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Final results of a phase II study of Taxotere (docetaxel, D), doxorubicin (Dx) and cyclophosphamide (CTX) (TAC) in the treatment of metastatic breast cancer (MBC)

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We conducted a phase II study of D (75 mg/m2, 1 hour i.v. infusion) with Dx (50 mg/m2, i.v. bolus) and CTX (500 mg/m2, slow i.v. bolus) q.3 weeks for a maximum of 8 courses in patients (Pts) with MBC without prior anthracyclines or taxanes. Fifty four patients with MBC were enrolled and received 339 courses. Pts characteristics are as follows: mean age: 53 years (33–70), prior adjuvant chemotherapy (CMF): 17 Pts (32%), visceral involvement: 33 Pts (62%), bone metastases: 32 Pts (60%), more than 3 metastatic sites: 28 Pts (52%), median follow-up 14 months (9–18). Forty eight Pts are evaluable for response (median number of courses: 7). The major response rate is 79% in patients with measurable disease and 73% overall with Stable Disease in 9 Pts (19%) and Progressive Disease in 4 Pts (8%). Time to progression and survival data will be presented at the meeting. Toxicity was evaluable in 54 Pts. Neutropenia is the main toxicity (grade 4: 70%, lasting less than 7 days) with febrile neutropenia seen in 6% of courses. There was no grade 4 toxicity, while grade 3 toxicity was limited (nausea: 9.2%; diarrhea: 3.7% and stomatitis: 5.5%)). Taxotere-specific toxicity was mild with 2% severe fluid retention (no Pt discontinued for toxicity). No severe skin, hypersensitivity or nail toxicity was observed. One Pt presented with a reversible CHF (2%). TAC is a well tolerated and active regimen with no unexpected cardiac toxicity and is the base of 2 large international multicentric randomized trials comparing TAC to FAC in metastatic and adjuvant setting.

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Serum tumor markers in metastatic breast cancer comparative study between CEA, CA-15.3 and MCA

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Purpose: Tumor markers are frequently requested at the time of Breast Cancer (BC) relapse and during treatment. To compare the sensitivity of the serum tumor markers CEA, CA-15.3 and MCA for the presence of metastatic disease, we performed a cross-sectional study.

Material and Methods: One-hundred and thirty-six BC patients with advanced disease were included in the study. Serum determinations of CEA, CA-15.3 and MCA, were performed using ELISA test. CEA, CA-15.3 and MCA were considered abnormally elevated if above 2.5 ng/ml, 28 U/L and 11 U/L respectively.

Results: The three tumor markers had different sensitivity for the presence of metastatic disease ($p < 0.0000008$, Cochram Q test). CEA was the tumor marker most frequently elevated (59.8%), followed by CA-15.3 (46.4%) and MCA (35.7%). The combination of CEA and CA-15.3 had the highest sensitivity (66.1%). However, when compared with CEA plus MCA the difference didn't reach statistical significance ($p = 0.08$, McNemar test). The three tumor markers combined had the same sensitivity as CEA plus CA-15.3. Any combination of tumor markers that includes CEA, increases significantly the sensitivity when compared with CEA alone.

Tumor Markers	Sensitivity (%)	CI 95%
CEA + CA-15.3	66.1	57.2 75.0
CEA + MCA	63.4	54.3 72.5
CA-15.3 + MCA	47.3	37.9 56.7
CEA + CA-15.3 + MCA	66.1	57.2 75.0

Conclusions: In BC patients with advanced disease CEA is the single tumor marker with highest sensitivity. The combination of CEA with another tumor markers increases significantly sensitivity, suggesting that a first determination of tumor markers in BC with metastatic disease, should include CEA and another tumor marker.

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Meta-analysis of dose intensity in breast cancer neoadjuvant chemotherapy (1997 update)

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Dose intensity (DI) in chemotherapy is defined as the amount of drug delivered per unit time and is usually standardized to body surface area as mg/m2/wk. A positive relation between DI and treatment outcome has been demonstrated not only in advanced breast cancer (BC) but also in adjuvant setting. Only few trials using DI concepts have been performed in neoadjuvant chemotherapy for BC. To determine if chemotherapy DI influences treatment outcome in BC, 52 published trials (8 randomized trials included two regimens) from 1984–1997 (including ASCO-97) were retrospectively analyzed (4857 patients). Regimens included such agents as Cyclophosphamide (43 trials) or Tiotepa (1), Fluorouracil (34), Doxorubicin (28) or Epidoxorubicin (20), Methotrexate (13), and Vinca alkaloids (9, Vincristine – 7) (from single drug therapy to five-drugs combinations). Relative DI (RDI) of each study regimen was calculated against commonly used doses of each drugs in single regimens (eg, 25 mg/m^2/wk for Doxorubicin, 400 for Cyclophosphamide, 25 for Methotrexate, etc.). Meta-analysis of chemotherapy trials for BC with some various regimens have suggested that higher total RDI correlated strongly with improved response rate (51 trials, $r = 0.43$, $p = 0.0016$) and complete response (40 trials, $r = 0.42$, $p = 0.0065$). Meta-analysis demonstrated that response rate in neoadjuvant chemotherapy of BC correlates with DI. A randomized controlled trial targeted for DI itself will be necessary to confirm the usefulness of DI concepts in neoadjuvant chemotherapy in BC.

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Vinorelbine in combination with 5-fluorouracil in metastatic breast cancer (MBC)

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Between March 1996 and December 1997, 27 consecutive patients (pts) with MBC were treated with Vinorelbine 20 mg/m^2 on days 1 and 8 as a short intravenous infusion and 5 Fluorouracil 350 mg/m^2 i.v. + folinic acid 100 mg/m^2 i.v. on days 1° to 5° every three weeks. Patients characteristics: median age 56 years (range 32–73); median ECOG PS 1 (range 0–2). The sites of metastatic disease were: liver (6 pts), lung (6 pts), bone (21 pts), lymphonodes (5 pts), skin (10 pts). 15/27 pts (55%) had $\geq$2 metastatic sites; 22 of the 27 pts (81%) had received prior chemotherapy in adjuvant setting (11 with anthracycline). 14/27 (52%) pts had received prior chemotherapy for advanced disease (only one chemotherapy regimen), 8 of them with anthracycline. All pts are presently evaluable for toxicity assessment and 25/27 are evaluable for response (1 pt presented with severe cutaneous allergy after the first cycle and discontinued the treatment). A total of 126 cycles was administered (median 6; range 1–9). Overall response rate was 44% (11/25): 1 CR and 10 PR. 9 pts achieved a stabilisation of metastases and 5 progression of disease. This regimen appeared to be well tolerated with mild to moderate toxicity: nausea and vomiting grade (G) 1 and 2 in 18/27 pts (67%), peripheral neuropathy G1 in 5/27 pts (18%); diarrhea G3 occurred in 1 pt. The main toxicities (G3 and 4) were mucositis in 6/27 pts (22%) and neutropenia 14/27 pts (52%).

To conclude, the association of 5 Fluorouracil and Vinorelbine is an active and tolerable regimen for metastatic breast cancer even in anthracycline pre-treated pts.

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Early breast cancer: How long should tamoxifen continue?

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The recent overview by the Early Breast Cancer Trials Collaborative Group analysed data on – 37,000 women in 55 trials of adjuvant tamoxifen (TAM). For women with receptor positive disease, or with unknown receptor status, TAM is of substantial benefit, regardless of age or nodal status. 5 years of TAM appears better than 2 years. There is inadequate evidence on the effects of 10 compared with just 5 years of TAM. 1 million women worldwide are now on TAM, with most clinicians prescribing TAM for ~5 years. Whilst there is good reason to believe that 10 years might confer extra benefit, the balance of long-term benefits and risks must be established. Trials to

reliably assess the optimal duration of TAM must be large with long follow-up if any worthwhile benefit is to be detected. So, results of small trials of 5 versus 10 years of TAM are conflicting with some studies, perhaps wrongly, suggesting that 5 years is sufficient.

ATLAS is an international randomised trial of longer versus shorter hormonal therapy. It aims to assess reliably the effects of prolonging TAM by an extra 5 years in women who have already had some years of treatment and for whom there is uncertainty as to whether they should stop now. 10–20,000 women will be randomised, usually after 5 years of TAM, to either stop, or continue TAM for 5 more years. This large, simple trial is designed to integrate into routine clinical practice with almost no documentation; since the main analysis will be of all-cause mortality. ATLAS will also provide information on both cause-specific mortality and non-fatal, but important events. If, by 2020, ATLAS shows improved long-term survival with 10 years of TAM (e.g. 27.5% vs. 30% dead), this result will save thousands of lives annually, and will be relevant to the appropriate use of hormonal therapies in general.

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Dose-dense weekly docetaxel and CBDCA in adriamycin-resistant metastatic breast cancer (MBC)

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We have studied 60 Pts. with MBC with the following characteristics: median age 55 (range 30–73) ECOG-PS 0:10 1:38 II:12

Protocol Design: Docetaxel (D) 60 mg/m^2 as one hour infusion followed in one hour by Carboplatin (C) 200 mg/m^2 as 30 min infusion weekly for 6 wks. Median dose intensity (mg/m^2/week, based on 6 wks of treatment and 2 wks rest period): Docetaxel: 42 mg/m^2, Carboplatin 142 mg/m^2. Hematoligical toxicity (WHO-Grading): Hbl:12 (20%); II:8 (13%) III:6 (10%); Leukocytes 21 (35%); II:8 (13%); III:6 (10%); Platelets I:14%; II:6%.

Peripheral Side Effects: Alopecia I:20 (33%), II:30 (50%); Sensory neuropathy I:10 (16%), II:5 (8%), no other side effects other than the above-mentioned observed.

Response Analysis: CR: 15 (25%), PR:33 (55%), NC:7 (11%), PD:5 (8%).

Conclusions: Dose-dens weekly Docetaxel/Carboplatin is active in Adriamycin-resistant MBC. Hematological and peripheral toxicities are not significant. A platelet sparing effect seems to exist with this regimen. Overall treatment time is shortened in comparison with Q.3 WK schedules, whereas dose intensity for Docetaxel is increased. The excellent tolerability recommends weekly D/C for ambulatory treatment.

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Hormonotherapy with goserelin depot after adjuvant chemotherapy in premenopausal women with early breast cancer: Is there any benefit?

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There is the definite evidence that adjuvant chemotherapy can affect both recurrence and survival with 21% reduction for recurrence and 11% reduction for mortality. Ovarian ablation in women aged under 50 was associated with 6% fewer recurrence and deaths after 15 years. Adding hormonotherapy to chemotherapy theorically could improve results depriving ER+ cells of oestrogen stimulus. In order to evaluate the effectiveness of hormonotherapy with Goserelin depot given soon after adjuvant chemotherapy with Epirubicin (110 mg/sqm) d 1 q 3 weeks × 4 followed by CMF d 1,8 q 4 weeks × 4 cycles, 92 premenopausal patients with ER+ breast cancer were randomly allocated after chemotherapy to stop therapy or to receive Goserelin depot 3.6 mg s.c. q 28 d × 2 years. In our experience the addition of Goserelin depot to sequential chemotherapy Epirubicin and CMF showed no benefit in terms of overall survival and DFS after a median follow-up of 46 months. This is not surprising if we keep in mind that chemotherapy caused amenorrhoea in up to two thirds of our patients during adjuvant treatment. Therefore, adding LHRH analogues may not result in significant additional benefit in the majority of women treated, but we can also hypotize that very large numbers of patients may be required before such a benefit can be seen.

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Second- and third-line treament of metastatic breast cancer with gemcitabine

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In the present study, 24 female breast cancer patients with visceral metastases were treated with intravenous gemcitabine 1250 mg/m2 on days 1, 8, and 15, q28d. In 6 patients gemcitabine was administered as second-line chemotherapy, whereas 18 patients received gemcitabine as third-line chemotherapy with previous chemotherapeutic regimens containing an anthracycline in all patients and taxanes in 8 patients.

2 (33%) of the 6 patients receiving gemcitabine as second-line chemotherapy showed a PR, and 4 patients (67%) developed SD. The median overall survival was 15.1 ± 6.7 months (range: 11.4–27.3), the median time to progression was 12 ± 3.4 months (range: 5.6–15.1). In the third-line setting, 1 (6%) out of 18 patients gained CR, 6 (33%) SD and 11 (61%) PD with a median overall survival of 6.3 ± 5.9 months (range: 2.4–23.8) and a median time to progression of 3.9 ± 1.7 months (range: 1.5–8) ($p < 0.01$).

Treatment-related toxicity in the two subgroups was similar. Second-line: anemia WHO grade I or II occurred in 3 (50%) patients; leukopenia grade I or II in 2 (34%), grade III in 4 (67%) patients; thrombopenia grade I or II in 4 (66%) patients, grade IV in 1 (17%) patient. In patients receiving gemcitabine as third-line therapy, 11 (61%) patients developed anemia WHO grade I or II, 2 (11%) patients anemia grade III. Leukopenia grade I or II was observed in 10 (55%) patients, grade III or IV in 4 (23%) patients. Thrombopenia grade I or II occurred in 9 (50%), grade III in 3 (17%) patients.

We thus conclude that gemcitabine was an effective therapy in patients with advanced breast cancer after previous chemotherapeutic agents including anthracyclines and taxanes. When administered early, gemcitabine led to a prolonged interval until progression occurred.

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Mitomycin (M), epirubicin (E) and vinorelbine (V) first-line chemotherapy for metastatic breast cancer (MBC). A feasibility study

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In our experience the combination of M and E showed high activity and good tolerability in MBC (Pacini P., EJC, 1994), with a response rate of 70%. The addition of V to E and M could improve these results without compromising tolerability. In order to evaluate the feasibility and compliance of MEV combination, a pilot study started on June 1996. Treatment schedule was: E 75 mg/sqm and M 10 mg/sqm on d. 1; E 75 mg/sqm and V 25 mg/sqm on d. 21; V 25 mg/sqm on d. 28 (1 cycle). Cycles were repeated every 3 weeks. G-CSF administration was planned according to the hematologic toxicity observed during the treatment. So far 16 patients (pts) were enrolled. Median age was 56 ys (37–70), median PS was 1 (0–3); all pts had visceral metastases. No pt was excluded from evaluation for response and toxicity. Patients received a median of 3 cycles (2–4). We observed 2 CR, 9 PR, 5 NC, no pts showed disease progression. As for toxicity, alopecia was universal, granulocytopenia grade 3–4 occurred in 8 pts, no other grade 4 toxicity was recorded; G-CSF was administered to 7 pts. On conclusion, MEV is a safe and probably very active chemotherapy for MBC as outpatients. Accrual of pts is ongoing in oredr to fully assess activity in a large series.

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Sequential or simultaneous chemo-radiotherapy in operable breast cancer. A French multicentric phase III study – State of inclusions

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Purpose: We compare two adjuvant modalities in operable breast cancer patients. After initial surgery (tumorectomy or mastectomy) with axillary