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## Elderly patients with advanced breast cancer: safety and efficacy of capecitabine

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**Background:** Capecitabine is a selectively tumor-activated fluoropyrimidine which demonstrates a good activity in a wide range of solid tumors. This study tested the global therapeutic index of orally administered capecitabine in elderly patients (pts) with advanced breast cancer (ABC).

**Methods:** From May 99 to October 2002, 73 consecutive pts were treated. The median age was 72.9 yrs (range 65-89). All the pts had measurable or evaluable advanced disease, PS $\leq$ 2,adequate bone marrow, renal and hepatic functions. The first 30 pts received 2500mg/sqm/day; then the dosage was reduced at 2000mg/sqm/day to improve the safety profile. Pts could received 1 prior chemotherapy and/or 2 hormonal regimens for metastatic disease. A previous therapy containing 5-fluorouracil was permitted but a 12 months minimum period was required starting from the last dosage of the previous treatment. The metastatic sites were soft tissue (28), bone (28), liver (26), lung (20), others (20).

The primary end-points were the safety profile and tolerability, the secondary end-points being the response rate (RR) and time to progression (TTP).

**Results:** All pts were evaluable for toxicity and 65 for response (7 did not received 2 cycles). Toxicity according to NCI-CTC Bethesda was: grade 3-4 diarrhea (6%), grade 3 vomiting (7%), grade 2 (10%) and grade 1 (22%) hand-foot syndrome, grade 2-3 asthenia (26%), grade 2 stomatitis (11%). There was a treatment related death for gastrointestinal toxicity.

The objective responses were documented in 26 ABC (35%), 3% complete remission, stabilizations of disease were 23 (34%) and progressions 13 (17%). The median time to progression was 77 days (range 14-139).

**Conclusions:** These results suggest that Capecitabine is feasible and active in elderly pts with ABC.

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## Osteoprotegerin (OPG) and osteopontin (OPN): their usefulness in monitoring the Anastrozole (AN) treated advanced breast cancer (ABC) patients bearing bone metastases

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**Background:** Osteoclast formation can be effectively blocked with OPG, a 55 kD protein that dimerizes, binds to receptor activator NF-kappaB ligand and strongly inhibits osteoclastogenesis. OPG production is regulated by a number of cytokines and hormones, including sex steroids. OPN is an integrin-binding phosphoprotein involved in various physiological and pathological pathways, in particular tumorigenesis and metastatization. OPN serum level is associated with tumour burden and survival in ABC pts. The AN short term effect on OPG and OPN serum levels, and the usefulness of these analytes in monitoring follow-up were evaluated.

**Material and methods**: 34 consecutive ABC pts receiving AN 1 mg/day were studied. Blood samples were collected at baseline and at 2, 4, 8 and 12 weeks during the treatment. OPG and OPN levels were measured by ELISA assay. We analyzed the results for all pts, and also separately for pts with (group A, 22 pts) or without (group B, 12 pts) bone metastases.

**Results**: Considering all pts no significant changes in OPG and OPN levels were observed during treatment. Sharing pts in group A and B there was no difference in baseline OPG and OPN levels. Nevertheless, in group A a significant increase in the levels of both OPG and OPN was detected as percentage of variations *vs.* baseline during the treatment, whether no significant changes was reported for group B pts. Furthermore, in group A a significant increase of both analytes was evident just for pts with PD as reported in table.

| | Clinical response | No. pts | 2 weeks % p | 4 weeks % p | 8 weeks % p | 12 weeks % p |
|---|---|---|---|---|---|---|
| OPG | PD | 7 | 120 0.085 | 129 0.013 | 135 0.004 | 131 0.007 |
| | NC | 10 | 100 | 101 | 108 | 100 |
| | CR + PR | 5 | 105 | 113 | 109 | 101 |
| OPN | PD | 7 | 116 0.23 | 106 0.29 | 174 0.77 | 237 0.042 |
| | NC | 10 | 90 | 51 0.005 | 94 | 82 |
| | CR + PR | 5 | 148 | 125 | 116 | 86 |

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**Conclusions**: In the short term AN doesn't seem to affect bone metabolism measured as OPG and OPN variations. OPG and OPN appear to be useful predictors of the outcome in skeletal disease.

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## Phase I study of vinorelbine (VRL) alternating i.v. and oral in combination with docetaxel (DTX) as 1st line chemotherapy (CT) of metastatic breast cancer (MBC)

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**Background:** VRL and DTX target tubulin-microtubule system, either inhibiting tubulin polymerisation (VRL) or microtubule depolymerisation (DTX). Both agents have proven activity in MBC.

**Material and methods:** The aim of this study is to determine the maximum tolerated dose (MTD) and the recommended dose (RD) of i.v. VRL and DTX given on day 1 (D1) and oral VRL on D8 every 3 weeks, maximum of 6 cycles. Eligibility criteria included no prior CT for MBC. Three to six patients (pts) per cohort are treated. Dose-limiting toxicity (DLT) is assessed during the first cycle and defined as grade 4 neutropenia >= 7 days, grade 3 thrombocytopenia, neutropenic infection, febrile neutropenia, any grade > 2 non-haematological toxicity except asthenia and inadequately treated nausea/vomiting and diarrhoea, omission of oral VRL, and a delay of >= 1 week in starting cycle 2 for haematological reason.

**Results:** Eleven pts were treated in the first 2 cohorts (i.v. VRL/DTX/oral VRL, doses expressed in mg/m2): 25/60/60 and 25/70/60. In the second cohort, 8 pts were treated, 2 pts being non evaluable for MTD, and 5 of them presented a DLT consisting of 2 febrile neutropenia and 3 omissions of oral VRL. Moreover one patient from this cohort died from septic shock after having received her second cycle. Therefore 25/70/60 was the MTD. Because 59% of oral VRL administration scheduled on D8 were delayed to D15, a new schedule of i.v. VRL and DTX on D1 and oral VRL on D15 every 3 weeks was tested. Twelve pts were treated in 3 additional cohorts as follows (i.v. VRL/DTX/oral VRL): 25/60/60 in cohort 3, 20/60/60 in cohort 4 and 22.5/60/60 in cohort 5. Criteria of MTD were achieved in cohorts 3 and 5: in cohort 3, 2 of the 3 enrolled pts had DLT consisting of febrile neutropenia and grade 4 neutropenia > 7 days; and in cohort 5, 2 of the 3 treated pts presented DLT consisting of febrile neutropenia and omission of oral VRL. Consequently the recommended dose for further clinical testing is currently i.v. VRL 20 mg/m2 and DTX 60 mg/m2 on D1 and oral VRL 60 mg/m2 on D15 of an every 3 week cycle. Two partial responses were seen in the 6 pts treated at the RD. The co-administration of VRL and DTX is unlikely to drug-drug interact on pharmacokinetics.

**Conclusion:** This phase I study has established a recommended regimen of VRL (20 mg/m2 of the i.v. form on D1 and 60 mg/m2 of the oral form on D15) and DTX (60 mg/m2 on D1). This study is still ongoing with increasing doses of DTX.

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## A phase II study of vinorelbine (VRL) alterning oral and intravenous (IV) plus epirubicin (EPI) as first line chemotherapy of metastatic breast cancer (MBC)

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**Background:** The combination of IV VRL 25 mg/m$^2$ on days 1 and 8 and EPI 90 mg/m$^2$ on day 1 every 3 weeks is an effective option for the treatment of MBC. In an effort to improve patient convenience, the day 8 administration of VRL was given orally while IV VRL was used the day of EPI infusion. The dose of oral VRL 60 mg/m$^2$, which is equivalent to 25 mg/m$^2$ of IV VRL, was administered on day 8 (possibly day 15 if neutrophils < 1500/mm$^3$).

**Material and methods:** A phase II, multicenter study tested this regimen in patients who had not received prior chemotherapy (CT) for MBC, presented a PS of 0 - 1 and normal ventricular function at study entry.