of tumor grade. If PgR negative, A-CMF CHT was given, while in a case of PgR positive disease, adjuvant endocrine therapy was introduced. A group of patients with SR-positive tumors defined as ER-positive/PgR-positive, ER-positive/PgR-negative, and ER-negative/PgR-positive were separated and divided according to menopausal status. Among these premenopausal (N = 196) and postmenopausal (N = 193) women disease-free survival (DFS) and overall survival (OS) were compared between women treated with A-CMF CHT and adjuvant endocrine therapy.

Results: Significantly more premenopausal patients treated with A-CMF CHT had grade 3, PgR negative breast tumors (Chi-square tests $p = 0.049$, $p < 0.001$ respectively), while significantly more women treated with OA had positive lymph nodes (Chi-square test, $p = 0.007$). In postmenopausal groups, significantly more women treated with A-CMF CHT had lower PgR (Chi-square test, $p < 0.001$), node negative status (Chi-square test, $p = 0.003$) and less frequently received postoperative radiotherapy (Chi-square test, $p < 0.001$) compared to postmenopausal patients treated with adjuvant TAM. There was no difference in DFS and OS between premenopausal women treated with A-CMF CHT and those treated with OA. However, significantly more postmenopausal patients, treated with A-CMF CHT, developed disease relapse comparing to postmenopausal women treated with adjuvant TAM (Chi-square test, $p < 0.001$), with local recurrences and bone metastases occurring significantly more frequently (Chi square tests, $p = 0.01$, $p = 0.006$, respectively). Furthermore, postmenopausal women treated with A-CMF CHT had significantly worse DFS (Log rank test, $p = 0.013$) compared to TAM group, while there was no difference in OS between the two groups.

Conclusion: Our results showed that SR might have some value as a predictive factor for the response to A-CMF CHT at least in postmenopausal women with SR-positive breast cancers.

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Prospective phase II study of: neo-adjuvant doxorubicin followed sequentially by cisplatin/docetaxel in locally advanced breast cancer

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Background: Neoadjuvant (primary) chemotherapy as part of multimodality treatment is increasingly used as standard of care for patients (pts) with locally advanced breast cancer.

We conducted a prospective study using Doxorubicin 75 mg/m^2 q 3 weeks × 3 cycles followed sequentially by Docetaxel 75 mg/m^2 and Cisplatin 75 mg/m^2 q 3 weeks × 3 cycles. All pts had definitive surgery followed by Radiation therapy, +/− Tamoxifen. Primary end points were pathologic complete response (pCR), secondary endpoints were, safety, rate of conservative surgery and overall survival.

Material: Eligible pts included biopsy proven invasive breast cancer, T2-T4 (primary ⩾4−10 cm) N0-N2, M0. 59 of 60 enrolled pts completed treatment one patient refused surgery after the completion of 6 cycles of chemotherapy were excluded from the analysis, Premenopausal: 68%, median age: 41 yrs (24−60), median tumor size: 6.0 cm (4−10), Stage IIB: 31% and IIIA/IIIB: 68%, both ER/PR positive: 53%, Her2/neu (3+) by IHC staining: 29%, Her2/neu (+2) equivocal: 20% were all are FISH negative. All patients had negative metastatic workup.

Results: 59 pts are evaluable for analysis: clinical complete response was seen in: 44%, clinical partial response in: 56%. Breast conserving surgery was performed in: 44%, and MRM in: 56%. Pathological complete response (pCR) in the breast was: 31%, in axilla were: 37%, breast and axilla were 22%.

Grade 3−4 Toxicities: febrile Neutropenia (13%), nausea−vomiting (12%), mucositis (10%), weakness/asthenia/weight loss (12%). Overall at follow up of 50 months the DFS & OS (62% and 87%).Patients who achieved complete pathologic response both in breast and axilla the DFS and OS were (100%).

Conclusion: Sequential combination of Doxorubicin followed by Docetaxel/Cisplatin is a safe, feasible and active combination, that offer the possibility of conservative surgery and associated with high clinical and pathologic response, further investigation of this combinations are warranted.

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Improving breast cancer survival – trends in node negative and node positive disease

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Aim: To determine any improvement in recurrence and survival in node negative and node positive breast cancer patients between 1988 and 1999.

Methods: The study was a retrospective database review of 890 breast cancer patients diagnosed between 1988 and 1999. Patients were divided into 2 groups according to the year of diagnosis (group I: 1988–1994; group II: 1995–1999). Recurrence free survival (RFS), breast cancer specific survival (BCSS) and overall survival (OS) was calculated by Kaplan-Meier life table analysis and compared using the log rank test with both groups stratified for lymph node status.

Results: There were 404 patients in group I and 486 patients in group II. 273 patients in group I and 320 patients in group II were node negative.

5-year RFS in node negative patients was 84% in group I versus 87% in group II ($p = 0.20$), BCSS was 92% in both groups ($p = 0.89$) and OS was 85% in both groups ($p = 0.95$). In node positive patients the 5-year RFS was 57% in group I and 69% in group II ($p = 0.01$), BCSS was 70% versus 78% ($p = 0.047$) and OS was 67% versus 73% ($p = 0.10$).

The use of systemic adjuvant therapy was significantly increased in group II, for node negative (chemotherapy 6% versus 18%, $p < 0.001$; endocrine therapy 74% versus 90%, $p < 0.001$) and for node positive patients (chemotherapy 33% versus 55%, $p < 0.001$; endocrine therapy 81% versus 92%, $p = 0.004$)

Conclusion: The increased use of systemic adjuvant therapy in node negative and node positive breast cancer patients between 1995 and 1999 was reflected in a significant improvement in RFS and BCSS in patients with node positive disease. Patients with node negative disease did not demonstrate any significant differences in recurrence or survival.

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Neoadjuvant capecitabine (X), docetaxel (T) ± trastuzumab (H) for patients (pts) with locally advanced breast cancer (LABC): preliminary safety and efficacy data from a multicentre phase II study

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Background: 3-weekly XT is highly active in metastatic breast cancer, with significantly superior response rates, time to progression and overall survival vs. T alone. X and T are synergistic with H in HER2-positive tumours. We evaluated the efficacy and safety of XT±H as neoadjuvant therapy for LABC.

Materials and Methods: Pts with newly diagnosed invasive stage III inoperable LABC (cT4 and/or cN2−3) received X (900 mg/m^2 orally bid d1−14) + T (36 mg/m^2 i.v. d1&8) q3w x6, followed by surgery and radiotherapy. Pts with HER2-positive tumours (IHC 3+ or FISH+) also received H (8 mg/kg on d1 of the first 3w cycle and 6 mg/kg on d1 of subsequent cycles). Safety was evaluated after each cycle, clinical response after 3 and 6 cycles, and pathological complete response (pCR) postoperatively. pCR was defined as no residual invasive tumour in breast and axilla.

Results: To date, 30/51 pts have completed neoadjuvant chemotherapy (26 pts XT, 4 pts XT+H) and surgery. Baseline characteristics are: median age 50 years (range 25−74), median ECOG PS 0 (range 0−1), ER/PR/HER2+ status 74/61/16%. The most frequent grade 3/4 treatment-related toxicities were diarrhoea (16%), HFS (10%) and stomatitis (10%). Dose reductions were applied because of grade 2−4 adverse events (stomatitis, HFS, diarrhoea, vomiting, peripheral neuropathy and skin rash) in 11 pts and because of neutropenic fever in 2 pts. Therapy was prematurely interrupted because of disease progression (1 pt), capillary leak syndrome (1 pt), infection (1 pt), fever of unknown origin (1 pt) and psychological intolerance (1 pt). The overall response rate was 90%, including 2 CRs (7%) and 25 PRs (83%). A further 2 pts had stable disease (7%). pCR was achieved in 2 pts who completed 6 cycles of XT (8%) and in 2/4 pts (50%) after 6 cycles of XT+H. Most pts received postoperative anthracycline-based chemotherapy (4−6 cycles of

FEC100) ± H without unexpected toxicity. All pts with hormone receptor-positive tumours received adjuvant hormonal therapy.

Conclusions: These preliminary data confirm the safety of the proposed XT±H combination as neoadjuvant therapy for LABC, with promising pCR rates in the XT+H arm. Weekly XT is particularly attractive for treating HER2-positive tumours because it can be combined with H, the latter being cleared during the perioperative phase, thereby avoiding the risk of overlapping cardiac toxicity with anthracyclines. Additional data on recent pts will be presented at EBCC.

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Switching from tamoxifen (TAM) to aromatase inhibitors (AIs) in the adjuvant treatment of breast cancer (BC) patients (pts). Results from the NORA study

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NORA study aimed at investigating modalities of treatment and pattern of relapse in 3511 BC pts, radically treated with surgery during the period 2000–2004, in 77 Oncological Centres.

Switching from TAM to AIs is one of the currently available options for the treatment of BC pts for whom hormone therapy is indicated. Recent trials are suggesting that switching to an AI during the period of the adjuvant therapy improves Disease-Free Survival (DFS) and Time to Distance reccurrence (TTDR). We analysed the switching from TAM to AIs in those patients who received either hormone therapy (HT) alone or chemotherapy (CHT) followed by HT as adjuvant treatment for early BC. 2388 out of 3511 (68%) started TAM, either as the sole therapy (35.3%) or after CHT. AIs have been administered as front-line choice in 392 pts (14.1%). Median age of pts receiving TAM was 58.6 (24–92). Switch was applied in 357 pts (17.2%). Median age of the switched pts was 62 (31–92). TN stage was T1N0 (34.6%), the therapy they have received was CHT followed by HT (59.7%). Median time to switch was 14.8 months (6.9–25.5). Main reasons for switching were gynecological toxicity (47%) and cardiovascular events (11.4%).

Switching from TAM to AIs was a current practice already some years ago, mainly due to TAM adverse events on gynecologic and vascular districts. Estimated DFS in the switched pts are currently under evaluation.

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Preoperative dose-dense sequential chemotherapy of epirubicin/cyclophosphamide followed by docetaxel/capecitabine in patients with early breast cancer: preliminary results

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Aims: To evaluate the activity and safety of a dose-dense, sequential chemotherapy of epirubicin/cyclophosphamide (EC) followed by docetaxel/capecitabine (DXe) given preoperatively in patients with early breast cancer not candidate to breast-conserving surgery.

Patients and Methods: This was a Simon's two-step phase II study, recruiting 24 patients in the first step, and an additional 17 patients in the second step (total of 41 patients). Patients with untreated operable breast cancer (T2–3, N0–2, M0) received four cycles of EC (cyclophosphamide, 600 mg/m^2 and epirubicin, 90 mg/m^2) q2 weeks, followed by two cycles of DXe (docetaxel, 36 mg/m^2 days 1, 8, and 15 and capecitabine, 1250 mg/m^2 days 5–18) q 28 days, with pegfilgrastim support. The primary end point was the incidence of pathological complete response (pCR) in the breast. Secondary end points were clinical response, rate of breast conservation, and safety.

Results: Twenty-four out of 26 enrolled patients were evaluable for response to treatment (one patient withdrew from the study for G4 neutropenia after the first EC cycle, and the other for therapy refusal after the 4 EC cycles). A pCR was observed in 6 patients for a total pCR rate of 25%. This met the requirements of the study design for the first step. A clinical response (CR or PR) detected by palpation and by imaging was observed in 23 patients, for an overall response rate of 96%. The rate of breast-conserving surgery was 75%. The treatment was well tolerated: one patient experienced G3 mucositis and another patient required a 25% dose reduction of capecitabine because of hand-foot syndrome.

Conclusion: The dose-dense sequential combination EC/DXe is endowed with good antitumor activity and limited toxicity, allowing a high rate of pCR and breast conservation. Accrual is continuing up to the estimated sample size.

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The expression of Her-2, IGF-1R, IGF-1, ER alpha and ER beta in tamoxifen resistant breast cancers

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Introduction: Tamoxifen resistance poses a significant problem in treating certain oestrogen receptor(ER) positive breast cancers. Recent evidence suggests that over expression of HER-2 receptors and increased signaling in growth factor receptor pathways (EGFR-HER-2, IGF-1R) are responsible for this resistance. The role of ER-beta in Tamoxifen resistance remains controversial. This study examines the gene expression difference in Tamoxifen sensitive and resistant breast cancer.

Methodology: Tamoxifen-resistant breast cancer samples from 11 patients who failed to respond to neoadjuvant Tamoxifen (*Group A*) were obtained. Samples were also obtained from 11 patients who developed recurrence or metastasis at least 1 year after surgery and taking adjuvant Tamoxifen(*Group B*). Samples from 14 patients who had these criterias were employed as Tamoxifen-sensitive controls (*Group C*): considered high risk of developing further metastasis (grade 3 with lymph node metastasis); started on adjuvant Tamoxifen; did not develop evidence of recurrence or metastasis at 6-year follow-up. All samples were ER positive on immunostaining. Relative expressions of ER-alpha, ER-beta, HER-2, IGF-1 and IGF-1R in all these samples were measured using real-time quantitative PCR.

Results: Mean ER-alpha expression was slightly lower in Group A when compared to Group B and C. However, there was little difference in the other gene expressions in all the groups. In Group A, IGF-1R levels significantly increased with HER-2 levels ($P = 0.010$). IGF-1R increased marginally with ER-alpha in Group C ($P = 0.098$) and Group A ($P = 0.000$). In Group B and C, IGF-1 increased significantly with HER-2 and ER-alpha but not in the Group A samples. Only Group C showed a positive correlation between ER beta and IGF-1 ($P = 0.003$) samples. ER-beta increased with IGF-1R in all groups.

Conclusion: Mean ER-alpha was lower in tamoxifen resistant breast cancers. However a larger sample size in future studies is required to detect significant difference in gene expression in these groups. The relationship between (EGFR-)HER-2 and IGF-1R in Tamoxifen-resistance the samples suggests that cross-talk between the two growth factor pathways may contribute to tamoxifen resistance. The stimulatory effect of IGF-1 on ER alpha and ER beta expression may be lost in Tamoxifen-resistant cancers. The role of ER beta in tamoxifen resistance may lie in this relationship.

Thursday, 23 March 2006 16:00–16:45

POSTER SESSION

Locally advanced and recurrent disease

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The effect on survival of local recurrence (LR) after breast conserving surgery

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This study is of 687 consecutive cases treated at Nottingham City Hospital in 1990–96 by breast conserving surgery (BCS). Cases were analysed by the Nottingham Prognostic Index (NPI).

Local recurrence (LR) is defined as recurrence within the parenchyma or skin of the treated breast; nodal recurrence is NOT included.