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## CONTINUOUS IV INFUSION OF VINORELBINE (VNB) AND BOLUS CISPLATINUM (CDDP) (CIVIC REGIMEN) AN EFFICIENT REGIMEN IN HORMONO RESISTANT METASTATIC BREAST CANCER (MBC), AFTER FAILURE OF ANTRACYCLINE AND/OR PACLITAXEL

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We have investigated a new chemotherapy regimen (CT) in patients (pts) previously treated with CT and/or hormonotherapy. CDDP of 20 mg/m$^2$/day was given, (D1 to D5) every 21 days in 1 H iv infusion and VNB was given with the dose of 6 mg IVD bolus, followed by VNB 6 mg/$^2$/day in continuous iv infusion (D1 to D5) every 21 days. 59 pts were included in this trial (median age: 46 years, range 28–49; premenopausal: 40 pts). Respectively 44 and 12 pts had previously anthracyclines (adm) and paclitaxel containing regimens. Overall 212 courses were given (median 3, range 1–6): myelosuppression was the most frequent side effect: neutropenia WHO grade III occurred in 41 courses (20%) on 212 and grade IV for 64 courses (31%). Thrombopenia WHO grade III and IV for 23 courses (12%). No cumulative toxicity was observed on bone marrow. Grade II peripheric neuropathy was observed in 12 of 212 courses (6%) and grade III in 4 of 212 courses (2%) with correlation between toxicity and numbers of courses. Neuropathy (grades II and III) occurred most often after 4 courses (CHI 2: 30.2; $P < 0.001$). Nausea and vomiting: grade II and III in 106 courses (50%). 56 pts were evaluable for response: CR-PR (complete response-partial response: objective response) in 24 pts (43%) (95% ci 23–63%), CR rate was 4%, MR-SD (minimal response-stable disease) in 24 pts (43%). The median time for response was 10 weeks. The median duration of response was 18 weeks. Response by sites: 16 CR-PR in 37 responses for pulmonary site (44%); 8 CR-PR in 18 for cutaneous site (45%); 19 CR-PR in 48 for hepatic (40%); 18 CR-PR in 49 for bone (37%). Response rate after the 2 first courses was 41% in ADM resistant and 58% in ADM + paclitaxel resistant pts.

CIVIC is an effective and well tolerated regimen in MBC resistant to previous anthracylines and/or paclitaxel containing CT.

A number of 4 courses seems to give the best toxicity-efficacy ratio.

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

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A hundred twenty-one patients (pts) were included in a phase II trial of Taxol (T) 225 mg/m$^2$ by 3-h infusion q3w, without G-CSF, as 1st line treatment for MBC. We report here the preliminary results on the first 50 pts. Eligibility criteria were: age 18–75, ECOG PS $\leqslant 2$, measurable disease, disease-free interval $\geqslant 12$ months and adequate organ function. Pts characteristics were: median(med) age 51 years (range 27–71); med ECOG PS 0 (0–2); 23 pts received prior neoadjuvant/adjuvant CT and 27 pts received no prior CT. A total of 297 cycles have been administered with a med number of T courses/pt of 6 (1–12). All pts are evaluable for toxicity and 47 for efficacy.

Grade III/IV neutropenia was seen in 27% cycles with febrile neutropenia in only 3 courses (1%). Treatment was never delayed because of slow hematologic recovery. Peripheral neuropathy grade $\geqslant$ II was noted in 25 pts: 18 (36%) grade II and 7 (14%) grade III. The med cumulative dose of T at appearance of grade III neurotoxicity was 1125 mg/m$^2$ (675–2475).

There were 4 CR, 17 PR, 12 SD and 14 PD for an objective response rate of 45%.

*Conclusion:* These preliminary results confirm that Taxol is a very active drug as a first-line therapy for MBC. It can be administered as a 3-hour infusion at a dose of 225 mg/m$^2$ q3w with an acceptable safety profile.

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## A RANDOMIZED PILOT CLINICAL TRIAL COMPARING 5 VERSUS 10 μG/KG FILGRASTIM (NEUPOGEN) AFTER FEC CHEMOTHERAPY IN ORDER TO COLLECT PERIPHERAL BLOOD STEM CELLS (PBSC)

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Chemotherapy followed by hematopoietic growth factor (HGF) is a effective way to collect PBSC. The optimal dose of HGF for mobilizing PBSC is not yet known. We conducted a randomized pilot clinical trial comparing two doses of filgrastim administered after FEC chemotherapy in breast cancer patients (pts). Sixteen pts were randomized to receive either 5 (group I) or 10 (group II) μg/kg filgrastim (Neupogen, Amgen). Eight pts were enrolled in each arm. FEC chemotherapy combined 5-FU, epirubicin, and cyclophosphamide. Filgrastim was administered daily subcutaneously until the second day of leukapheresis. Three Leukaphereses were performed. Pts characteristics were comparable in the 2 groups. Thirteen pts were fully evaluable; 7 in group I and 6 in group II. Total numbers of CD34 + cells collected after 3 leukaphereses were significantly greater in group II than in group I: 4.26 $10^6$/kg (9–81 $10^6$) versus 1.377 $10^6$/kg (0.3–5.3 $10^6$) $P < 0.05$. All but one pts were autografted after high dose chemotherapy (STAMP V). No difference was seen between the two groups in term of hematologic recovery. We can conclude that it seems to exist a dose-dependent effect of filgrastim for mobilizing PBSC. Ten ug/kg after FEC chemotherapy allow to collect significantly more CD34+ cells than 5. No advantage in term of hematologic recovery is observed.

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## A RANDOMISED, DOUBLE-BLIND, MULTICENTRE CROSSOVER TRIAL TO EVALUATE *IN-VIVO* INHIBITION OF AROMATASE BY ARIMIDEX (ZD1033) (1 MG AND 10 MG PO OD) IN POSTMENOPAUSAL WOMEN WITH BREAST CANCER

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ARIMIDEX (A) is a new aromatase inhibitor which has been shown to be a potent and highly selective in Phase I studies. It has also been evaluated in multicentre studies in the US and Europe for comparative clinical efficacy against megestrol acetate in postmenopausal women with advanced breast cancer.

In this study we have compared the effect of once daily orally administered A (1 and 10 mg) on whole body aromatisation in 10 pts with breast cancer using a modification of the method described by Jacobs et al. (1991). A was well tolerated at both doses.

Whole body aromatase was reduced by approx 95% after 28 days of treatment with either dose of A and the plasma concentration of oestrone, oestrone sulphate and oestradiol by >80; >90 and >80% respectively. Whereas the levels of AD showed no consistent change.

These data indicate that 1 mg OD PO of A can maximally inhibit aromatisation in pts and that this is associated with a profound decrease in circulating estrogens.

Jacobs S *et al.* Journal of enzyme inhibition 4:315–325 (1991)

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## LONG-TERM SURVIVORS AFTER HORMONOTHERAPY (HT) IN METASTATIC BREAST CANCER (MBC). A RETROSPECTIVE STUDY

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From a data base of 1724 patients (p) with MBC, we have analyzed a group of 436 p (25.3%) treated with HT as single first-line treatment. Patients who received simultaneous local therapy or chemotherapy were excluded. Treatment was elected according to clinical criteria.

*Pretreatment characteristics:* Mean age was 57 years (26–88), 429 p (98.4%) were female and 50% underwent adjuvant treatment of the primary tumor (median disease free interval: 24 months (m), range 0–276). Eighty-three percent (356 p) had suppressed ovarian function at the time of metastatic disease. One single metastatic site was seen in 66% of p.

Metastatic sites were: bone (54%), skin (32%), lymph nodes (27%), lung (20%), pleura (7%), liver (2%) and other sites (1%).

*Treatment results:* All p were evaluable for response. Overall response (OR): 151 p (34.7%), Complete Response (CR): 57 p (13.1%), No Changes (NC): 116 p (26.6%), and Progressive Disease (PD): 169 p (38.8%). At the end of the study, 28 of the 57 p (49%) remained in CR, after a median follow-up for response of 10 m (2–153). The median CR duration was 73 m (95% CI: 50–96).

After a median follow-up for survival of 21 m (2–216), 248 p (56%) have died.

Median overall survival (and 95% CI) was 36 m (31–41) for the whole series, 128 m (86–170) for CR; 39 m (35–43) for PR, 46 m (39–53) for NC and 14 m (12–16) for PD.

Differences in survival with statistical significance were found between CR vs PR, CR vs NC, CR vs PD, PR vs PD and NC vs PD.

We conclude that long disease-free and overall survival can be seen in selected patients who obtain CR after HT as first line therapy.

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## NAVELBINE (NVB) PLUS MITOMYCIN (MMC) OR MITOXANTRONE (MTZ): A RANDOMIZED TRIAL IN ANTHRACYCLINE BREAST CANCER RESISTANT (ABCR) PATIENTS. PRELIMINARY REPORT

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NVB, a new semisynthetic Vinca alkaloid is one of the most useful new drugs in breast cancer. The response rate (RR) in pretreated patients (pts) is between 17% and 35%. Combination chemotherapy in ABCR pts with NVB and MMC provided a RR of 46% (R. Santos et al., EJC 29A: 78, 1993, Suppl. 6 n° 407), or with MTZ, RR 40% (Silvestro P. *et al.*, EJC 29 A: 85, 1993, Suppl. 6 n° 449) in two phase II studies. Both combinations are associated with high RR and tolerable toxicity (T), but they have not been compared in a randomized trial. Between 8–1993 and 12–1994, 69 pts. with ABCR non suitable for hormonotherapy were randomized to A: NVB 25 mg/m$^2$ IV days 1–8 plus MMC 7 mg/m$^2$ IV day 1, or B: NVB as above plus MTZ 8 mg/m$^2$ IV day 1. A and B each 28 days, until progression or toxicity grade 4. Number of patients: A: 35; B: 34. Median age: A 55 y; B 54.4 y. Premenopausal: A: 8; B: 5. Adjuvant chemotherapy: A: 26; B: 23. Previous homonotherapy: A: 6; B: 4; Metastatic sites: soft tissue: A: 30; B: 28,; Lung: A: 9; B: 8; Liver: A: 10; B: 10; Number of metastatic sites: One: A: 13; B: 10; Two: A: 16; B: 21; Three: A: 6; B: 3. *Results:* RR: A: 14/35 (48%); CR: 0; PR: 14. B: 18/34 (58%), CR: 1; PR: 17. Median survival A: 7.24 months; B: 6.94 months. T: a total of 128 cycles in arm A and 127 cycles in arm B are comparable. Hematological grade 3–4 were seen in 18 cycles of A and 13 cycles of B and one phlebitis grade 3 in arm B. There were no drug related deaths. *Conclusion:* 1—Both second line schedules are active in ABCR (A: 48%, B: 58%, p:NS). 2—T was manageable. 3—To this date there are no differences in survival. Study is still ongoing.

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## PACLITAXEL BY 3-H ON DAY 1 & 8 EVERY THREE-WEEKS IN WOMEN WITH ANTHRACYCLINE-RESISTANT METASTATIC BREAST CANCER

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Frequent administration by 3-h infusion should result in prolonged and intense tumor exposure to active concentrations of P. In May 1994 we started a trial to assess feasibility, maximum tolerated dose (MTD) and antitumor activity of P on day 1 and 8 q 3 wk schedule. After standard premedication P was infused in 3-h starting at 100 mg/m$^2$. Dose escalation by 25 mg/m$^2$ steps in subsequent cohorts of patients (pts) was planned. Twenty pts with metastatic breast cancer were accrued so far (10 at 100, and 10 at 125 mg/m$^2$). Median age was 50 (22–59) and ECOG PS 0 (0–2). Thirteen pts had relapsed and 7 progressed within median 7 months (1–20) of prior anthracyclines. Fourteen pts and 70 cycles are presently evaluable for rexicily and 13 pts for activity. Main toxicities according to WHO scale were:

| dose | patients | neutropenia | | neuropathy | | myalgias | |
|---|---|---|---|---|---|---|---|
| (mg/m$^2$) | (n.) | III | IV | I | II | I | II |
| 100 | 10 | 3 | 1 | 6 | 1 | 2 | 2 |
| 125 | 4 | 2 | - | 2 | 1 | 2 | - |

All patients had grade 3 alopecia. Nansea was rare. Dominant sites of measurable disease in 13 pts were: lung (n = 7), liver (n = 2), pleura (n = 1), and soft tissue (n = 4). Three CR and 8 PR (84%, C.I.: 55–98%) were observed. Sites of response were lung (6/7), liver (2/2), soft tissue (3/3), and bone (3/4). Median duration of response is 5 months (2$^+$–10$^+$). Four pts had CNS progression while still responding on extra-CNS sites. These preliminary data indicate that the new schedule of P is feasible and very active. The accrual continues to define the MTD and assess the actual duration of responses.

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## PHASE I/II STUDY WITH PACLITAXEL IN COMBINATION WITH WEEKLY HIGH DOSE 5-FU/FOLINIC ACID IN THE TREATMENT OF METASTATIC BREAST CANCER

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*Introduction:* Based on the results of a phase II study with a weekly (x6) schedule of a 24 h infusion of high dose 5-FU/Folinic acid (HDFU/FA) demonstrating high efficacy (RR 41% 13/32 pts) and low toxicity in intensively pretreated metastatic breast cancer patients (pts), we added Paclitaxel (P) to HDFU/FA in a phase I/II trial. P was chosen because of its activity in pretreated metastatic breast cancer pts, different mode of action than HDFU/FA and the lack of overlapping hematologic toxicities between the combination partners. Since 9/93, 51 pts with at least one prior chemotherapy regimen were entered.

*Treatment:* Pts were treated with HD5-FU (24 h infusion)/FA (2 h infusion prior to FU) weekly for six weeks (d1, 8, 15, 22, 29, 36) and P (3 h infusion) was administered additionally on day 1 and day 22. Each cycle comprised of six weeks followed by two weeks rest. Number of cycles depending on response and toxicity. All pts were treated under outpatient conditions using i.v. port systems and portable pumps. During Phase I we chose the following dose levels (dl): Fixed doses of FA dl1–4 500 mg/m$^2$ followed by HDFU 24 h infusion dl1: 1.5, dl2: 1.8, dl3 and dl4: 2.0 g/m$^2$. .3 h infusion of P, given prior to HD5-FU/FA on d.1 and d.22 dl1–dl3: 135, dl4: 175 mg/m$^2$. Dl 4 was chosen to be further evaluated during phase II.

*Patient Characteristics:* 51 pts entered this ongoing trial. Up to now 48 pts were evaluable for response and toxicity. 12 ps entered dl1–3 (4 pts each dl) and 39 pts dl4; age 47 yrs (26–63). WHO PS 1 (0–2), metastatic disease sites 2 (1–4). All pts had bidimensionally measurable disease.

*Pretreatment:* Pts had adjuvant chemotherapy 17/51, prior chemotherapy for metastatic disease 12/51, chemotherapy both adjuvant and for metastatic disease 22/51; prior treatment with anthracyclines 34/51, resistance to anthracyclines with disease progression while treatment prior to study entry 29/51.

*Toxicity:* (n = 51). No dose limiting toxicities occurred during dl1–3. 153 treatment cycles at dl4 had the following toxicities (WHO grade) in (n) cycles: leucopenia 3°/4° (28); mucositis 2° (49); diarrhea 2° (35), 3° (15); hand-foot syndrome 2° (85); PNP 2° (41); nausea/vomiting 2° (37); myalgia 2° (66).

*Results*: (n = 48). CR 4% (2/48), PR 58% (28/48), SD 34% (16/48), PD 4% (2/48). RR (Response rate) 62%, 95% confidence interval 48–76%. Responses (PR) at dl1–3: 2/4 patients. Response concerning 29 patients with anthracycline refractory disease (26 pts were evaluable for response so far): RR 58% (15/26), 95% confidence interval 38–78%. Time to maximum response 2 months (1–5), remission duration 8+ months (2–11). Median survival time not yet reached.

*Conclusions:* The combination of P with weekly HDFU/FA is well tolerated and indicates high efficacy also in anthracycline refractory metastatic breast cancer. In addition the regimen can safely be administered under outpatient conditions.