37 ORAL

Family history of breast cancer and local recurrence after breast conserving therapy

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Purpose: We investigated the impact of family history of breast cancer (BC) on local recurrence (LR) risk after breast conserving therapy (BCT).

Methods: The study was performed within the framework of a multicenter case-control study (BORST) of risk factors for LR after BCT. Family history (BC in first and/or second degree relatives) was assessed for 218 BC patients with LR (cases) and 480 BC patients without LR (controls). Detailed histological features were assembled by revision of the primary tumour.

Results: The risk of LR was not significantly different between familial and sporadic breast cancer patients (OR 0.65 (95% C.I. 0.39–1.06)). Familial patients tended to have a smaller tumour diameter ($p = 0.12$) and lower histological grade ($p = 0.08$). Adjustment for these factors and age at onset did not essentially alter the results (OR_{adj} 0.68 (0.37–1.26)). Separate analyses according to age at onset $<$ and >50 years and time and location of LR did not show different results.

Conclusions: The presence of a positive family history of BC is no risk factor for LR after BCT. This might be different in (subgroups of) truly hereditary cases.

38 POSTER

Epirubicina (EPI) and vinorelbine (VNR): High activity, dose dense regimen for primary breast cancer

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Neoadjuvant/adjuvant chemotherapy studies generally employ regimens that have appeared to be the most active against the same tumor in advanced stages. In a previous study, we showed the efficacy and tolerance of EPI and VNR plus G-CSF in untreated metastatic breast cancer patients, obtaining a 77% response rate (ASCO '97). We therefore wanted to examine this combination in a neoadjuvant setting. Between January 1997 and January 1998, 48 patients (pts.) with locally advanced breast cancer were treated with EPI, 60 mg/m^2 on days 1 and 15 and VNR 25 mg/m^2/week plus G-CSF; 150 mcg/m^2 on days 2, 4, 9 and 11. Therapy was administrated for three months.

Patient Data: Median age: 48 years (range: 29–72 yrs.), PS 0: 46 pts.; PS 1: 2 pts.; Premenopausal status: 30 pts.; Postmenopausal status: 18 pts.. The diagnosis of a carcinoma was always confirmed by cytology.

Toxicity: All the pts. are evaluable for toxicity. Neither febrile neutropenia nor infection were observed, although grade 3–4 neutropenia affected 17 pts. (35%). No other serious hematologic toxicity was present. Four pts. had grade 3 nausea and vomiting and two pts. had grade 3 stypsis.

Results: response was evaluated in 36 pts. A pathological complete response (CR) was opteined in 5 pts. (14%), a partial response (PR) in 30 pts. (83%) and stable disease (SD) in one pts. (3%). The overall response rate was 97%. There were no cases of progressive disease (PD). Conservative surgery could be performed in 8 of the pts. (22%).

After primary chemotherapy plus surgery the following stages and node involvement were determined: stage 0: 2 pts., I: 4 pts., IIA: 23 pts., IIB 6 pts. and IIIB 1 pt.. N_0 10 pts., N+ 1–3 14 pts. ($N_{0/1-3}$: 67%); N+ 4–9: 8 pts., N+ $\geq$ 10: 4 pts.

Conclusions: The combination of EPI. VNR and G-CSF appears to be highly effective and well tolerated in a neoadjuvant setting.

39 POSTER

Concurrent paclitaxel and radiation in locally advanced breast cancer

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Purpose: 1) To study primary paclitaxel during radiation as a first-line treatment for locally advanced breast cancer, 2) to obtain pre-treatment tumor biopsies to explore molecular determinant of pathological response, 3) to measure in selected patients the kinetics of paclitaxel effects on cell cycle.

Methods: Locally advanced Stage IIIA or IIIB breast cancer patients are eligible. We measured tumor mitotic and apoptotic indexes by obtaining sequential fine needle biopsies of breast cancers at 24 h, 48 h, 72 h and 96 h after paclitaxel. The data generated supported the design of a regimen of twice a week paclitaxel (30 mg/m2 over one hour) and RT (50.40 Gy/ 28 fractions) to the breast and regional nodes.

Results: A total of 15 patients were accrued, so far. The preliminary clinical and pathological results from the first ten evaluable patients are available. No grade IV toxicities occurred. The only grade III toxicity consisted of in field wet desquamation in one patient. One patient developed grade II esophagitis. All patients achieved a clinical response: 4 CR, 6 PR. Two of the ten patients achieved pathological complete response (clearance of invasive cancer in the breast and axillary contents) and 4 achieved a pathological partial response (residual microscopic foci of invasive cancer).

Conclusion: The combination of twice a week paclitaxel and radiation is well tolerated and constitutes a promising primary management for locally advanced breast cancer.

40 POSTER

Combination of oral idarubicin and cyclophosphamide in the treatment of advanced breast cancer

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Background: Oral idarubicin has been shown to be an effective treatment option especially in older patients with advanced breast cancer. In this study an oral combination therapy of idarubicin and cyclophosphamide was performed.

Patients and Methods: 49 patients with stage IV breast cancer were treated with oral idarubicin 25 mg/d on two consecutive days followed by oral cyclophosphamide 200 mg/d for 3 days, every 21 days.

Results: Out of 40 Patients that received at least 2 cycles, 17 showed an objective response rate with 3 complete remissions. In 3 patients therapy had to be stopped because of grade 4 myelotoxicity. Nausea and vomiting as well as alopecia was generally low and tolerance was good.

Conclusion: Combination of oral idarubicin and cyclophosphamide is a safe and effective treatment, that may improve the quality of live of breast cancer patients with poor venous access.

41 POSTER

Combination chemotherapy with paclitaxel (T) and epirubicin (E) for metastatic breast cancer (MBC): A phase I–II study

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Aim: to evaluate response rate and toxicity of a regimen including administration of (E) followed by (T).

Methods: 48 patients (pts) with MBC previously untreated for metastatic desease entered our study. 37 pts received adjuvant therapy, including 7 pts treated with anthracyclines (there had been twelve or more months of desease free survival after adjuvant therapy). Pts characteristics included. median age 54.6 y (30–73), ECOG $\leq$ 2, visceral (56.8%) and bone (43.2%) metastases. Pts were treated every three weeks with (E) day one 60–90 mg/m^2 and (T) day two 175–200 mg/m^2; (E) and (T) were administered by 30' and 3 hours standard i.v. infusion respectively and pts were premedicated with standard antiallergic and antiemetic regimens.

Results: actually 48 pts are evaluable for toxicity and 39 for response. A total of 309 courses of chemotherapy was administered (1–8, average 6.5).

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