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Decreased Efficacy of Cyclophosphamide, Epirubicin and 5-Fluorouracil in Metastatic Breast Cancer when Reducing Treatment Duration from 18 to 6 months

Bent Ejlertsen, Per Pfeiffer, Dorte Pedersen, Henning T. Mouridsen, Carsten Rose, Marie Overgaard, Erik Sandberg and Bent Kristensen

The impact of treatment duration on survival and progression-free survival is uncertain in metastatic breast cancer. In this trial 359 patients were randomised to receive cyclophosphamide, epirubicin and 5-fluorouracil (CEF) once every 3 weeks for a maximum of 18 months or identical chemotherapy for a maximum of 6 months. Following progressive disease (PD) or severe toxicity CEF was discontinued before the scheduled maximum duration. A second series of CEF continued for a maximum of 12 months was offered to patients with PD more than 3 weeks after completing a maximum of 6 months of CEF. Both groups received tamoxifen (30 mg daily) until PD, and premenopausal patients also received ovarian irradiation. After 6 months 254 evaluable patients were unprogressive. Survival and progression-free survival were significantly longer in 127 patients continuing CEF than in 127 patients interrupting CEF at 6 months ($\chi^2 = 17.6$, $P = 0.00003$ and $\chi^2 = 4.7$, $P = 0.03$, respectively). The results of the second series of CEF were discouraging with only one complete response in 44 evaluable patients. In conclusion, prolonged chemotherapy for 18 months is superior to identical chemotherapy for 6 months in the treatment of metastatic breast cancer.
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INTRODUCTION

METASTATIC ADENOCARCINOMA of the breast is associated with a poor prognosis, and only minor therapeutic advances have been made over the past two decades [1]. Definite cure is reported only sporadically [2] and despite the currently used therapy, the median survival from the first metastatic manifestation is between 1 and 2 years [3, 4]. The available cytotoxic and endocrine treatments have been introduced without clinical trials involving comparison with untreated control patients. Thus there is no well defined measure of a possible beneficial effect on survival. A reliable effect of chemotherapy is prolongation of progression-free time and tumour shrinkage [5, 6]. Side-effects may outbalance the palliative benefits of cytotoxic drugs. Reducing the duration of chemotherapy decreases the toxicity, but it is uncertain whether the efficacy is mediated by treatment duration. The present study was initiated to elucidate this question.

PATIENTS AND METHODS

Criteria of eligibility

Women with histologically verified adenocarcinoma of the breast were considered for the trial provided that they were less than 70 years of age, had progressive disease with measurable and/or evaluable lesions according to the UICC criteria [7], a performance status ≤3 [8], oestrogen receptor negative or unknown tumours, and white blood cell counts (WBC), platelet counts, serum calcium, and serum creatinine within the reference levels of each of the participating institutions.

Criteria of ineligibility

Patients who had received systemic adjuvant therapy within the previous 12 months or systemic therapy for locally recurrent or metastatic disease, or who had other prior or concomitant malignant disease with the exception adequately treated and cured *in situ* carcinoma of the uterine cervix and basal or squamous cell carcinoma of the skin.

Trial design

Verbal informed consent was obtained before initiation of treatment with prior registration and randomisation. Patients were stratified according to institution only. Eligible patients were randomly allocated to one of the two following treatment groups: (a) 24 cycles of cyclophosphamide, epirubicin, and 5-fluorouracil (CEF) for 18 months or until progressive disease (PD), or (b) eight cycles of CEF for 6 months or until PD, and resumption of CEF with 16 cycles for 12 months or until subsequent PD.

The therapeutic regimen

The therapeutic regimen consisted of cyclophosphamide 600 mg/m^2, epirubicin 60 mg/m^2, and 5-fluorouracil 600 mg/m^2 administered as intravenous (i.v.) bolus injections with repetition every 3 weeks. Epirubicin was replaced by methotrexate (40 mg/m^2 with reduction according to prior reduction of epirubicin) when a cumulative dose of 1000 mg epirubicin/m^2 had been administered or if symptoms of cardiac toxicity developed. In addition, all patients received tamoxifen 30 mg daily until PD, and premenopausal patients also received ovarian irradiation. Women were defined as being postmenopausal when menostasia has persisted for at least 5 years, or when hysterectomised women were older than 55 years.

Dose modification

The dose of CEF was adjusted according to platelet and WBC counts (× 10^9/l) on the scheduled day of treatment as follows: platelets ≥100 and WBC ≥3, 100%; platelets 75–99 or WBC 2.0–2.9, 50%. If platelets were <75 or WBC were <2.0, the treatment was delayed 1–2 weeks. The dose was escalated to 125% if platelets were ≥150 and WBC were ≥4.0 in three successive cycles.

Pretreatment and follow-up investigations

This included physical examination, chest X-ray, radiographic bone survey and/or bone scintigraphy, serum creatinine, calcium, alkaline phosphatase, transaminase and bilirubin. Positive bone scans were verified by radiography. Computer tomography scans or ultrasound scans of the liver or other regions in the case of suspicion of metastases. All tumour-positive examinations were repeated every 12 weeks.

Endpoints of the study

These were duration of survival and progression-free time (PFT). Responses were defined according to the UICC criteria [7]. Toxicities were graded according to the WHO criteria [8].

Ethics

The protocol and the procedures followed were according to the Helsinki Declaration of 1975, as revised in 1983 and were sanctioned by the regional and national Committee on Human Experimentation.

Statistical analyses

Breslow's generalised Wilcoxon test was used for comparison of the survival distributions [9]. Restriction was used with exclusion of patients with PD during the first 6 months of identical treatment. Reported P values are two-tailed. 95%-confidence intervals (CI) for medians, proportions and their differences were calculated according to Gardner and Altman [10]. Body surface area was estimated from height and weight according to Gehan [11]. For each drug the actual dose intensity was calculated as the total number of mg/m^2 administered over the eight cycles in each 6-month period divided by the number of weeks of the period.

RESULTS

From February 1986 to September 1989 five institutions entered 359 patients in this trial. 180 patients were randomised to a maximum of 18 months of CEF, and 179 patients to a first series of CEF for a maximum of 6 months. On revision 318 patients were evaluable (Table 1).

During the first 6 months both groups received identical treatments. The characteristics of the evaluable patients at randomisation and the characteristics of non-progressive patients at 6 months are given in Table 2. Recurrence-free interval, time from first recurrence until randomisation and dominant sites of metastases were evenly distributed.

Among the patients randomised to CEF for 18 months, the overall rate of complete responses (CR) was 22.3% (CI: 16–30) compared with 18.6% (CI: 13–26) among patients randomised

Table 1. Patients' details

	Duration of CEF		Total
	18 months	6 months	
Evaluable patients	157	161	318
Ineligible patients	22	15	37
Not accepting randomisation	7	4	11
Adjuvant treatment within 1 year	3	6	9
Previous systemic treatment	3	2	4
Performance 4 (WHO)	2	2	4
No evaluable lesions	7	1	8
Lost to follow-up	1	3	4
Randomised patients	180	179	359

Correspondence to B. Ejlertsen.
B. Ejlertsen, H.T Mouridsen and B. Kristensen are at the Department of Oncology 5-07-4, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, 2100 Copenhagen 0, Denmark; P. Pfeiffer and C. Rose are at the Department of Oncology, Odense University Hospital; D. Pederson and M. Overgaard are at the Department of Oncology, Aarhus Municipal Hospital, University of Århus; and E. Sandberg is at the Department of Oncology, Esbjerg Municipal Hospital, Denmark.
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Table 2. Patients' characteristics

	Evaluable patients at randomisation		Non-progressive at 6 months	
	Duration of CEF 18 months	6 months	Duration of CEF 18 months	6 months
Evaluable patients	157	161	127	127
Median age (years)	56	56	55	55
Performance (WHO)				
Grade 0	71	70	62	58
Grade 1	38	39	33	35
Grade 2	22	29	17	17
Grade 3	15	15	6	10
Unknown	11	8	9	7
Menopausal status				
Premenopausal	48	52	40	41
Postmenopausal	109	109	87	86
ER and PgR status				
Positive	10	14	7	11
Unknown	119	118	97	94
Negative	28	29	23	22
Sites				
Soft tissue	41	44	37	34
Lymph nodes	52	57	41	46
Lung	45	43	39	35
Bone	86	86	61	67
Liver	23	23	14	14
Other	4	4	4	4
RFI (months, median)	47	45	36	33
TFFR (months, median)	7	6	1	1

RFI = Recurrence free interval, TFFR = time from first recurrence, ER = oestrogen receptor, PgR = progesterone receptor.

to discontinuation of CEF at 6 months. The corresponding figures were 29.3 (CI: 22–37) vs. 32.9% (CI: 26–41) for partial responses (PR), 34.3 (CI: 27–42) vs. 34.2% (CI: 27–42) for no change (NC) and 14.0 (CI: 9–20) vs. 14.3% (CI: 9–21) for PD. In terms of CR rates the therapeutic gain of continuing CEF beyond 6 months is limited to a difference of 6% (CI: −7–20) [10].

Median survival times in all evaluable patients were 23 and 18 months in the two groups allocated to 18 and 6 months of CEF, respectively (Fig. 1). Following exclusion of patients with PD during the first 6 months of identical treatments (early failures), duration of survival in patients allocated to 18 months was significantly longer than in patients allocated to 6 months of CEF ($\chi^2 = 4.7$; $P = 0.03$).

Median PFT were 14 and 10 months in the groups allocated to 18 and 6 months of CEF, respectively (Fig. 2). PFT was significantly longer in the patients randomised to 18 months of CEF ($\chi^2 = 17.6$; $P = 0.00003$), following exclusion of early failures. PFT without chemotherapy was independent of the scheduled treatment duration (Fig. 3) and it was of short median duration (2–3 months).

During the first 6 months comparable drug doses were administered in the two treatment groups and during the two subsequent 6-month treatment periods the median drug doses were gradually decreased in the group allocated to 18 months of

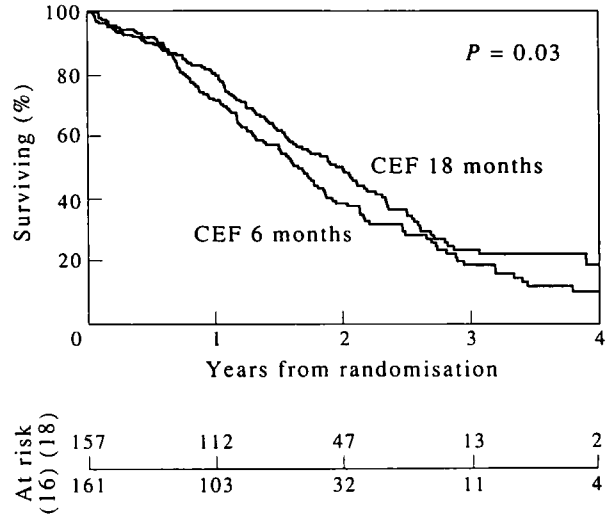

Fig. 1. Duration of survival for each duration of CEF. Number of patients at risk is given below the horizontal axis.

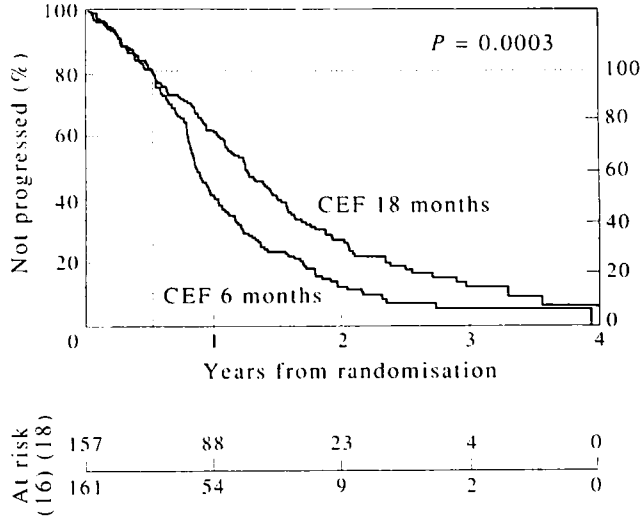

Fig. 2. Progression-free survival for each duration of CEF. The right vertical axis and the dotted line reflect the non-identical treatment periods. Number of patients at risk is given below the horizontal axis.

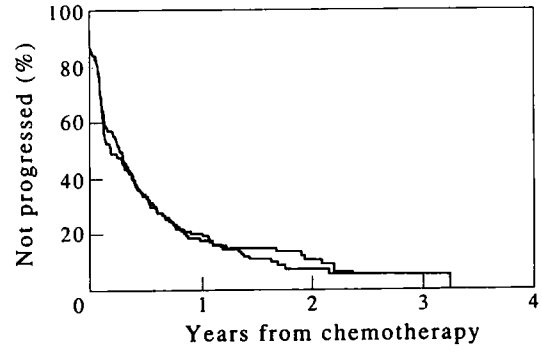

Fig. 3. Progression- and chemotherapy-free survival for each duration of CEF.

Table 3. Weekly administered drug doses

	Duration of CEF 18 months	6 months
0–6 months (cycles 1–8)		
Cyclophosphamide	176.0 (164–182)	179.6 (173–186)
Epirubicin	17.6 (17–18)	17.8 (17–19)
5-Fluorouracil	176.0 (164–182)	179.6 (173–186)
6–12 months (cycles 9–16)		
Cyclophosphamide	128.0 (116–152)	
Epirubicin	10.8 (17–12)	
5-Fluorouracil	128.0 (116–152)	
12–18 months (cycles 17–24)		
Cyclophosphamide	100.0 (66–155)	
Epirubicin	4.9 (3–8)	
5-Fluorouracil	100.0 (66–155)	

The observed dose intensity was calculated as the median mg/m^2 delivered weekly during eight cycles of CEF.

Table 4. Reasons for dose reduction

	Duration of CEF 18 months	6 months
Patients without reduction	76 (48%)	121 (75%)
Patient's request	15 (10%)	7 (4%)
Toxicities	47 (30%)	28 (17%)
Bone marrow suppression	13 (8%)	2 (1%)
Nausea and vomiting	3 (2%)	0
Stomatitis	1 (1%)	1 (1%)
Genitourinary	2 (1%)	2 (1%)
Cardiopulmonary		
Evaluable patients	157 (100%)	161 (100%)

CEF (Table 3). Only a few patients received more than one injection of methotrexate during the second 6-month period, and in the third period 15 patients received a median dose of methotrexate of 9.6 mg/m^2 (CI: 5–11). All patients were evaluated every 3 months, but only patients who completed each 6-month period without PD are included in the calculations. Reasons for chemotherapy dose reduction are summarised in Table 4, and the justifications for arresting chemotherapy are shown for each group in Table 5.

Patients allocated to 6 months of CEF were offered reinstitution of CEF for a maximum of 12 months in the case of PD. CEF was not resumed in 27 of the 72 patients eligible for a second series, and 89 patients were not eligible on account of the reasons listed in Table 6. During the second series of CEF 1 patient with soft tissue metastases only achieved CR, 2 patients PR, 21 patients NC, and 21 patients PD.

Table 5. Motivations for withdrawal of chemotherapy

	Duration of CEF 18 months	6 months
Scheduled duration	112 (71%)	115 (96%)
Patient's request	37 (23%)	5 (3%)
Toxicities		
Bone marrow suppression	0	0
Nausea and vomiting	3 (2%)	0
Stomatitis	1 (1%)	0
Genitourinary	0	1 (1%)
Cardiopulmonary	4 (3%)	0
Evaluable patients	157 (100%)	161 (100%)

DISCUSSION

In the present study reduction of the treatment period with CEF from 18 to 6 months was associated with diminished efficacy in terms of both duration of survival and PFT. With reduction of median survival from 23 to 18 months, and median PFT from 14 to 10 months without a corresponding reduction in time free from both progression and chemotherapy, the participating institutions will continue the treatment of advanced breast cancer for a maximum of 18 months or until either PD, or severe toxicity.

Randomised clinical trials comparing different durations of the same treatment are more complex than trials comparing different treatments. Several design elements, e.g. sample size, the experimental and control treatment duration, endpoints, and statistics are of great importance to the conclusions that might be drawn from the study. The analysis of the present study confirmed that the choices of treatment durations and simultaneous endocrine therapy in both groups were optimal. In agreement with our intentions the use of CEF for a maximum of 6 months produced a number of responding patients similar to the number achieved with CEF for a maximum of 18 months. Two possible sources of bias have arisen during the 12-month period with different treatments in the two groups.

First the weekly administered drug doses were reduced during the last 12 months in the 71% of unprogressive patients who completed the scheduled duration of CEF to a maximum of 18 months. Furthermore, 74 patients endured PD for more than 3 weeks after completing the scheduled 6 months of CEF but the second 12-month series was not initiated in 27 of these eligible patients. The main reason for both was the protocol item of stopping treatment whenever the patient or the attending physician judged that the toxicity might outbalance the benefits of continued treatment. The main goal of the treatment was palliation of tumour-induced symptoms and in our opinion it would be unethical to continue treatment in patients with severe toxicity. The two sources of bias have opposite directions and probably introduced only minor moderations of the treatment effect. In spite of the possible selection of good responders the results of the second series of CEF were dubious.

Table 6. Patients' details for a second series of CEF

Patients eligible for a second series of CEF	72
CEF restarted and at risk of PD	9
CEF restarted amd PD observed	38
Eligible but CEF not restarted	27
CEF interupted without PD	27
Patients not eligible for a second series of CEF	62
Death or PD during first CEF	36
Death less than 3 weeks after PD	15
Not evaluable	7
WHO performance 4	2
Low cardiac performance	2
Evaluable patients	161

The survival and PFT observed with 18 months of CEF are comparable with those observed in other trials. Early randomisation was used to ensure the generalisability of the trial. Only patients with PD during the non-identical treatment periods contribute with any knowledge. Exclusion of early failures increases the statistical power of the analysis, but may introduce bias [12]. In the present study, the equal numbers and course of events ratified that comparability of the two groups was maintained following the exclusion of patients with PD during the first 6 months of identical treatment.

Few studies have approached the question of duration of chemotherapy in metastatic breast cancer. The present study confirms the results of the Australian–New Zealand Breast Cancer Trials Groups [13] regarding time to treatment failure. They reported a difference in median PFT of only 2 months (6 months for continuous, 4 months for intermittent treatment), in a patient population where 56% received previous endocrine therapy for metastatic disease. The Australian–New Zealand Group randomised the patients to continuous treatment vs. three cycles of chemotherapy and resumption on PD. They did not obtain comparable response rates before discontinuation of the intermittent treatment, which introduced difficulties with interpretation of the results. In a British study, Harris *et al.* [14] found no significant differences in PFT comparing four courses of mitozantrone with continuous treatment. The analyses in the British study had, however, a low statistical power with logrank comparison based on 43 randomised patients.

Trials comparing different treatments for a duration of 6 months or less may not be able to detect even a major difference in survival. This must be considered in the interpretation of studies using short-term chemotherapy, where even highly aggressive chemotherapy regimens have failed to demonstrate any beneficial effects [15, 16].

In our study the continuation of chemotherapy was based on the judgment of both the patient and the attending physician and therefore the quality of survival was not recorded. The time free from both progression and chemotherapy was not significantly shorter in the group treated with CEF for a maximal duration of 6 months. In the Australian–New Zealand study the patients' qualty of life improved during chemotherapy. This necessitates implementation of quality of life in future studies.

In conclusion, in patients with metastatic breast cancer continued chemotherapy with CEF until PD or for a maximum of 18 months is superior to CEF until PD or for 6 months and resumption of CEF for 12 months in case of PD. Thus the efficacy of chemotherapy seems to be moderated through the duration of the treatment.

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