Pathological response was evaluated in 13 pts, 1 pt was additionally treated by preoperative locoregional radiotherapy, 1 pt continue the treatment.

pCR = 9/13 pts (69.2%) − complete disappearance tumor in the breast and lymph nodes occurred in 8 pts (61.5%) and 1 pt (7.6%) had pCR + in situ (in situ lesions only in breast tissue).

Toxicity was assessed for 75 treatment cycles. Grade III–IV neutropenia was observed in 76% of cycles. Febrile neutropenia was observed in 14.7% of cycles, no intravenous antibacterial therapy was required. Grade I−II transaminase increase and/or bilirubin was recorded in 29.3% of cycles; grade II mucositis − 10.7%. Only 1 pt had asymptomatic LVEF decrease on 10%.

Conclusion: the combination of Docetaxel 75 mg/m^2 + Carboplatin AUC 5 + Trastuzumab every 3 weeks is promissing regimen (pCR − 69.2%) with manageable toxicity for treatment of locally advanced HER-2 overexpression breast cancer.

Wednesday, 24 March 2010 18:15–19:15

POSTER SESSION

Predictive and prognostic factors

121 Poster

A prognostic model for breast cancer-related events in primary operated invasive lobular breast cancers from one centre

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Background: Invasive lobular breast cancers (ILA) differ from non-ILA in many perspectives. ILA are a heterogeneous group with a large variety in histologic subtypes and disease free survival (DFS); a prognostic model for ILA is not available. We propose a model based on demographic and clinicopathological features.

Material and Methods: A retrospective cohort study of 380 consecutive patients treated between Jan 2000 and Dec 2006 for primary operable ILA, none E-cadherin positive, and all receiving local and systemic adjuvant therapy (108/380 or 28.4% had chemotherapy). None received neo-adjuvant therapy and those with a bilateral or multifocal disease with the non-ILA having a higher NPI than the ILA were not in this cohort. We investigated independent demographic and clinic-pathological variables for relapse.

Results: After a mean follow-up of 5.3 yrs, 37 patients (9.7%) experienced a breast cancer-related event. In a univariate setting, variables considered as significant ($p < 0.05$) were: node positivity (np), tumor size, grade (1−2 vs 3), mitotic count (1 vs 2−3, mito), the amount of nuclear pleomorfism (1−2 vs 3, pleo) and subtype, classical ILA or not. The tubule formation was not considered as a variable since 98.4% of the patients had less than 10% of the tumor forming tubules. A multivariate Cox model revealed that np, nuclear atypia and mitotic count are independent prognostic factors. We propose to divide patients into risk groups as illustrated in Table 1. Patients in group 1 (node negative) are considered as low risk, patients in group 3 are high risk. Table 1 also describes the predicted (S_{COX}) and observed survival (S_{KM}).

Conclusions: Our prognostic model of operable ILA showed that nor histological grade or subtype nor nuclear atypia nor mitotic activity are prognostic in node negative ILA. In node positive ILA, the combination of nuclear atypia and mitotic index distinguished a medium and high risk group. Risk groups can be defined without the complex definition of classical ILA.

Table 1: Categorizing patients into risk groups

Nuclear atypia	Mitotic count	Node positive	Risk group	N$^+$	# events	Event rate*	S_{KM} (5-yr)	S_{COX} (5-yr)
1 of 2	1, 2 of 3	no	1					
3	1	no	1					
3	2 of 3	no	1	211	8	0.01	0.95	0.95
1 of 2	1, 2 of 3	yes	2	136	21	0.03	0.84	0.86
3	1	yes	2					
3	2 of 3	yes	3	29	8	0.07	0.68	0.62

[a]4 patients had no value for one or more model variables.
[b]Expected percentage of events per year of follow-up.

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Bevacizumab combined with chemotherapy as first-line treatment of metastatic breast cancer patients: a meta-analysis based on studies having randomized 2,695 patients

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Background: Bevacizumab, a monoclonal antibody against VEGF, has been shown to improve the outcome of patients with metastatic breast cancer. We conducted a meta-analysis of randomized trials to assess the magnitude of the benefit of adding bevacizumab to chemotherapy in the first-line treatment of metastatic/recurrent breast cancer (MBC) in terms of progression-free and overall survival as well as tumour response rate. The commonest side-effects of bevacizumab were also evaluated.

Methods: Randomized phase III trials evaluating the addition of bevacizumab to chemotherapy for the first-line treatment of MBC were identified using PubMed and/or abstracts presented at major oncology meetings. Hazard Ratios (HR) for time-to event endpoints and odds ratios (OR) for binary endpoints were calculated or retrieved from each study and combined using the fixed-effects or random-effects whenever indicated.

Results: Three studies were selected with a total of 2,695 randomized patients; only one study was published in a peer review journal at the moment this meta-analysis was performed. The addition of bevacizumab to chemotherapy improved progression-free survival (PFS) (HR 0.69; 95% CI 0.63–0.76) and response rates (OR 1.84; 95% CI 1.56–2.18) in patients receiving the combination compared to chemotherapy alone. A trend towards better overall survival was also observed (HR 0.88; 95% CI 0.78–1.00). The benefit of adding bevacizumab to chemotherapy was observed in all subgroups (ER positive or negative, age <65 or $\geqslant$65, short or long disease-free interval, prior adjuvant chemotherapy, and prior taxanes). As expected, toxicity profile included hypertension, proteinuria, sensory neuropathy and left ventricular dysfunction, and was significantly more pronounced in patients receiving bevacizumab.

Conclusion: In our meta-analysis the addition of bevacizumab to chemotherapy in the first-line treatment of patients with MBC significantly improves PFS and response rates in all patient population and across different subgroups. A trend towards better overall survival was also observed. Side effects were more often observed in patients receiving bevacizumab.

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Preoperative capecitabine and docetaxel followed by 5-FU/epirubicin/cyclophosphamide (FEC) and predictive value of protein biomarkers

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Background: Capecitabine (X) and docetaxel (T) have demonstrated synergistic effect in preclinical models and survival benefit in metastatic breast cancer. Useful predictive marker is necessary for breast cancer patients treated with preoperative chemotherapy. This study's purpose was to determine the efficacy of X and T followed by 5-FU/epirubicin/cyclophosphamide (FEC) in the preoperative setting and to evaluate the correlation between protein biomarker expression and pathological complete response (pCR).

Patients and Methods: Patients with stage II/III breast cancer received 4 cycles of XT (capecitabine 1650 mg/m^2 on days 1−14 and docetaxel 60 mg/m^2 on day 8 every 3 weeks), followed by 4 cycles of FEC (fluorouracil 500 mg/m^2, epirubicin 90 mg/m^2, cyclophosphamide 500 mg/m^2 on day 1 every 3 weeks). Primary endpoints were the pathological complete response (pCR) rate and adverse drug reactions. pCR was defined as no microscopic evidence of residual viable tumor cells, invasive or noninvasive, in all resected specimens of the breast. Expression analysis using immunohistochemistry was performed in core needle biopsy samples at baseline.

Results: Seventy-two patients were enrolled and 71 patients were assessable for clinical and pathologic responses. The median age was 51 years (range, 27−69 years). The median tumor size was 3.5 cm (range, 2−8.3 cm). Forty-six (64.8%) patients were clinically node-positive. Overall, 50 (50.1%) patients had hormonal receptor (HR)-positive tumors, and 21 (29.6%) had HR-negative tumors. A HER2 overexpression was detected in 19 cases (26.8%). Ki67 expression ranged from 0 to 92.3% and 34 cases showed 20% and higher of positive nuclei. The overall response rate was 91.5%, including a complete response in 29 patients and a partial response in 36 patients. No patients showed clinical progression of disease. The pCR rate was 14.1% (10/71). Grade 3/4 neutropenia was observed in 32.4%

of patients, and febrile neutropenia was observed in 5.6% of patients. The most common grade 3/4 non-hematologic adverse event was hand-foot syndrome, observed in 11.3% of patients. The median relative dose intensities of FEC, T, and X were 0.982, 0.968, and 0.933, respectively. Patients with HR-negative tumors had significantly higher pCR rate than HR-positive tumors (35.3% vs. 10.5%, p = 0.03). HER2 status was not significantly correlated with pCR rate. Patients with Ki67 expression >20% revealed significantly higher pCR rate than <20% (23.5% vs. 8%, p = 0.02). In HR+negative subgroup, Ki67 expression were significantly correlated with pCR (p = 0.02).

Conclusions: Our data indicate that the sequential combination of XT followed by FEC is a well-tolerated, effective preoperative treatment for stage II/III breast cancer and HR status and Ki67 expression are useful predictive biomarkers.

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Estrogen receptor-negative tumour and positive family history for breast cancer highly modify the risk of second contra-lateral breast cancer

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Background: A recent study reported an increased risk of contra-lateral estrogen-negative breast cancer after a first primary estrogen-negative breast cancer. Our study aims to confirm this result and to evaluate how the risk of second breast cancer occurrence is affected by family history of breast cancer and anti-estrogen treatment.

Patients and Methods: We included in the study all 4152 women diagnosed with breast cancer between 1994–2007, using data from the population-based Geneva Cancer Registry. We compared the incidence of second breast cancer among patients according to estrogen receptor (ER) status with that expected in the general population by age-period Standardized Incidence Ratios (SIRs).

Results: Among the cohort, 63 women developed second breast cancer. Patients with ER-positive first tumors had a decreased risk of second breast cancer occurrence (SIR: 0.67, 95% CI: 0.48–0.90), whereas patients with ER-negative primary tumors had an increased risk (SIR: 1.98, 95% CI: 1.19–3.09) limited to ER-negative second tumors (SIR: 7.94, 95% CI: 3.81–14.60). Patients with positive family history had an 8-fold (SIR: 7.67, 95% CI: 2.49–17.90) higher risk of ER-negative second tumor, which increased to nearly 50-fold (SIR: 46.18, 95% CI: 12.58–118.22) when the first tumor was ER-negative. Treatment with anti-estrogen decreased the risk of second ER-positive tumors but not ER-negative tumors.

Conclusions: The risk of second ER-negative breast cancer is very high after a first ER-negative tumor, in particular among women with strong family history. Surveillance and prevention of second cancer occurrence should consider both ER status of the first tumor and family history.

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The effect of lymphovascular invasion (LVI) on survival

M. Sundquist, S. Bianchi, A. Douglas-Jones, I. Ellis, A. Lee, S. Pinder, S. Thorstenson, G. Ball, R. Blamey, on behalf of the ONCOPOOL Consortium

The ONCOPOOL database (n = 17,000) is compiled from primary operable (⩽5 cm) breast cancers in women aged ⩽70, from 12 European Breast Units, treated by first line operative treatment and entered in 1990−99 inclusive.

Method: LVI was regularly measured in 4 units (n = 5195) on H & E staining. Scoring was to definite positive or negative. 20% were LVI+.

Results:

- Relation to Nottingham Prognostic Index (NPI). A highly significant rank order from 7% LVI+ lying in Excellent NPI group to 60% and 62% in the Poor and Very Poor groups.
- Overall survival by both LN stage and LVI (Table 1): survival by LN status was moved down one stage by LVI+ positivity.
- LVI positivity lowers survival within all Nottingham Prognostic Index (NPI) groups: Cox Analysis entering NPI and LVI shows both to have p values of <0.000 with hazard ratios of 1: 7 and 1: 6 respectively.

Table 1

LN group	Stage	LVI	n LN/LVI		10 yr OS (%)	LVI+ .v. Neg
1	LN Neg	Neg	2359	1	86±1	p < 0.000
2	LN Neg	Pos	429	2	78±3	
	LN 1 Pos	Neg	413		80±2	p = 0.025
3	LN 1 Pos	Pos	245	3	73±4	
	LN 2−3 Pos	Neg	307		72±3	p = 0.025
4	LN 2−3 Pos	Pos	266	4	65±4	
	LN 4+ Pos	Neg	574		69±2	p < 0.000
5	LN 4+ Pos	Pos	508	5	44±3	

Conclusion: LVI is an important additional independent variable to NPI for survival.

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P-cadherin, Osteopontin and MIB1 as prognostic factors for loco-regional relapse in breast cancer

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Introduction: Loco-regional relapse in breast cancer is considered to be an independent predictor of subsequent metastization and death. As a consequence, one of the current pathways of research stands on the discovery of new risk factors for local relapse due to the significant discrepancy in prognosis of patients with identical staging and similar pattern of known molecular markers.

Three new molecular markers have been associated in previous studies to worst outcomes in breast cancer patients: P-cadherin has been identified as an independent prognostic factor in breast cancer; Osteopontin in breast cancer stroma has been related with the expression of genes associated with worst prognosis; Proliferation index (MIB1) is also considered to be inversely related with survival. The purpose of this work was to study the value of these three markers as possible determinants factors for loco-regional relapse in breast cancer.

Material and Methods: We retrospectively analyzed the clinical records of 1432 patients treated at our institution between January 1998 and June 2008. The case group consisted of 101 patients (7%) with local relapse as first new related event. The control group, consisted of 92 patients, from the same series with a disease free survival longer than 10 years.

Clinical data and classical pathological factors were retrieved for cases and controls. We performed Tissue MicroArrays and Immunohistochemistry for estrogen and progesterone receptors, HER2, Ck-5, P-cadherin, Osteopontin and MIB1.

Results: The average time to recurrence was 41 months; the mean survival after relapse was 33 months and the 5-year survival was 55%. On multivariate analysis tumour size, nodal status, histological grade and P-cadherin showed independent prognostic value for disease-free survival. None of the studied markers had a significant association with local relapse.

The aberrant expression of P-cadherin was related to higher histological grades and estrogen-receptor negativity; Osteopontin expressing tumours had more advanced disease at diagnosis and the MIB-1 was associated with tumours negative for estrogen receptors.

Conclusion: P-cadherin is a promising marker for loco-regional disease prognosis and a putative novel therapeutic target. Its real biological value is still undetermined and further studies are required.

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Cyclin A − an alternative to gene expression profiling for subdividing histological grade 2 breast cancer into groups with different prognosis

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Background: Ki67 has recently been included in the St Gallen guidelines as a prognostic factor, but the role of other proliferation markers, such as cyclin A, is still under debate. We investigated the prognostic importance of cyclin A, and if this was dependent on estrogen receptor (ER) status. Gene expression profiles, consisting mainly of genes associated to proliferation can subdivide histological grade 2 into two groups, one with a good