Results: Between 1994 and 2005 breast cancer incidence increased significantly among women 40 years or older with oestrogen positive tumours. However, the incidence of oestrogen negative tumours seems to be constant. The increase in breast cancer incidence has solely arisen among oestrogen positive tumours in both pre-menopausal and post-menopausal women. Hence, the relative amount of ER positive tumours rose from 70.1% to 81.5%.
Conclusion: The finding that the rapid increase in breast cancer incidence has solely occurred within ER positive cancers suggests that it may be related to changes in life style and environmental factors rather than a genetic or biological change of the disease itself.

Poster presentations (Wed, 26 Sep, 14:00–17:00)
Breast cancer – pre-clinical science

2006 POSTER

The potential role of bone derived cells in the development of breast cancer metastases

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Despite advances in treatment, over 80% of patients with advanced breast cancer will develop bone metastases for which there is no cure. Thought to involve a complex cascade of cell-cell interactions, the mechanisms of bone metastases are still largely unknown. Bone is a very dynamic environment with continuous cell turnover, which may play an important role in directing the homing and engraftment of circulating breast cancer cells. Mesenchymal Stem Cells (MSCs) and osteoblasts are two subpopulations of cells that exist within bone. MSCs have the potential to differentiate into a range of cell types, and when cultured under appropriate conditions will develop into osteoblasts.
The aim of this project was to investigate the potential role of bone derived MSCs and osteoblasts (NHOst) in directing breast cancer cell migration, and to identify factors mediating their interactions.
Primary culture of MSCs, NHOsts and breast cancer cell lines (MDA-MB-231 and BT-474) was performed. Breast cancer cell migration in response to MSCs and NHOsts was measured using Transwell™ inserts. Media containing β-Glycerophosphate, ascorbic acid and dexamethasone was used to induce MSC differentiation into osteoblasts. MCP-1 and VEGF were quantified using ChemiArray™ and ELISA™ at various stages of differentiation. The potential role of MCP-1 in breast cancer cell migration was investigated using a monoclonal antibody to the chemokine.
There was a significant increase in migration of both breast cancer cell lines in response to factors secreted by NHOsts (5–10 fold increase) and MSCs (6–10 fold increase). MSCs were shown to secrete a range of chemokines including IL-6 & 8, TIMP 1 & 2 and MCP-1. Levels of MCP-1 secreted by differentiating MSCs increased from 319 pg/ml (Day 3) to 12,280 pg/ml (Day 21), while VEGF increased from 100 pg/ml (Day 3) to 1040 pg/ml (Day 21). MSC differentiation into osteoblasts was confirmed by the presence of calcium deposits following Von Kossa staining. A monoclonal antibody to MCP-1 resulted in inhibition of MDA-MB-231 (20% reduction) and BT-474 (30% reduction) migration in response to NHOst cells, confirming a role for this chemokine in the migratory effects seen.
Bone derived MSCs and osteoblasts secrete varying levels of chemokines throughout differentiation that play a potentially important role in mediating breast cancer cell migration. Further investigation of the specific mode of action of these chemokines may provide novel therapeutic targets for treatment of advanced breast cancer.

2007 POSTER

Recommendations for the prevention of aromatase inhibitor-associated bone loss in women with breast cancer

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Background: Patients with breast cancer are at increased risk for fracture compared with healthy age-matched women; however, there is currently no guidance for identification of women at high fracture risk. It is well established that osteoporotic women (T-score ⩽2.5) require bisphosphonate therapy to increase bone mineral density (BMD) and reduce the risk of fracture, yet this threshold appears inadequate for averting fractures in breast cancer patients, particularly those receiving aromatase inhibitor (AI) therapy.
Material and Methods: We performed a literature review to identify factors that contribute to the increased risk of fracture observed in women with breast cancer. Using an evidence-based medicine approach, we selected risk factors that can be used to determine when to initiate bisphosphonate treatment and to identify the appropriate bisphosphonate for AI-associated bone loss treatment.
Results: With the exception of AI treatment, risk factors for fracture were chosen based on their validation in large populations of postmenopausal women. Risk factors for fracture in patients with breast cancer were AI therapy, T-score ⩽1.5, age >65, family history of hip fracture, personal fragility fracture history after age 50, or oral corticosteroid use of >6 months. Additional risk factors were identified for which guidance could not be provided because available data were insufficient: chemotherapy, radiotherapy, low body mass index, low weight, family fracture history, and smoking. Available data clearly suggest that combined risk factors contribute to fracture risk independent of BMD; therefore, BMD measurement should not be the sole criterion to assess fracture risk in this patient population. Randomized clinical trials support zoledronic acid 4 mg every 6 months for prevention of AI-associated bone loss when a patient is identified to be at risk, and data with other bisphosphonates are emerging.
Conclusions: Our guidance for the treatment and prevention of AI-associated bone loss is as follows: In addition to calcium and vitamin D, any patient initiating AI therapy with a T-score ⩽2.0 should receive zoledronic acid 4 mg twice per year. In addition, any patient receiving AI therapy with any 2 of the following risk factors, T-score ⩽1.5, age >65 years, family history of hip fracture, personal history of fragility fracture after age 50, or oral corticosteroid use of >6 months, should receive zoledronic acid as preventative therapy.

2008 POSTER

The E-ZO-FAST trial: Zoledronic acid (ZA) effectively inhibits aromatase inhibitor associated bone loss (AIBL) in postmenopausal women (PMW) with early breast cancer (EBC) receiving adjuvant Letrozole (Let)

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Background: Letrozole is safe and effective in the treatment of receptor positive EBC in PMW. But like other aromatase inhibitors (AIs), long-term letrozole is associated with loss of bone mineral density (BMD) and a higher incidence of fractures. This multicenter open-label randomized study evaluates an immediate or delayed strategy of bone protection therapy with ZA in preventing AIBL in PMW with EBC who are receiving adjuvant Let therapy.
Material and Methods: 522 PMW with stage I-IIIa ER+ and/or PR+ EBC starting Let (2.5 mg qd x 5 yrs) were randomized to immediate ZA (4 mg IV infusion q 6 mos) vs delayed ZA in 66 centers in South America, Europe, the Middle East, Korea, and South Africa and received Let. The delayed group received ZA when either post-baseline T-score decreases to less than −2.0 SD or if a non-trauma fracture occurs. The primary endpoint is the percent change in lumbar spine (LS) BMD with key secondary endpoints of percent change in total hip (TH) BMD and safety.
Results: Patient enrollment started 9 April 2004 and ended 11 August 2005. The median age on both arms was 58 (range 40–81). Baseline characteristics were similar between arms. Patients were stratified by prior adjuvant chemotherapy, menopausal status, and baseine BMD T-Score. The 12 mos LS BMD revealed that the upfront ZA group shows a mean increase of 2.7%, the delayed group had a mean decrease of 2.7%, resulting in a significant difference of 5.4% between groups ($p > 0.0001$). For the 12 mos TH BMD, upfront arm results were a mean increase of 1.7%; the delayed arm had a mean decrease of 1.6%. This is a significant difference of 3.3% between groups ($p < 0.0001$). The median duration of Let therapy was similar in both arms (18.5 vs 18.6 months). Patients on the immediate arm had received a median of 3 dose of ZA at the time of this analysis. Only 35 patients on the delayed arm had started ZA. At month 12, the most common adverse event was arthralgia, as expected. The incidence was similar in both arms (35.7% vs 38.9%). Seven patients had a clinical fracture (2 in the immediate group and 5 in the delayed group).

No serious renal disorders or ONJ cases were reported during this time frame. Overall, the incidence of adverse events was not different between the two arms.
Conclusion: This geographically diverse study confirms the effectiveness of the zoledronic acid to prevent AIBL as documented in the North American Z-FAST study and the rest of world study, ZO-FAST.

2009 POSTER

Safety of the combination of lapatinib (L) plus trastuzumab (T) in patients (pts) with HER2-Positive (+) metastatic breast cancer (MBC)

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Background: L, an oral, dual EGFR/HER2 tyrosine kinase inhibitor, and T, a humanized anti-HER2 antibody, are approved in HER2+ MBC. Based on preclinical synergy and different mechanisms of action, L+T was studied in HER2+ MBC. Data from 4 trials were analyzed to assess safety of L+T.
Methods: From July 2003 to Mar 2007, 393 women of median age 51 years (range: 22−81 years) with HER2+ MBC received L±T (n = 351) or L+T+ paclitaxel or docetaxel (n = 42). L dose range: 500–1500 mg/day; 297 pts received ⩾1000 mg. T dose: 2 mg/kg/week. Drug-related adverse events (AE) graded by NCI CTCAE were analyzed. Cardiac function (LVEF) was assessed at screening, 8 weekly after starting L+T, and at withdrawal via MUGA or echocardiogram. Rate of symptomatic cardiac events (CE; CTCAE Grade 3/4 LV systolic dysfunction) or asymptomatic LVEF decreases (⩾20% relative to baseline and below institution's lower limit of normal) were assessed.
Results: Common drug-related AEs were diarrhea (53%), rash (25%), nausea (24%), fatigue (19%), and vomiting (13%). Maximum grade (G) reported by most was G1 or G2. G3 AE rate was ⩽3% except diarrhea in 12% (including G4 in <1%). Eight pts had single asymptomatic LVEF decreases, 2 had 2 asymptomatic decreases, and 2 (0.5%) had symptomatic CEs, totaling 14 decreases in 12 (3.1%) pts. Pts received prior T± anthracyclines (A; n = 8), A (n = 2), or unknown therapy (n = 2). For asymptomatic events, mean baseline and nadir LVEFs were 65.3% (range: 58−74%) and 46.1% (range: 42.5−51%), respectively. Mean absolute decrease was 19.4% points (range: 13−29%). Median time to onset and duration of LVEF decrease was 55 (range: 18–282) and 9 days (range: 4–113), respectively. L+T was interrupted in 4 pts and continued in 4 despite LVEF decrease. Two events occurred after L was discontinued. Asymptomatic LVEF decrease resolved without sequelae in 7 pts, unresolved in 2, ongoing at death (disease progression) in 1. Two pts had symptomatic CEs (LVEF 58% to 25% and 69% to 25%) after 365 and 42 days of L+T, respectively. L+T was discontinued in both; 1 recovered after 17 days and 1 died (cardiac insufficiency/pulmonary thromboembolism).
Conclusion: Preliminary data indicate L+T was well tolerated in pts with HER2+ MBC. Rates of drug-related AEs were consistent with those reported for L and T alone. Combined HER2 inhibition with L+T does not unexpectedly increase the risk of CE. L+T is currently being studied in neoadjuvant and adjuvant trials in HER2+ BC.

2010 POSTER

Comparative analysis of circulating tumor cells (CTCs) in peripheral blood and disseminated tumor cells in the bone marrow (DTC-BM) of breast cancer patients

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Background: The detection of Disseminated Tumor Cells in the Bone Marrow (DTC-BM) of breast cancer patients is an independent prognostic factor in all stages of the disease. As less invasive procedure the analysis of Circulating Tumor Cells (CTCs) in Peripheral Blood (PB) could be an alternative especially for repeated follow up examinations. Automated systems und molecular methods (PCR) could increase sensitivity and offer the possibility of further characterizations of those cells.
Methods: BM aspiration and blood draw is performed simultaneously. Immunocytochemical examination of DTC-BM with the anti-Cytokeratin (CK) antibody A45B/B3 follows a standardized protocol. Analysis of PB (7.5 ml) for the presence of CTCs is performed with the CellTracks Analyzer system (Veridex, NJ, USA). After immunomagnetic enrichment by anti-Epcam antibodies CTCs are stained against CK, CD 45, and, optionally, HER2 by immunofluorescence. Positive events are recognized automatedly and presented on a screen for evaluation.
Results: Up to now, comparison of BM and PB of 44 patients could be performed. DTC-BM and CTCs in PB were detected in 15/44 (34%) cases each. Overall congruence of positive and negative findings was 68% (p = 0.05). 32 pts were examined at primary diagnosis. Of those, 19 (59%) showed both negative BM and PB, 6 (19%) DTC-BM (1−11) with negative PB, 6 (19%) CTCs (2–123) with negative BM, and 1 (3%) both. Patients with presence of CTCs at primary diagnosis tended to have higher tumor stage (T2-T4), Grading 2/3, 4 presented with lymph node metastases. Of 6 patients at recurrence free follow up examination, 3 had both positive BM and PB and 3 both negative status (100% congruence). Of the 6 pts with distant metastases, 5 showed DTC-BM (1–>1000) and 5 CTCs (2−77), all 4 patients with visceral metastases both.
Conclusion: If our results can be confirmed in a larger series, examination of CTCs in PB could add valuable information and allow monitoring of the disease during follow up. Further characterization of CTCs might enable risk stratification and application of targeted therapies. Aim of our ongoing research is the detection and characterization of CTCs by rt-PCR for tumor specific mRNA.

2011 POSTER

Serum BCL-2 and VEGF in women with breast cancer – can they detect the recurrence before CEA and CA15−3?

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Purpose: The purpose of our study is to investigate if serum VEGF and bcl-2 can be used as prognostic factors during the follow-up of the patients with breast cancer and to compare these two factors with CEA and CA15−3.
Patients and Methods: 200 patients with breast cancer stage I and II are enrolled in our study. The mean age of the patients was 59.65±11.65 years. 102 patients had quadrectomy and axillary lymph node dissection and 98 had mastectomy. After the surgical treatment they had supplementary therapy. The size of the tumor was <2 cm in 105 patients and >2 cm in 95 patients. The histological type was ductal carcinoma in 169 patients, lobular in 10 and DCIS in 2 patients. 54 patients had <3 lymph node positive, 46 had >3 positive lymph node and 100 had negative lymph node. 14 patients had recurrence of the disease after the 18 months of the surgical treatment. We measured serum VEGF and bcl-2 before and after the operation and the first and second year of their follow-up with ELISA. CEA and CA15−3 were measured every 4 months after the surgical treatment until the two years. The results have been analysed with curves ROC and Pearson method to find if VEGF and bcl-2 can be used during the follow up of the patients to investigate the recurrence of the disease before the clinical appearance. Also we examine if they can detect the recurrence earlier of CEA and CA15−3.
Results: After the analysis with ROC curves we found that bcl-2 can detect the recurrence of breast cancer preoperative (p = 0.066) and also postoperative (p = 0.037) and at second year (p = 0.029) of the follow-up of the patients. VEGF can detect the recurrence after the operation (p = 0.003). On the other side CEA can detect the recurrence in 20 months after the operation (p = 0.098) and CA15−3 in 8 (p = 0.045). There was no correlation with the size of the tumor, the histological type and the lymph node status.
Conclusion: These results shows that bcl-2 and VEGF in serum can be used in the follow-up of the patients with breast cancer as they can detect the recurrence of the disease much earlier of the clinical appearance. CEA and CA15−3 can also detect the recurrence before the clinical appearance but later of the other two factors. Serum bcl-2 is the most significant factor as it can detect the recurrence in three measurements.

Poster presentations (Mon, 24 Sep, 14.00−17.00)
Breast cancer – pre-clinical science

2012 POSTER

Activity of capecitabine (C) and docetaxel (D) doublets with and without trastuzumab (T) in a breast cancer xenograft model

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Background: In the setting of pretreated metastatic breast cancer, C is highly active, well tolerated, and extends survival when D is added to C. Preclinical data on C+D doublets ± T, a humanized monoclonal antibody