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Randomised adjuvant trial comparing two dose intensities of epirubicin and cyclophosphamide (EC) in high-risk breast cancer

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Due to bad prognosis therapy of breast cancer patients at high risk of recurrence and death remains challenging. Dose-intensification and dose-density are promising concepts to improve survival of these women.

Purpose: Our trial served the purpose, to define the role of a dose-intense and dose-dense regimen in adjuvant breast cancer treatment.

Methods: Between 3/1993 and 8/1997 we randomised 182 patients with high-risk breast cancer defined by >9 positive axillary lymphnodes or extracapsular involvement to either 4 cycles EC 120/600 mg/m" q2w with G-CSF-support (HDI-EC) or 4 cycles EC 90/600 mg/m" q3w followed by three cycles CMF (EC/CMF).

Results: At present 174 patients are evaluable. During a median follow-up of 24 months (range 3 to 54 months) 38 recurrences and 18 deaths were observed. Multivariate analysis revealed progesteron receptor and nodal status (1–9 vs. 10+) as significant prognostic factors. Intention to treat evaluation, performed by Kaplan-Meier estimates, showed a mean DFS of 44 months for patients receiving HDI-EC versus 37 months for patients receiving EC/CMF (p = 0.03), OAS was 49 versus 44 months (p > 0.05). Benefit was seen in patients with 1 to 9 positive lymphnodes as well as patients with 10 or more positive lymphnodes. Hematologic toxicity in the HDI-EC arm was present as leucopenia WHO grade III in 13%, grade IV in 8.3% and thrombopenia WHO grade III/IV in 1.2% of all cycles. Anemia was found in 2.8% of all patients receiving HDI-EC. Non hematologic toxicity mainly consisted of nausea (53%), vomitus (34%) and alopecia (100%). One treatment related death was due to acute dilatative cardiomyopathia at a cumulative Epirubicin dose of 480 mg/m".

Conclusions: Regarding the short follow-up we conclude, that HDI-EC is feasible regimen with considerable shorter time of treatment. DFS is significantly superior at present, longer follow-up will reveal, whether this favourable trend will persist.

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Comparison of 3 versus 6 cycles CMF in node positive breast cancer patients based on 10 years follow-up

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Purpose: In 1984 the GBSG started a multicenter randomized trial to compare in 2 × 2 study the effectiveness of three versus six cycles CMF and the additional effect of tamoxifen.

Materials and Methods: During 5 years, 41 institutions randomized 473 patients. In the first analysis, based on follow-up until March 1992, no significant difference in recurrence free survival (RFS) was observed for duration of chemotherapy (Schumacher et al. 1994; JCO, 12: 2086–2093). Based on follow-up until December 1997 an updated analysis for RFS and overall survival (OS) will be presented.

Results: Based on 271 events for RFS and 226 deaths, the estimate of the relative risk for the effect of 3 versus 6 cycles CMF is 0.96 (95% confidence interval 0.76–1.22) for RFS and 0.94 (0.72–1.22) for OS. Adjustment for prognostic factors has hardly any influence on these estimates..

Conclusion: The results of this study support a reduction of duration of CMF to cycles only.

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Doxorubicin (A) followed by docetaxel (T) versus doxorubicin + docetaxel (AT) in the adjuvant treatment of breast cancer (BC)

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We evaluated the two following regimens: 1) A 75 mg/m^2 q 3 wks × 3 → T 100 mg/m^2 q 3 wks × 3 → CMF i.v. days 1 + 8 q 4 wks × 3; 2) AT (50/75 mg/m^2) q 3 wks × 4 → CMF (as for 1) × 4. A factor to note is that, cumulative doses of A and T in the two arms were nearly identical. Pts with N-positive BC aged ≤ 70 y.o. were eligible.

Data regarding A → T and AT are compared below. Data related to CMF are not reported.

	A → T	AT
N° treated pts/.N° cycles	20/118	29/95
% of pts withdrawn	5	7
% cycles with RDI < 75%	1	1
% pts reporting:		
– vomiting/stomatitis (%G3)	60 (5)/65 (20)	31 (3)/52 (3)
– skin/neuro-toxicity (%G3)	35 (5)/55 (–)	17 (–)/17 (–)
– neutropenic fever	30	48

These data suggest that when A and T are given sequentially rather than in combination, there is a higher incidence of single drug-related side effects and a lower incidence of neutropenic fever. Both strategies are feasible in the adjuvant treatment of BC. A comparison in terms of activity is ongoing in a phase III trial.

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Doxorubicin vs CMF in the adjuvant tratment of high risk breast cancer

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This trial was activated to compare the efficacy of Doxorubicin vs CMF in adjuvant treatment locally-advanced breast cancer T1-2N2M0, T3N0-2M0. From 1985 to 1990, 349 pts aged 27–57 years, who had undergone preoperative radiation therapy (60 Gy to the breast and 40 Gy to the axillary lnd) followed by modified radical mastectomy, were randomized to receive either Doxorubicin 50 mg/m^2, iv, on day 1 and 8, every 4 weeks, to total dose 500 mg/m^2 (165 pts), or classical CMF regimen up to 6 cycles (184 pts). Mean duration of follow-up was 68.8 months. The overall (OS) 5-years survival rate was 73% in the Doxorubicin group and 62% in CMF group (P = 0.12). The disease free (DFS) survival was 62.8% in the Doxorubicin group and 55% in the CMF group (P = 0.06).

Only in subgroup of pts with tumor pN2 was estimated significant improvement DFS in Doxorubicin group (86.3%) vs CMF (58%), P < 0.01. But this phenomena requires further study with more number of events.

In spite of appreciable absolute difference in rates of OS (11%) between treatment groups, it has statistically doubtful.

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A randomized phase III trial of adjuvant endocrine therapy with tamoxifen for one year (TAM1) vs tamoxifen for two years (TAM2) in postmenopausal high risk patients with estrogen receptor positive or estrogen receptor unknown breast cancer. A DBCG study

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Purpose: To evaluate whether adjuvant TAM2 is superior to TAM1 using disease free (DFS) and overall survival (OS) as end points in postmenopausal high risk patients with operable breast cancer.

Methods: The study was conducted in the years 1990 to 1996. Following surgery and adjuvant radiotherapy postmenopausal high risk patients with estrogen receptor positive or estrogen receptor unknown breast cancer