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RANDOMIZED TRIAL BETWEEN SELECTIVE AROMATASE INHIBITOR FORMESTANE (®LENTARON) VS TAMOXIFEN AS FIRST-LINE HORMONAL THERAPY IN POSTMENOPAUSAL PATIENTS WITH ADVANCED BREAST CANCER: CONFIRMATION OF BIOEQUIVALENCE IN SURVIVAL

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409 patients were randomly allocated to receive either formestane (f) 250 mg i.m. fortnightly or tamoxifen (t) 30 mg orally o.d. in a multinational, prospective, open trial. The efficacy and tolerability results were previously reported in the Annals of Oncology 1994, Vol 5 (Supp 7) 519–524. Further analysis has been performed to confirm the survival data now that it has matured, including 218 additional visits from 67 patients. There was no difference between treatments in survival, (1062 (f) vs 1079 (t) days).

During the follow-up period of this trial, 84 patients, (48 (f), 36 (t)) achieved further response to other anticancer therapy, indicating that these patients remained responsive regardless of which endocrine therapy they received for first-line.

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WHICH PATIENTS DEVELOP AN EARLY LOCAL RECURRENCE AFTER BREAST CANCER?

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In a retrospective study of breast cancer patients, the disease course was examined in 137 pre- and postmenopausal patients with a local recurrence. Here especially the dependency of a recurrence-free interval on biological parameters of the primary tumor was investigated. It was found that in 23% of the cases the local recurrence expressed tumor generalization with the simultaneous occurrence of distant metastases. The average recurrence-free interval was 4 years, whereby more than half of the recurrences took place in the first two postoperative years. A statistically significant relationship to the recurrence-free interval could be demonstrated for the following parameters: Primary tumor size (P = 0.0003), node status (P = 0.0006) as well as the number (P = 0.0002) and level (P = 0.00001) of metastatically involved lymph nodes. The immunohistochemical estrogen and progesterone receptors (P = 0.0005) and the growth factor obtained with the monoclonal antibody Ki67 (P = 0.0005) also significantly correlated with the length of the recurrence-free interval. The type of operative primary therapy did not have an effect on recurrence-free survival. However, adjuvant therapy had a decisive influence—patients developed a local recurrence significantly later after adjuvant radiotherapy (P = 0.00001).

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INFUSIONAL 5-FLUOROURACIL (F) WITH EPIRUBICIN (E) AND CARBOPLATIN (ECARBOF) IN ADVANCED/METASTATIC BREAST CANCER (ABC)—CAN CARBO REPLACE CISPLATIN (C)?

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Infusional ECF is an active new schedule against ABC with a response rate of 84% in 43 patients (Jones *et al.*, *JCO* 1994; 12:1259–65). Cisplatin however is a major contributor to toxicity and usually requires inpatient treatment. We have investigated the substitution of carboplatin (AUC 5 iv 4-weekly) replacing C, in combination with E 50 mg/m^2 iv 4-weekly bolus and F 200 mg/m^2 daily. Fifty pts, with ABC median age 48 yrs (range 33–62 yrs) have been treated in a phase II trial. At a median follow-up of 9 mths (range 4–27 mths), there are 9 CR, 34 PR and 7 NC to give a RR of 86% (95% CI 70–97%) with responses in all sites. The median PFS is 11 mths and median survival is 17 mths. Grade 3/4 toxicities in the two non-randomised sequential studies were as follows: ECF v ECarboF: emesis 28% v 2%, alopecia 56% v 22%, lethargy 14% v 3%, plantar-palmar rash 26% v 6%, stomatitis 12% v 8%, neuropathy 2% v 0% and Hickman line complication 28% v 26%. These results suggest a regimen that is as active as ECF and has less toxicity.

368 POSTER

EFFECT OF ORAL CLODRONATE IN WOMEN WITH RECURRENT BREAST CANCER IN THE ABSENCE OF SKELETAL METASTASES

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Clodronate reduces morbidity in women with breast cancer and skeletal metastases. In this double blind controlled study, we examined the effect of clodronate on the incidence of skeletal metastases and morbidity in recurrent breast cancer without radiographic or scintigraphic evidence of skeletal disease.

In addition to anti-tumour therapy, 133 women received either clodronate 1600 mg daily by mouth (n = 66) or an identical placebo (n = 67). Fewer patients developed skeletal metastases during clodronate treatment (15 vs 19, NS) and the total number of skeletal metastases was significantly decreased (32 vs 63, $P < 0.005$). Treatment also reduced the number of hypercalcaemic episodes (10 vs 17) and vertebral deformities (35 vs 54). The latter effect was most marked in those with vertebral deformities at entry (41.9 vs 150.0 fractures/100 patient years, $P < 0.005$). The combined rate of all morbid skeletal events was reduced by 26% ($P < 0.01$). We conclude that oral clodronate reduces the progression of skeletal metastases in patients with recurrent breast cancer and may provide a useful adjunct in the management of these patients.

369 POSTER

ADVANCED BREAST CANCER: A PHASE II TRIAL WITH GEMCITABINE (GEM)

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A phase II study is being conducted to investigate the efficacy of the novel nucleoside analogue, GEM, in advanced breast cancer. At present, this condition is incurable and most current treatment is given with the expectation of palliating symptoms and improving quality of life. Female patients (pts) with progressive advanced or metastatic breast cancer which is not amenable to curative surgery or radiotherapy will be recruited to this 2 stage study. Inclusion criteria: life expectancy of at least 3 months; Karnofsky Performance status $\geq$60; WBC $\geq 3 \times 10^9$/L; Hb $\geq$ 10 g/dL; platelets $\geq 100 \times 10^9$/L. GEM (starting dose 1000 mg/m^2) was administered as a 30-min infusion once weekly for 3 weeks followed by a week of rest (1 cycle). To date, 33 pts have entered the study. There have been 6 PRs after treatment with GEM. In 13 other pts the disease stabilized. Toxicity was generally mild: no grade 4 WHO symptomatic toxicity was reported. Only 1 pt suffered grade 3 nausea and vomiting. Therefore, this study confirms that GEM is active in breast cancer. Further studies are warranted, particularly to evaluate the use of GEM in earlier stages of breast cancer and in combination with other cytotoxic drugs.

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TAXOL® (PACLITAXEL) AND FARMORUBICIN® (EPIRUBICIN) IN METASTATIC BREAST CANCER (MBC): PRELIMINARY RESULTS OF A PHASE I STUDY

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TAXOL® (T) (3 hour infusion) given immediately after FARMORUBICIN® (F) (IV bolus) every 3 weeks for MBC was explored in a phase I study:

Dose level	TAXOL® (mg/m^2)	FARMORUBICIN® (mg/m^2)	N pts	N cycles
1	110	50	3	14
2	135	50	4	19
3	175	50	6	37
4	200	50	6	29
5	200	60	3	4
6	225	50	3	6
			25	109

Patients (pts) characteristics: mean age was 52 (33–68), ECOG PS0: 13, PS1: 12, 17/25 pts received prior CT for their primary disease (with anthracyclines in 16 cases). In all cases, the left ventricular ejection fraction (LVEF) was ⩾50% at the entry.

The dose limiting toxicity evaluated at the first cycle being reached at dose level 5 (with 2 febrile neutropenias without documented infection), dose level 6 tested T 225 mg/m^2 and F 50 mg/m^2. So far, 78 courses have been analyzed: 26 grade 3 (33%) and 14 grade 4 (18%) neutropenias have been observed (only 3 courses with fever). Extrahematological toxicities were 1 grade 3 nausea / vomiting, 1 grade 3 asthenia, 5 grade 2 and 1 grade 3 neurotoxicities. Three pts previously treated by anthracyclines experienced cardiac toxicity: 1 myocardial ischemia, 1 heart failure and 1 asymptomatic decrease of LVEF at 41%.

To date, 22 pts are evaluable for response: 9 partial (41%) (PR), 11 (50%) stabilisations.

For the dose levels 3, 4 and 5, PR rate is 60%.

In conclusion, TAXOL® dose escalation is still being investigated with FARMORUBICIN® kept at 50 mg/m^2.

371 POSTER

LHRH AGONIST ANALOGUE FUNCTIONAL TEST IN ADVANCED BREAST CANCER PATIENTS TREATED WITH TOREMIFENE (TOR)

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In order to differentiate the antagonistic and agonistic effect of TOR at the level of the hypothalamus-hypophysis (HT-HP) axis, LHRH test was performed during a phase II clinical trial. In 15 postmenopausal patients with advanced breast cancer FSH and LH release—induced by LHRH agonist (Suprefact-R 0.5 mg sc.)—was monitored during a 16-week TOR treatment (60 mg/day po). The functional test was carried out prior TOR therapy and then 4, 8, 12, 16 weeks afterwards. FSH and LH were measured by RIA method.

On the basis of our endocrine study, TOR has a strong antagonistic (antiestrogenic) mechanism of action at the level of the HP, and a tissue-specific agonistic effect in the periphery. The drug sensitizes the HP for the LHRH stimulus without eliciting any clinical or hormonal side effect.

The LHRH test supported our earlier findings, obtained by the TRH provocation test, i.e. TOR exerts its effect predominantly at the level of the pituitary gland.

372 POSTER

NEO-ADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED BEAST CANCER (LABC): FEC (5FU, EPIRUBICIN, CYCLOPHOSPHAMIDE) VS HIGH DOSE INTENSITY EC + G-CSF (FILGRASTIM). AN EORTC—NCIC—SAKK STUDY. PRELIMINARY RESULTS OF DOSE INTENSITY (DI)

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Patients: Since May 1993, 205 patients (pts) with LABC (clinical inflammatory, T_4 N_x M_0 or any N_2/N_3 M_0) have been randomized into the study. *Treatment:* F (500 mg/m^2 i.v. d 1, 8), E (60 mg/m^2 i.v. d1, 8) and C (75 mg/m^2 p.o. d 1–14) q 28 d × 6 (arm A) *vs* E (120 mg/m^2 i.v. dl), C (830 mg/m^2 i.v. d 1) and G-CSF (5 μg/kg/d s.c. d 2–13) q 14 d × 6 (arm B). *Results:* In arm A (43 pts off-treatment), the delivered DI (mg / m^2 / week, median value) for F, E and C were respectively 212 (range: 152–264), 26 (18–31) and 220 (156–293). The corresponding figures in arm B (56 pts) for E and C were 57 (29–62) and 384 (206–426). The percentage of delivered DI relative to the theoretical DI was around 85% for all drugs in arm A and 94% for both drugs in arm B. Relative to arm A, the DI for E and C in arm B were increased by 119% and 75% respectively. Hematological grade 3–4 toxicities were (% pts, arm A/ B): neutropenia (86%/ 61%), thrombocytopenia (26%/ 36%) and anemia (26%/ 55%). 1 pt in arm A and 11 pts in arm B experienced a significant but asymptomatic decrease in left ventricular ejection fraction. *Conclusion:* Dose intensification of E and C with G-CSF support in LABC pts is feasible, with acceptable toxicity.

373 POSTER

PHASE II TRIAL OF LETROZOLE (A NOVEL ORAL NONSTEROIDAL AROMATASE INHIBITOR) IN POSTMENOPAUSAL PATIENTS WITH ADVANCED OR RECURRENT BREAST CANCER

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64 Japanese postmenopausal patients (pts) (median age 59: range 38–76) with advanced or recurrent breast cancer who had received more than 1 prior regimen (hormonotherapy and/or chemotherapy) were randomized between 2 oral regimen of letrozole for more than 8 weeks, 33 pts (ER+: 18, ER−: 3, unknown: 12) being given 0.5 mg of letrozole daily and 31 pts (ER+: 15, ER−: 3, unknown: 13), 1 mg daily. The tumor responses were peer reviewed and response rates (CR + PR) in evaluable cases were 28% (3CR + 6PR/32, 95% C.I.: 14–47%) in 0.5 mg group and 39% (5CR + 6PR/28, 95% C.I.: 22–59%) in the 1 mg group, respectively. Stabilization of the disease for more than 6 months (long NC) was obtained in 19% for the 0.5 mg group and in 29% for the 1 mg group, respectively. Progressive disease was noted in 31% for the 0.5 mg group and in 21% for the 1 mg group, respectively. Clinical adverse experiences were observed in 6% of pts (2/33, 5 events) for the 0.5 mg group and in 6% of pts (2/31, 2 events) for the 1 mg group, all being only of mild severity (grade 1) except one event of grade 2 itching in the 1 mg group. Laboratory test abnonnalities were found in 9% of pts (3/33, 6 events) for the 0.5 mg group and in 10% of pts (3/31, 6 events) for the 1 mg group, respectively. Except for one event of grade 2 GOT and GPT elevation noted in the 0.5 mg group, all other events were of either grade 0 or grade 1 severity. Estrone levels were maintained below the detection limit (2.5 pg / ml) and a sustained estradiol suppression was observed, with levels near the detection limit (1 pg / ml) during treatment. There was no clinically relevant changes in the other hormones (aldosterone, cortisol, FSH, LH, testostetone, androstenedione). These highly promising results support further extensive clinical evaluation.

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VINORELBINE, 5 FLUOROURACIL, LEUCOVORIN AND CYCLOPHOSPHAMIDE AS FIRST LINE CHEMOTHERAPY IN METASTATIC BREAST CANCER (MBC)

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Vinorelbine (Navelbine) alone or in combination with Adriamycin or 5 FU has major activity in MBC. From 06.92 to 04.94, 60 patients were included. Eligibility criteria: MBC, no prior chemotherapy for metastatic disease, measurable target lesion, WHO PS ⩽ 2, informed consent, 55 patients are eligible. Patients characteristics: median age: 52.3 years (33–74) PS 0: 35 (63.6%) 1: 16 (29.1%) 2: (7.3%). Prior treatment: surgery 40 (72.7%), post operative radiotherapy 32 (58.2%), adjuvant chemotherapy 27 (49.1%), hormonotherapy 23 (41.8%). Metastatic at diagnosis: M0: 39 (70.9%) M1: 15 (27.3%) unknown: 1 (1.8%). Hormonal status at inclusion: premenopausal 14 (25.5%), post menopausal 41 (74.5%). Median metastatic sites 3 (1–6). Visceral metastases: 65%. Treatment schedule: Cyclophosphamide 500 mg/m^2 D1—Vinorelbine IV 25 mg/m^2 D1, 8—5 FU 500 mg/m^2 D1, 8—leucovorin 200 mg/m^2 D1, 8—repeated every 21 days. Total number of courses: 276—mean number of courses: 5.7. Treatment was very well tolerated with no grade superior to 2 except for alopecia. Efficacy: Number of patients: 60: OR rate: 45% (95% CI 32.4–57.6). CR: 6.7% (0–13). PR: 38.3% (22.5–54.1). Median time to first response: 26.7 w (r: 13–36). Median duration of: CR: n = 4–45.4 w (r 20.3–45.4+) – PR: n = 23–37.4 w (r 15.1 – 75.1+) OR: n = 27 44.1 w (r 15.1–75.1+). Median survival: 66.4 w (r 3+ – 80+). Alive: 34 patients (56.7%). Median remission duration: 187 days (91–222). *In conclusion:* efficacy in terms of both O.R. rate and duration of O.R. is within the range of expected results with multidrug regimens without anthracyclins.