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).