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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

irradiated with CT-based planning. After completetion of Radiotherapy, hormonal agent was continued unless the patient has to be withdrawn earlier owing to progressive disease (as per RECIST criteria).

Results: Tumor response was evaluated by monthly clinical examination till Radiotherapy begins (to asses the response to the hormonal agent alone) and after completion of Radiotherapy (to find the final response to hormone + concurrent Radiotherapy as per RECIST criteria). More than 50% tumor shrinkage was noted prior to Radiotherapy in 48/156 (31%) patients on tamoxifen and 18/65 (27%) on letrozole. Complete remission was achieved in 137/217 (63%) patients at a median interval of 3 months after completion of Radiotherapy i.e. about 7−8 months of commencement of hormonal therapy. Partial response was recorded in 64/217 and Stable disease in remaining 16/217 patients. Median time to progression was found to be a median 13 months for those having overall response and 8 months for those having stable disease. Although 2 year DFS was noted in only 42/217 patients, 2 year OS was recorded in 203/221 patients − 13/17 deaths were of unrelated causes. Surprisingly systemic metastasis was recorded in only 6/217 patients who completed Radiotherapy.

Conclusion: For estrogen receptor positive inoperable locally advanced elderly patients or those who refuse surgery, primary radio-hormone therapy proves to be a non-toxic well-tolerated inexpensive patient-compliant treatment option, which, till date remains nearly untrodden ground in world literature.

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Monthly versus three-monthly goserelin treatment in premenopausal patients with oestrogen receptor-positive early breast cancer

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Background: Goserelin is a luteinising hormone-releasing hormone agonist often used in combination with tamoxifen to treat premenopausal women with oestrogen receptor-positive (ER+) breast cancer. Due to its less-frequent administration schedule, a three-month goserelin 10.8 mg depot may provide a more convenient treatment option versus the current 3.6 mg monthly depot.

Materials and Methods: This multicentre, open-label, randomised study of premenopausal Japanese women with ER+ early breast cancer compared patients receiving goserelin 3.6 mg once every 4 weeks with patients receiving 10.8 mg once every 12 weeks. All patients received concomitant tamoxifen (20 mg/day). The primary endpoint was oestradiol suppression occurring over the first 24 weeks (area under the concentration time curve [AUC]). Secondary endpoints included: oestradiol and follicle-stimulating hormone (FSH) levels; the proportion of patients with oestradiol levels <30 pg/mL; menstruation; disease-free survival (DFS); and safety/tolerability. Treatment continued for 96 weeks or until discontinuation criteria were met.

Results: A total of 170 patients were randomised (84 to the 3.6 mg group; 86 to the 10.8 mg group). The mean AUCs for oestradiol serum concentration were 18.95 pg/mL·week (3.6 mg group) and 18.32 pg/mL·week (10.8 mg group). The baseline adjusted AUC ratio (10.8 mg/3.6 mg) was 0.974 (95% CI: 0.8, 1.19). Oestradiol and FSH levels were suppressed in both treatment groups; $\geqslant$98.8% of patients had oestradiol-serum concentrations <30 pg/mL by Week 4. Menstruation had ceased by Week 16 in both groups. Median follow-up periods for DFS were 675.5 days (3.6 mg group) and 675.0 days (10.8 mg group); a total of four recurrence events were observed during the study (one in the 3.6 mg group and three in the 10.8 mg group, respectively); plus one new cancer (in the 10.8 mg group). The incidence of adverse events (AEs) was similar between treatment groups. The most common AEs were hot flushes, nasopharyngitis and headache. No clinically important differences in the safety and tolerability profiles were found between treatment groups.

Conclusions: In terms of oestradiol suppression, goserelin 10.8 mg is non-inferior to goserelin 3.6 mg in premenopausal patients with ER+ early breast cancer. Both treatments have similar efficacy and similar tolerability profiles.

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Gemcitabine, carboplatin and paclitaxel as neoadjuvant combination chemotherapy in patients with locally advanced (stage III) or inflammatory breast cancer − a non-anthracycline alternative

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Background: The gemcitabine/paclitaxel combination is a highly effective regimen in metastatic breast cancer. Preclinical studies have demonstrated synergistic action, when combining a platin-derivative and paclitaxel. We examined the activity of combining gemcitabine, carboplatin and paclitaxel (GCP) in patients (pts) with locally advanced or inflammatory breast cancer (LABC or IBC).

Material and Methods: In the period 2002−6, 44 consecutive pts with LABC or IBC entered a phase II protocol of neo-adjuvant GCP (G, 800 mg/m^2 d1+8; C, AUC 4.5 d8; P, 175 mg/m^2 d1) every 3 weeks for 4−6 cycles. Median (range) age was 57 (32−76) years and 76% were postmenopausal. Tumor size (median): 80 mm range 7–150 mm; 74% were node positive; 10 had IBC; 85% were hormone receptor positive and 14% were HER2 positive. If there was no sign of response after two cycles of GCP treatment was shifted to CEF (750/60/750 mg/m^2) d1 q3w. After surgery, radiotherapy and adjuvant systemic treatment were given according to standardized guidelines (total of 9 cycles of chemotherapy).

Results: A total of 139 cycles (median 4 cycles (range, 1−6)) were given before surgery; 44 pts was evaluable for toxicity and survival and 39 pts for response. Non-haematological toxicity was mild: no grade 3−4 toxicity was found except that 3% had transient grade 3 increase of transaminases. Most common grade 1−2 toxicities were parestesia (47%) fatigue (36%), myalgia/arthralgia (38%), nausea/vomiting (16%), diarrea (7%) and allergic reactions/hypersensitivity (8%). Grade 1−2 haematological toxicity comprised neutrocytopenia, 21% and thrombocytopenia, 2%; grade 3−4 neutrocytopenia occurred in 12% (one grade 4) and thrombocytopenia in 1%. After two cycles a PR or a minor response (justifying continued GCP) were seen in 64% of the 39 evaluable pts, while NC were observed in 33% of the pts; no complete responses; one patient had progressive disease. A total of 22 pts shifted to CEF before final surgery due to insufficient response (14 pts) or toxicity (8 pts). At surgery 33% obtained a PR and 23% had NC. Radical surgery was possible in all pts. Median follow up time was 48 mos. The 5-year survival was 61% (95CI: 42−80 mos.). In the same period, 47 pts non-eligible to the present protocol or who did not wish to participate in the protocol received CEF (750/60/750 mg/m^2 d, 1q3w x 4−6). The 5-year survival of this (non-randomized) comparable group was 74% (95% CI: 49−89%).

Conclusion: As non-anthracycline drug combinations may be indicated in some clinical settings, we examined the activity of GCP in pts with LABC or IBC. The three drug combination can obtain comparable efficacy and an obvious decreased toxicity compared to traditional anthracyline containing regimens, making this combination an alternative when anthracyclines are not warranted. Updated results in relation to hormone receptor, HER2, P53 and TOP2A status will be presented.

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Locally advanced breast cancer; twelve years results from a single institution

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Background: The management of locally advanced breast cancer (LABC) requires a combined modality treatment approach involving surgery, radiation and systemic therapy. The introduction of new modalities in the adjuvant treatment of primary breast cancer treatment, such as taxanes, aromatase inhibitors and targeted treatments has made a major improvement in recurrence-free and overall-survival. These modalities have been passed on to the locally advanced setting. We now report treatment results for LABC patients treated in a single institution in the county of Funen, Denmark.

Material and Methods: Through a cross check from the national database (Danish Breast Cancer Cooperative Group − DBCG) and the treatment files of our department in the period 1.1.97–31.12.08, 111 patients were identified with LABC. LABC includes any **T3,** any **T4,** any **N2, M0**.

The chemotherapy regimens were mainly anthrycyline based whereas taxanes in the second half-part of the study were used either if no response where observed or in the adjuvant setting. Trastuzumab was used from 2005 in patients with HER-2 positive tumors, either preoperatively with a taxane or in the adjuvant setting.

The patients were analyzed according to treatment period (first vs last half-part) and response to treatment (pCR, PR, NC and PD).

Results: Patient characteristics: age median 58 (27−88), primary treatment chemotherapy 101 vs endocrine therapy only 10. Ninety seven