Toxicity was assessed according to WHO criteria. Grade III–IV transitory neutropenia was identified in 29.8% and 19.4% of the courses administered respectively, only 5 pts received bone marrow rescue (G-CSF). Peripheral neuropaty grade I–II was seen in 36.6 pts and III–IV in two pts; one patient went out of study for neurotoxicity. No patient had evidence of cardiac toxicity. We achieved: 61.5% OR (20.5% CR, 41% PR), 25.7% SD and 12.8% PD; 75% of CR received (E) 90 mg/m^2 and (T) 200 mg/m^2. At the present time of the study the duration of response is as follows: CR median 10.4 months (6–18), PR median 8.7 months (6–13). Paclitaxel in combination with Epidoxorubicin represents an active and tolerable regimen for women with metastatic breast cancer. Further studies are warranted in order to modulate the neurotoxicity observed in our study by weekly administration of drugs.

42 POSTER

Timing of combined chemoradiotherapy in the conservative treatment of locally advanced breast cancer (LABC)

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The aim of this study was to compare the initial combination of chemotherapy and irradiation to a delayed association after neoadjuvant chemotherapy (CT) in a conservative treatment of LABC. From 1988 to 1993, 65 patients with stage III breast cancer were included in this randomised study. Median age was 49 years, 71% of the patients were premenopausal. In group 1, patients (N = 34) received a split course radiotherapy (RT) of 18 Gy during 2 weeks, on week, 1, 5 and 9 with concomitant CT (VCF) that consisted of vindesin (V) 3 mg/m2 day (d) 1 and 5, cyclophosphamide 300 mg/m2 d 1 and 5 intravenously and fluorouracil (FU) 600 mg/m2 continuous infusion from d 1 to 5, every 3 weeks. Boost RT of 18 Gy was delivered on tumour site at week 13. Three weeks after RT, patients received monthly (AVCF) Adriamycin (A) 25 mg/m2 d 1 and 2, C 400 mg/m2 d1, 2 and 3, V3.5 mg/m2 d 1 and FU 500 mg/m2 from d1 to 5 during 8 months. In group 2, patients (N = 31) received 3 monthly neoadjuvant AVCF, followed by RT of 54 Gy during 6 weeks associated with VCF, each 3 weeks. Three weeks after a boost RT of 18 Gy, 5 monthly AVCF were delivered. Total treatment duration was 12 months in both groups. Median follow-up time is 7 years. Objective response rates were 88% in group 1 and 77% in group 2. Mastectomy had to be performed after RT in 3 cases (9%) and in 7 (23%) respectively. Five years probabilities for survival without local recurrence were 74% and 78% in group 1 and 2 respectively (p = 0.38), 63% and 66% for survival without metastases (p = 0.56), 52% and 58% for disease-free survival (p = 0.24), 73% and 79% for overall survival (p = 0.77) and 72% and 60% for breast conservation (p = 0.67). In conclusion, combined chemoradiotherapy with prolonged adjuvant CT has efficacy in LABC, with a high 5-year survival rate of 76% and a breast conservation rate of 66%. We did not to find any difference between initial versus delayed radiotherapy in this study.

43 POSTER

Primary chemotherapy for locally advanced breast cancer using film as a novel regimen

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Sixty nine patients with locally advanced carcinoma of the breast were treated with Neo Adjuvant combination chemotherapy regimen between October 1993 and October 1997. The median age of the patients was fifty three (25–70). All patients received Neo Adjuvant chemotherapy consisting of 6 cycles of 5 FU, Ifosfomide, Leucovorin and Mesna at three weekly intervals. At alternate cycle Mitomycin C was added. Following chemotherapy 77% (53) underwent surgery [75.5% (40) received radiotherapy and 24.5% (13) did not receive radiotherapy] and 23% (16) patients did not undergo surgery [81.25% (13) received radiotherapy]. 46.4% (32) patients underwent mastectomy, 30.4% (21) underwent breast conservation surgery and 23.2% (16) had no surgery. The median disease free interval is 20 (6–51) months and the median survival period is 22 (7–53) months. The clinical response in these patients is 90% (23 CR, 39 PR). The pathological response in these patients is 85.5% (5 CR, 54 PR). The response rate and survival data are encouraging. Further trial are needed to confirm results.

44 POSTER

Letrozole as primary medical therapy for locally advanced and large operable breast cancer

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The aim of this study was to investigate the efficacy of letrozole given as primary systemic therapy and to compare responses with those obtained with tamoxifen. 24 patients were treated with letrozole (12 at 2.5 mg, 12 at 10 mg) and in a separate but identical protocol 65 patients were treated with tamoxifen. All were similar stages $T_2 > 3$ cm, T_3, T_{4b}, N_{0-1}, M_0. All tumours were ER +ve. Patients were monitored by monthly ultrasound and change in volume over a 3 month period calculated. The median percentage reduction in tumour volume with letrozole was 81, 95% CI 69–86. Prior to letrozole 15 patients would have required mastectomy but after 3 months therapy all were suitable for treatment by breast conservation. There was 1 complete pathological response and 3 patients had residual microscopic tumour foci only at the time of definitive surgery. In a series of 65 patients treated with tamoxifen, the median percentage reduction in tumour volume was 48, 95% CI 27–48. Although not a randomised study this was a much lower reduction than that obtained by letrozole. Letrozole is highly effective as primary systemic therapy and appears at least as good as tamoxifen in this setting.

45 POSTER

Weekly cisplatin-epirubicin-paclitaxel in advanced breast cancer: A phase I study

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Purpose: To determinate the MTDs of epirubicin (EPI) and paclitaxel (PTX) given weekly with a fixed dose of cisplatin (CDDP).

Methods: Breast cancer patients with advanced disease received CDDP at the dose of 30 mg/m2 togheter with escalating doses of PTX and EPI, weekly for a minimum of 6 cycles.

Results: To date 57 patients have been entered onto this phase I study, for a total of 410 weekly cycles delivered. Both hematological and non-hematological toxicity have been manageable. Overall 8 pts. have shown DLT (neutropenia causing a >2-week cumulative delay in 4 pts, peripheral neuropathy, cardiac ischemia, and severe diarrhoea in 1, 1, and 2 pts. respectively). Only 2 pts. have required hospitalization because of sepsis. Grade 4 thrombocytopenia has never occurred, but severe anemia has occurred quite frequently as the treatment went on, with 18 pts. requiring blood transfusions. Alopecia has been almost universal. Other nonhematologic toxicities have been generally mild except for grade 3 fatigue, vomiting and diarrhoea occurring in 4,7, and 3 cycles respectively. Peripheral neuropathy has occurred in 12 pts., but was severe in 1 case only. 12 complete and 35 partial responses have been registered for an 82% ORR.

Conclusions: The recommended doses of EPI and PTX to combine weekly with CDDP 30 mg/m2 are 40 mg/m2 and 85 mg/m2 respectively, in absence of G-CSF support. Although less than 33% of pts. enrolled at level 5 showed DLT during the firs 6 cycles, we stopped the escalation since the actually delivered dose intensity was less than 70% of that planned in more than 50% of pts. The escalation still continues with the concomitant administration of G-CSG (5 mg/kg d 3–5 of each week), and the PTX and EPI doses can be safelty escalated to 120 mg/m2 and 50 mg/m2/week in this way. This approach appears to be higly effective (82% ORR with 22% CRR) and deserves a further evaluation in large phase II/III trials either in advanced or inoperable breast cancer.

46 POSTER

Long duration of response with letrozole 2.5 mg (Femara®) in two trials in postmenopausal women with advanced breast cancer after anti-estrogen therapy

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Purpose: Subset analyses on duration of response and time to progression

(TTP) comparing letrozole 2.5 mg with megestrol acetate (MA) (AR/BC2) and aminoglutethimide (AG) (AR/BC3).

Methods: Tumor response and TTP (UICC criteria) were defined by independent, treatment-blinded peer review based on tumor imaging and tumor measurements. Median times were estimated by the Kaplan-Meier product-limit method. Treatments were compared by Cox proportional hazards regression.

Results: Duration of response (CR + PR) was significantly longer for letrozole 2.5 mg compared with MA (medians 33 and 18 mos respectively) but not with AG (median duration of response (MDR) 24 mos for letrozole, 15 mos for AG). In the trial against MA, MDR was 33 mos for patients with predominant soft tissue disease (19 mos MA), 27 mos for bone (18 mos MA), 33 mos for visceral (15 mos MA). In patients with lung metastases, MDR was not reached for letrozole (16 mos MA), and in liver metastases, was 33 mos for letrozole (13 mos MA). Median TTP in predominant soft tissue disease was 17 mos for letrozole, 8.6 mos for MA. In the trial against AG, MDR was 38 mos for letrozole 2.5 mg, 24 mos for AG in patients with visceral metastases. Median TTP in patients with predominant soft tissue disease was 11.3 mos for letrozole, 3.5 mos for AG.

Conclusion: Letrozole 2.5 mg appears to provide long duration of response, irrespective of the predominant site of disease.

47 POSTER

Serum hepatocyte growth factor (HGF) levels in patients with progressive metastatic breast cancer

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Purpose: Several studies have shown that HGF plays a crucial role in carcinogenesis and malignant progression. To investigate a possible impact of serum HGF levels on the clinical course, serum HGF levels in patients with metastatic breast cancer were examined.

Patients and Methods: Between September 1996 and January 1998, 80 patients with metastatic breast cancer were enrolled in this study. The sites of metastasis included soft tissues in 22 patients, bone in 37, lung and/or pleura in 30, liver in 19, brain in five, and ovarium in one. Twenty-two patients had multiple metastatic organs. Serum HGF levels were evaluated using ELISA kit.

Results: The average level of serum HGF in all the patients was 0.80 ± 0.52 ng/ml (average ± SD, 0.15–2.87). Circulating HGF levels in patients with liver metastasis (1.14 ± 0.67) were significantly higher than those without liver metastasis (0.69 ± 0.41). Significantly higher levels in serum HGF (1.0 ± 0.56) were also observed in patients with progressive disease compared with those with stable disease (0.53 ± 0.30). The patients with high HGF levels (more than 1.0 ng/ml) exhibited a significantly shorter survival rate than those with low HGF levels. Sequential monitoring revealed that circulating HGF levels significantly elevated in patients with progressive metastasis associated with disease progression.

Conclusion: Serum HGF level may be a useful indicator for the progression of metastatic lesions, existence of liver metastasis, and prognosis of patients with metastatic breast cancer.

48 POSTER

High-dose chemotherapy with peripheral blood stem cell transplantation as adjuvant therapy for primary breast cancer

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Twenty patients with breast cancer involving more than 10 regional lymph nodes were treated by high-dose chemotherapy (HD-CT) supported by peripheral blood stem cell plantation (PBSCT) as adjuvant therapy. After radical mastectomy, the combination chemotherapy with adriamycin 50 mg/m^2, cyclophosphamide 1,000 mg/m^2, vincristine 1.0 mg/m^2 and methotrexate 200 mg/m^2 with leucovorin rescue was started, and repeated every 3 weeks for 3 courses. G-CSF was also given. After the 2nd and 3rd courses, PBSCs were collected and cryo-preserved. Tamoxifen was also given to patients with breast cancer containing a high concentration of estrogen receptor, and radiation therapy for supraclavicular and parasternal lymph nodes was also combined. Finally, HD-CT with thio-TEPA 200 mg/m^2/day, etoposide 300 mg/m^2/day, and CPA 2,000 mg/m^2/day were administered for 3 consecutive days, and after 72 hours of final doses, frozen-thawed PBSCs were administered.

HD-CT with PBSCT was well tolerated, and recovery from myelosuppression of the HD-CT was rather quick and no serious side effects were observed. Seventeen patients remained in remission with a median follow-up of 40 months after mastectomy, and three relapsed at 13, 19 and 21 months after surgery. According to Kaplan-Meyer analysis, the probability of disease-free survival was significantly higher in patients treated by HDCT with PBSCT as compared with those treated by conventional chemotherapy in our division, showing 79.3% and 25.3%, respectively, at 5 years after mastectomy.

HD-CT with PBSCT as adjuvant therapy for primary breast cancer involving extensive lymph nodes may improve the supposed poor prognosis of such patients.

49 POSTER

Sequential administration of paclitaxel and doxorubicin followed by CMF in women with advanced breast cancer

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Purpose: The purpose of our study was to evaluate the activity of paclitaxel/doxorubicin combination in patients with advanced breast cancer but to avoid excessive cardiotoxicity.

Methods: We administered 4 cycles of doxorubicin/paclitaxel followed by 6 cycles of standard CMF regimen. Study medication consisted of doxorubicin 60 mg/m^2 as a 15-minute intravenous infusion followed by paclitaxel 175 mg/m^2 as a 3-hour infusion.

Results: The main toxicity of doxorubicin/paclitaxel treatment phase was neutropenia (WHO grade 3/4, 58%) but we observed only one cardiac adverse event. Toxicities of the CMF treatment phase were not significant. Of 24 patients evaluable for response, two (8%) had complete response and 11 (46%) achieved partial response. Ten additional patients (42%) had stable disease. The median time to progression was 12 months and the median overall survival was 18.5 months.

Conclusion: The sequential administration of doxorubicin and paclitaxel followed by CMF appeared active and well tolerated in patients with metastatic breast cancer.

50 POSTER

A randomised clinical trial of primary chemotherapy (PC) with taxol + epirubicin (TE) V. 5-FU + epirubicin + cyclophosphamide (FEC) in stage III_A breast cancer: A preliminary report

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Introduction: The possible contribution of (PC) in the management of breast cancer has been investigated since 1980 following the hypothesis that (PC) might alternate cancer cell behavior.

Aim: The aim of this study was to determine the incidence of satisfactory response to (PC) treatment and prolongation of disease free survival and overall survival rates using a new combination (TE) as compared to the standard approach (FEC).

Material and Patients: In this trial 30 patients 35–70 yeasrs of age (mean 52) with stage III_A breast cancer were included. Of these 11 were pre and 19 post-menopausal and they were randomised in two groups. Arm A (TE, n = 16) and arm B (FEC, n = 14). Two cases from each arm were not evaluable. Patients in both arms received 3 courses of pre-operative chemotherapy at a dose of 200 mg/m^2 Taxol + 75 mg/m^2 Epirubicin and 5-FU 600 mg/m^2 + Epirubicin 75 mg/m^2 + Cyclophosphamide 600 mg/m^2 every three weeks respectively. Following modified radical mastectomy they had 3 additional courses of chemotherapy. All patients received a course of radiation therapy and 20 mg Tamoxifen daily regardless of receptor status.

Results: 1) Clinical response rates: Arm A: CR 4 (28.5%), PR 9 (64.5%), SD 1 (7%). Overall response rate 93%. Arm B: CR 1 (9%), PR 5 (45.5%), SD 4 (36.5%), PD 1 (9%) overall response rate 54%. 2) Pathological complete response rates: Arm A: 4 (28.5%) Arm B: 0 (0%).

Conclusion: The preliminary results of this trial demonstrate that combination of Taxol + Epirubicin seems to have a better activity in clinical and pathological response rates. However conformation of these observations