Proffered Papers

Optimizing systemic therapy for early and advanced breast cancer

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Reassessment of adherence to a guideline for primary breast cancer

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In 1988 the Comprehensive Cancer Centre East of the Netherlands, which comprises of 10 hospitals (including 1 university hospital), produced a guideline for the treatment of primary node positive premenopausal breast cancer patients. In 1993 all hospitals agreed to a retrospective assessment of guideline adherence over the period 1988-1992 (P1). The preliminary results were reported in 3 regional meetings, and in 1 international and 2 national conferences between 1993 and 1996. In the same period 3 papers on the relevance of dose intensity(2)and timing of chemotherapy (CT)(1) were published in leading journals. As part of a prospective intervention study to improve guideline implementation, a reassessment of adherence was done for the period 1996-1998 (P2).

From the patients records were abstracted: menopausal state, type and date of surgery, tumour size and histology, number and level of metastatic lymph nodes,type, dates of start and stop and ideal and given dose of adjuvant CT. The percentage of intended dose (DI) was calculated as well as the relative dose intensity (RDI= DI x (ideal/actual duration of CT)x (actual/ideal number of courses). A Fisher Exact Test was done to estimate significant differences.

In P1 323 and in P2 155 patients were eligible for treatment according to the guideline. The percentage of patients who underwent breast conservative treatment did not change significantly, from 39% in P1 to 35% in P2. Ablation after breast conservative surgery increased from 4% to 10% (P=0.01). The percentage of operations with less than 10 investigated lymph nodes decreased from 35% to 19% (P=0.0004). The percentage of patients who did not receive CT did not change signficantly, from 9% to 12%, neither did the percentage of patients for whom the interval between surgery and start of CT exceeded the advised 28 days: 73% in P1 and 75% in P2. The percentage of patients with a DI ≥85% and a RDI≥ 85% increased from 75% in P1 to 94% in P2 (P=0.000003) and from 59% to 78% (P=0.0003), respectively.

The quality of surgery and adjuvant CT increased significantly over time, probably due to an increased awareness of both personal functioning due to the feed back of results and of the importance of optimal surgery and CT. However multidisciplinary processes were not changed significantly. It could be hypothesised that these more complex processes are more difficult to change or that they reduce personal feelings of responsibility to change them.

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Randomised trial of two versus five years of adjuvant tamoxifen for postmenopausal early stage breast cancer: preliminary results of the SITAM-01

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Purpose: While tamoxifen (TAM) adjuvant therapy in early breast cancer is widely accepted as a standard treatment, the optimal treatment duration has not been well established yet. The results of two randomised clinical trials comparing 2 versus 5 years of TAM treatment and the indirect comparisons of the last overview suggested that a longer treatment might produce better outcomes than a shorter one. In 1989 the Italian Interdisciplinary Group for Cancer Care Evaluation (GIVIO) launched the Italian Study of Adjuvant Treatment in Breast Cancer (SITAM-01), a multicentre randomised clinical trial comparing 2 years versus 5 years of TAM treatment.

Methods: All women with operable invasive breast carcinoma T1-3 N0-3 M0 aged between 50 and 70 years were eligible, irrespective of tumour grade or estrogen receptor (ER) status. Randomisation to stop or continue treatment was performed following two years of TAM therapy in event-free patients. Treatment allocation was stratified by centres, prior chemotherapy and lymph nodal status.

Results: From 1989 through 1996, 2551 patients were entered in the trial, of whom 1901 were alive and event-free after 2 years of TAM therapy and were randomised to stop (N=958) or continue TAM for an additional 3 years (N=943). The median duration of post-randomisation follow-up was 70 months. Patients had a mean age of 60.9 years; 45% were node positive, 60% were ER positive and 25% had unknown ER status. Five years of treatment with TAM significantly improved DFS among ER positive patients (HR=0.78; 95% CI 0.62-0.99), while no benefit could be seen among ER negative/unknown patients. No significant overall survival differences were demonstrated, irrespective of ER status. Patients allocated to 5 years of TAM also showed a reduced risk of contralateral breast cancer (HR= 0.69; 95% CI 0.36-1.34) and an increased risk of thromboembolic events (2.3% vs. 1%; p=0.03).

Conclusion: Five years of tamoxifen significantly reduce the risk of relapse in post-menopausal ER positive patients with early breast cancer and should thus be considered standard treatment. Our findings also stress the importance of ER status measurement as a fundamental factor in prescribing hormone treatment.

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The effect of adjuvant treatment on minimal residual disease (MRD) in patients with primary breast cancer: 2 years follow-up data

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Purpose: The presence of MRD in the bone marrow of women with breast cancer is an indicator of poor prognosis. Monitoring MRD may be a useful way to improve disease staging and evaluate the effectiveness of therapeutic strategies.

We have developed a quantitative polymerase chain reaction (QPCR) to detect MRD and this is used in conjunction with immunocytochemistry (ICC) to monitor patients with primary breast cancer and hence determine the effect of adjuvant treatment on MRD.

Methods: Bilateral bone marrow aspirations (BMA) were performed on 103 women with primary breast cancer at the time of surgery. Follow up BMA (unilateral) were subsequently obtained at 3, 6, 12 and 24 months (m) following surgery. The samples were tested for MRD using QPCR for Cytokeratin-19 mRNA (Slade et al., J. Clin. Oncol. 1999) and ICC for cytokeratins 8,18 and 19 (Pantel et al., J. Haematother. 1994). The immunostained slides were analysed using an automated imaging system. 76% of the patients received tamoxifen; 10% adjuvant cytotoxic therapy and 14% received both.

Results: We have to date obtained follow up BMA from 84 women at 3m, 64 at 6m, 56 at 12 m and 45 at 2 years. The QPCR and ICC results agreed in 65% of cases at the time of surgery, 69% at 3m, 75% at 6m, 57% at 12 m and 73% at 24m.

Percentage of women with a positive BMA by:

QPCR:	41% at surgery; 32% at 3m; 20% at 6m; 44% at 12m and 27% at 24m.
ICC:	29% at surgery; 20% at 3m; 18% at 6m; 37% at 12m and 24% at 24m.
ICC or QPCR:	50% at surgery; 40% at 3m; 31% at 6m; 59% at 12m and 40% at 24m.

The differences between 3 and 24m (p= 0.6671), the 6 and 24m (p= 0.5024) and the 12 and 24m (p = 0.1927) samples were not statistically significant. There have been no clinical relapses to date.

Comment: These data show that MRD persists in a proportion of patients despite ongoing adjuvant treatment, suggesting that disseminated tumour cells are relatively resistant to such treatments. Detection of MRD may therefore be used to identify a subgroup of patients who would not benefit from cytotoxic or hormonal therapy. Our results support those of a previous study, which found that tumour cells persisted in the bone marrow after chemotherapy (Braun et al. J. Clin. Oncol. 2000). These findings may be a reflection of the dormant nature of these cells and alternative therapeutic strategies will be required to eliminate them.

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ICI 182,780 (Faslodex™) versus anastrozole (Arimidex™) for the treatment of advanced breast cancer in postmenopausal women - prospective combined analysis of two multicenter trials

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ICI 182,780 (Faslodex, FAS), a novel Estrogen Receptor Downregulator, is the first in a new class of antiestrogen. We report the prospectively planned combined analysis of two phase III trials, comparing FAS 250 mg once monthly and 'Arimidex' (anastrozole, AN) 1 mg once daily in postmenopausal women progressing on prior endocrine treatment for advanced breast cancer.

The trials compared the efficacy and safety of FAS with AN. The primary endpoint was time to progression (TTP). Secondary endpoints included objective response (OR), duration of response (DOR), clinical benefit (CR+PR+SD*24 weeks) and tolerability. Patients were randomised to either FAS 250mg (n=428) by intramuscular injection once monthly or AN 1mg (n=423) taken orally daily. Patients were followed for a median of 15.1 mo. Most (98%) patients had been treated with tamoxifen. At the time of analysis, approximately 83% of patients in each treatment arm had progressed. Median TTP was 5.5 mo and 4.1 mo for FAS and AN, respectively (Hazard Ratio 0.95; CL 0.82*1.10; p = 0.48). The OR (CR+PR) rates were 19.2% and 16.5% (Odds ratio 1.21; CL 0.84*1.74; p= 0.31) and clinical benefit rates were 43.5% and 40.9% for FAS and AN respectively. Both drugs were well tolerated. Withdrawals due to adverse events (drug related) were 2.8% (0.9%) in the FAS group and 1.9% (1.2%) in the AN group. Only 0.5% (2/423) FAS-treated patients withdrew because of an injection site reaction.

At the outset of the trial 7 adverse events were pre-defined for statistical analysis. Incidences of adverse events for FAS vs. anastrozole, which in the majority of cases were mild to moderate were as follows: gastrointestinal disturbances 46.3% vs. 43.7%; hot flushes 21.0% vs. 20.6%; vaginitis 2.6% vs. 1.9%; weight gain 0.9% vs. 1.7%; thromboembolic disease 3.5% vs. 4.0%; urinary tract infection 7.3% vs. 4.3%, and joint disorders (including arthalgia, arthrosis and arthritis) 5.4% vs. 10.6% which is the only adverse event to be significantly different between the two treatments (p=0.0036). Quality of life was maintained to a similar extent with both agents

In conclusion, FAS was found to be at least as effective as the aromatase inhibitor anastrozole in second-line advanced breast cancer in patients previously treated with tamoxifen. All efficacy endpoints are9 in favour of FAS. FAS was well tolerated. Based on these data FAS will provide a valuable new treatment option for advanced breast cancer in postmenopausal women.

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Survival update of so14999 a large phase III trial of capecitabine/docetaxel combination therapy vs docetaxel monotherapy in patients with locally advanced (LABC) or metastatic breast cancer (MBC)

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Capecitabine (Xeloda), an oral fluoropyrimidine, has substantial antitumor activity in colorectal cancer and heavily pre-treated MBC. Capecitabine plus docetaxel (Taxotere) has demonstrated synergy in preclinical studies. Patients with LABC and MBC in whom anthracycline treatment had failed were randomised to oral capecitabine 1250mg/m2 twice daily, days 1-14 plus i.v. docetaxel 75mg/m2 day 1 q3w (n=255), or i.v. docetaxel 100mg/m2 (n=256), day 1 q3w. The baseline patient characteristics in the treatment arms were balanced. Approximately 1/3 of the patients received study treatment as 1st and 1/2 as 2nd line therapy. With a minimum follow up of 15months, overall survival was superior in the combination arm (log rank p=0.0126; HR=0.775), median of 14.5 months (95% CI 12.3-16.3) vs. 11.5 months (95% CI 9.8-12.7) for single agent docetaxel with 72% and 79% of events reached, respectively. The survival curves separate early. One year survival was 56.8% (95% CI 51-63) in the combination arm and 46.9% (95% CI 41-53) in the monotherapy arm. Survival differences were evident in the 1st, 2nd and 3rd line treatment subgroups. Approximately 2/3 of the patients received post study chemotherapy in both treatment arms. The overall tumor response rate (RR) was superior for capecitabine/docetaxel 41.6% vs. for docetaxel 29.7% (p=0.006). Time to progression (TTP) was superior with the combination (log rank p=0.0001; HR=0.652), median of 6.1 months (95% CI 5.4-6.5) vs. 4.2 months (95% CI 3.4-4.5) with docetaxel. Multivariate Cox analysis revealed performance status, ER/PR status, number of metastatic sites and liver metastases as important baseline prognostic factors. Patients receiving monotherapy experienced a higher incidence (all grades) of neutropenia, complications of neutropenia, myalgia, and arthralgia. Diarrhoea, stomatitis, nausea/vomiting and hand-foot syndrome were more common with the combination therapy. The same pattern was generally noted for grade 3/4 adverse events.

Conclusion: The addition of capecitabine to 75mg/m2 docetaxel compared to docetaxel 100mg/m2 monotherapy led to significantly superior RR, TTP and survival, with a manageable safety profile.

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Weekly cisplatin - epirubicin - paclitaxel (PET) with G-CSF support vs. triweekly epirubicin-paclitaxel (ET) in advanced breast cancer (ABC). A SICOG phase III trial

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Background: In a previous study the PET weekly regimen gave an ORR of about 80% in breast cancer patients with metastatic disease, while the ORR exceeded 90% in locally advanced disease. (Frasci G. et al. Breast Cancer Res and Treat 62: 87-97; 2000). The present study aimed at evaluating whether this new regimen could produce a significant prolongation of TTP in ABC patients in comparison with standard ET.

Patients and Methods: ABC pts with locally advanced (T4 or N2) or metastatic disease, who had not received prior chemotherapy (except adjuvant) were considered eligible. Women were randomized to receive PET (P 30 mg/m2/week + E 50 mg/m2/week + T 120 mg/m2/week + G-CSF) or ET (E 90 mg/m2 + T 175 mg/m2 q3wk). A minimum of 6 cycles of PET or 3 cycles of ET were delivered, and the treatment was continued up to 12 and 6 cycles, respectively in absence of disease progression. Study design: Time to treatment failure was the chosen end point. A 3-month TTF prolongation was hypothesized with PET. Thus, at least 120 patients were required in each arm. An interim analysis was planned after the accrual of half of the total planned sample size.

Results: As of April 2001, overall 125 pts have been recruited (PET=61; ET=64), and 121 are evaluable for response (PET=60; ET=61). 65 patients showed locally advanced and 60 had metastatic disease at beginning of treatment. Overall, 17 CRs and 63 PRs have been recorded for a 66% ORR. 11 CRs and 35 PRs occurred in the 63 patients with locally advanced disease (ORR=73%) as compared to 6 CRs and 28 PRs in the 58 patients with metastatic disease (ORR=59%). 12 CRs and 31 PRs (ORR=72%)