoposide (E), mitomycin (Mi). This study was a further development of the cisplatin/etoposide combination, which was shown to be very active in metastatic (Cocconi et al.; JCO 1991; 9: 664) and of the classical MVAC combination, which was confirmed as very active even in breast carcinoma (Bisagni et al.; Annals of Oncol. 1994; 5: 93). We randomly administered these combinations, named MPEpiV, MPEpiE, MPEMi, to 101 patients with stage III (57) or with locally-recurrent breast carcinoma (44). After 4 cycles, patients received local treatment, surgery and/or radiotherapy. The toxicity of the three combinations was substantial but treatment was tolerable and no toxic deaths were observed. Bone marrow suppression, vomiting and mucositis were the most important side effects. The short-term objective response was very high, with no significant differences among the three schedules. Including in the denominator all 101 patients in an intention to treat analysis, the overall CR rate was 23%, and the CR plus PR rate 86%. In stage III, at time of surgery, 7 of 57 patients showed pathological CR (12%). Even the long-term results appeared as favourable compared with those usually reported in the literature in these situations. After a median follow-up of 56 months, in stage III disease 3 yrs and 5 yrs RFS were 60–49% and 79–63% respectively; in locally recurrent disease RFS were 40–26% and 89–64%.

In conclusion, these three new so-called MVAC-like combinations appeared very active in treating stage III and locally-recurrent breast carcinoma. Our results warrant further investigations using these schedules, compared to conventional chemotherapies, in phase III studies concerning metastatic disease and adjuvant/neoadjuvant setting.

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P80 Neoadjuvant chemotherapy in locally-advanced breast cancer: A preliminary report

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Eighty-five patients with locally-advanced (stage III) breast cancer were recruited to the study. Thirteen patients were subsequently excluded during follow-up. The median age was 50 (range: 28–70) in the remaining 72 patients. There were 33 premenapausal and 39 post-menapausal patients. The treatment protocol consisted of 3 consecutive cycles of neoadjuvant CEF (cyclophosphamide 500 mg/m2/d on day 1, epirubucin 50 rng/m2/d on day 1 and fluorouracil 600 mg/m2/d on day 1, to be repeated every 3rd week). Response to treatment was evaluated as a reduction of the initial size of breast mass evaluated by physical examination and mammography. In case of CR and PR, 4th cycle of CEF was given followed by modified radical mastectomy, 5th CEF, radiotherapy and 3 cycles of CMF chemotherapy, respectively. We obtained 16 (18.8%) CR, 60 (70.6%) PR, 7 (8.2%) stable disease and 2 (2.4%) progressive disease. Median disease-free survival (DFS) durations were 19.58 and 21.54 months in premenapausal and post-menapausal patients, respectively. Median overall survival (OS) durations were 19.64 and 22.78 months in these patients. In overall patient group, median DFS and OS durations were 19.78 and 21.54 months, respectively.

Further follow-up is needed to evaluate the results of this treatment protocol.

P81 Using high doses of 5-fluorouracil in patients with breast cancer: 3-Year results of the treatment

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The aim is studying the effectiveness of using the intensive regime of chemotherapy with high doses of 5-fluorouracil in treating patients having breast cancer (BC).

Material and Methods: There have been treated 24 patients with nodular forms of BC II (12) and III (12) stages of a disease. The treatment included the conducting of preoperative chemotherapy according to the scheme: 5-fluorouracil at a dose of 1000 mg/m2 per day as 120-hour infusion i/v on the 1-st to the 5-th days; methotrexate at a dose of 40 mg/m2 and cyclophosphamide at a dose of 600 mg/m2 on the 1-st, 8-th days. After performing a radical mastectomy in the postoperative period 5–6 courses of chemotherapy using the scheme CMF and radiotherapy by indications were also carried out. The control group consisted of 66 patients with BC having got a standard chemotherapy course according to CMF scheme in the preoperative regime.

Results: The efficiency of the neoadjuvant chemotherapy made up 79.2%, treatment without any effect was marded in 20.8% of patients. In the control group these indices corresponded to 53% and 47%. The most expressed effect of treating was observed in women younger than 50 years with a normal menstrual function. The results of the treatment did not depend on the histological type of a tumor. For patients having got the intensive regime of treatment the 3-years survival rate without signs of the tumor recurrence made up 95%, without metastases it was 90%. In the control group these indices made up 86.2% and 69.8%, respectively.

Conclusion: The obtained results testify to a high effectiveness of the proposed regime of neoadjuvant chemotherapy.

Friday, February 27, 1998 9.00–18.00

Adjuvant Conventional Chemotherapy

P82 Comparison of doxorubicin/cyclophosphamide versus doxorubicin/cyclophosphamide/tamoxifen and CMF-chemotherapy versus tamoxifen in node positve breast cancer. An up-date of the German adjuvant breast cancer group (GABG) trial

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Goal: To assess the effectivity of chemotherpy (CT) versus CT + Tamoxifen in a high risk (HR) group and CT versus Tamoxifen in a low risk (LR) group of women with node positive breast cancer.

Patients and Methods: Based on the extent of axillary lymph node involvement and hormone receptor status, patients were recruited to the LR and HR arm of a trial run between 1981 and 1986. Patients with oestrogen and/or progesterone receptor (R) positive ($\geq$20 fmol) tumors with less than 4 involved lymph nodes (n = 276) were randomized to either tamoxifen 3 × 10 mg/day for 2 years or 6 cycles of cyclophosphamide 500 mg/m^2, methotrexate 40 mg/m^2 and 5-fluorouracil 600 mg/m^2, all day 1 + 8 (CMF) intravenoulsy (i.v.). Patients with R negative tumors or more than 3 nodes involved were randomized to 8 cycles of doxorubicin 30 mg/m^2 day 1 plus cyclophosphamide 300 mg/m^2 day 1 + 8, (AC) i.v. or 8 times AC plus tamoxifen 3 × 10 mg/die orally for 2 years.

Results: In this up-dated analysis of a follow up of 10 years no difference in clinical outcome could be observed in the LR group. However in patients <50 years of age CMF significantly improves disease-free (DFS)(p = 0.05, log rank test) and overall survival (OS)(p = 0.008), whereas patients >50 years tamoxifen was more effective (DFS: p = 0.001, OS: p = 0.05). Due to this retrospective stratification and an imbalance of the age distribution in the 2 treatment arms these results have to be interpreted with caution. In the HR group a significantly prolonged disease-free survival (p = 0.03) and a trend for a longer overall survival (p = 0.1) for patients >50 years with the chemoendocine treatment. The same was found for patients with positive R (DFS:p = 0.03 and OS: p = 0.5).

Conclusions: The effect of chemo- and endocrine therapy in node positive breast cancer is dependent on patients age and the receptor content of the primary. CT is effective in younger patients, the combination represents the best choice for patients >50 years of age.

P83 Dose effect of epirubicin in amenorrhea induced by chemotherapy for breast cancer

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Purpose: To demonstrate the role of Epirubicin combined with Cyclophosphamide and 5 Fluorouracil (FEC regimen) in amenorrhea induced by chemotherapy.

Population: 269 premenopausal patients received FEC in neoadjuvant and/or adjuvant setting for breast cancer. Epirubicin was utilized at 50 mg/m^2, 75 mg/m^2 or 90 mg/m^2.

Method: amenorrhea was defined as discontinuation of menses for at least 60 days from the first day of the last menses. Mean dose (mg/m^2) of Epirubicin and Cyclophosphamide received at onset of amenorrhea, total dose of these two drugs administered were recorded. Dose intensity (dose/time) was evaluated

too. Amenorrhea according to doses of Epirubicin was evaluated in each group of age (<38 years, 38–41, 42–47, ≥48).

Results: 269 premenopausal women (range of age: 23–55 years, median age 43 yrs) received FEC regimen at various doses of Epirubicin. 191 patients became amenorrheic while on chemotherapy: 8/58 among women <38 yrs, 30/43 in 38–41 yrs, 106/119 in 42–47 yrs, 47/49 in ≥48 yrs. With an equal dose of Cyclophosphamide we observed no difference of mean total dose of Epirubicin received between patients with amenorrhea and without amenorrhea in each group of age.

As for Cyclophosphamide, the mean dose of Epirubicin at amenorrhea decreases as age increases. Three cycles of FEC regimen with 50 mg/m^2 per cycle (FEC 50) are similar to 3 cycles of FEC 90 to achieve amenorrhea in women 38–41 year old. In women 42–47 year old 2.6 cycles of FEC 50 and 2.3 cycles FEC 90 are needed to achieve amenorrhea this difference is not significant. There is no effect of the dose of Epirubicin in inducing amenorrhea in FEC regimen.

Conclusion: with an equal mean Cyclophosphamide dose in all age groups, increasing Epirubicin dose does not increase the rate of chemotherapy related amenorrhea. These results allow us to inform a patient who is about to receive chemotherapy combining Fluoro-uracil, Epirubicin and Cyclophosphamide, on the probability to become amenorrheic according to her age and the dose of Cyclophophamide whatever the dose of Epirubicin.

P84 High dose epirubicin and cyclophosphamide (EC) vs cyclophosphamide, methotrexate, fluorouracil (CMF) as adjuvant chemotherapy in high risk premenopausal breast cancer patients (PTS). A prospective randomized trial

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Two hundred and seven consecutive premenopausal breast cancer pts, pT1–3 with >3 involved lymphnodes, were randomized between 1/90 and 4/95 after radical surgery to classic CMF (C 100 mg/m^2 p.o. days 1–14, M 40 mg/m^2 and F 600 mg/m^2 i.v. on days 1 and 8 q 28) for 6 cycles or to EC (E 120 mg/m^2 and C 600 mg/m^2 day 1 q 21) for 4 cycles. One hundred and four CMF and 103 EC pts were enrolled overall; median age, tumor size, no. of involved lymphnodes (≤10, >10), ER status and type of surgery were well balanced. Toxicity (G 3–4, WHO) was significantly higher ($p < 0.001$) in EC compared with CMF pts, particularly for neutropenia (35 vs 14%), nausea and vomiting (39 vs 18%), alopecia (72 vs 15%), while amenorrhea was 38 vs 30%. No cardiotoxicity has been observed so far in any pt. The received dose intensity >80% was 86% in EC vs 87%in CMF pts (D.I. >90% 69% and 65%, respectively). After a median follow-up of 48 mos, 6 local relapses were observed in each treatment arm, whereas 37 EC (35.91%) and 47 CMF pts (45.14%) developed distant metastases ($p = 0.2$) in the bone (39%), viscera (51%), and soft tissue (10%). The projected 5-y DFS is 57% for EC and 45% for CMF pts (p = NS). The 5-y OS is 70% for EC and 71% for CMF pts. In conclusion, a trend in favor of EC has been consistently observed but, at the time of this analysis 4 cycles of EC appear as effective as 6 cycles of classic CMF in a much shorter treatment period (9 vs 22 w), with a higher but rapidly resolving toxicity; no cardiotoxicity has been observed so far. The different "costs" in terms of duration of treatment and pharmacoeconomic aspects are in the process of being evaluated.

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P85 Feasibility of docetaxel (D)-containing regimens in the adjuvant treatment (AT) of breast cancer (BC)

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In preparation for a phase III trial evaluating D in the AT of BC, we tested the feasibility of these regimens: I) A 75 mg/m^2 q 3 wks × 3 → D 100 mg/m^2 q 3 wks × 3 → CMF days 1.8 q 4 wks × 3; II) A 75 mg/m^2 q 2 wks + lenograstim (G) × 3 → D 100 mg/m^2 q 2 wks + G × 3 → CMF (as I) × 3; III) A 50 mg/m^2 + D 75 mg/m^2 day 1 q 3 wks × 4 → CMF (as I) × 4. Radiotherapy was given during/after CMF. Patients with stage II BC and age ≤70 years were eligible.

Main results are summarized in the table.

These data support the feasibility of Arms I and III in the AT of high-risk BC. In the phase III trial, it will be necessary to provide these regimens with an antibiotic prophylaxis, to reduce the incidence of neutropenic fever. The latter has been associated with hospitalisaiton and i.v. antibiotics only in a minority of cases. Arm II can not be recommended due to the unacceptable rate of early treatment discontinuation for severe skin toxicity.

Arm	I	II	III
No. pts/No. cycles	20/174	30/221	14/53
% cycles:			
– delayed	11	10	4
– dose-reduced	6	10	6
Median RDI*	100	100	100
No. pts withdrawn	2	8	–
G3–G4 toxicity % pts/% cycles:			
– diarrhea	–	10/2	–
– stomatitis	20/3	17/2	7/4
– skin	5/1	27/5	–
Neutropenic fever (%pts/%cycles)	30/3	10/1	57/15
% cycles with:			
– antibiotic therapy (oral)	10 (6)	9 (5)	11 (8)
– RBC transfusion	1	1	–
– hospitalization	5	4	8

* R.D.I. = relative dose-intensity

P86 Epirubicin as a single agent in comparison to CMF in adjuvant therapy of stage I and II breast cancer

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Anthracyclines are among the most effective single agents in the treatment of advanced breast cancer, but their use in an adjuvant setting is still undefined. While the Oxford overview found poli-chemotherapy (CT) superior to a single agent, anthracyclines as a single agent have not been previously evaluated. Relatively short regimens such as 4 courses of doxorubicin plus cyclophosphamide were proven to be equivalent to CMF for 6 courses. Therefore, we conducted a prospective randomized trial of weekly Epirubicin (E 30 mg/m^2) for 4 months vs CMF iv (C 600 mg/m^2, M 40 mg/m^2, F 600 mg/m^2, days 1–8, every 4 weeks) for 6 courses. A weekly schedule of E was chosen because of its reduced cardiac toxicity. From November 1990 to January 1994 a total of 348 pts with ER−N−, and ER− & ER+, N+ (<10) were accrued from eleven Italian Centers. Postmenopausal pts received concomitantly tamoxifen for 3 yrs. RT to conserved breast was given post-CT. Eight pts were ineligible. Median age was 50 yrs (range 30–70); 181 pts were premenopausal. The two arms were well balanced according to the most important prognostic factors. Ninety-seven percent of pts received six courses of CMF and 89% of pts received 16 wks of E. The planned and delivered dose intensities (mg/m^2/week) were calculated for each drug and the median ratio between delivered/planned dose was superior to 0.9 for all drugs. Toxicity in the two arms was superimposable except for more frequent grade 3 alopecia in E treated patients ($p = 0.001$). Two treatment-related deaths (congestive heart failure in the E arm and neutropenia septic shock in the CMF arm) were observed. Amenorrhea occurred in 52% of pts treated with CMF and 58% of pts treated with E. At median follow-up of 4.8 years there was no difference in OS and RFS between the two arms for all pts and in the analysis by menopausal status. Relapse free rates for all pts at 5 yrs were 70% ± 4% SD on CMF and 69% ± 4% SD on E; $p = 0.60$. We observed 6 second primary tumours: 4 in CMF treated pts (2 endometrial, 1 kidney and 1 LMA) and 2 in E treated pts (1 non-small cell lung cancer and 1 rectum). A longer follow-up is needed to draw definitive conclusions about the role of adjuvant monochemotherapy with anthracyclines.

P87 Adjuvant therapy of primary breast cancer with doxorubicin vs. pirarubicin in combination with cyclophosphamide and 5-fluorouracil (FAC vs. FPC)

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The aim of this study was to compare antitumour activity and toxicity of the two chemotherapeutical regimens, in adjuvant treatment of an early breast carcinoma (BC), stage II, with standard FAC vs. FPC.

Pirarubicin has been showen in clinical trials, as an anthracycline without significant cardiotoxicity and comparabile efficacy.

Between 1992–1997, 82 patients (pts.) with stage II BC., were enrolled in this open, comparabile study. The charactheristics of the pts. in both groups were well balanced: age <65, PS 0–1, no prior anthracycline therapy, absence of cardiopathy. Pts, were given cyclophosphamide and 5-fluorouracil 500 mg/m^2 each, and either doxorubicin or pirarubicin 50 mg/m^2, every 3 weeks, 6 cycles.

The median follow up was 32 months. Ove all disease free intreval (FAC 8/41 vs. FPC 10/41, N.S.) and survivall (FAC 4/41 vs. FPC 5/41, N.S.) were similar in the both groups. There was also no difference in loco-regional disease free interval (FAC 4/41 vs. FPC 3/41, N.S.).