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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

Data management by scientific service I.T.M.O. (Italian Trial Medical Oncology)

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.

In patients who had received anthracycline-containing adjuvant CT, the cumulative doses had not to exceed 180 mg/m^2 for doxorubicin, 360 mg/m^2 for EPI, and 72 mg/m^2 for mitoxantrone. Patients received a maximum of 6 cycles.

Results: Between October 2000 and March 2002, 49 patients have been enrolled. Median age was 55 years; 88% had visceral involvement (51% liver; 37% lung) and 37% had at least 3 organs involved. The most common toxicity was neutropenia with 65% of patients with grade 3-4, 8% of febrile neutropenia and 12% of neutropenic infection. The main non haematological toxicities included nausea (86% of patients), vomiting (59%) and fatigue (77%) but they were rarely severe. No cardiac toxicity except one transient episode of arrhythmia was seen. Twenty five patients responded, yielding a response rate of 51% in the intent-to-treat population and 55% in the 44 evaluable patients. Median duration of response was 8.5 months. With a median followup of 9.5 months, the median progression-free survival has not been reached.

Conclusion: VRL alterning oral and IV in combination with EPI is an effective and convenient therapeutic option for MBC. Its activity and safety profile are similar to those reported for the fully IV regimen.

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A phase II study of first-line combination chemotherapy with docetaxel and gemcitabine in anthracycline-pretreated, Her-2 negative metastatic breast cancer (MBC)

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Background: The combination of docetaxel (D) and gemcitabine (G) is particularly attractive as both agents are not completely cross-resistant and have been shown to be active in anthracycline-pretreated MBC. This phase II study evaluated the efficacy and safety of D and G in anthracycline-pretreated patients with MBC not overexpressing *Her-2/neu*.

Materials and methods: Patients with MBC (n=36) not overexpressing *Her-2/neu* and pretreated with an anthracycline-based adjuvant or neoadjuvant chemotherapy received D 75 mg/m^2 on Day 1 and G 1000 mg/m^2 on Day 1 and Day 8 every 3 weeks as first-line chemotherapy. The predominant metastatic sites were visceral (liver 36% and lung 30%); 10 (28%) patients had soft tissue metastases and 2 (6%) patients had bone lesions alone.

Results: All patients were evaluable for toxicity and 35 for response. A total of 184 cycles were given to 36 patients (median 6 cycles, range 1-6). A complete response was recorded in 8 (23%) patients and a partial response in 11 (31%) patients for an overall response rate of 54%. With a median follow-up of 11 (range 3-22) months, median time to progression was 8 (range 2-21) months. Median overall survival has not been reached so far. The predominant toxicity was leucopenia, however, no febrile neutropenia occurred. Haematological toxicity WHO grade 1-4 occurred as follows (% of patients/% of cycles): leucopenia grade 1, 14%/22%; grade 2, 33%/34%; grade 3, 47%/30% and grade 4, 6%/2%; thrombocytopenia grade 1, 28%/14%; grade 2, 8%/2%; grade 3, 14%/3%; grade 4, 0%/0%; anaemia grade 1, 47%/34%; grade 2, 19%/6%; grade 3, 3%/1%; grade 4, 3%/1%. The most common grade 1 or 2 nonhaematological toxicities per cycle were nausea and vomiting 21%, mucositis and stomatitis 20%, diarrhoea 15%, asthenia 28%, neurological symptoms 22%, pain 22%, nail and cutaneous disorders 21%, and dyspnoea 8%. Grade 3 or 4 toxicity per cycle included dyspnoea 3%, pain 2%, asthenia 2%, nausea and vomiting 2%, and constipation 1%.

Conclusion: The D-G combination regimen was active and well tolerated as first-line treatment of anthracycline-pretreated MBC not overexpressing *HER-2/neu*.

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Caelyx (pegylated liposomal doxorubicin hcl) and conventional doxorubicin have significantly different adverse event profiles

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In a previously reported randomized, phase III trial in first-line treatment of 509 women with metastatic breast cancer, CAELYX™ and conventional doxorubicin were shown to have comparable efficacy with respect to progression-free survival. There was a significantly greater risk of cardiotoxicity with conventional doxorubicin compared with CAELYX™ (P<.001). In order to ascertain whether there were other significant differences in toxicity between the 2 agents, a post-hoc analysis was performed using data from the trial. Twenty types of adverse events were reported in ≥5% of patients in either arm. Palmar-plantar erythrodysesthesia was the most frequently reported adverse event related to CAELYX™ treatment (48% of patients overall; NCI-CTC Grade 3 in 17%, and Grade 4 in 0%), whereas alopecia was the most frequently reported adverse event associated with conventional doxorubicin, (reported in 66% of patients overall; pronounced or total hair loss reported in 54%). Adverse events related to the skin or mucosa were significantly more prevalent in the CAELYX™ arm and included mucositis (CAELYX™ = 59 events, conventional doxorubicin = 33 events; P = 0.0026), stomatitis (CAELYX™ = 55 events, conventional doxorubicin = 38 events; P = 0.0487), palmar-plantar erythrodysesthesia (CAELYX™ = 123 events, conventional doxorubicin = 5 events; P<.0001), rash (CAELYX™ = 25 events, conventional doxorubicin = 4 events; P<.0001), erythema (CAELYX™ = 18 events, conventional doxorubicin = 3 events; P = 0.0008), and abnormal pigmentation (CAELYX™ = 21 events, conventional doxorubicin = 6 events; P = 0.0029). Alopecia (CAELYX™ = 51 events, conventional doxorubicin = 169 events; P<.0001), nausea (CAELYX™ = 94 events, conventional doxorubicin = 136 events; P = 0.0002), vomiting (CAELYX™ = 48 events, conventional doxorubicin = 78 events; P = 0.0022), and neutropenia (CAELYX™ = 10 events, conventional doxorubicin = 25 events; P = 0.0089) were more often associated with conventional doxorubicin treatment. In this posthoc analysis there were no other significant differences in adverse event frequency between the 2 groups. CAELYX™ and conventional doxorubicin have distinct toxicity profiles. Skin and mucosal toxicity are the most common type of adverse events associated with CAELYX™ whereas conventional doxorubicin is associated with significantly more alopecia, nausea, vomiting, and neutropenia.

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Multicenter phase II study of sequential hormonotherapy with Anastrozol/Exemestane (ARIM-AROM) in metastatic breast disease. Preliminary data of Goim 2107 study.

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The study was oriented to evaluate the overall response as primary endpoint, TTP, clinical benefit, toxicity and overall survival as secondary end-point.

Eligibility criteria: Advanced breast cancer or primary tumour or locally advanced not resectable, with positive or unknown ER/PgR, with interrupted TMX treatment and physiological, pharmacological, radiotherapeutic or surgical menopause.

Treatment: Anastrozol 1 mg/die up to progression, followed by Exemestane, 25 mg/die up to 2nd progression.

Recruitment time: 12 months.

Patient characteristics: 99 pts were recruited, median age 67 (range 36-93) with bone metastases (55%), skin and lymphonodes (27%), liver (33%) and PS 0 (58%), PS 1 (35%), PS 2 (17%) and 42 months median DFS.

Results: 73 valuable pts; CR 5 (7%), PR 18 (24,5%), OR 23 (31,5%), NC 24 (33%), PD 21 (29%). In 18 pts treated in second line with exemestane were registered 2 PR and 4 NC >4 months.

Conclusion: These actual data are on line with literature results. Very promising seem preliminary not shown data of median response duration and clinical benefit. The next update will be at the end of June 2003.

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Weekly paclitaxel plus trastuzumab in metastatic breast cancer (MBC): a multicentre German trial

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Background: Three-weekly paclitaxel plus weekly trastuzumab therapy has proven clinical benefit in metastatic breast cancer (MBC) (Slamon D, et al. New Engl J Med 2001:344;783-92). The current trial investigates the efficacy and safety of weekly administration of both paclitaxel and trastuzumab in MBC.