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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.

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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.

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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.

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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

171 days; P=0.015). Among patients with nonlytic lesions, multiple event analysis demonstrated a 12% reduction in the risk of skeletal complications for patients treated with zoledronic acid (n=188) compared with 226 pamidronate-treated patients (HR=0.878; P=0.385). Bone marker data for these patient subsets will be presented. Zoledronic acid was well tolerated with a long-term safety profile similar to that of pamidronate.

Conclusions: These data indicate that zoledronic acid is more effective than pamidronate for reducing the long-term risk of skeletal complications in patients with breast cancer, particularly those with at least 1 osteolytic lesion. Zoledronic acid is the only bisphosphonate to show superiority in a direct comparison with the active agent, pamidronate.

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Pre-operative chemotherapy with Navelbine (N) and Anthracycline in Locally Advanced Breast Cancer (LABC): A multicentric Egyptian Phase II trial

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Navelbine and anthracycline are among the most active agents in the management of advanced breast cancer. Several clinical trials have demonstrated the high efficacy of this combination in advanced breast cancer (Pawlicki, The Oncologist 2002; Vici, JCO 2002). We conducted a multicentric phase II study to evaluate the activity in terms of pathological response rate and downstaging of the combination in locally advanced breast cancer.

Patients and Methods: from June 2002, thirty-four consecutive patients (pts) among the 40 planned have been enrolled in the study. Median age: 46 years (29–63), WHO PS: 0–1, median tumor size: 8 cm, clinical TNM staging was T2: 2 pts (6%), T3: 19 pts (56%), T4: 13 pts (38%), N0: 3 pts (9%), N1: 18 pts (53%), N2: 13 pts (38%), all pts were M0. Histological confirmation was performed by biopsy showing SBR I: 4 pts (12%), SBR II: 20 pts (59%), SBR III: 10 pts (29%). The chemotherapy consisted of 3 cycles of the combination of N: 25 mg/m^2 on day 1 & day 8 plus A: 50 mg/m^2 on day 1 or E: 75 mg/m^2 on day 1 on 3 week schedule. All pts were restaged after 3 cycles; pts showing clinical CR or PR received 3 additional cycles of the combination.

Results: twenty-eight pts were evaluable for clinical response and 34 pts for toxicity; 15 pts achieved a partial response and 8 pts a complete response for an overall response of 82%. The primary chemotherapy has allowed an impressive downstaging in these bulky diseases by reducing to 2 cm the median tumour size. Twenty-one pts went under surgery, 9 pts had a pathological complete response. A total of 169 cycles were administered with a median of 5 cycle/pt. The regimen was well tolerated. WHO neutropenia grade 3/4 was seen in 3 pts, one pt experienced grade 3 mucositis and another one grade 3 phlebitis. Nausea vomiting was moderate and alopecia was universal.

Conclusion: our results confirm that navelbine + anthracycline as pre-operative chemotherapy is a very active and safe regimen in locally advanced breast cancer allowing a high rate of pathological complete response.

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Efficacy and tolerability of combination docetaxel and cisplatin regimen in anthracycline pre-treated patients with advanced breast cancer

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Introduction: The combination of docetaxel (DTX) and cisplatin (DDP) is interesting because both of agents are active in metastatic breast cancer and options of systemic therapy in anthracycline pre-treated patients (pts) are limited. The efficacy and safety of DTX and DDP combinations in anthracycline pre-treated patients with locally advanced or metastatic breast cancer.

Material and Methods: 12 pts with advanced breast cancer were treated with combination of DTX (75 mg/m^2 iv d1q3 weeks) and DDP (75 mg/m^2 iv d1q3 weeks). Median age was 55 (range 34–66). One patient was treated because of locally advanced breast cancer, 11 pts because of metastatic disease with median number of metastatic sites 1.5 (range 1–4). All pts were previous treated with anthracycline: 8 as an neoadjuvant treatment, 4 due to metastatic disease. Median number of previous chemotherapy regimen – 1. All of patients were evaluable for toxicity and tumour response. The response was assessed according to WHO criteria.

Results: A total of 72 cycles were given to 12 patients (median 6, range 3–8). The objective response (OR) was observed in 8 patients (67%): CR in 2 patients, PR in 6 patients, SD in 3 patients (25%) and progression of disease (PD) in 2 patients. In the median follow up 13.7 months, median time to progression (mTTP) was 9.5 months. One patient died because of progression. In our group no severe toxicity was observed. The most common (grade 1 or 2) were: nausea and vomiting, asthenia, arthralgia and myalgia, diarrhea, polineuropathy, oedemas.

Conclusions: Combination of docetaxel and cisplatin is effective and safety regimen in anthracycline pre-treated patients with advanced breast cancer.

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Metastases of adenocarcinoma in axillary lymph nodes of unknown origin

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Background: In patients presenting with metastases of adenocarcinoma in axillary lymph nodes, and no evidence of primary cancer on physical and radiological examination, the most probable source of metastases is undetected microfocus of breast cancer. Therefore in such patients, diagnosis of "occult" breast cancer is made. The incidence of the entity ranges form 0.3% to 1.0% of all breast cancers. However, the diagnosis of occult breast cancer does not necessarily mean that the primary focus must be in the ipsilateral breast. The best method of evaluation of such patients is magnetic resonance imaging of the breast. However the method is not universally available.

Objective: To summarize our experience with occult breast cancer patients in whom magnetic resonance was not performed.

Material and Methods: Study group was composed of twenty two patients with diagnosis of occult breast cancer operated on from January 1982 to December 2002 in our Clinic. The patients files were examined for details of treatment and results of pathological examinations.

Results: In 8 cases (36.4%) mastectomy was performed without the diagnosis of primary focus in the breast. In one case surgical biopsy of upper-outer quadrant of the breast revealed the presence of cancer. It was the only case when mastectomy was performed after the breast cancer diagnosis. Altogether, mastectomy was done in 9 women. In remaining 13 cases, mastectomy was not performed. In 63.5% of women (5/8) who underwent mastectomy despite lack of evidence of breast cancer, pathologic examination did not reveal the presence of cancer. In 53.8% (7/13) of women in whom mastectomy was not performed, primary focus was identified in the breast during follow-up. Altogether, the ipsilateral breast was identified as a source of axillary metastases in 50.0% of women from the studied group. In 45.5% of women the primary focus remained undetected. In one patient (4.5%), the primary focus of cancer was found 9 months after mastectomy in the ipsilateral kidney.

Conclusions: In patients with occult breast cancer efforts should be undertaken to identify the primary focus using modern imaging techniques. As mastectomy seems to be a gross over-treatment, more conservative methods of treatment are advised.

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Modalities in the routine use of trastuzumab (Herceptin®) in advanced breast cancer

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Background: Routine treatment of advanced breast cancer (BC) has been monitored in a postmarketing surveillance study in Germany.

Results: Data from 265 patients (pts) from 80 centers have been collected. About 75% of pts (n=196) received trastuzumab (T) plus concomitant chemotherapy (CT) (mainly paclitaxel, docetaxel, vinorelbine or capecitabine), and 69 pts received T alone. Endocrine therapy was administered for 55% of pts in the T alone group and 37% in the T+CT group. Mean age was 55.5 years (range 28–82). Mean time since initial diagnosis of BC was 4.1 yr in the T alone compared to 2.9 yr in the T+CT group. 84% of pts tested HER2 3+ by IHC, others were confirmed for HER2 positivity by FISH. ER/PR was positive in 59% of pts. Some pts had been pre-treated with cytostatic (53%) or endocrine (37%) treatment for advanced BC and with CT (70%) for early disease. Out of 94% of pts with distant metastasis at onset of T therapy, the liver was the most frequently involved organ in the T+CT group (52%). In contrast, T alone pts predominantly suffered from bone lesions (51%). Performance status at study entry was rather impaired with 53% categorized as ECOG 1 and another 21% as ECOG 2/3. Median duration of documented T treatment