243 POSTER HIGHLIGHT

A multinational phase II study of Navelbine (N) and Herceptin (H) as first-line therapy for patients with HER2-positive metastatic breast cancer (HER2+ MBC)

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The combination of Navelbine (N) and Herceptin (H) is an attractive regimen for HER2 positive MBC patients. Preclinical studies show synergistic activity between the two agents and several national studies have demonstrated that there is no overlapping toxicity. Here we report results of a large multinational phase II trial.

Patients and methods: MBC patients (pts) overexpressing HER2 (IHC 3+ or FISH+ by centralised testing), with measurable disease, KPS=70%, normal LVEF, no prior H or N, adjuvant chemotherapy allowed, were treated with N: 30 mg/m^2/week and H: 4 mg/kg on day 1 as loading dose and then 2 mg/kg/w starting on day 8 within 4 week-cycle. Patients were reassessed every 8 weeks.

Results: between October 2000 and June 2002, 69 consecutive patients were included in the study (from 147 screened pts), median age 53 years (30–74), prior neo/adjuvant chemotherapy: 65.2% (anthracycline: 51.1%, anthracycline + taxanes: 28.9%, CMF: 20%), prior hormonal therapy: 49.3%, visceral metastases: 75.4% (liver: 55.1%, lung: 27.5%). Sixty-six patients were evaluable for response and 68 pts for toxicity. Radiological assessments were reviewed by an independent review committee. The overall response rate is 58.5% including 14% complete responses. The clinical benefit (CR+PR+SD = 24 weeks) was 80%. The median time to response is 8.4 weeks, median duration of response is 11.7 months and median progression-free survival is 10 months. Median survival has not yet been reached. The median duration of treatment is 24 weeks (1–80+) with a median of 6 cycles/pt. Nine pts were treated with this combination for more than 1 year and 7 pts (10%) are still receiving treatment. The regimen is well tolerated, WHO grade 3–4 neutropenia was recorded in 44.6% of cycles with 2 episodes of febrile neutropenia, H infusion reactions were moderate (grade 3: 1.5% of pts), grade 3 asthenia was seen in 8.8% of pts, grade 3 neuropathy in 4% of pts and grade 3 infection in 6% of pts. One pt came off study for grade 3 cardiac toxicity with a decline in LVEF and symptomatic cardiac dysfunction that resolved with symptomatic therapy. No severe nausea, vomiting or alopecia has been reported.

Conclusion: our results confirm that N + H is one of the most active treatment regimens for pts with HER2 positive MBC, even after Anthracycline/Taxane pre-treatment and demonstrates a very favourable safety profile.

244 POSTER HIGHLIGHT

High incidence of cerebral metastases in patients with metastatic breast cancer treated with trastuzumab

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Trastuzumab is an effective treatment that can prolong survival in patients with metastatic breast cancer (MBC), which overexpresses HER-2. A high incidence of brain metastases has been noted in patients receiving trastuzumab therapy. A retrospective chart review was conducted of 100 patients who commenced trastuzumab therapy for metastatic breast cancer from July 1999 to December 2002, at the Christie Hospital, Manchester, UK. Five patients developed CNS disease prior to starting trastuzumab and were therefore excluded, as were 2 with incomplete data. Twenty-three of the remaining 93 patients (25%) have developed brain metastases to date. Forty-six patients have died, and of these, 18 (39%) have been diagnosed with brain metastases prior to death. Seventeen of 23 patients (74%) developed cerebral metastases whilst receiving trastuzumab therapy, and of these, 14 (83%) were responding to trastuzumab or stable at other disease sites at the time of the development of cerebral metastases. Of the 23 patients that have developed brain metastases, 18 (78%) had oestrogen receptor (ER) negative disease. Eighteen (78%) of the 23 patients developing CNS disease also had visceral disease. Univariate analysis has shown a significant association between the development of cerebral disease and both hormone receptor status, and the presence of visceral disease. In conclusion, a high proportion of patients with MBC treated with trastuzumab develop symptomatic cerebral metastases. HER-2 positive breast cancer may have a predilection for the brain, or trastuzumab therapy may change the disease pattern by prolonging survival. The data presented here also suggest that a particularly high-risk group with ER negative disease and visceral metastases may be identified. New strategies to address this problem require investigation in this group of patients.

245 POSTER HIGHLIGHT

A new mechanistic action of Zoledronic acid in the prevention of breast cancer bone metastasis: both decreased cell motility and SDF-1 directed cell migration

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Introduction: Zoledronic acid (ZA) is a nitrogen-containing biphosphonate wich reduces cancer-induced bone complications by an anti-proliferative and apoptotic effect on osteoclasts. Recently it has also been reported to prevent bone metastasis. In this work we provide mechanistic understanding of how ZA could prevent the development of bone metastasis in breast cancer.

Material and Methods: The effects of ZA were tested on a human breast-derived aggressive cancer cell line (MDA-MB231). Action on cell invasion was studied on matrigel-coated membrane in a Transwell, without and with the chemotactic cytokine stromal cell-derived growth factor-1 (SDF1).

The mechanism of the anti-invasive action of ZA was analysed by its effect on actin cytoskeleton visualised by confocal analysis. The role of RhoA in ZA effect on cell motility inhibition was investigated. As for cell signalling RhoA has to be prenylated to cell membrane, we determined by western blotting its repartition on particulate and cytosolic cell fractions in the absence or presence of ZA.

The mechanism of the ZA-induced modulation of SDF-1chemotactic effect on cancer cells was investigated by the measurement by flow cytometry analysis of the membrane-expression of its receptor CXCR-4.

Results: Low concentrations (1 μM) of ZA inhibited cancer cell invasion and SDF-1 induced chemotactic effect. It was related 1) to the inhibition of actin cytoskeleton organisation due to inhibition of the cell signalling induced by RhoA consecutive to a defective prenylation; 2) to an important decrease in CXCR-4 cell expression independent of RhoA inhibition.

Conclusion: ZA induced a decrease in cell motility by inhibiting RhoA cell signalling and a decreased expression in SDF-1 receptor. As SDF-1 is greatly involved in breast cancer bone metastasis, our results suggest a new mechanistic explanation of the anti metastatic activity of ZA in breast cancer.

246 POSTER HIGHLIGHT

Zoledronic acid has long-term efficacy in reducing skeletal complications in patients with bone metastases from breast cancer

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Background: The long-term efficacy and safety of 4 mg zoledronic acid for the prevention of skeletal complications from bone metastases in patients with breast cancer was demonstrated in a large, multicenter, randomized, phase III trial compared with pamidronate.

Materials and Methods: Patients were randomized to receive 4 mg zoledronic acid (via 15-minute infusion) or 90 mg pamidronate (via 2-hour infusion) every 3 to 4 weeks for up to 25 months. Data presented are from the stratified subset of 766 patients with breast cancer who were treated with 4 mg zoledronic acid or pamidronate, including subset analysis of patients with either osteolytic or nonlytic bone lesions, and including data from core and extension phases.

Results: A total of 454 patients completed the 13-month core phase, and 165 patients completed the 12-month extension phase. The preplanned multiple event analysis (Andersen-Gill method), which provides comprehensive assessment of skeletal morbidity, demonstrated that 4 mg zoledronic acid significantly reduced the risk of developing skeletal complications throughout the 25-month study. Among all patients with breast cancer, zoledronic acid reduced the risk of skeletal complications by an additional 20% over that achieved with pamidronate (hazard ratio [HR] = 0.799; P=0.025). Among patients with ⩾1 osteolytic lesion (47% of total), those treated with zoledronic acid (n=190) had a significantly (32%) lower risk of developing skeletal complications compared with 162 pamidronate-treated patients (HR=0.683; P=0.003). In this subset, zoledronic acid also significantly delayed the time to first skeletal complication (median, 296 vs