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.