Randomised trials with impact on breast cancer *

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Comparison of adjuvant therapy with tamoxifen and goserelin vs. CMF in premenopausal stage I and II hormone-responsive breast cancer patients: Four-year results of Austrian Breast Cancer Study Group (ABCSG) trial 5

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Adjuvant chemotherapy is still the treatment of choice in premenopausal patients with stage I and stage II breast cancer. To test the efficacy of the endocrine combination of tamoxifen (TAM) and goserelin (GOS) compared with chemotherapy, the ABCSG has conducted a prospective randomized trial beginning in 1990. Representing 28% of all suitable patients in Austria, 1,045 patients with estrogen and/or progesteron receptor-positive, radically operated breast cancer were randomly allocated to cyclophosphamide (C, 600 mg/m^2), methotrexate (M, 40 mg/m^2) and 5-fluorouracil (F, 600 mg/m^2) days 1 and 8 i.v. for 6 cycles, or GOS 3.6 mg subcutaneously every 28 days for 3 years and TAM 20 mg orally for 5 years. 51% of the patients had a T1 lesion, 46% had node-negative disease and 58% underwent breast-conserving surgery. The median follow-up was 42 months. Within this follow-up, 157 patients experienced a recurrence and 56 patients died. Patients treated with combination endocrine treatment showed a significantly improved recurrence-free survival (RFS) compared with CMF (p lesser than 0.02), yet overall survival (OS) was not statistically different. The prognostic factors for RFS in multivariate analysis were age (0.0001), tumor stage (0.01), nodal stage (0.0001) and therapy (0.02); and those for OS were tumor and nodal stage (0.0003 and 0.0001). Patients who developed amenorrhea following CMF had a significantly better RFS and OS than those who did not (0.001 and 0.05 respectively). 20.9% of all patients with endocrine treatment terminated the therapy prematurely due to side effects and 72% of the CMF patients received full dose. Although premature, these data indicate a significant benefit of the GOS + TAM combination over CMF. Four-year results will be presented.

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Adjuvant treatment of premenopausal breast cancer with zoladex and tamoxifen: Results from randomised trials by the Cancer Research Campaign (CRC) Breast Cancer Trials Group, The Stockholm Breast Cancer Study Group, the South East Sweden Breast Cancer Group and Gruppo Interdisciplinare Valutazione Intervention Oncologia (GIVIO)

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In the late 1980's, following publication of the results of ovarian ablation and tamoxifen in the World Overview, four collaborative groups began pragmatic trials evaluating both tamoxifen and Zoladex in premenopausal women operated for early breast cancer. All the trials used 2 x 2 factorial designs. Participating centres were allowed to randomise just to Zoladex, electively recommending tamoxifen or not. The use of adjuvant chemotherapy was also permitted according to local protocols. The current analysis includes 2,631 patients; 1,082 (44%) were node positive and 1,128 (43%) received adjuvant chemotherapy. In the 60% of patients of known ER status, 74% were ER positive. In 833 (35%) of patients the decision to give tamoxifen or not was made electively. These patients are not included in the tamoxifen analysis.

A main effects analysis for Zoladex showed a significant increase in relapse-free survival (relative risk [RR] = 0.77; 95% CI 0.66–0.90; p = 0.001) with 261 first events in the patients allocated to Zoladex and 330 in the control group. For survival the RR was 0.84 (95% CI 0.67–1.05; p = 0.12) with 104 deaths in the Zoladex group and 165 in the control group. The main effects comparison for tamoxifen did not show any significant advantage for either relapse or survival.

Endocrine ablation using Zoladex in premenopausal breast cancer patients increases the relapse-free interval and may be considered as adjuvant treatment.

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Improvement of bone pain, quality of life and survival time of breast cancer patients with metastatic bone disease treated with intravenous ibandronate

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Purpose: Bisphosphonates reduce tumor-induced skeletal complications in metastatic bone disease and have an effect on aspects of palliation. In addition to investigating the reduction in skeletal complications, the aim of the present study was to evaluate the improvement in quality of life, the reduction of bone pain and the effect on survival time following interval therapy with the bisphosphonate ibandronate (IBN).

Methods: 462 patients with bone metastases due to breast cancer were randomized in a double-blind, placebo-controlled, multicenter study. 153 patients received 2 mg IBN every 4 weeks for a maximum of 2 years, 152 patients received 6 mg IBM iv monthly, and 157 received a placebo. Quality of life was assessed using the EORTC quality of life scale (QLQ-C30). Bone pain was assessed by recording a pain score (0–4). Survival was compared by Kaplan-Meier estimates and the proportional hazard model.

Results: A significant ($p < 0.05$) improvement in quality of life was demonstrated for IBN for almost all functions and for global health status. The same effect was seen for most symptoms (fatigue, insomnia, etc.), although the improvements with the 6 mg dose were more pronounced than with 2 rag. There were also significant improvements in the bone pain score (p = 0.0006; 6 mg vs. placebo). The survival time for all IBN-treated patients was 774.3 days (SD = 24.0) compared with 741.7 days (SD = 34.9) in controls. In the soubgroup of patients with soft tissue metastases after 6 months the survival was improved significantly ($p < 0.01$).

Conclusion: Quality of life was clinically significantly improved in patients treated with 6 mg IBN as compared to placebo. Bone pain was reduced significantly (6 mg vs. placebo). IBN-treated patients had a slightly better survival compared to the placebo group. IBN administered doses of 2 mg (bolus) and 6 mg is well tolerated and safe.

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Adjuvant anthracycline in breast cancer. Improved outcome in premenopausal patients following substitution of methotrexate in the CMF Combination with epirubicin

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The study analyzed whether the therapeutic gain with anthracycline combinations in advanced breast cancer could be translated to the adjuvant setting in three subgroups of patients. Group A: premenopausal with node-negative, grade II–IIItumor, group B: premenopausal with node-positive, receptor-negative or unknown tumor, group C: postmenopausal with node-positive, receptor negative tumor. Following primary local treatment patients were randomized into a 2 times 2 factorial designed study to either CMF (cyclophosphamide, methotrexate, fluorouracil), or to CEF (cyclophosphamide, epirubicin, fluorouracil) or to CMF + PAM (oral pamidronate 150 mg 2 times daily for 4 yrs) or to CEF + PAM. Only the results comparing CMF with CEF will be addressed. Both regimes were administered intravenously d. 1 every 3 weeks times 9. Doses (mg/m^2) were, CMF. 600, 40,600 and CEF: 600, 60,600. From January 1990 to May 1998 1195 patients were randomized. The present analysis dates to October 1995 and median follow-up is 61 months. At 6 years survivals with CMF vs CEF were 83% vs 93% ($p < 0.01$) in group A (n = 343), 60% vs 66% (p = 0.2) in group B (n = 531) and 48% vs 50% (p = 0.3) in group C (n = 321). In the combined premenopausal groups (groups A + B) survivals were 69% vs 76% (p = 0.01). 95% of scheduled CMF dose was given compared with 96% of scheduled CEF. Dose intensities were identical. Hematologic toxicities were evenly distributed in the two groups. Alopecia and amenorrhoea occurred more frequently in the CEF group (87% vs 7% and 80% vs 60%). In conclusion adjuvant CEF is superior to CMF in terms of survival in premenopausal patients with intermediate and high risk breast cancer, but no difference was observed in postmenopausal patients with high risk breast cancer.

* This session will be held on Tuesday 14 September 1999