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POSTER DISCUSSION

Association Between Circulating Tumour Cells and Bone Turnover Markers in Patients With Breast Cancer and Bone Metastases on Treatment With Bisphosphonates (ZOMAR Study)

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Background: Quantification of Circulating Tumour Cells (CTC) has demonstrated an important role in assessing disease progression and outcomes, and pathological CTC levels are an independent prognostic factor of disease progression. The presence of bone metastases alters the balance of bone remodeling and consequently, levels of bone turnover markers (BTM). Increased levels of these biomarkers have been associated with the risk of skeletal-related events (SREs), disease progression and death. The aim of this study is to determine the relation between BTM, CTC and SREs in patients with bone metastatic breast cancer (mBC) treated with zoledronic acid.

Patients and Methods: Observational, prospective and multicenter study. Patients with mBC; no previous bone treatment in the last 6 months prior to study entry. CTC (fluorescently labelled with nucleic acid dye 4,6-diamidino-2-phenylindole DAPI, monoclonal antibodies specific for leukocytes CD45-allophycocyanin and epithelial cells cytokeratin 8,18,19 – phycoerythrin. Cell Search System Veridex); urinary aminoterminal telopeptide of collagen I (NTX, Osteomark NTx Urine, Wampole Laboratories, USA); urinary alpha-alpha-isomer of carboxyterminal telopeptide of collagen I ($\alpha\alpha$ -CTX, ALPHA Crosslaps EIA, ids, UK) and serum bone alkaline phosphatase (BALP, OSTASE BAP, ids, UK) were determined at baseline (V0) and after 3 mo of treatment (V1). Pts were treated with zoledronic acid (ZOL) at inclusion and every 3–4 weeks.

Results: Data of CTCs and BTM at basal visit (V0) and after 3 mo of treatment (V1) are presented. Population basal characteristics: mean age: 61 years; ER+: 80%; PR+: 67%; HER2+: 18%. 52% of patients (n = 102) had detectable CTC (CTC ≥ 1) at V0, and 70% of them presented pathological (CTC ≥ 5) at V0. A significant decrease was observed at V1, 27% of patients with pathological CTC levels (p < 0.05). 55%, 29% and 81% patients (n = 83) presented elevated levels of NTX, $\alpha\alpha$ -CTX and BALP at V0. A significant decrease was observed between V1 vs V0, of 16%, 6% and 54% of NTX, $\alpha\alpha$ -CTX and BALP levels respectively (p < 0.05). A positive correlation was observed between CTC and each time point with BTM (p < 0.05). At V1 the positive significant correlation remained for CTC and NTX and BALP (p < 0.05). 17 patients presented SRE between V0 and V1.

Conclusion: Over 50% mBC patients presented basal detectable CTC levels (CTC ≥ 1), and the majority – 70% had pathological levels (CTC ≥ 5). A significant decrease was observed at V1 in 27% patients with pathological CTC levels (p < 0.05). ZOL significantly reduced CTC and BTM levels after 3 mo of treatment. Due to the low number of SRE, no correlation was observed either with CTC or with BTM after 3 mo of treatment. Longer follow up is needed.

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Cyfra 21-1 Correlation With Circulating Tumour Cells (CTC) Detection and Patient Outcome in Metastatic Breast Cancer: Results of a Substudy of the Prospective IC 2004-06 Trial

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Background: The Cyfra 21-1 epitope is a polypeptide originating from cytokeratin-19 fragments possibly released by cell death and was an

interesting serum marker in small and/or retrospective studies in breast cancer. On the back of circulating tumour cell (CTC) detection, the prospective IC 2006-04 study planned serum markers (CEA, Ca15.3, Cyfra 21-1) measurements.

Methods: Metastatic breast cancer patients were included in a multicentric non-interventional study before the start of the 1st line chemotherapy. Blood biomarkers, including CTC detection (CellSearch, 5CTC/7.5 ml), were analyzed at 4 different times: before the start of the chemotherapy, before cycle 2 (ie mostly at day 21), at first tumour evaluation (ie before cycle 3/4) and at tumour progression.

Results: 191 of the 267 patients included had Cyfra 21-1 assessed at inclusion. CTC level was 5CTC/7.5 ml in 44% of the cases. Cyfra 21-1 > ULNV (in 65% of pts) was not correlated with tumour ER/PR/HER2 status but strongly correlated with PS (p = 8×10^{-4}), number of metastatic sites (p = 0.0001), Ca15.3 (p = 0.009), CEA (p = 0.005), LDH (p = 7×10^{-8}) and CTC detection (p = 2×10^{-6}).

Logistic regression showed that LDH (p = 0.0005) and CTC (p = 0.0004) were the two independent predictors of Cyfra 21-1 elevation. Baseline Cyfra 21-1 > ULNV was associated with early tumour progression (RECIST, p = 0.03). In multivariate analysis including standard biomarkers (without CTC), baseline Cyfra 21-1 was independently associated with PFS (p = 0.008, RR), together with PS (p < 0.001), triple-negativity (p < 0.001) and CEA (p = 0.02). Multivariate analysis with CTC, subsequent Cyfra 21-1 analyses (cycles 2, 3–4 and progression) and correlation with tumour response and PFS will be shown at the meeting.

Conclusion: Cyfra 21-1 is a commonly elevated serum marker in metastatic breast cancer and has an independent prognostic value. Although highly correlated, Cyfra 21-1 appears to be more frequently positive in metastatic breast cancer patients than CTC count. Multivariate analyses comparing CTC and Cyfra 21-1 at different time points will be shown at the meeting.

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POSTER DISCUSSION

Clinically Used Breast Cancer Markers are Heterogeneous Throughout Tumour Progression

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Background: As of today, clinical management of metastatic breast cancer patients is frequently based on primary tumour marker status.

Methods: The cohort includes breast cancer patients in the Stockholm health care region who relapsed during January 1, 1997 to December 31, 2007. Biochemical or immunohistochemical (IHC)/ immunocytochemical (ICC) methods were used for determination of oestrogen receptor (ER), progesterone receptor (PR) and Her2-neu amplification (HER2) (confirmed also by Fluorescence In Situ Hybridization for IHC/ICC 2+ and 3+).

Results: Information on ER and PR in multiple relapse sites was assessed in 119 and 116 patients, respectively. Interestingly, the markers were unstable throughout tumour progression also in the advanced setting. For ER, 33.6% of patients had discordant ER status between different sites of relapse, whereas 36.1% and 30.3% of patients were stable positive and negative, respectively. Further, 16.0% of patients changed ER status from positive to negative, 12.6% changed from negative to positive, and 5.0% altered ER status forth and back throughout tumour progression (labelled heterogeneity in table). For PR, 30.2% of patients altered their hormone receptor status with a majority of the change from PR positive to negative (19.8%).

Table: Information on multiple sites of relapse in the same patient: Hormonal receptor discordance in the relapse setting

ER*	Hormonal receptor status			
	PR*			
	Number of patients	Percent	Number of patients	Percent
Between relapse sites				
Stable positive	43	36.1	15	12.9
Stable negative	36	30.3	66	56.9
Positive to negative	19	16.0	23	19.8
Negative to positive	15	12.6	8	6.9
Heterogeneity	6	5.0	4	3.5
Total	119	100.0	116	100.0

*Cut-off value of 0.05 fmol/ μ g DNA and 10%, for monoclonal antibody based biochemical and IHC/ICC methods, respectively.

Conclusions: Breast cancer patients alter hormone receptor status throughout tumour progression. Hence, this dynamics will make clinical