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FEC (5-FLUOROURACIL-EPIRUBICIN-CYCLOPHOSPHAMIDE) MONTHLY VERSUS FEC WEEKLY IN METASTATIC BREAST CANCER.

First results of a randomized trial

CARL BLOMQVIST, INKERI ELOMAA, PENTTI RISSANEN, PÄIVI HIETANEN, KAISU NEVASAARI and LEENA HELLE

Patients (n = 174) with metastatic breast cancer previously untreated with anthracycline cytotoxic agents were randomized into two groups: Group 1 received FEC (5-flourouracil 500 mg/m^2, epirubicin 60 mg/m^2 and cyclophosphamide 500 mg/m^2) once every fourth week and group 2 received the treatment once weekly in the same monthly dosage. Treatment was recommended to continue until disease progression or to a cumulative epirubicin dose of 1 000 mg/m^2, but could be discontinued at any time at the patient's request or at the treating physician's judgement. An interim analysis was made when 131 patients were evaluable for response, and 128 patients for toxicity. Hematological toxicity was significantly more severe in the monthly group, as was nausea and vomiting. Of the monthly treated patients 76% had total alopecia compared to 14% in the weekly group. There were no statistically significant differences in the occurrence of mucositis. Monthly FEC gave significantly higher response rate than weekly treatment (52 vs 34%, p = 0.01). Time to progression was significantly (p = 0.004) longer with monthly FEC. Patients in the monthly treated group lived significantly (p = 0.02) longer than patients in the weekly group. These results indicate that both toxicity and efficacy of epirubicin-containing combination therapy in breast cancer is dependent on the treatment schedule, not merely on dosage. Both efficacy and toxicity increased when the treatment was given once monthly compared to the weekly schedule.

Key words: Breast cancer, metastatic disease, epirubicin, 5-FU, cyclophosphamide.

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Traditionally cytotoxic treatment of metastatic breast cancer has been carried out using combinations of drugs once a month or once three-weekly. Anthracycline combinations including doxorubicin(Adriamycin) or epirubicin are among the most potent and widely used regimens. Cyclophosphamide and 5-fluoruracil with either doxorubicin or epirubicin (FAC and FEC respectively), yield objective responses in previously untreated advanced breast cancer in about 50% of patients (1-5). Due to the considerable toxicity associated with this combination, less toxic alternatives have been introduced, including low-dose single doxorubicin and epirubicin given weekly. A randomized Norwegian trial has reported equal efficacy of weekly single doxorubicin and monthly combination chemotherapy with considerably less toxicity of the weekly regimen (19). The response rate in the Norwegian trial, however, was modest (31 vs 35%) in the two study arms. Uncontrolled studies of weekly doxorubicin or epirubicin have reported objective response in between 12 and 47% (6-22).

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Correspondence to: Carl Blomqvist Department of Radiotherapy and Oncology, University of Helsinki, Haartmanninkatu 4 SF-00290 Helsinki Finland
Addresses: Dept of Radiotherapy and Oncology, as above (C. Blomqvist, I. Elomaa, P. Rissanen, P. Hietanen), Central Hospital of Central Finland (K. Nevasaari), Central Hospital of Kymenlaakso (L. Helle).

The dependency of efficacy on the schedule of combination chemotherapy including doxorubicin or epirubicin has, however, never been properly tested in a randomized trial. The efficacy has traditionally been assumed to be determined solely by the drug concentration expressed as 'the area under the curve' of doxorubicin or epirubicin concentration versus time, i.e. independent of infusion time or fractionation of the dose (23). On the other hand, certain side-effects, especially cardiac toxicity, have been assumed to be more dependent on peak drug concentration, i.e. on treatment fractionation (24). The present trial was started in order to study whether weekly administration of drugs affected the toxicity and efficacy of FEC chemotherapy in breast cancer.

Material and Methods

Patients with measurable or evaluable metastatic disease from breast cancer eligible for combination chemotherapy in three Finnish oncological centers were included in the study. The patients were required to be ambulant (WHO performance index ≤ 2), and were not allowed to have been pretreated with anthracycline chemotherapy. Other chemotherapy, including CMF adjuvant therapy, was allowed, as was previous hormonal therapy. One hundred and seventy-four patients were included in the study between November 1987 and January 1991. The patients were randomized to once 4-weekly or once weekly FEC in the same monthly dosage. Cyclophosphamide and 5-fluorouracil were given a 4-weekly dosage of 500 mg/m^2 and epirubicin in a dosage of 60 mg/m^2 every fourth week. Dose reduction by 20 or 40% was performed in case of unexpected toxicity according to a dose reduction scheme. Treatment was recommended to continue until progression or until a total epirubicin dose of 1 000 mg/m^2 was reached, but treatment could be discontinued earlier according to the clinical judgement of the treating physician.

Three patients were excluded from response and toxicity evaluation because they never received the assigned treatment due to avert psychosis, rapidly deteriorating performance and mistake in randomization. They were, however, included in the analysis of time to progression and survival.

Complete blood counts, serum alkaline phosphatase and 5-nucleotidase were recorded before treatment once 4-weekly, and blood counts were also recorded weekly in the weekly schedule and 10 days after treatment in the monthly treated group. Physical examination and toxicity analysis including performance status, alopecia, nausea, stomatitis, GI-toxicity and infections were performed every fourth week. Diagnostic tests appropriate for response evaluation (radiography, ultrasound or scintigraphy, measurement of visible lesions) were performed every third month or on suspicion of disease progression.

The present first analysis is based on 131 patients evaluable for efficacy. Data on hematological toxicity were available in 128 patients and on non-hematological toxicity, including nausea, vomiting and alopecia in 117 patients. Analysis of survival and time to progression is based on 157 patients with follow-up data available.

Results

Pretreatment characteristics are shown in Table 1. There were no statistically significant differences in prognostic factors between the two groups. Ten patients in the weekly and 7 patients in the monthly treated group had been pretreated with non-anthracycline chemotherapy, most commonly in the adjuvant setting.

The response rate was 34% in the weekly and 52% in the monthly group ($p = 0.06$; x^2). The occurrence of progressive disease, no change, partial and complete response in the two groups is shown in Table 2. The Mann-Whitney test for differences in response categories (PD, NC, PR and CR) between the two groups gave a statistically significant result ($p = 0.01$).

The occurrence of hematological toxicity, nausea and vomiting, alopecia and stomatitis is shown in Table 3. There was statistically significantly more hematological toxicity and alopecia in the monthly treated group. Dose limiting hematological toxicity was mainly seen as leukopenia; only three patients had trombocyte nadir values below $50 * 10^9$/l. Time to total alopecia in the two groups is shown in Fig. 1. Significantly more frequent and earlier alopecia ($p < 0.0001$, Mantel-Cox) was seen in the monthly group, while the majority of patients in the weekly treated group retained at least some hair even after more than 6 months of treatment.

Time to progression (Fig. 2) was significantly longer in the monthly group ($p = 0.004$, Mantel-Cox). Median time to progression was 10.6 and 5.5 months in the monthly and weekly groups respectively. The patients in the monthly group had a significantly ($p = 0.02$) longer survival (Fig. 3). Median survival were 21.5 and 13.4 months in the monthly and weekly treated groups respectively.

The actual amount of monthly delivered drugs was similar in the two treatment groups (58 vs 59 mg/m^2 epirubicin for the weekly and the monthly groups respectively, $p = 0.59$, Mann-Whitney), and there were no differences in total treatment time between the two groups (medians 5.89 and 4.90 months in the monthly and weekly groups respectively, $p = 0.34$, Mantel-Cox).

Discussion

Doxorubicin is one of the most active single drugs in the treatment of advanced breast cancer. Randomized comparisons of two of the most popular regimens CMF (cyclophosphamide, methotrexate and 5-fluorouracil) and FAC (cyclophosphamide, doxorubicin and 5-fluorouracil)

Table 1

Pretreatment characteristics

	Monthly	Weekly	Statistics	
			p	Test
Mean age, years	54	53	0.87	Student's t-test
Premenopausal, %	51	55	0.53	χ^2
ER-positive, %	40	53	0.16	χ^2
PgR-positive, %	73	67	0.75	χ^2
Median DFI, months	16.5	18.5	0.25	Mann-Whitney
Previous treatment regimens, median (range)	1 (0–4)	1 (0–6)	0.50	Mann-Whitney
Previous cytotoxic regimens, median (range)	0 (0–1)	0 (0–3)	0.19	Mann-Whitney
Number of metastatic sites, median (range)	2 (0–5)	2 (0–6)	0.37	Mann-Whitney
Soft tissue metastases only, %	8	14	0.30	χ^2
Bone metastases only, %	12	10	1.0	χ^2
Viceral metastases, %	81	76	0.56	χ^2

Table 2

Treatment response

Response	Weekly		Monthly	
	n	(%)	n	(%)
Progression	29	(41)	14	(23)
No change	18	(25)	15	(25)
Partial response	20	(28)	21	(35)
Complete response	4	(6)	10	(17)

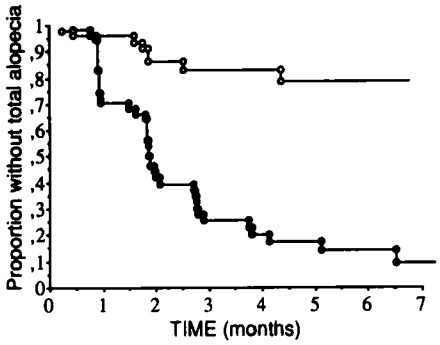

Fig. 1. Time to total alopecia by treatment group. $p < 0.0001$, Mantel-Cox. ● monthly treatment; ○ weekly treatment.

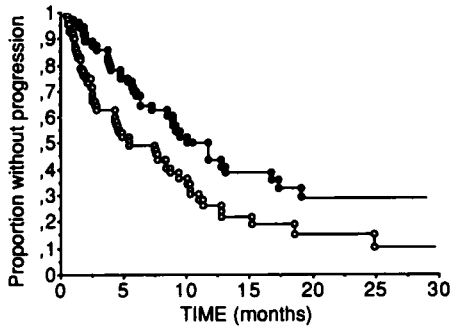

Fig. 2. Time to progression by treatment group. $p = 0.004$, Mantel-Cox. ● monthly treatment; ○ weekly treatment.

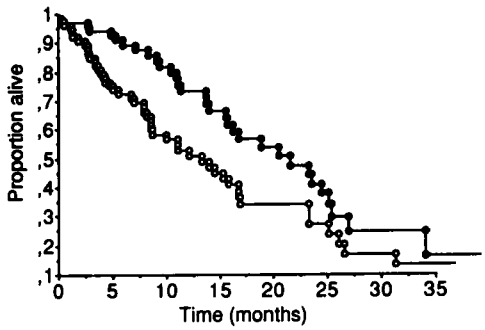

Fig. 3. Survival from randomization by treatment group. $p = 0.002$, Mantel-Cox. ● monthly treatment; ○ weekly treatment.

have shown that the doxorubicin-containing regimen gives about 15% higher response rate and 3 to 4 months' longer time to progression (25). Lately a derivative of doxorubicin, epirubicin, has been introduced, which has been associated with considerably less cardiotoxicity (23). In five randomized trials the efficacy of standard dosage FEC and FAC given in identical doses every third to fourth week has been the same, the response frequency to FEC varying between 44 and 57% (mean: 48%) (1–5).

In spite of the fact that doxorubicin-based chemotherapy has been widely used in breast cancer for several decades little is known of the optimal way of administering the drugs. Traditionally the drugs have been given as 2- or 3-drug combinations with bolus or short infusions once every three or four weeks. Weekly administration of single-drug doxorubicin has gained popularity during the last decade due to the favourable toxicity profile. In a Norwegian randomized trial comparing weekly doxorubicin with three-weekly VAC less alopecia, nausea and vomiting was

Table 3

Toxicity

Toxicity (%), WHO grade	G0	G1	G2	G3	G4	p-value Mann-Whitney
Hematologic, weekly	29	23	31	15	2	0.0001
Hematologic, monthly	8	19	27	41	5	
Nausea, weekly	15	36	39	10	0	0.006
Nausea, monthly	10	26	24	34	5	
Alopecia, weekly	29	40	17	14		0.0001
Alopecia, monthly	7	7	10	76		
Stomatitis, weekly	64	29	7			0.1
Stomatitis, monthly	48	43	9			

Table 4

Treatment response to weekly doxorubicin or epirubicin. Literature survey

Study	Ref.	Regimen	n	Response %
Castiglione et al.	(9)	A 20 mg/m^2		29
Scheithauer et al.	(18)	A 8–12 mg/m^2	17	12
Namer et al.	(16)	A 12 mg/m^2	42	42
Gundersen et al.	(14)	A 20 mg	62	31
Gundersen et al.	(15)	A 20 mg/m^2	81	36
Sigurdsson et al.	(20)	A 20 mg	48	19
Nylén et al.	(17)	A 15–20 g	50	14
Elomaa et al.	(11)	A 12 mg/m^2	47	23
Elomaa et al.	(11)	A 12 mg/m^2 + other CT	52	33
Creech et al.	(10)	A 20 mg/m^2	60	27
Frenay et al.	(12)	A 12 mg/m^2	84	32
Gasparini et al.	(13)	A 20 mg/m^2	21	38
Gasparini et al.	(13)	E 20 mg/m^2	22	36
Tucci et al.	(21)	E 15 mg/m^2	29	35
Beretta et al.	(8)	E 20–30 mg/m^2	29	29
Scheulen et al.	(19)	E 20 mg/m^2	44	18
Castiglione et al.	(9)	E 20 mg/m^2		20
Barni et al.	(6)	E 25 mg/m^2	21	47
Beex et al.	(7)	E 20 mg	33	15
Jones et al.	(26)	E 12 mg/m^2	42	43
Twelves et al.	(22)	E 25 mg/m^2	36	30

A: Doxorubicin (Adriamycin)
E: Epirubicin
CT: Chemotherapy

seen in the weekly arm. The response rate was comparable in the two study arms, but only 31 and 35%, which is lower than the response rate reported with FAC or FEC-combinations given three-weekly (14). Several uncontrolled studies of weekly doxorubicin or epirubicin have reported response rates between 12 and 47% with a mean of 29% (Table 4). Many of these studies included mainly previously treated patients, which tends to decrease the response rate.

Thus, there still remains some uncertainty of whether weekly single doxorubicin or epirubicin is as effective as three- or four-weekly administered 2- or 3-drug combinations. It has usually been assumed that the effectivity of anthracycline treatment is independent of the administration rate as long as drug concentration per unit time is unchanged. Toxicity, on the other hand, has been reported to be dependent also on peak drug concentration. This is almost certainly true for cardiac toxicity (24), and possibly also for other side-effects (23). The present trial was performed in order to study the effect of the schedule of FEC administered once every fourth week compared to weekly administration of the same drug in the same monthly dosage. Pretreatment characteristics were comparable in the two treatment groups. Although the disease-free interval was somewhat shorter in the monthly group, this adverse fact was counterbalanced by a somewhat more heavy previous treatment in the weekly group.

A special characteristic of this trial was the rather low median age (54 years) of the patients, and the high frequency of visceral metastases. The amount of delivered drug per time and the total treatment time was almost equal in the two treatment groups.

The toxicity profile was significantly more favourable with weekly than with monthly FEC. This was especially pronounced for the occurrence of alopecia and leukopenia, while the difference in nausea and vomiting was less pronounced although statistically significant. Thus it seems as a considerably part of the lower toxicity of weekly single doxorubicin or epirubicin is due to drug scheduling, not merely to the use of single-drug therapy instead of combination treatment.

The considerably lower efficacy of FEC when delivered in four-dose fractionations instead of one was surprising. We know of no other controlled trial reporting this striking effect of drug fractionation of epirubicin combination therapy on antineoplastic potency. At present it is unknown whether the loss of efficacy with drug fractionation is due only to some or all three drugs in combination. Although the 20% difference in response rate between the two study arms is only modestly statistically significant, several facts indicate that the difference may be true. Firstly, the response rate in the monthly arm is comparable to the response rate of FEC in other randomized studies (2–6) while the 20% lower response rate of weekly FEC is typical of the response rate with weekly epirubicin.

Secondly, the lower response rate in the weekly arm is accompanied by a statistically highly significant decrease in time to progression.

Although the effect of FEC or FAC scheduling alone on antineoplastic efficacy has not to our knowledge previously been tested in a controlled study, several findings from other studies may have a bearing on this question. A study of Ebbs et al. (27) utilizing long-term infusion of doxorubicin or epirubicin reported a very low response rate. A Norwegian study comparing weekly doxorubicin bolus with epirubicin in a 3-h infusion, reported a low response rate of only 22% in the infusion arm (15). However, three other randomized studies of various doxorubicin or epirubicin combinations in different schedules have not reported any evidence of diminished efficacy with more prolonged schedules (28–30). Although inconclusive, these studies in addition to the present one raise the question whether the antineoplastic efficacy of doxorubicin and epirubicin is related only to the amount of drug delivered by time unit or whether the peak drug levels have an effect on efficacy as well as on toxicity.

An unexpected finding was the increase in total survival in the monthly group. Although an impact of chemotherapy on survival in advanced breast cancer has only rarely been reported, this result is not totally unprecedented. One early study by Canellos et al. (31) reported significantly increased survival in patients treated with combination chemotherapy (CMF) compared to monotherapy with L-PAM. Lately a small study by Carmo-Pereira et al. (32) reported significantly longer survival in patients treated with epirubicin and cyclophosphamide in a higher dosage (response rate 58%) compared to a low-dose regimen (response rate 25%). In the latest report from the French Epirubicin Study Group a survival advantage of borderline statistical significance was found in favour of the more effective high-dose FEC compared to epirubicin monotherapy (3). The Danish breast cancer group has reported a longer survival of borderline significance associated with 18 months of FEC compared to 6 months of treatment (33).

Moreover, in an overview analysis of randomized chemotherapy trails in breast cancer A'Hern et al. (34) found a statisitcally significant association between response rate and survival. According to the regression equation proposed by A'Hern et al. the prolongation of median survival in the present trial should be about 3 months with the ratio of response rates given. In fact the difference was about twice as large. The explanation for this discrepancy is not obvious. One factor, however, which may be of importance is the predominance of visceral (potentially life-threatening) metastases in the patients of the present trial. In the study by Canellos et al (31) the survival advantage with the more effective regimen was most pronounced in patients with liver metastases. The statistical significance of the survival difference between our two treatment groups is not overwhelming, however, and therefore it cannot be totally excluded that it is due to chance. A definitive analysis of the trial, with longer follow-up, may possibly confirm or refute this finding.

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