375 POSTER

EFFECT OF ADJUVANT CHEMOTHERAPY (ACT) WITH OR WITHOUT ANTHRACYCLINES ON FIRST LINE CEF IN METASTATIC BREAST CANCER PATIENTS (PTS)

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The effect of previous ACT with or without anthracyclines on the overall survival (OS), progression free survival (PFS) and response rate (RR) was evaluated in 326 metastatic breast cancer pts entered into 4 consecutive randomized trials and treated with CEF (Cyclophosphamide, Epidoxorubicin, 5-Fluorouracil) as first line CT. 154 (44%) pts did not receive previous ACT, 143 (44%) and 39 (12%) pts received CMF-based and anthracycline-based ACT, respectively. Response to CEF was observed in 161 (49.4%) pts. At univariate analysis, pts who received prior ACT had a significantly lower probability of response than pts who did not: 43% versus 58% ($P = 0.02$). No difference between CMF-based (RR 43%) and anthracycline-based (RR 44%) ACT was observed. Stepwise logistic regression analysis indicated that ACT, metastatic site and previous hormonotherapy for metastatic disease, were the most important factors in predicting the RR. At the multivariate analysis ACT was one of the strongest factor associated with a poor PFS. Median OS was 17.9 months. Pts who did not receive ACT had a longer survival (21.1 months) compared to pts previously treated with CMF-based (15.3 months) or anthracycline-based (15.8 months) ACT. Previous ACT adversely affects RR, PFS and OS in metastatic breast cancer pts treated with CEF regimen as first line chemothorapy. No difference between pts previously treated with CMF-based or anthracycline-based ACT was observed.

376 PUBLICATION

ORAL DOXIFLURIDINE PLUS LEUCOVORIN IN ELDERLY PATIENTS WITH ADVANCED BREAST CANCER

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In an ongoing phase II study, 37 elderly patients (≥70 year) have been treated with oral doxifluridine 600 mg/m^2 plus oral l-leucovorin 25 mg, both q 12 hours days 1–4. The courses are repeated every 12 days. A total of 230 courses have been given, with a median of 4 cycles per patient (range 1–14). The main patient characteristics are a median age of 76 years (range 70–88), median ECOG performance status 0 (range 0–2), soft tissue, viscera and bone involvement in respectively 81%, 46% and 27% of patients. Seventeen of the 37 patients have previously received chemo and/or hormonotherapy for metastatic disease.

The grade 1–2 (NCI) side effects are: nausea and vomiting (37%), diarrhea (26%), mucositis (14%), gastric pain (3%), leukopenia (11%), piastrinopenia (9%), anemia (9%). Grade 3 nausea and vomiting has been observed in 1 patient and grade 3 diarrhea in 4 patients. Only 1 patient has experienced grnde 4 diarrhea.

In the 32 evaluable patients, 1 CR, 8 PR (CR + PR = 28%, C.I. 95% = 28 ± 15), 11 SD and 12 PD have been recorded. The 17 previously untreated patients show a response rate of 35% (1 CR + 5 PR) with a median response duration of 4 months (1+ – 15+); the 15 pretreated patients include 3 PR (20%) with a median duration of 2 months (1+ – 4). Doxifluridine plus l-leucovorin is a treatment with promising activity and good compliance when delivered in an out-patient setting.

Data management by ITMO (Italian Trials in Medical Oncology) Scientific Service.

377 PUBLICATION

THERAPEUTIC EFFECTS OF THE AROMATASE INHIBITOR FADROZOLE (F) HYDROCHLORIDE IN ADVANCED BREAST CANCER

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In order to determine the endocrine effects and evaluate tumour response of the 3 doses of fadrozole (F), a new potent oral non-steroidal aromatase inhibitor, a multi-centre randomised double-blind study has been performed in post-menopausal (PM) patients (pts) with recurrent breast cancer after tamoxifen failure. Treatment allocation was randomly 0.5, 1.0 or 2.0 mg orally bd. Toxicity was assessed using WHO criteria and the response was assessed using UICC criteria. The endocrine component of the trial lasted for 3 months. 80 pts were entered on study. 8 are not assessable for toxicity or response; 3 have no measurable or evaluable disease, 2 received trial treatment for less than 27 days due to disease-progression, 1 stopped trial treatment after 6 days due to disease-progression, 1 was lost to follow-up and 1 had hypercalcaemia the day after the start of trial. In general the pt characteristics (dose of F, age, disease-free interval, performance status, menopausal status, years PM, ER status, metastatic sites, dominant site of metastatic disease and previous treatment for metastatic disease) were well balanced between the 3 randomised groups. We have previously reported that F achieves near maximal suppression of oestrogen at 1 mg bd. The objective response rate (RR) was 17% (95% CI: 8.9–27.3%) with no complete responders. 15 pts (21%) had stable disease (NC) and 45 pts (63%) had progressive disease (PD). There was no significant difference in the RR between pts receiving 0.5 mg, 1 mg and 2 mg of F bd. The median duration of objective response was 36 weeks (wks). The median time to treatment failure was 12.7 wks. The log rank test showed no statistical difference between the dosage groups. The main adverse events reported were of mild to moderate severity; nausea in 11 pts (15%), hot flushes in 4 (5%) and somnolence in 3 (4%). 2 pts stopped therapy because of side-effects (somnolence, depression) but the causal relationship remained uncertain. No serious adverse events were reported. In conclusion F is a clinically active aromatase inhibitor with a low incidence of side-effects and phase III clinical trials in PM patients are currently underway.

378 PUBLICATION

TAXOL® (PACLITAXEL) 225 MG/M^2 BY 3-HOUR INFUSION WITHOUT G-CSF AS A SECOND LINE THERAPY IN PATIENTS (PTS) WITH METASTATIC BREAST CANCER (MBC)

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We report the preliminary results on 50 out of 86 pts enrolled to an ongoing trial of Taxol (T) as 2nd line treatment for MBC. T dose is 225 mg/m^2 (3-h infusion) q3w without G-CSF. Eligibility criteria: age 18–75. ECOG PS ≤ 2, measurable disease and adequate organ function. Pts characteristics are: median (med) age 55 (range 36–76); med ECOG PS 1 (0–2); 24 pts received prior adjuvant + metastatic CT (group A) and 26 pts received only 1 prior metastatic CT (group B). Patients received a total of 217 cycles with a med number of T courses/pt of 4 (1–11). Fourty-nine pts are evaluable for toxicity and 46 for efficacy.

Grade III/IV neutropenia was observed in 58% cycles. Febrile neutropenia was reported in only 3% cycles and grade III anemia in 5% cycles. No thrombocytopenia grade ≥ 3 was reported. Peripheral neuropathy grade ≥ 2 was noted in 31 pts: 20 (41%) grade II and 11 (22%) grade III. The med cumulative dose of T at appearance of grade III neuropathy was 900 mg/m^2 (450–1350). There were 2 CR, 11 PR, 22 SD and 11 PD, for an objective response rate of 28% (group A: 15%; group B: 38%).

Conclusion: Taxol 225 mg/m^2 as a 3-h infusion is a safe schedule for 2nd line pts with MBC. These preliminary results suggest an encouraging efficacy in this setting.

379 PUBLICATION

L-FOLINIC ACID (FA), FLUOROURACIL (FU), ESCALATING DOSES OF MITOXANTRONE (N), CICLOPHOSPHAMIDE (C) AND G-CSF IN ADVANCED BREAST CANCER PATIENTS (ABC). A PHASE II STUDY

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In order to verify if an increased dose intensity is associated with higher response rate and improved survival, starting from September 1993 untreated patients (pts) with ABC were enrolled in a multicentric study of GOIM (prot. n 9304). Chemotherapy consisted (mg/mq) of L-FA 100 iv d 1–3, F 340 iv d 1–3, N 12 iv d 1 and C 600 iv d 1. G-CSF was administered sc at 0.5 μgr/kg from day 5 to 14. Mitoxantrone was escalated by one dose level (2 mg/mg) up to a maximum of 18 mg/mq according to nadir toxicities. Treatment was repeated every 3 weeks or was moved up

in the presence of good hemometry values. To date fifty-three pts entered into the study and 32 are evaluable for response and toxicity. The main characteristics of the evaluable pts were: median age 50 yrs; median Karnofsky PS 90; dominant site of disease: viscera 21 (62%), bone 4 (12%), soft tissue 9 (26%) of which 2 pts with locally advanced breast cancer (LABC), multiple site of disease 22 (65%). Globally 4 CR and 19 PR were observed for an ORR of 68%; there were 8 SD and 3 PD. Both the LABC pts achieved a PR and underwent to the surgery. Median duration of response was 9 months (range 4+–17+). A total of 188 cycles were administered: in 107 cycles (57%) it was possible to increase the mitoxantrone dosage and in 28 cycles (15%) the maximal dosage of 18 mg/mq was reached. In 43 cycles (23%) the interval among cycles was reduced. Toxicity was mild and gastrointestinal and hematological toxicity of grade (G) 3–4 was not observed. At nadir the most important hematological toxicity was leucopenia (85%), followed by anemia (76%) and thrombocytopenia (53%). Alopecia of grade G3 was seen in only 3 cases. The study is ongoing, but preliminary data show the F-FNC combination as a well tolerated and effective form of palliative treatment in ABC.

380 PUBLICATION

PHASE I STUDY WITH WEEKLY PACLITAXEL (1 H) INFUSION IN HEAVILY PRETREATED ADVANCED BREAST CANCER AND OVARIAN CANCER PATIENTS

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Introduction: With the introduction of Paclitaxel (P) severe acute hypersensitivity reactions (HSR) attributed to the drug during phase I clinical trials led to subsequent changes. First, premedication was initiated prior to treatment and second, the duration of paclitaxel infusion was lengthened mostly up to 24 h. Recently in randomised trials the 3 h schedule and as well the 1 h schedule have proven to be safe there was no significant difference in acute HSR's, but a significant reduction of myelosuppression with the shorter infusion schedules. The optimal dose and schedule of P remained undefined especially with regard to combination chemotherapy. Therefore we performed a phase I study with a weekly 1 h infusion of P in heavily pretreated breast and ovarian cancer patients.

Treatment: Patients (pts) were treated with P (1 h infusion) once weekly. Each treatment cycle comprised of six weeks followed by two weeks rest. All pts were treated under outpatient conditions. Predmedication: dexamethason 8 mg p.o. 12 h and 6 h prior to each paclitaxel infusion and 30 min before treatment 400 mg cimetidine and 2 mg clemastine i.v. During Phase I we chose the following dose levels (dl): dl1 70 mg/m^2, dl2 80 mg/m^2, dl3 90 mg/m^2, dl4 100 mg/m^2. Maximal tolerable dose was defined: neutropenia 4°, thrombopenia $\geqslant$ 3°, other organ toxicity >2° according to WHO criteria.

Patient characteristics: 19 pts entered this trial (15 pts with advanced breast cancer, 4 pts with ovarian cancer): dl1 7 pts [86 single weekly doses (SWD) of P], dl2 5 pts (51 SWD), dl3 3 pts (37 SWD), dl4 4 pts (12 SWD). The characteristics were: age 54 yrs (32–73). WHO performance status 1 (0–2), metastatic disease sites 2 (1–4). Pts had a median number of 3 pretreatment regimens (1–4). All pts had anthracycline refractory disease in case of breast cancer and cisplatinum refractory disease in case of ovarian cancer.

Toxicity and results: No dose limiting toxicities occurred during dl1–3. With regard to the reduced premedication program in order to avoid corticosteroid side effects using the weekly schedule, it must be emphasized, that neither mild nor severe HSR's occurred. The following toxicities could be observed in 15 pts (dl1–3), 29 treatmeant cycles and 174 weekly doses of paclitaxel [grade WHO (number of cycles)]: neutropenia 3° (1), 2° (5), nausea/vomiting 1° (3); myalgia 1° (3); peripheral neuropathy 1° (6); mucositis 1° (7). After the second weekly application of paclitaxel at dl4 in 3 out of 4 pts the next infusion had to be postponed for 1 week because of neutropenia grade 4 WHO. So far no hospitalisations must be performed. Pts received a median of 2 treatment cycles. At all dl's responses could be observed, dl1: PR 1, SD 5, PD 1; dl2: PR 1, SD1, PD 3; dl3: PR 1, SD 1, PD 1; dl4: PR 1 not evaluable 3. MTD was reached using dl4, Dl 3 is recommended for phase II.

Conclusions: As with other antineoplastic agents, P is likely to make an impact when used in combination therapy. Our phase I study underlines that P, given in a weekly 1 h infusion, is safe and active in heavily pretreated breast cancer and ovarian cancer patients. Its moderate toxicity, especially with regard to myelosuppression, should lead to further studies using dl3 in order to better define the value of this schedule for the use in combination protocols.

381 PUBLICATION

HIGH DOSE CHEMOTHERAPY (HDC) WITH G-CSF AND PERIPHERAL BLOOD STEM CELL SUPPORT (PBCS) IN ADVANCED BREAST CANCER (ABC)

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There is a dose-response relationship in ABC. HDC with autologous bone marrow transplantation, after conventional induction chemotherapy enhance complete response rate, but we still ignore the long term survival benefit. Another approach is to use very HDC at induction with PBCS.

We have begun a trial with epirubicin (100 mg/sqm) and cyclophosphamide (3000 mg/sqm) q 2 week × 4. PBCS were collected after the 1st course and reinfused after course 3 and 4.

As for February 1995, 12 ABC pts have received 42 courses. Relative dose-intensity was 92%. Median duration of grade 4 leukopenia lasted 3, 5, 8 and 8 days after successive courses with a median duration of fever of 3–5 d. However rehospitalization for IV antibiotics was required in less than 33 % of pts. Grade 3–4 thrombocytopenia appeared after cycle 3. Other side effects were grade 0–3 and manageable. 6/18 pts achieved a PR. This treatment appears feasible and further pts will receive 6 courses. Actualized results will be presented.

382 PUBLICATION

PRELIMINARY EFFICACY AND TOLERANCE RESULTS OF DOCETAXEL (TAXOTERE) (TXT) IN HEAVILY PRETREATED METASTATIC BREAST CANCER PATIENTS (MBC)

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The activity/safety profile of TXT in heavily pretreated MB pts is of interest to the practicing oncologist. *Pts char:* From Aug 1994 to Feb 1995, 29 women with heavily pretreated MBC, have received TXT: 24 pts with 100 mg/ and 5 pts with 70 mg/sqm q 3 weeks given with steroids premedication: median age 53 years [42–75]; PS (WHO) 0–1: 16 pts (55%), 2: 9 pts (31%), 3: 4 pts (14%), median time diagnosis first relapse: 28 months (m) [1–216]; median time first relapse/TXT: 40 m [1–164]; Metastatic Sites: liver: 17 pts (58%), bone: 16 pts (55%), lung: 14 pts (48%), skin: 12 pts (41%), lymph nodes: 2 pts (6%), CNS: 4 pts (14%), miscellaneous: 1 (3%). Number of sites/pt: 1: 6 pts (20%), 2: 13 pts (45%), $\geqslant$3: 9 pts (31%); CA 15-3 was increased in 20 pts (68%). Median nb previous chemotherapy (CT) lines: 4 [2–11], with anthracyclines 27 pts (93%); 16 pts (55%) had also Mitoxantrone; previous hormonotherapy in 25 pts (86%). *Toxicity:* 123 cycles (cy); median (cy) nb/pt: 4 [1–10]; 84 (cy) and 28 (pts) evaluable for hematol Tox, 13 cy (23%) grade III and 44 cy (52%) grade IV neutropenia, 5 cy (6%) grade III–IV thrombocytopenia; 106 cy and 28 pts evaluable for non hematol Tox: asthenia (100%); 5 episodes of mucositis grade III, other Tox: edema: 15 pts (53%) (1 severe); nail changes: 12 pts (42%). *Activity:* 22 pts evaluable (2 early death and 5 too early): 4 PR (6+, 7+, 7+, 8), 11 Minor Response, 7 PD. Median TIP (all pts) 3 months (1–8). Encouraging results and acceptable toxicity in a multitreated cohort confirm the value of TXT and its interest as second or first line treatment in MBC.

383 PUBLICATION

COMPARATIVE STUDY: PIRARUBICIN VS DOXORUBICIN IN COMBINATION WITH CYCLOPHOSPHAMIDE AND FLUOROURACIL IN THE TREATMENT OF BREAST CANCER

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Pirarubicin, an anthracycline antibiotic without significant cardiotoxicity in preclinical and clinical trials, showed equal antineoplastic effect but less alopecia than doxorubicin in patients with breast cancer. A prospective, randomised phase III study of FPC versus FAC in the treatment of advanced breast cancer was carried out in Croatia in 9 clinical centres during 2 years. A total of 94 patients was entered into the trial and 87 patients were evaluable for responses. The patients characteristic were