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Capecitabine given concomitantly or in sequence with EC → docetaxel as neoadjuvant treatment for early breast cancer: GeparQuattro – a GBG/AGO intergroup-study

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Background: Integration of new cytotoxic agents is possible by either simultaneous or sequential addition to established regimens. Direct comparison of these strategies is biased by differences in treatment duration. A three-arm neoadjuvant study (GeparQuattro) was designed to address this question by adding capecitabine (X) to docetaxel (D) after pretreatment with epirubicin/cyclophosphamide (EC).

Patients and methods: Patients (pts) were eligible in whom adjuvant chemotherapy would be considered otherwise. Therefore, either large operable (T3) and locally advanced (T4), or estrogen (ER) and progesterone (PR) negative receptor status, or ER/PR positive tumors but clinically node-positive disease were recruited to receive 4 cycles of EC (90 mg/m^2/600 mg/m^2) and to be then randomized to either 4 cycles of D (100 mg/m^2) or 4 cycles of DX (75 mg/m^2/1800 mg/m^2) or 4 cycles of D (75 mg/m^2) followed by 4 cycles of X (1800 mg/m^2) (D → X). Pts with HER-2 positive tumors received trastuzumab concomitantly with all regimens. The primary endpoint was pathologic complete response (pCR) at surgery. The co-primary objectives were to assess the effect of X by comparing EC → D vs. EC → DX + EC → D → X (effect of X) and to assess the effect of time (24 vs 36 weeks) by comparing EC → D + EC → DX vs EC → Doc → X. The trial was designed to detect an increase in pCR from 17% to 23.5% (OR 1.5) for each comparison.

Results: Between 08/05 and 12/06 1510pts were recruited in 115 centers and after receiving 4 cycles EC, 1421 pts were randomized to D (N = 471), DX (N = 471), and D → X (N = 479). pCR was observed in around 21% in all three treatment groups. No statistically significant difference neither for the effect of capecitabine or for the effect of treatment duration was found. Breast conserving surgery was possible in 65% of these patients. Hematological toxicity was similar among the three arms. Only leucopenia was more frequent in the docetaxel monotherapy arm. Febrile neutropenia was observed in around 7% of patients. The simultaneous administration of docetaxel and capecitabine was associated with significantly more non haematological toxicities (i.e. diarrhea, nail changes, hand-foot-syndrome).

Conclusions: Addition of X to EC-T does not allow administration of T and X at full dose, leads to more non-hematologic toxicities and does not improve pathologic response in general. Prolongation of neoadjuvant chemotherapy reduces patient's compliance and does not improve pathologic response.

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Decrease in tumorigenic breast cancer stem cells – final results of a neoadjuvant trial in primary breast cancer patients

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Background: Previously, we have shown that tumorigenic breast cancer cells (CD44+/CD24−/low) were resistant to conventional chemotherapy. Residual cancers showed an increase in tumorigenic CD44+/CD24−/low cells, enhanced tumor-initiation by mammosphere (MS) formation, and increased new tumor formation by xenograft transplantation assays. Molecular pathways like EGFR/HER2 have been shown to be aberrant in CSCs.

Methods: We performed a neoadjuvant clinical trial in 45 patients with locally advanced HER-2 overexpressing breast cancers who received lapatinib (EGFR/HER2 tyrosine kinase inhibitor) given initially as a single agent for the first 6 weeks, followed by a combination of weekly trastuzumab and 3-weekly docetaxel for 12 weeks before primary surgery. Pathologic response in the surgical specimens after neoadjuvant therapy was assessed. Sequential core biopsies of the primary cancers were taken in patients at time of diagnosis and after week 6 of lapatinib, and assessed for tumorigenic CD44+/CD24−/low cells by flow cytometry, and MS formation. Global gene expression differences between cancer cells bearing CD44+/CD24−/low cells and all other sorted cells, and between cancer MS and the primary bulk invasive cancers were analyzed.

Results: Significant tumor regression in the product of bidimensional tumor measurements with a median decrease of −60.8% (range 0, −86.5%, p = 0.001) was observed in primary tumors after only 6 weeks of single agent lapatinib. Unlike with chemotherapy, lapatinib treatment decreased tumorigenic CD44+/CD24−/low breast cancer cells from 10.6% to 4.7%, and also reduced self-renewal capacity measured by MS assays (30 to 15 MS/10,000 cells, p = 0.01). The pathologic complete response rate after lapatinib and trastuzumab/docetaxel was much higher than expected, at 63% (16/25). The gene transcription pathways that underlie chemoresistant, MS-forming CD44+/CD24−/low cells involve genes belonging to stem cell self-renewal, Notch (Jagged-2, Hes1, Lunatic fringe, mastermind-like 2), Hedghog (Cyclin B1, CDC2), and Wnt pathways, FOXP1, growth factor/PI3K/AKT signaling (AKT3, BCL2, CTNNB1, FGFR2, FOXO1A, FOXO3A, PIK3R1, PTEN), and early development pathways (JARID2, JMJD2C, and MBNL1), regardless of HER2 expression in the primary tumor.

Conclusion: Contrary to conventional chemotherapy, human breast cancer specimens obtained from this prospective in vivo study has demonstrated for the first time, that lapatinib decreases tumorigenic breast cancer stem cells in the primary breast cancers of women receiving neoadjuvant treatment. This data suggests that specific signaling inhibitors of the pathways responsible for stem cell self-renewal could provide a therapeutic strategy for eliminating tumorigenic cells in order to achieve long-term eradication of cancer.

Thursday, 17 April 2008 16:00–17:30

CLINICAL SCIENCE SYMPOSIUM

New developments in the management of early metastatic breast cancer

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Recent developments in the management of metastatic bone disease

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Bone is the most common site for metastasis in cancer and is of particular clinical importance in breast cancer due to the prevalence of the disease. Bone metastases result in considerable morbidity and complex demands on health care resources. Additionally, in many patients metastatic bone disease is a chronic condition affecting their lives over years rather than months. Multidisciplinary management including oncologists, palliative care specialists, orthopaedic surgeons, radiologists and specialist nurses are required to optimise individual patient care. Metastatic bone disease results from the interactions between cancer cells in the bone marrow microenvironment and normal bone cells. These growth factor and cytokine-mediated interactions lead to stimulation of osteoclastic bone resorption and both uncoupled and unbalanced bone remodeling. This underlying mechanism provides the rationale for bone-targeted therapies such as bisphosphonates as an adjunct to traditional anticancer agents. Multiple, randomised controlled trials over the past two decades have clearly demonstrated that bisphosphonates are effective in reducing skeletal morbidity from breast cancer. Zoledronic acid is the most potent bisphosphonate, and has shown superior efficacy to pamidronate in the management of both hypercalcaemia of malignancy and the prevention of skeletal complications. Oral agents such as ibandronate and clodronate provide a useful alternative for some clinical situations. Quite appropriately, bisphosphonates are increasingly used alongside specific anticancer treatments to prevent skeletal complications. However, bisphosphonates are relatively expensive supportive care drugs, and it is simplistic to assume that all patients require the same dose or schedule of bisphosphonate treatment. Recent studies indicate that the risk of skeletal complications is strongly related to the rate of bone resorption. Additionally, clinical benefit from bisphosphonates appears to be related to the effective suppression of accelerated bone resorption. A tailored approach to therapy may be more appropriate, safer and cost-effective. It seems likely that the efficacy of bisphosphonates in metastatic disease has reached a therapeutic ceiling. Recently, the biological importance of the RANK ligand-RANK-OPG system in metastatic bone disease has been defined. Early phase studies of an antibody to RANK ligand (denosumab) have been completed, and denosumab is now in phase III development.