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A systematic review of the impact of breast surgery on survival of patients with distant metastases at initial presentation

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Background: According to current treatment standards, patients with distant metastatic breast cancer at diagnosis receive palliative therapy. Local treatment of the breast is only recommended if the primary tumor is symptomatic. Recent studies suggest that surgical removal of the primary tumor has a favorable impact on the prognosis of patients with primary metastatic breast cancer. We performed a systematic review of the literature to weigh the evidence for and against breast surgery in this patient group.

Methods: A search was performed in PubMed in May 2009. The following search strategy was used: breast cancer AND (stage IV OR metastatic) AND surgery AND ("primary tumour" OR "primary tumor"). English journals were taken into account, and only full papers were included. This resulted in 784 hits. After reviewing the abstracts, ten retrospective studies were found in which the use of local therapy in primary metastatic breast cancer and its impact on survival was examined. The results and conclusions of the studies were analyzed and the hazard ratios of the studies were pooled to provide an estimate of the overall effect of surgery.

Results: A crude analysis, without adjustment for potential confounders, showed that surgical removal of the breast lesion in stage IV disease was associated with a significantly higher overall survival rate in seven of the ten studies, and a trend towards a better survival in the three remaining studies. These three studies concluded that the positive effect on survival in the surgery group was caused by stage migration bias, treatment with chemotherapy in the same period as the surgery was performed and/or case selection bias. But in multivariate analyses, conducted in eight out of ten studies, surgery of the primary tumor appeared to be an independent factor for an improved survival, with hazard ratios ranging from 0.47 to 0.71. The pooled hazard ratio for overall mortality was 0.65 (95% CI 0.59–0.72) in favor of the patients undergoing surgery.

Conclusion: This systematic review of the literature suggests that surgery of the primary breast tumor in patients with stage IV disease at initial presentation does have a positive impact on survival. In order to provide a definite answer on whether local tumor control in patients with primary metastatic disease improves survival, a randomized controlled trial comparing systemic therapy with and without breast surgery is needed.

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p27 expression predicts clinical outcome and resistance to doxorubicin treatment in locally advanced breast cancer

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Preoperative chemotherapy is often used in patients with locally advanced breast cancer. However, commonly used clinical parameters poorly predict response to therapy. Recent studies have suggested that altered regulation of the cell cycle in cancer may be involved in resistance to chemotherapy. Loss of the cell cycle inhibitor $p27^{Kip1}$ is associated with poor prognosis in early breast cancer. The purpose of the present study was to examine the role of $p27^{Kip1}$ in chemoresistance and as a predictor of response to chemotherapy in locally advanced breast cancer.

Materials and Methods: Tumor expression of $p27^{Kip1}$ was determined by immunohistochemistry before preoperative chemotherapy in 40 patients with locally advanced breast cancer. All patients were treated with doxorubicin and cyclophosphamide (AC). Expression data were compared with patients' clinical outcome and response to chemotherapy. In addition, doxorubicin-treated MCF7 breast cancer cell were transfected with p27siRNA to assess the effect of p27 downregulation on chemoresistance.

Results: $p27^{Kip1}$ levels were found to be accurate prognostic markers for disease-free and overall survival in locally advanced disease ($p < 0.01$). $p27^{Kip1}$ expression was high in 95% of the tumors responding to AC. In contrast, low expression of $p27^{Kip1}$ was associated with response to AC in one patient only, thus correlating with poor response to AC in 85.7% of cases. Downregulation of $p27^{Kip1}$ by siRNA transfection resulted in a 10-fold increase in cell survival following doxorubicin treatment.

Conclusions: $p27^{Kip1}$ expression may have a causative role in chemoresistance and may be a useful marker for predicting response to doxorubicin-based preoperative chemotherapy and clinical outcome in patients with locally advanced breast cancer.

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Preliminary results of a phase II study of lipoplatin (liposomal cisplatin)–vinorelbine combination as first line treatment in HER2/neu negative metastatic breast cancer (MBC)

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Background: The frequent use of anthracyclines & taxanes in breast cancer's adjuvant setting has lead to drug resistance & cardiac toxicity. This has raised the need for new agents in the metastatic setting. Cisplatin-vinorelbine combination recently showed interesting results with an overall response rate of 64%. Nevertheless, the use of cisplatin was limited by the frequently induced nausea, vomiting, & nephrotoxicity. Lipoplatin is a non-toxic alternative agent to cisplatin. The aim of this study is to evaluate the efficacy & safety of lipoplatin-vinorelbine combination in first line metastatic breast cancer (MBC) patients (pts).

Methods: From Aug 2007 to July 2009, we included 35 pts with MBC & no prior treatment for their metastatic disease, PS 0−2, HER2/neu negative, & at least one measurable lesion, were enrolled. Treatment included I.V. vinorelbine 30 mg/m^2 on days 1 & 8, and lipoplatin 120 mg/m^2 on days 1, 8 & 15. Cycles were repeated every 3 weeks for a total of 6 cycles. Primary objectives: objective response rate, time to treatment failure (TTF) & time to progression (TTP). Secondary objectives: overall survival & treatment-related toxicity.

Results: The median age was 49 years (29−74). 74% of pts had visceral metastases. 31% had one metastatic site, 49% had 2, 20% had 3 or more. A total of 157 cycles were administered with a median number of 5 per patient [1−6]. At the time of the analysis 30 pts were evaluable for response. An objective tumor response was observed in 16 pts (53.3%) & complete response in 2 pts (6.7%). Eleven (36.7%) pts had stable disease. The median TTF & TTP were 7 & 8 months respectively. All pts (35) were evaluable for toxicity. The majority of adverse events were mild to moderate. No WHO G3−4 nephrotoxicity or neuropathy was noted. G3−4 nausea/vomiting was observed in 5 pts (14.3%). Four pts (11.4%) had G3 asthenia. Four pts (11.4%) had G3 anemia & 21 pts (68.6%) had G3−4 neutropenia. Three pts (8.6%) developed febrile neutropenia with no secondary mortality.

Conclusion: The new combination of lipoplatin & vinorelbine shows promising activity & good tolerance as first line treatment for HER2/neu negative MBC. Updated results will be presented at the meeting.

Friday, 26 March 2010 18:15–19:15

POSTER SESSION

Locally advanced and recurrent disease

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Evaluation of concomitant radio-endocrine therapy as primary treatment modality for elderly receptor positive locally advanced breast cancer patients

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Background: Judicious integration of systemic and local therapy for elderly locally advanced breast cancer patients (LABC) are often a therapeutic challenge. Benefit: risk ratio remains debatable with chemotherapy, particularly for receptor positive geriatric patients. The study aims to explore the efficacy of combined radio-endocrine treatment, followed by continuation of endocrine treatment alone in elderly LABC patients with strong ER positivity, who are not considered for surgery either for inoperability or medical co-morbidities. Study end points are tumor response, time to progression, and overall survival.

Materials and Methods: Between May 2004 and January 2007, a total of 221 elderly inoperable LABC patients (T_4 or $N_{2)}$ with age >65 years with core needle biopsy confirmed, estrogen receptor positive invasive adenocarcinoma of breast were enrolled in the study and were placed on tamoxifen 20 mg daily (n = 156) if HER 2 negative or Letrozole 2.5 mg, if HER 2 positive (n = 65). Concomitant Radiotherapy (50 Gy in 25 F over 5 weeks) was started after 3 months of hormone therapy in 217/221 patients, remaining 4 patients were excluded from the study as they developed systemic metastasis. Whole breast, axilla and supraclavicular area were