Results: Prophylactic treatment with pegfilgrastim alone or pegfilgrastim with C was associated with a lower incidence of febrile neutropenia, first cycle febrile neutropenia, hospitalization, and anti-infective use compared with daily G-CSF (see table). Pegfilgrastim alone or with C also showed a lower incidence of grade 3/4 stomatitis and diarrhea ($p < 0.05$) compared with daily G-CSF.

Conclusion: Pegfilgrastim alone or in combination with ciprofloxacin was a more effective treatment for prevention of neutropenia and its related complications than daily G-CSF in early stage breast cancer patients treated with TAC chemotherapy.

	Cohort A G-CSF (n = 385) 2086 cycles	*Cohort B* pegfilgrastim (n = 311) 1631 cycles	*Cohort C* pegfilgrastim + ciprofloxin (n = 219) 1074 cycles	Statistical comparison
Patient incidence of FN	17%	6%	5%	*** A vs B *** A vs C ns B vs C
Incidence of FN in the first cycle	9%	2%	0%	*** A vs B *** A vs C * B vs C
Number of hospitalizations	391	210	161	*** A vs B ** A vs C ns B vs C
Number of anti-infective[a] administrations	88	44	25	** A vs B ** A vs C ns B vs C

***$p < 0.001$; **$p < 0.01$; *$p < 0.05$; ns: not significant; FN: febrile neutropenia.
[a]defined as antibiotic, virostatic, or antifungal medications

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Amenorrhea as a prognostic factor in premenopausal endocrine responsive early breast cancer patients

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Objectives: Amenorrhea (Am) seems to be a prognostic factor in early breast cancer (EBC), especially in endocrine responsive disease. Aim of our analysis was to evaluate prognostic value of Am in premenopausal patients (pts) treated for EBC at Institute of Oncology in Ljubljana from 1986 to 1998.

Patients and Methods: To assure complete menstrual data, only 204 premenopausal HR positive pts included into international prospective trials evaluating the role of adjuvant systemic therapy (ChT alone n = 120, ChT plus Tam n = 19, ChT plus goserelin n = 37, goserelin alone = 28) were reviewed. Median age was 45 (27–54) years, majority of tumors (53%) were classified as T2, of median grade (43%), half of pts had positive lymph nodes. Amenorrhea was defined as a cessation of menstruation for at least 2 years. Endocrine responsive disease was defined as ER and/or PR $\geqslant$ 10 fmol/mg protein in primary tumor. Kaplan-Maier method and log-rank test were used for statistical analyses.

Results: Amenorrhea occurred in 85% (174/204) of all pts (in 76% of pts on ChT +/− Tam and in all patients on goserelin, respectively). Pts with Am had significantly higher 5-year DFS compared to pts without Am (75% vs. 53%; $p = 0.0081$). Also in the group of pts with Am induced by ChT alone, higher 5-year DFS rates were observed (76% vs. 57%; $p = 0.06$). Recovery of menstruation after 2 years of goserelin treatment did not affect 5-year DFS rates significantly ($p = 0.44$). After adjusting for ChT and Tam Am still showed borderline significance for DFS ($p = 0.06$). In Cox multivariate analyses with tumor size, tumor grade, nodal status and Am included, only nodal status retained independent prognostic value.

Conclusions: In our cohort of endocrine responsive premenopausal EBC patients, treatment related amenorrhea showed a prognostic impact on DFS. Also when Am was achieved only by ChT, it had a favorable effect with a trend to better DFS. No significant difference in DFS according to recovery of menstruation after goserelin cessation was observed.

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Cost-effectiveness of exemestane versus tamoxifen as adjuvant therapy for early-stage breast cancer after 2–3 years treatment with tamoxifen in Sweden

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Breast cancer is the most common cancer in Swedish women, with about 7000 new cases annually. Aromatase inhibitors are rapidly becoming the cornerstone of hormonal treatment for advanced disease and are now also used as adjuvant treatment in early-stage disease. The Intergroup Exemestane Study (IES) trial was a double-blind, randomized controlled trial in which postmenopausal women who had received two to three years of tamoxifen therapy following primary treatment of early-stage breast cancer were randomized to either continue on tamoxifen therapy or be switched to exemestane therapy. The results showed a disease-free survival hazard ratio of exemestane relative to tamoxifen in IES of 0.69.

The objective of this study was to assess the cost-effectiveness of adjuvant treatment with exemestane versus tamoxifen for early-stage breast cancer after 2–3 years treatment with tamoxifen in Sweden, based on findings in the IES. A Markov-type state-transition model was developed to simulate consequences after the end of the clinical trial, and to integrate the trial data with external data on mortality, costs and quality of life specific for Swedish women. The model used a life-long time horizon and the primary clinical outcome measure was quality adjusted life-years (QALYs).

Locoregional and distant recurrences occurred in about 18% of the patients, while new contralateral cancer occurred in 1–2%. Treatment of cancer recurrences contributed most to the total cost, while the largest difference in cost between the exemestane and tamoxifen groups was incurred by the adjuvant hormone treatments. The cost per QALY gained was about €20,000 in the base case analysis without inclusion of consequences of coronary heart disease. Inclusion of these events increased the cost-effectiveness ratio to about €31,000 for the base case assumption. Exemestane treatment in early breast cancer may therefore be a cost-effective option compared with tamoxifen, depending on the long-term effect of tamoxifen on coronary heart disease.

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Preoperative concomitant hormone-radiotherapy for locally advanced breast cancer: Long-term clinical results of the Montpellier feasibility study

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Purpose: To evaluate, with a 6-year median follow-up our data concerning survival and locoregional control in a pilot study of locally advanced breast cancer after primary hormonoradiotherapy (HT-RT).

Patients and Methods: Between 1987 and 2002, 80 patients (33 stage IIA, 27 stage IIB, 16 stage IIIA, and 4 stage IIIB according to AJCC staging system 2002) were treated by tamoxifen 20 mg daily and preoperative radiotherapy (50 Gy to the breast and nodal areas). Tamoxifen was started the first day of radiotherapy and was delivered for 3 months (median 90 days, range 60–130) before surgery.

Before any treatment, all patients were clinically evaluated by a surgeon and an oncologist and were considered not suitable for a conservative surgery. In all cases, primary tumors were histologically proven and were positive for estrogen (RE) and/or progesterone receptors (RP).

After surgery, tamoxifen was continued for 5 years, or until disease progression. Fifteen patients (19%) received adjuvant anthracyclin-based chemotherapy. Only four patients stopped tamoxifen before 5 years for toxicities.

Results: The median age of the patients was 60 years (range, 32–80 years). Sixteen (20%) patients were premenopausal and received LHRH analogues with tamoxifen. Compliance to neoadjuvant treatment was excellent and all patients received the complete sequence of preoperative radiotherapy and tamoxifen. Overall clinical response rate was 75% (64 patients), including a complete response rate of 8% (6 patients). Mastectomy and axillary dissection were performed in 44 patients (with clinical residual mass larger than 3 cm or central tumors), and conservative treatment in 36 patients (22 of them achieved clinical complete response or

partial response > 50%). Pathological complete response was obtained in 3 patients (4%). Postoperative complications occurred in 19 patients (24%). These complications included 7 infections with delayed wound healing, and 9 persistent lymphorrea. None required a second surgery.

Local relapses after breast conserving surgery and mastectomy were 4 and 4, respectively. Nine-year local and metastatic disease-free survival rates were 87% (95%CI [74–94]) and 60% (95%CI [46–73]), respectively.

Cosmetic results were satisfactory in 80% of patients after conservative surgery.

Conclusion: For many years, preoperative hormonal therapy is an interesting alternative to neoadjuvant chemotherapy for RE/RP positive tumors. In our experience, combined pre-operative hormone-radiotherapy is well tolerated with very few postoperative complications and may render more locally advanced tumors to conserving surgery. In this setting, we are conducting a pilot study with concurrent radiotherapy and a non-steroidal aromatase inhibitor, letrozole.

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A computer programme to calculate for the individual the expected improvement in survival chance from adjuvant therapies

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The EBCTCG overviews of adjuvant therapies provide figures of relative risk reduction (RRR). Applied to the survival chance of the individual, shown by the Nottingham Prognostic Index (NPI) the absolute improvement expected from therapies for that individual, may be calculated.

The baseline figure ('observed 1980–86') is the survival in NPI groups in patients treated without any adjuvant systemic nor local (RT) therapies. (1) The 'Expected' figures are the effects on these from the relative risk reductions (RRR) demonstrated in the EBCTCG overviews for each therapy.

Example: Women 50+, % 10 year survival

NPI group	Observed 1980–6 (No Adj: local/systemic)	Tam 5 Yr (ER+) RRR 27%	CMF RRR 11%
EPG	88	91	89
GPG	72	80	75
MPGI	61	72	65
MPGII	42	58	48
PPG	14	37	23

Patient age and pathological tumour characteristic (grade, LN stage, size, ER, VLI) must be entered. The expected improvements will be given for individual NPI values rather than for groups (Blamey, 2005).

Survivals have improved in the 1990's in all prognostic groups to a greater degree than predicted by the EBCTCG estimate of risk reduction for adjuvant systemic therapies.

A further calculation is given for the gain in survival expected from the selected systemic therapy plus the survival gain from a recommended programme of local and regional management (based on free margins, case selection for breast conservation, selective local and regional RT or clearance).

The combined figure gives the present day expected Breast Cancer Specific (BCS) survival from modern therapeutic management, which is specified for each case.

Example: Age 60 years. Inv. Ca, 2 cm, LN +ve (1/4), Grade II → NPI 4.4. ER +ve
Expected 10 yr BCS survival without adjuvant treatments = 61%
with 5 years Tam = 72%
with clear margins and intact breast RT
with Ax clearance or RT
Expected 10 yr BCS survival with above therapeutic program = 81%
Expected 10 yr BCS survival after age correction = 73%

The programme will be accessible at http://www.absolutegain.com

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Dose intensity and outcomes of epirubicin-based adjuvant breast cancer therapy: FEC100 vs CEF/PO

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Adjuvant therapy with Epirubicin-based chemotherapy is standard in many jurisdictions. While there has been no direct, head-to-head comparisons made of CEF/PO and FEC100, the two regimens have been assumed to be equivalent. FEC100 has been shown to be easier to deliver and better tolerated than CEF. We have undertaken a retrospective analysis indirectly comparing CEF and FEC100.

In this analysis, 391 pts were prescribed FEC100 or CEF and received a full 6 cycles of adjuvant therapy. 220 pts were treated with FEC100, and 171 pts were treated with CEF. Patients treated with CEF had a longer median follow-up (50.6 months) than FEC100 (34 months) due to an earlier adoption of CEF. More pts that received CEF developed recurrences (46/171, 26.9%) compared to FEC100 (31/220, 14.1%). Kaplan-Meier analysis did not demonstrate statistical superiority (Log Rank p = 0.2436) but differences in length of followup may account for this.

Patients were balanced for nodal status, hormone receptor status as well as disease stage in this analysis. Patients that received a high relative dose intensity (RDI) of FEC100 (>95%) demonstrated a trend towards superiority in recurrence free survival (p = 0.07371, see Figure 1).

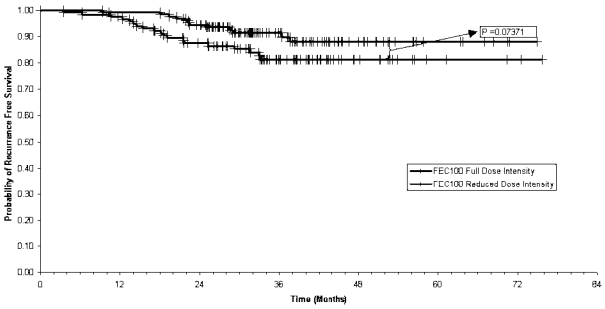

Figure 1. FEC100 adjuvant therapy – dose intensity.

Patients treated with CEF that received a high RDI (>85%) did not show a statistical recurrence free survival advantage (p = 0.7548) despite a higher proportion of patients that developed a recurrence in the low dose intensity group (34/107 vs 12/64, p = 0.01746). Overall, all patients with a high RDI of therapy with either FEC or CEF demonstrated a trend towards superiority in recurrence free survival when compared to a lower RDI (p = 0.1708). However, when patients that had a high RDI delivered for FEC100 were compared to patients that received a low RDI for FEC and any dose intensity of CEF, they demonstrated a statistically significant improvement in recurrence free survival (p = 0.04359, see Figure 2).

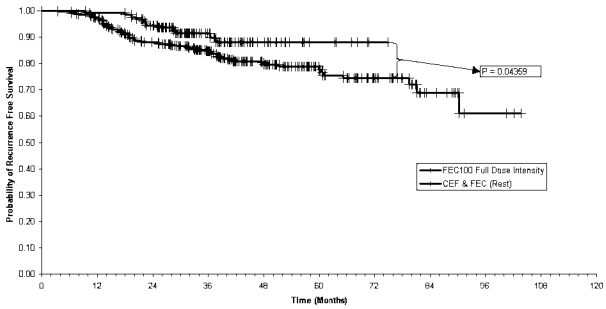

Figure 2. Epirubicin adjuvant therapy – dose intensity.

In conclusion, Epirubicin-based adjuvant therapy is an effective chemotherapy treatment. In this retrospective study, a higher RDI appears to improve recurrence-free survival. As well, CEF does not appear to be any more effective than FEC100. In the absence of prospective trials comparing the two regimens, a meta-analysis of Epirubicin-based therapies may potentially confirm or corroborate these observations