Proffered Papers

(Neo)adjuvant medical treatment of early breast cancer

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Are international guidelines on adjuvant treatment for early breast cancer followed in clinical practice? A multicenter observational study on 1547 patients treated in 1997

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Purpose: To evaluate the consistency of clinical patterns of care, in the prescription of Medical Adjuvant Treatment (MAT) for Early Breast Cancer (EBC), with widely accepted international guidelines (JNCI 87: 1441–1445, 1995).

Methods: Within the framework of a prospective, multicenter, observational study performed by the AIRO-L cooperative group, data collected by 12 Radiotherapy centers on 1547/1610 pts with stage I–II breast cancer and irradiated to the breast in 1997 after conservative surgery have been analyzed (63 pts with no axillary dissection are excluded from this analysis).

Results:

(1) N+, premenopausal group: MAT was chemotherapy (CT) in 96%, hormonal (HT) in 0%, none in 4% of ER– pts; MAT was CT in 92%, HT in 4%, none in 4% of ER+ pts.
(2) N+, postmenopausal group: MAT was CT in 85%, HT in 10%, none in 5% of ER– pts; MAT was CT in 56%, HT in 40%, none in 4% of ER+ pts.
(3) N–, ER– group (high risk): MAT was CT in 59%, HT in 7% and none in 34% of pts.
(4) N–, ER+ group: the use of CT ranged from 0% (low risk pts) to 51% (high-risk, pre-menopausal pts); the option of no MAT ranged from 21% (high-risk pts) to 70% (low-risk pts).

Conclusions: A composite picture emerged from this analysis, with both over- and under-prescription of medical adjuvant treatment in different subsets of EBC patients, as compared with a specific example of international guidelines.

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Early breast cancer: How long should tamoxifen continue?

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The overview by the Early Breast Cancer Trials Collaborative Group analysed data on ~37,000 women in 55 trials of adjuvant tamoxifen (TMX). For women with receptor positive disease, or with unknown receptor status, TMX is of substantial benefit, regardless of age or nodal status. 5 years of TMX appears better than 2 years. The effects of more than 5 years of TMX could not be assessed because there was insufficient randomised evidence to look at this reliably. Until trials that randomise 5 years versus longer hormonal therapy have entered and followed large numbers of women for many years, this question will remain unanswered. In particular, trials of this question that have already closed leave major uncertainty as to whether treatment should routinely continue beyond the fifth year.

ATLAS is an international trial of longer versus shorter hormonal therapy to assess reliably the effects of an extra 5 years of TMX in women who have had some years of treatment and for whom there is uncertainty as to whether they should now stop, or continue. 10–20,000 women will be randomised, usually after about 5 years of TMX, to either stop, or continue TMX for 5 more years. This large, simple trial addresses a question of relevance in routine clinical practice into which it is easily integrated. The main analysis will be of all-cause mortality, but ATLAS will also provide information on cause-specific mortality and non-fatal, but important, events. If, by 2010, ATLAS shows improved long-term survival with 10 years of TMX, this result will save thousands of lives annually, and will be relevant to the appropriate use of hormonal therapies in general. By September 1999, more than 5000 women will have entered ATLAS making it the largest ever study of tamoxifen duration. Still however, many thousands more need to be randomised to answer this question definitively. New collaborators are invited to join the study.

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Adjuvant CMF (cyclophosphamide, methotrexate, fluorouracil) in breast cancer. Is it cost-effective?

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Introduction: Today, adjuvant chemotherapy (ACT) consisting of CMF is standard practice in several countries. Benefits in delayed time to recurrence and prolonged survival has been documented. The incidence of breast cancer suggests a significant financial burden to the health care system.

Material and Methods: The cost-effectiveness analysis included data from the English speaking literature on efficacy, tolerability and quality of life (QoL) and Norwegian data on age, survival, drug charges and production gains/losses. The median age of women undergoing ACT in Norway was 50 years, the CMF regimen saved 0.51 years per woman treated during 10 years (Milan study), a survival gain of 8.5% after 10 years and a life expectancy of women aged 60 of 22.8 years. The efficacy was then measured 2.45 years saved per patient treated. The QoL was assumed diminished by 0.33 (0–1 scale) for 6 months during ACT, the life years (LY) gained valued Q = 0.86 and the dose intensity 85%. It was calculated 1 BP (£) = 12NOK and a 5% discount rate.

Results: The total cost of adjuvant CMF was calculated £1,976. Money spent on drugs alone constituted 41%. The cost per LY saved was measured £1,784. A sensitivity analysis was done. An off by 10% on drug charges indicated a cost per LY gained of £1,280. If the women were not cured by CMF, but lived half of their expected life span, the figure was £1,830. If 2% of ACT patients had been hospitalised due to sepsis, the total cost per patient had raised by £89.

Conclusion: Adjuvant CMF in breast cancer is cost effective in Norway.

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Neoadjuvant chemotherapy for breast cancer (BC): Is doxorubicin-cyclophosphamide (AC) combination still a standard regimen?

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Purpose: The NSABP B18 trial established AC as a standard neoadjuvant regimen for BC. In a randomized phase II trial, AC was evaluated Vs doxorubicin – TAXOL® (AT). Primary objective: pathological complete response (pCR); secondary: clinical response and safety.

Methods: Prospective, unbalanced randomized (2AT:1AC), parallel, multicenter trial. Pts were stratified according to center and tumor size (T2, T3). Treatment consisted of 4 cycles of AT: doxorubicin 60 mg/m^2 and TAXOL® 200 mg/m^2 as a 3-hour-infusion, or AC: doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2, followed by surgery, radiotherapy and tamoxifen for postmenopausal ER+ pts.

Results: A planned interim analysis (AC: 40 pts – AT: 80 pts) was performed according to early stopping rule of less than 7.5% of pCR: AC arm was stopped (5% pCR). Accrual continued in AT arm up to 180 pts. As

AC toxicity profile is well known, results are presented for the AT arm only. Pts characteristics (n = 180): median age: 47 (24–66); premenopausal: 66%, lobular. 13%; SBR III: 36%; T3: 38%; N1: 56%. Transient hematologic toxicity was observed without any toxic death: 56% of pts (32% of cycles) had grade 3–4 leucopenia, 3% of cycles had short-duration febrile neutropenia, grade 3 vomiting occurred in 3% of pts only. No clinical cardiotoxicity was observed. Efficacy: pts achieved 16% of pCR. Eighteen pts (10%) were devoid of any tumor cells in both breast and lymph nodes, 11 pts (6%) had only in situ carcinoma in the breast; for T2 pts, pCR rate was 20%. Clinical response was 83% and breast-conserving surgery was performed in 56% pts with AT vs 45% with AC.

Conclusion: Doxorubicin-TAXOL® appears to be highly effective and well tolerated in the neoadjuvant setting. Therefore AT will be the standard arm in our future trial.

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Primary chemotherapy in breast cancer: Significantly enhanced clinical and pathological response with docetaxel

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Introduction: Primary chemotherapy is increasingly being used in the treatment of patients with breast cancer. The most efficacious drug regimens employed have utilised anthracyclines alone or in combinations. However, many breast cancer patients fail to respond to such therapies.

Aim: The aims of this study therefore were (1) to determine the efficacy of primary docetaxel in patients that initially fail to respond to such combination chemotherapy, and (2) to compare the efficacy of docetaxel with conventional anthracycline combination regimens in patients that are initially responsive to such therapy.

Methods: Patients with large (>3 cm) or locally advanced (T3, T4, Tx, N2) breast cancers received 4 pulses of combination CVAP (cyclophosphamide 1000 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.5 mg/m^2, prednisolone 40 mg for 5 days) primary chemotherapy. After 4 cycles (3 weekly) clinical tumour response was assessed (UICC criteria). Those with a partial (PR) or complete response (CR) were randomised to receive either 4 further pulses of CVAP or 4 pulses of docetaxel (100 mg/m^2). All patients in whom stasis or progression of disease had occurred received 4 further pulses of docetaxel (100 mg/m^2). Following completion of the chemotherapy regimen, tumour response was assessed (as above) and appropriate surgery performed. Pathological response was assessed in excised specimens.

Results: To date, 130 patients have completed 8 cycles of primary chemotherapy. 83 women were suitable for randomisation (PR or CR) and 47 women were unsuitable. In randomised patients, after completion of chemotherapy, the clinical PR/CR rate was 66% in the CVAP group and 95% (p = 0.001) in the docetaxel group. Non-randomised patients had a clinical PR/CR of 37%. Pathological response (CR/PR) in randomised patients was 56% with CVAP and 80% with CVAP and docetaxel (p = 0.019); in non-randomised responders it was 43%. Patients receiving docetaxel experienced more onycholysis (p = 0.003) and less nausea (p = 0.009). Standardised measures of quality of life revealed no difference between the two regimens.

Conclusion: Primary docetaxel therapy resulted in a statistically significant improvement in clinical and pathological response. This was not at the expense of quality of life.

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Randomised controlled trial of high dose chemotherapy (HD-CNVp) versus standard dose (CAF) chemotherapy for high risk, surgically treated, primary breast cancer

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Purpose: To investigate the efficacy of high dose as compared to standard dose adjuvant chemotherapy for patients with surgically treated high risk breast cancer.

Method: 154 patients were entered into a randomised controlled clinical trial comparing 2 cycles of HDC-CNVp (cyclophosphamide 4.4 g/m^2, mitoxantrone 45 mg/m^2, VP16 1.5 g/m^2) together with peripheral blood stem cell rescue (PBCSR) to standard CAF chemotherapy for patients with surgically treated high risk breast cancer [T1-3a, $\geq 10^+$ Nodes or T $\geq$ 5 cms plus 7–9 nodes plus one additional poor risk factor (ER negative and or family history of breast cancer)].

Results: The study population was balanced for pre-treatment prognostic variables. At a median duration of follow up of 278 weeks 19/75 patients receiving HD-CNVp relapsed as compared to 52/70 receiving CAF (p < 0.001). Relapse free-survival (400$^+$ weeks vs 190 weeks) overall survival (400$^+$ weeks vs 320 weeks) were significantly better for HD-CNVp.

Conclusion: High dose chemotherapy is an effective treatment for high risk primary breast cancer.

Cervical, ovarian and gestational trophoblastic disease

903 ORAL

Cervix cancer (CxCa) and pregnancy (pregn)

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Purpose: How can the therapeutical approach be organized? Is the prognosis different? What are the possibilities for pregn?

Population: 1985–1997: 487 patients (pts) with Cx Ca operated at IGR, among them, 19 (4%) were pregnant. Stages IB: 14, II: 5. Squamous cell ca 18/19. Period of diagnosis according to the pregn: 1rst trimester (T1): 11 pts, T2: 5 pts, T3: 2 pts, post partum: 1. Mean delay for treating: 4 months in 5 pts. Ca treatment radiosurgical procedure: surgery: hysterectomy + lymphadenectomy (19 pts), ovarian transposition (13 pts). N$^+$: 9 pts. EBI: 10 pts. Brachytherapy: 19 pts. Pregn management: cesarian 7, hysterectomy 4, abortion 5, delivery 3, giving birth to 7 children.

Results: 1) Survival rate according to * Stage: IB: 93%, II: 60%, * Nodes: N$^-$: 100%, N$^+$: 67%, * Treatment delay: without delay: 82%, with delay: 88%. 2) Complication: Gr 1: 2, Gr 2: 5.

Conclusion: Same treatment were applied in these pregnant pts as in other pts, with same stages. No difference in survival, in complication rate; no influence for cases with delayed treatment. For the pregn aspect: 7 children are alive.

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Clinical value of screening for cytokeratin (CK)-positive bone marrow micrometastases in stage I–II cervical cancer

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Purpose: In spite of the lack of lymph node metastasis, some stage I–II cervical cancer patients succumb to distant metastases (e.g. in liver and lung), suggesting the existence of early hematogenous tumor cell spread. Immunocytochemical screening of BM aspirates, an easily accessible site of potential metastasis, might elucidate the presence of such minimal residual disease.

Methods: We analysed bone marrow aspirates from 93 newly diagnosed cervical cancer patients with stage I–II disease. We applied the monoclonal antibody A45-B/B3 directed against CK to detect tumor cells, and evaluated 2 × 10^6 BM cells per patient. At the time of this analysis, complete follow-up was available on 61 cancer patients. The median follow-up time was 20 months (range, 6–52).

Results: CK$^+$ tumor cells were detected in 28 (30%) of 93 cervical cancer patients. This finding was not correlated to established risk parameters, neither to lymph node metastasis, histological type, tumor lymphangiosis carcinomatosa nor to tumor differentiation grade. Surprisingly, at the time of follow-up, the OS rate in 21 CK$^+$ patients was 48% (5 events) compared to 89% in 40 negative patients (3 events) with a tendency towards significance (P = 0.075; log-rank test). DFS and DDFS were not significantly different in CK$^+$ and CK$^-$ patients (P = 0.19 and P = 0.22, respectively).

Conclusions: Our study clearly shows that hematogenous dissemination of tumor cells occurs early during tumor development of cervical cancer. This tumor cell spread can be detected in bone marrow, though bone is not a preferred site of distant metastasis. Nevertheless, bone marrow may indicate the presence of relevant and viable residual tumor cells that might have clinical value if the observed trend for reduced survival of CK$^+$ patients can be confirmed.