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.