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Original Paper

Doxorubicin Versus Methotrexate Both Combined with Cyclophosphamide, 5-fluorouracil and Tamoxifen in Postmenopausal Patients with Advanced Breast Cancer—a Randomised Study with more than 10 Years Follow-up from the Danish Breast Cancer Cooperative Group

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To evaluate the substitution of methotrexate with doxorubicin (Dox) in CMF-(cyclophosphamide, methotrexate, 5-fluorouracil) containing regimen for advanced breast cancer, 415 postmenopausal patients below the age of 66 years, naïve to chemotherapy, were accrued from 1980 to 1984 and followed-up until 1995. They received tamoxifen 30 mg daily orally and by randomisation either 400 mg/m^2, cyclophosphamide, 25 mg/m^2 doxorubicin and 500 mg/m^2 5-fluorouracil (CAF) or 40 mg/m^2 methotrexate instead of Dox (CMF) intravenously (i.v.) days 1 + 8 repeated every 4 weeks. Dox was substituted by methotrexate at a cumulative dose of 550 mg/m^2. Among 341 eligible patients the response rate and median time to progression was significantly in favour of CAF: 53% CAF versus 36% CMF ($P = 0.002$) and 11.8 months CAF versus 6.5 months CMF ($P = 0.001$). Median duration of response was 19.5 CAF versus 18.0 CMF months, and survival 20.8 CAF versus 17.4 CMF months (non-significant). The two regimens were equimyelotoxic. There were no treatment-related fatalities but 1 patient with congestive heart failure on CAF was reported. Nausea/vomiting, stomatitis and infections were modest in both groups, whilst alopecia was more common with CAF. Regression analysis showed that long recurrence free interval, good performance status, and no visceral involvement was significantly related to long-term survival, whilst the treatment regimen was not. It is concluded that in chemotherapy-naïve patients with advanced breast cancer Dox-containing regimens are superior and remain the first choice of chemotherapy, especially in patients with visceral metastases, until newer drugs and combinations have been proven to be superior. © **1999 Elsevier Science Ltd. All rights reserved.**

Key words: breast-neoplasms, chemo-endocrine therapy, doxorubicin, methotrexate, cyclophosphamide, 5-fluorouracil, tamoxifen
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INTRODUCTION

FROM THE introduction of cytotoxic therapy in the treatment of solid tumours in the 1960s, it became obvious that disseminated breast cancer in comparison with many other types of cancer was responsive to such treatment. Accordingly, chemotherapy became the standard treatment even though no randomised comparisons between no treatment and chemotherapy were, in fact, performed. It was soon demonstrated that combination chemotherapy was superior to single agent treatment [1] and preferred combinations usually included drugs such as cyclophosphamide, methotrexate,

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5-fluorouracil (5-FU), vincristine, and prednisolone [2]. Later, however, it appeared that doxorubicin (Dox) was the most effective single agent in the treatment of advanced breast cancer [3] and a number of studies were conducted where Dox was compared with methotrexate combined with some or all of the above mentioned drugs.

Since the last century it had been recognised that a proportion of breast cancer cases is sensitive to endocrine manipulation [4], and in a randomised study it was shown that the addition of the anti-oestrogen tamoxifen (TAM) to CMF (cyclophosphamide, methotrexate, 5-FU) in the treatment of advanced breast cancer in postmenopausal patients was superior to CMF alone with regard to response [5].

In 1980 the Danish Breast Cancer Cooperative Group (DBCG) initiated a nationwide study comparing CMF with CAF (cyclophosphamide, doxorubicin, 5-FU) both with the addition of TAM in the treatment of postmenopausal patients with advanced breast cancer (Protocol DBCG 80R2). This is the largest study ever reported on comparing methotrexate with Dox in combination chemotherapy and the follow-up period is almost complete as 98% of the patients have died. Details have until now only appeared in abstract form [6, 7].

PATIENTS AND METHODS

Patients were considered for the trial provided they had locally advanced or metastatic histologically confirmed adenocarcinoma of the breast with measurable or evaluable lesions according to UICC criteria [8], postmenopausal status, age less than 66 years, WHO performance status of 0–3 [9], and normal serum creatinine. Exclusion criteria were cerebral metastases, present or previous congestive heart failure, other malignancies with the exception of adequately treated carcinoma *in situ* of the uterine cervix and non-melanoma skin cancer, ascites, pleural effusion or osteoblastic bone lesions as only manifestation of disease, prior cytotoxic treatment for recurrent disease, or first recurrence within one year after completed adjuvant treatment with tamoxifen.

Patients were randomised in the participating departments by a sealed envelope system to treatment with either 400 mg/m^2 cyclophosphamide, 40 mg/m^2 methotrexate, and 500 mg/m^2 5-FU; or 400 mg/m^2 cyclophosphamide, 25 mg/m^2 Dox, and 500 mg/m^2 5-FU (i.v. bolus injections on days 1 and 8). Cycles were repeated every 4 weeks and all patients in addition received TAM 10 mg three times daily orally. When a cumulative dose of Dox of 550 mg/m^2 was reached, it was substituted by 40 mg/m^2 methotrexate.

Chemotherapy doses were adjusted according to platelet and white blood cell counts (WBC) on day 1 as follows: platelets > 100 (10^9/L) and WBC > 4 (10^9/L): 100%; platelets 75–100 (10^9/L) or WBC 2.5–3.9 (10^9/L): 50%; platelets < 75 (10^9/L) or WBC < 2.5 (10^9/L): treatment postponement 14 days. For day 8, dose adjustment was as for day 1 except for treatment being given as a 25% dose if platelets were 50–74 (10^9/L) or WBC 1.0–2.4 (10^9/L). No chemotherapy was given if values were lower.

A minimum of three cycles were required for patients to be considered fully evaluable. In case of progressive disease (PD) at that time, the treatment was discontinued and further therapy was at the discretion of the physician. In all other cases treatment was to be continued until progressive disease or in case of complete remission (CR) for another 12 months.

Pretreatment and follow-up investigations included physical examination, chest X-ray, radiographic bone survey (or bone scintigraphy to be verified by X-ray if positive), serum creatinine, calcium, alkaline phosphatase, bilirubin and transaminases. Examinations were repeated every three months. If there were no bone lesions at entry, however, bone X-ray survey or scintigraphy were repeated only every 6 months.

Treatment response was evaluated according to UICC criteria (8). The endpoints of the study were the rate of response in evaluable patients, the duration of response (i.e. time from start of treatment to PD for responding patients (i.e. patients with CR or partial remission (PR)), and the time from start of treatment to progression (TTP) and survival (time from start of treatment to death) for all eligible patients and for all randomised patients. Toxicities were graded according to WHO [9] with the exception of alopecia and infections where a simplified grading was used.

The study was performed according to the Helsinki Declaration of 1975. All patients gave informed, oral consent. The Ethical Committee System was not yet established at that time.

In the statistical analysis, continuous variables were compared by the Mann–Whitney two-sample rank sum test. Categorical variables were compared by the chi-square or Fisher's exact test (2×2 tables). Survival distributions were analysed by Kaplan–Meier estimates and compared by log-rank tests. The importance of age, time from diagnosis of breast cancer to first recurrence, time from first recurrence to entry in protocol, performance status, visceral involvement, and treatment regimen on response (CR + PR versus NC + PD) was evaluated by multiple logistic regression [10]. The same variables' importance for TTP and survival was evaluated by univariate analyses and variables with a P-value less then 0.05 were included in a Cox proportional hazards model [11].

RESULTS

Eligibility

From April 1980 to August 1984, a total of 415 patients were randomised and treated at four institutions (Table 1; Figure 1). Patient and treatment characteristics were assessed by review of hospital records and X-rays through 1989, and patients were followed-up with regard to vital status up to 1995. The number of ineligible patients was relatively high ($n = 74$, 18%), and the distribution among the treatment arms not equal as 23% on CAF and 13% on CMF were ineligible ($P = 0.008$). No obvious explanation for this inequality was found. Among 341 eligible patients, 329 (79%) were evaluable for response. Evaluable patients included 33 patients with early death (before first evaluation) who in the analyses of response were rated as PD. 12 of these received CAF and 21 received CMF. Reasons for non-eligibility and non-evaluability are given in Table 1. Eligible patients were well balanced (Table 2) between the two treatment arms with regard to age, performance status and prior therapy. Previous adjuvant systemic treatment and treatment for recurrent disease were only used sporadically. Information on oestrogen receptor status was only infrequently available and was not analysed. 45% of patients in the CMF + TAM group had visceral involvement compared with 35% in the CAF + TAM arm (not statistically different). The median recurrence free interval was longer in the CMF + TAM arm, 25.5 months compared with 18.1 months in the CAF + TAM group, but this difference was also not significant (Table 2).

Table 1. *Eligibility of patient*

	CAF + TAM *n* (%)	CMF + TAM *n* (%)	All *n* (%)
Randomised	209 (100)	206 (100)	415 (100)
Ineligible	48 (23)	26 (13)	74 (18)
Premenopausal status	5	0	5
Age > 65 years	1	3	4
Performance status > 3	1	3	4
Cardiovascular disease	2	0	2
CNS metastases	1	1	2
Other malignancies	4	0	4
Previous chemotherapy	7	2	9
Progression on tamoxifen	16	12	28
No evaluable disease	11	5	16
Eligible	161 (77)	180 (87)	341 (82)
Treatment institution:			
Finsen Centre, Rigshospitalet University Hospital	84 (40)	94 (46)	178 (43)
Department Oncology, Herlev University Hospital	19 (9)	22 (11)	41 (10)
Department Oncology, Odense University Hospital	24 (11)	31 (15)	55 (13)
Department Oncology, Aarhus University Hospital	34 (16)	33 (16)	67 (16)
Non-evaluable	6 (3)	6 (3)	12 (3)
Protocol violation	4	2	6
Missing data, lost to follow-up	2	4	6
Evaluable	155 (74)	174 (84)	329 (79)

CAF, cyclophosphamide, doxorubicin, 5-fluorouracil, TAM, tamoxifen; CMF, cyclophosphamide, methotrexate, 5-fluorouracil.

Response

The overall objective response rate (Table 3) was highly significantly in favour of CAF + TAM, 53 versus 36% for eligible patients ($P = 0.002$). The rate of CR was 27 versus 16%, and the rate of PR 25 versus 20%. This difference was partially accomplished by a relatively high response rate for CAF-treated patients with visceral involvement, 55%, compared with 28% for CMF ($P = 0.002$) (Table 4). The isolated response rate in lungs was 66 versus 38% and in liver 50 versus 26%. Response rates for patients with soft tissue or bone as the dominant site did not differ significantly. Multiple logistic regression was performed for all eligible patients, for patients alive after 3 months and after 6 months both with continous and dichotomised variables, taking into consideration patients with locally advanced or metastatic disease at diagnosis. Consistently, only performance status and treatment regimen were demonstrated to be independent prognostic factors for response ($P < 0.05$).

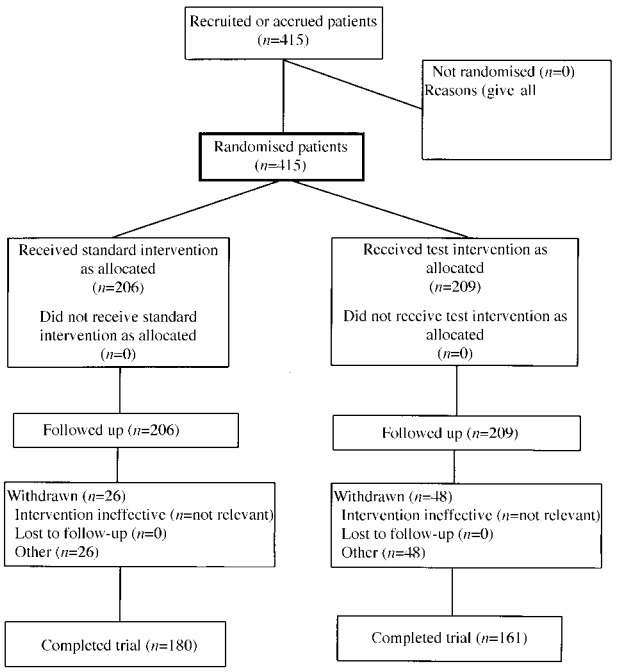

Figure 1. Flow chart of the progress of patients through the trial. (Adapted from Begg C, Vho M, Eastwood S, *et al.* Improving the quality of reporting of randomised controlled trials. The CONSORT statement. *JAMA* 1996, 276, 637–639.)

Time to progression

The median duration of response (time from start of treatment to progression in responding patients) for CAF-treated patients was 19.5 months compared in 18.0 months for CMF ($P = 0.2$) (Figure 2a). At the end of follow-up 1 patient in each group was still in remission after 14 and 15 years, respectively.

The median TTP for eligible patients was significantly longer for CAF, 11.8 versus 6.5 months, $P = 0.001$ (Figure 2b). All patients had recurrence/progression or died during the follow-up period except the two patients still in remission. Median TTP for all randomised patients (i.e. eligible as well as non-eligible patients where information on time of PD was available) was 12.7 versus 6.8 months, $P = 0.001$. Information on time of PD was not available for 15 patients on CAF and 8 on CMF. In the proportional hazards model performance status (0-1, unknown versus 2-3), dominant site of disease (soft tissue or bones versus viscera) as well as treatment (CAF + TAM versus CMF + TAM) were significant independent variables (Table 5).

Survival

The median survival for eligible patients was 20.8 CAF versus 17.4 CMF months. Figure 3 shows that the survival curve for CAF is consistently above the curve for CMF but

Table 2. Characteristics of 341 eligible patients

	CAF + TAM ($n = 161$) *n* (%)	CMF + TAM ($n = 180$) *n* (%)	*P*
Age at entry (median, range)	58 (45–65) years	58 (43–65) years	0.12
Time from breast cancer diagnosis to first recurrence	18.1 (0–189.0) months	25.5 (0–195.0) months	0.25
Months from first recurrence to entry	1.0 (0–132.6) months	0.9 (0–111.1) months	0.46
Previous Treatments			
Adjuvant			
Radiotherapy	91 (57)	106 (59)	0.74
Cyclophosphamide	5 (3)	9 (5)	0.55
Tamoxifen	8 (5)	11 (6)	0.97
Ovarian ablation	3 (2)	3 (2)	1.00
Treatment for recurrent disease			
Ovarian ablation	7 (4)	2 (1)	0.25
Other endocrine	3 (2)	2 (1)	0.90
Chemotherapy	0 (0)	0 (0)	
Performance status			
0	84 (52)	93 (52)	
1	45 (28)	57 (32)	
2	17 (11)	18 (10)	0.88
3	8 (5)	6 (3)	
Unknown	7 (4)	6 (3)	
Dominant site of disease			
Soft tissue	49 (30)	37 (21)	
Locally advanced	18 (11)	11 (6)	
Other soft tissue	31 (19)	26 (14)	
Bone	55 (34)	60 (33)	0.08
Viscera	57 (35)	81 (45)	
Lung	38 (24)	52 (29)	
Liver	16 (10)	22 (12)	
Lung + liver	3 (2)	6 (3)	
Ovaries	0 (0)	1 (1)	
Non-evaluable sites			
Pleural effusion	27 (17)	24 (13)	0.46
Bone marrow carcinosis	4 (2)	5 (3)	1.00
Ascites	4 (2)	5 (3)	1.00
Pulmonar carcinosis	6 (4)	5 (3)	0.85

CAF, cyclophosphamide, doxorubicin, 5-fluorouracil; TAM, tamoxifen; CMF, cyclophosphamide, methotrexate, 5-fluorouracil.

the difference was not statistically significant by log-rank test ($P = 0.17$). The median survival for all randomised patients was 21.1 for CAF versus 17.4 months for CMF ($P = 0.12$). In the survival model, performance status, dominant site of disease and length of recurrence free interval proved to be independant variables (Table 5). At the end of follow-up, 3 patients on CAF and 4 patients on CMF were still alive.

Table 3. Response to treatment in 341 eligible patients

	CAF + TAM *n* (%)	CMF + TAM *n* (%)	All *n* (%)
Eligible patients	161 (100)	180 (100)	341 (100)
Complete response (CR)	44 (27)	28 (16)	72 (21)
Partial response (PR)	41 (25)	36 (20)	77 (23)
No change	42 (26)	52 (29)	94 (28)
Progressive disease (PD)	28 (17)	58 (32)	86 (25)
Non-evaluable	6 (4)	6 (3)	12 (4)
Objective response (CR + PR)	85 (53%)	64 (36%)	149 (44%)

*$P = 0.002$, CAF + TAM versus CMF + TAM. CAF, cyclophosphamide, doxorubicin, 5-fluorouracil; TAM, tamoxifen; CMF, cyclophosphamide, methotrexate, 5-fluorouracil.

Chemotherapy cycles and dose intensity

The number of administered chemotherapy cycles is given in Table 6. The median number was 10 versus 6.5 cycles for CAF and CMF, respectively, reflecting the shorter time to progression for CMF. The reason for stopping chemotherapy was progression or death for all patients except 19 on CAF and 12 on CMF. The reasons in these cases were patient preference (7 CAF, 4 CMF patients), protocol violation or lost to follow-up (6 CAF, 6 CMF patients), and long-lasting remission or unknown reasons (6 CAF, 2 CMF patients). The median cumulative administered dose of Dox was 300 mg/m^2 (range 24–550).

The treatment intensity whilst on trial as estimated by the dose rate of cyclophosphamide was significantly higher for CMF although the absolute difference was not large (median 22.4 for CMP versus 20.3 mg m^2/day for CAF, $P = 0.042$). This difference was mainly due to a borderline significantly higher relative cumulative dose of cyclophosphamide (i.e. actually received cumulative amount of cyclophosphamide relative to the maximum dose provided no dose adjustments, CMF 68.9% versus CAF 63.8%; $P = 0.077$), whilst the median relative number of cycles (i.e. percentage of received number of chemotherapy cycles compared with the theoretical

maximum number while on study did not differ, CMF 95.4% versus CAF 95.7%, $P = 1.00$).

Toxicity. The haematological toxicity, however, was comparable in the two groups and relatively modest (median leucocyte nadir 2.8 versus 2.8×10^9/l, $P = 1.00$; median platelet nadir 147 versus 150×10^9/l, $P = 1.00$) indicating that the two regimens were equimyelotoxic. Non-haematological toxicities were also modest (Table 7). No life-threatening complications were reported. Treatment with Dox was discontinued prematurely in one patient who, at a cumulative dose of 346 mg/m^2, developed congestive heart failure. There were no major differences between the two regimens except that alopecia necessitating a wig was more common among patients treated with CAF.

At the time of PD further treatment was at the discretion of the treating physicians. From review of hospital records, it appears that 77 of the patients on CMF received anthracyclines or antracendiones as second- or third-line treatment.

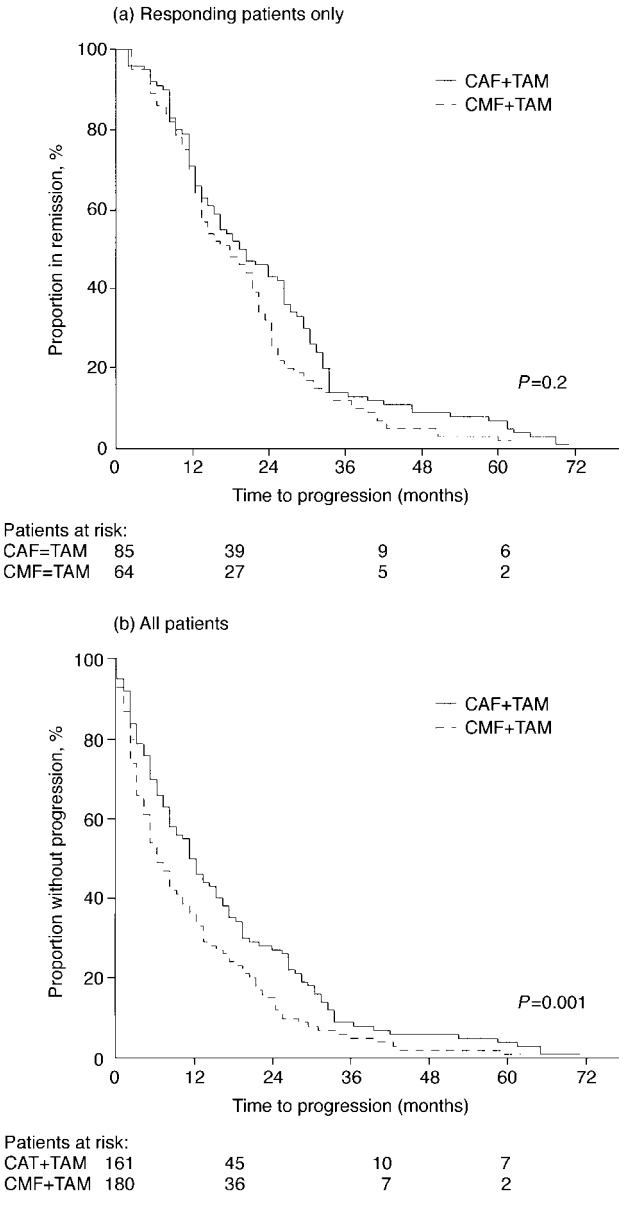

Figure 2. Time from start of treatment to progression for (a) responding patients and (b) all eligible patients. Kaplan–Meier estimates, log-rank test. CAF, cyclophosphamide, doxorubicin, 5-fluorouracil; TAM, tamoxifen; CMF, cyclophosphamide, methotrexate, 5-fluorouracil.

DISCUSSION

It is generally believed that metastatic or locally advanced breast cancer is incurable. Realistic treatment goals are, therefore, palliation of symptoms and discomfort, induced by the neoplastic process, whilst major prolongation of survival is rarely if ever reported.

The principal findings from the present study of postmenopausal patients naïve to chemotherapy are that the two similarly scheduled treatment regimens, CAF + TAM and CMF + TAM, in the administered doses were both relatively

Table 4. Response to treatment in 329 evaluable patients according to dominant site of disease

	CAF + TAM *n* (%)	CMF + TAM *n* (%)	All *n* (%)
Soft tissue, all patients	48 (100)	36 (100)	84 (100)
Complete response	29 (60)	13 (36)	42 (50)
Partial response	7 (15)	10 (28)	17 (20)
No change	7 (15)	8 (22)	15 (18)
Progressive disease	5 (10)	5 (14)	10 (12)
Objective response rate	36 (75)*	23 (64)	59 (70)
Bone, all patients	51 (100)	57 (100)	108 (100)
Complete response	5 (10)	7 (12)	12 (11)
Partial response	13 (25)	11 (19)	24 (22)
No change	18 (35)	19 (33)	37 (34)
Progressive disease	15 (29)	20 (35)	35 (32)
Objective response rate	18 (35)†	18 (32)	36 (33)
Viscera, all patients	56 (100)	81 (100)	137 (100)
Complete response	10 (18)	8 (10)	18 (13)
Partial response	21 (38)	15 (19)	36 (26)
No change	17 (30)	25 (31)	42 (31)
Progressive disease	8 (14)	33 (41)	41 (30)
Objective response rate	31 (55)‡	23 (28)	54 (39)

*$P = 0.389$. †$P = 0.916$. ‡$P = 0.002$. CAF + TAM versus CMF + TAM. CAF, cyclophosphamide, doxorubicin, 5-fluorouracil; TAM, tamoxifen; CMF, cyclophosphamide, methotrexate, 5-fluorouracil.

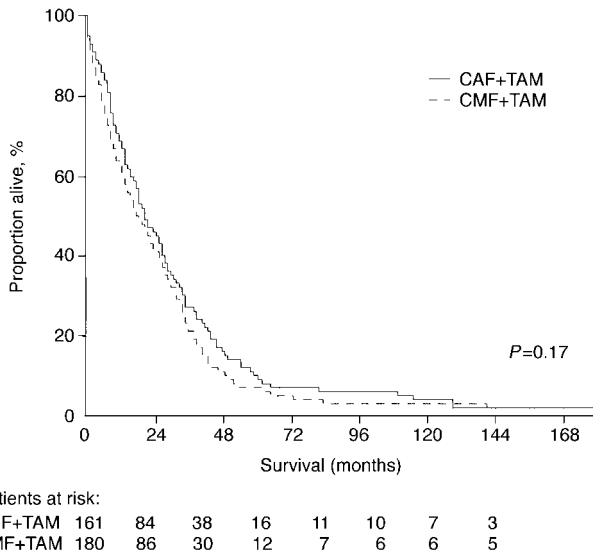

Figure 3. Survival from start of treatment for eligible patients. Kaplan–Meier estimates, log-rank test. CAF, cyclophosphamide, doxorubicin, 5-fluorouracil; TAM, tamoxifen; CMF, cyclophosphamide, methotrexale, 5-fluorouracil.

Table 5. Prognostic variables for time to progression and survival among 341 eligible patients. Univariate and multivariate analyses

		Time to progression			Survival		
		Univariate	Cox model		Univariate	Cox model	
	n	*P*	Hazard rate	*P*	*P*	Hazard rate	*P*
Performance status							
0-1, unknown	292	0.0001	2.4986	< 0.0001	< 0.0001	2.3445	< 0.0001
2-3	49						
Dominant site of disease							
Soft tissue, bones	201	0.0067	1.3697	0.0065	0.0002	1.6046	< 0.0001
Viscera	140						
Age at entry, years							
≤ 58.01	170	0.0838			0.1249		
≥ 58.02	171						
Recurrence free interval, days							
0-670	171	0.0604			0.0141	0.7508	0.0111
≥ 671	170						
Days from first recurrence to entry							
0-28	169	0.2154			0.1386		
≥ 29	172						
Treatment							
CAF + TAM	161	0.0011	1.4476	0.0012	0.1670		
CMF + TAM	180						

CAF, cyclophosphamide, doxorubicin, 5-fluorouracil; TAM, taxoxifen; CMF, cyclophosphamide, methotrexate, 5-fluorouracil.

atoxic as the reported side-effects were modest with no treatment-induced fatalities. Treatment intensity was almost identical and the doses given were equimyelotoxic but the treatment results, especially in patients with visceral dominant disease, in terms of rate of response (53 versus 36%) and median time to progression (11.8 versus 6.5 months) were significantly in favour of CAF + TAM. A similar but non-significant trend was observed for the duration of response and for overall survival.

Table 6. Numbers of administered chemotherapy cycles among eligible patients

	CAF + TAM (*n* = 161) *n* (%)	CMF + TAM (*n* = 180) *n* (%)
No. of cycles		
0–3	30 (19)	49 (27)
4–6	25 (16)	41 (23)
7–9	23 (14)	24 (13)
10–12	24 (15)	17 (9)
13–18	45 (28)	31 (17)
19 +	14 (9)	18 (10)

CAF, cyclophosphamide, doxorubicin, 5-fluorouracil; TAM, tamoxifen; CMF, cyclophosphamide, methotrexate, 5-fluorouracil.

The present study was large and randomised but the two treatment groups differed from each other in that the proportion of ineligible patients, in general high, was for unknown reasons significantly higher for CAF (23%) than for CMF (13%). Further, among eligible patients, the proportion with viscera as dominant site of disease was almost significantly higher for CMF than for CAF. These inequalities could be considered to influence treatment outcome. However, both in multiple logistic regression of response and in the proportional hazards model of time to progression, the treatment regimen proved to be an independant prognostic factor. Furthermore, in the univariate analysis of the time to progression for all randomised patients (eligible as well as ineligible) TTP was significantly longer for CAF.

The substitution of methotrexate by Dox in combination chemotherapy has been investigated in several other studies (Table 8) [12–19]. The treatment results both in terms of rate of response and time to progression but also for survival

Table 7. Non-haematological toxicity among eligible patients graded according to WHO or as indicated (number of patients shown)

	CAF + TAM 161 patients						CMF + TAM 180 patients					
	WHO grade						WHO grade					
	0	1	2	3	4	NR*	0	1	2	3	4	NR
Nausea/vomiting	8	34	86	25	0	8	15	47	81	25	0	12
Stomatitis	70	26	9	4	0	52	74	29	15	5	0	57
Urological	130	9	6	2	0	14	132	20	8	0	0	20
	0	1	2	NR			0	1	2	NR		
Infections†	122	29	4	6			135	26	7	12		
Alopecia‡	13	11	93	44			47	44	12	77		

*Not reported. †0, none; 1, trivial; 2, treatment for febrile neutropenia/septicaemia. ‡0, none; 1, slight; 2, severe necessitating a wig. WHO, World Health Organisation; CAF, cyclophosphamide, doxorubicin, 5-fluorouracil; TAM, tamoxifen; CMF, cyclophosphamide, methotrexate, 5-fluorouracil.

Table 8. *Randomised combination chemotherapy studies comparing doxorubicin with methotrexate. Data for evaluable patients in all trials but the present, where data for eligible patients were given*

Reference	Regimen	*N* of pts	Rate of response (%)	TTP (median, months)	Survival (median, months)
Muss [12]	CAFVP	76	58	NI	NI
	CMFVP*	72	57		
Bull [13]	CAF	38	82	10†	27
	CMF‡	40	62	6	17
Smalley [14]	CAF	135	55†	7†§	15†§
	CMFVP‖	130	40	5	12
Tormey [15]	CAFVP	107	71†	11†	19†
	CMFVP¶	109	50	8	14
Cummings [16]	CAF	79	53	8	19
	CMFP**	76	53	6	16
Parvinen [17]	CA	47	32	NI	NI
	CMFVP††	55	35		
Aisner [18]	CAF	82	55†	10†	26
	CMF#	99	37	6	16
Falkson [19]	CAF	38	82†	NI	21
	CMF§§	40	62		17
Present study	CAF + TAM	161	53†	12†	21
	CMF + TAM‖‖	180	36	7	17

*C: 2 mg/kg p.o. days 1–14, then 100 mg daily, F: 12 mg/kg i.v. days 1–3, then q 2 wk, V: 25 mg/kg i.v. day 1, then q 2 wk x 3, then q 4 wk, P: 0.75 mg/kg p.o. days 1–14, then 10 mg daily *plus either* A: 20 mg/m^2 i.v. day 1 q 2 wk *or* M: 0.2 mg/kg i.v. day 1 q 2 wk. †Difference between regimens significantly different at 0.05 level. ‡C: 100 mg/m^2 p.o. days 1–14 *plus either* A: 30 mg/m^2 and F: 500 mg/m^2 *or* M: 40 mg/m^2 and F: 600 mg/m^2 i.v. days 1 + 8, all q 4 wk. §Values estimated from figures. ‖C: 500 mg/m^2, A: 50 mg/m^2, F: 500 mg/m^2 all day 1 i.v. q 3 wk *or* C: 400 mg/m^2 day 1, M: 30 mg/m^2 days 1 + 8, F: 400 mg/m^2 days 1 + 8, V: 1 mg days 1 + 8, all i.v. q 4 wk, P 20 mg qid p.o. days 1–7. ¶P: 40 mg/m^2, C: 100 mg/m^2 p.o. days 1–14, F: 500 mg/m^2 i.v. days 1 + 8 *plus either* A: 25 mg/m^2 or M: 40 mg/m^2 i.v. days 1 + 8, all q 4 wk. **C: 100 mg/m^2 p.o. days 1–14 *plus either* A: 30 mg/m^2, F: 500 mg/m^2 i.v. days 1 + 8 or M: 40 mg/m^2, F: 600 mg/m^2 i.v. days 1 + 8, P: 40 mg/m^2 p.o. days 1–14, all q 4 wk. ††C: 200 mg/m^2 p.o. days 3–5, A: 40 mg/m^2 i.v. day 1, all q 3 wk *or* P: 60 mg, C: 150 mg p.o. days 1–14, M: 50 mg/m^2 i.v. day 1, F: 700 mg/m^2, V: 1 mg i.v. days 1 + 8, all q 4 wk. #C: 100 mg/m^2 p.o. days 1–14, F: 500 mg/m^2 i.v. days 1 + 8 *plus either* A: 25 mg/m^2 *or* M: 40 mg/m^2 i.v. days 1 + 8, all q 4 weeks. §§C: 100 mg/m^2 p.o. days 1–14 *plus either* A: 30 mg/m^2, F 500 mg/m^2 or M: 40 mg/m^2, F: 600 mg/m^2 i.v. days 1 + 8, all q 4 wk. ‖‖TAM 30 mg p.o. daily, c: 400 mg/m^2, F: 500 mg/m^2 i.v. days 1 + 8 *plus either* A: 25 mg/m^2 *or* M: 40 mg/m^2 i.v. days 1 + 8, all q 4 wk. p.o., oral; q, every; i.v., intravenous. TTP, time to progression; C, cyclophosphamide; A, doxorubicin; M, methotrexate; F, fluorouracil; V, vincristine; P, prednisolone; TAM, tamoxifen; NI, no information.

are surprisingly in accordance. In the largest studies [14, 15, present study] response rates for the Dox-containing regimen were 37–47% higher than the reference group, median time to progression 38–71% longer and the median survival 24–36% longer. In a statistical overview [20] of published summary results from five of the studies [13–16, 18], it was concluded that the inclusion of Dox significantly reduces both the hazard of treatment failure by 31% but also the hazard of dying by 22%, resulting in a significant increase in median survival of approximately 20% from 14–18 months. The results of the present series are similar to these observations.

The follow-up with regard to survival is almost complete in the present study as only 7 patients are still alive. This enables an analysis of long-term survivors. In this connection, information about the treatment received subsequent to the present trial is important. Unfortunately, this information is scarce, but there is evidence that most of the patients for whom chemotherapy was indicated after progression on CMF were in fact treated with anthracyclines or antracendiones as 77 patients among the 153 evaluable patients in the CMF-group did receive either Dox, epirubicin or mitoxantrone subsequent to progression on CMF. Information about therapy after the trials were usually not given in the other published studies, but it can be hypothesised that similar treatment principles were commonly applied. If this is the case, then the results in terms of survival may be interpreted as a comparison of Dox-containing combination chemotherapy as first-or second-line treatment. It seems as if Dox as first-line treatment imposes a certain, though not large, survival advantage.

In the present series, the factors significantly disposing to long-term survival were the classic ones: long recurrence-free interval, absence of visceral involvement and good performance status. The treatment arm was not significantly related to longer survival but a trend in favour of CAF was seen. In the only other study with a long follow-up, similar observations were made [19].

The introduction of CMF-containing combination chemotherapy for advanced breast cancer was not preceded by any controlled trials with comparisons with the standard treatments at that time. However, the inclusion of Dox in treatment has been investigated in several randomised studies which accrued patients in the 1970 and 1980s including the present one, which is the largest. It can be concluded that in patients naïve to chemotherapy, especially with visceral metastases, regimens containing Dox are superior to non-Dox containing combinations. Since then, efforts have been made to improve the treatment by varying the schedules, by introducing high-dose chemotherapy with haematopoietic support and by introducing new drugs alone or in combination. The most mature, promising results come from studies with taxanes and vinorelbine, but the superiority of such drugs and of high-dose chemotherapy as well, both with regard to classical endpoints such as rate of response, time to progression and survival, but also as concerns quality of life, has to be demonstrated in randomised comparisons, some of

which are ongoing [21]. Until then, in patients not treated adjuvantly with antracyclines, anthracycline-containing regimens should remain the first choice of treatment when chemotherapy is considered for advanced breast cancer outside the scope of controlled trials.

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