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.).

Cardiotoxicity was not seen, probably due to low cumulative dose of the anthracyclines, 300 mg/m^2. Toxicity (myelosupression, nausea/vomiting, stomatitis, diarrhoea) was similar in both groups.

Alopecia: FAC group – 10/41 grade II, 31/41 grade III

FPC group – 10/41 grade II, 2/41 grade III

$p < 0.001$, significantly favouring FPC

Conclusion: Pirarubicin gives the same efficacy like doxorubicin, but better life quality, to high risk patients with breast cancer, especially in young women, causing less alopecia.

P88 Adjuvant chemotherapy of primary breast cancer: 20 Years follow up

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Breast cancer ranks the second among all cancers: 14%, and the first among females: 34% at the NCI, Cairo. Average age of onset is 46 years, mostly; 65% in premenopause status. At presentation tumours are bulky mean diameter 6.5 cm, at an advanced stage:T3 and T4 represent 68%, and positive nodes in 75%, with a mean number of 13.4. There is always a high risk of recurrence after primary therapy. In 1976 we started a prospective randomized study comparing one year of adjuvant cobination chemotherapy CMFVP to two years of L-PAM in women with operable breast cancer with histologically positive axillary lymph nodes. In fully evaluable 80 patients for a follow up of 20 years, recurrence was observed in 20 patients who received L-PAM and 42 patients who received CMFVP. There is a significant difference in the disease free survival in favour of CMFVP compared to L-PAM (p 0.001); 30% versus 9%. The most common site of recurrence was local 37%, followed by nodal 27%. Toxicities in both treatments were acceptable and reversible. Although these results showed that continuous CMFVP is far superior than the L-PAM in decreasing recurrences and increasing survival in comparison to no adjuvant chemotherapy: 10% at 5 years, yet they are still far from we expect for our patients. In fact several trials followed using chemo-radiotherapy, and adjuvant high dose chemotherapy followed by autologous bone marrow transplantation with overall promising preliminary results. Follow up of these trials is ongoing at the present time.

P89 Reduction of metastases in breast cancer patients by adjuvant bisphosphonate treatment

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Bisposphonates (BPS) can obviously inhibit osteoclastic activity. This is the reason why they are widely used in the treatment of tumorassociated-osteolysis. In the palliative setting of metastasized breast cancer BPS decrease skeletal-related events. Animal experiments could already proove that osteoprotection with BPS leads to a reduction of number and incidence of bone metastases. From 1991–1995 we performed a prospective randomized study including 142 primary breast cancer patients with positive tumor cell detection in bone marrow (at the time of primary surgery). They were treated with the Bisphosponate Clodronate (1600 mg/d, orally) over 2 years. The identical number of patients was used as controls. Prognostic factors and adjuvant systemic treatment of both groups showed no significant differences as well. Follow-up data were evaluated after a median of 36 months. 22 patients treated with Clodronate developed distant metastasis compared with 41 women without BSP-treatment ($p < 0.001$); 11 of the BSP-group showed bone metastases, whereas 24 of the controls displayed osseous metastases ($p = 0.002$). The average number of bone metastases in every individual differed between 3.1 (clodronate-group) and 6.8 (control-group). Also the bone relapse-free interval was longer (32 months) in the BSP-group compared with the controls (17.5 months). For the first time our study showed, that a reduction of number and incidence of bone metastases is possible by adjuvant treatment with the BPS Clodronate (orally administered over 2 years). It is surprising that even non-bone metastases were reduced. However, it must be mentioned, that the number of patients was limited ($n = 284$) and the time of follow up was moderate. Prospective placebo-randomized studies should be performed to confirm our results.

Friday, February 27, 1998 9.00–18.00

High-Dose and Novel Therapy

P90 Does the mobilization regimen influence peripheral blood stem cell (PBSC) tumor contamination in early breast cancer patients that undergo high dose chemotherapy? A comparison of chemotherapy plus G-CSF vs G-CSF mobilized PBSC

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High dose chemotherapy with PBSC support is being widely used as adjuvant treatment for high risk breast cancer. Tumor cell contamination has been described in PBSC, but its clinical relevance its still unknown. Some authors have speculated that chemotherapy plus G-CSF could act as an "in-vivo" purging, but no data that compare G-CSF plus chemotherapy vs G-CSF mobilized PBSC are available. In 57 high risk breast cancer patients undergoing adjuvant high dose chemotherapy, we compared PBSC collection and tumor cell contamination after Cyclophosphamide 4 g/m^2 (CTX) plus G-CSF vs G-CSF alone. CD34$^+$ CD38$^-$ cells, week-5 cobblestone area forming cells (CAFC) and contaminating breast cancer cells were enumerated in PBSC collections obtained after CTX plus G-CSF ($n = 27$) or G-CSF alone mobilization ($n = 30$). CD34$^+$ cell collection was 1.9 fold higher after CTX plus G-CSF (11 ± 7.9 vs $5.8 \pm 3.5 \times 10^6$/Kg, $p < 0.001$). Similarly the total CD34$^+$ CD38$^-$ cell number and CAFC collection was significantly higher in patients mobilized with CTX plus G-CSF. Among patients mobilized with G-CSF alone, more than 1 collection procedure was necessary in 73% of patients and 7 patients failed to collect more than 5×10^6 CD34$^+$cells/Kg and underwent chemotherapy plus G-CSF mobilization with success. Nonetheless, cytokeratin-positive tumor cells were found in the apheresis products in 29% of patients mobilized with CTX plus G-CSF and in 10% of patients mobilized with G-CSF alone ($p = 0.12$). In conclusion CTX plus G-CSF is a very effective mobilization protocol, but tumor cell contamination was not different when compared to G-CSF alone. These data suggest that G-CSF alone can be safely used to mobilize PBSC, without increasing the risk of tumor cell contamination in the apheresis product.

P91 High-dose chemotherapy with stem cell support in breast cancer: Does cyclophosphamide alter high-dose thiotepa pharmacokinetics?

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Introduction: The alkylating agent thiotepa (TT) is ideal in high-dose treatment of breast cancer. TT can be escalated by a factor of 20 without relevant organ toxicity. It is metabolized by hepatic cytochrome P450 oxidases. Cyclophosphamide is well known to induce several cytochromes after repeated application. There are few data about pharmacokinetic interactions of these drugs in the high-dose setting. This study was initiated to evaluate individual TT plasma concentrations and possible interactions between TT and other drugs, which potentially may modulate effects and toxicity of the treatment.

Materials and Methods: Data from 12 randomized patients with high-risk breast cancer receiving tandem ECTT (epiadriamycin 90 mg/m^2, cyclophosphamide 1000 mg/m^2 × 3, thiotepa 133 mg/m^2 × 3) and autologous bone marrow support are actually available. Serial post infusion blood samples were analysed for TT using HPLC with UV-detection. Pharmacokinetic data were derived by noncompartmental methods.

Results: Maximum postinfusion TT concentrations were 3.17 ± 1.34 μg/ml on day 1 and 2.52 ± 0.75 μg/ml on day 3; terminal half-life was 1.97 ± 1.18 h on day 1 and 2.13 ± 0.84 h on day 3; total body clearance was 222 ± 67 ml/min/m^2 on day 1 and 259 ± 103 ml/min/m^2 on day 3;, volume of distribution was 0.98 ± 0.34 l/kg on day 1 and 1.25 ± 0.38 l/kg on day 3 and extrapolated AUC were 10.76 ± 2.98 μg h/ml on day 1 and 9.73 ± 3.54 μg h/ml on day 3 (mean ± S.D.).

Conclusion: Considerable interindividual differences were noted There was no statistical difference between measurements on day 1 and 3 of HD-therapy in non-parametric tests.. Our data on HPLC are in concordance with already reported results, which were obtained using gas chromatography.

Thiotepa metabolism seems not to be altered by simultaneous cyclophosphamide treatment.