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COMBINED CYTOTOXIC AND ENDOCRINE THERAPY IN POSTMENOPAUSAL PATIENTS WITH ADVANCED BREAST CANCER

A RANDOMIZED EORTC STUDY OF CMF vs CMF + TAMOXIFEN

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Summary—Two hundred and sixty-three patients with advanced measurable breast cancer were randomized to receive cyclophosphamide, methotrexate and 5-fluorouracil (CMF) or CMF + tamoxifen (T). Each cycle of CMF (C, 100 mg/m² p.o. days 1–14, M, 40 mg/m² i.v. days 1 and 8, F, 600 mg/m² i.v. days 1 and 8) was repeated every 4 weeks. Tamoxifen, 20 mg twice daily, was given continuously. The treatment results as assessed by external reviewing were as follows in the CMF and CMF + T groups, respectively: PD 24 and 10%, NC 27 and 15%, PR 29 and 44%, CR 20 and 31%. The difference between response (CR + PR) rates is highly significant ($P = 0.0001$). Derived from life-table analysis, the median duration of remission was 12 months in the CMF-treated group and 18 months in patients treated with CMF + T ($P = 0.04$). Median duration of survival was 19 and 24 months, respectively ($P = 0.12$), but in the group of responders CMF + T was significantly superior to CMF (32 months vs 21 months, $P = 0.03$). The addition of T was of benefit to all subgroups but the difference only reached statistical significance in patients with the dominant site of disease in viscera, in patients with a Karnofsky index of 100 and in patients of more than 60 years of age. The amount of CMF given was identical in the two groups with a trend for a decrease in dose with increasing age. No relation between response rate and amount of dose given was observed. In conclusion, the addition of T to CMF improves the therapeutic results in patients with advanced breast cancer although the superiority of the combined treatment is statistically significant only in some subsets of patients.

INTRODUCTION

Cytotoxic and endocrine therapies play an important role in the management of advanced breast cancer. When used as first-line therapies remissions are achieved in approx. 60 and 30% of the patients, respectively.

While cytotoxic drugs affect all cells participating in the cell cycle, hormone therapy only affects the hormone-sensitive cells. Experimental and pathological data indicate that breast tumors are heterogeneous. This concept of tumor heterogeneity provides a rationale for combining endocrine and cytotoxic chemotherapy. Theoretically the different modes of action of endocrine therapy and cytotoxic drugs should lead to a higher rate of remission for the combined therapy. Furthermore, the two treatment modalities have different spectra of toxicity thus adding a clinical rationale for the combination.

The antiestrogen tamoxifen has become the most commonly used endocrine therapy in advanced breast cancer due to its few side effects and an overall response rate of 30–40% [1]. A large number of cytotoxic combinations, most of which include cyclophosphamide, metotrexate, 5-fluorouracil or adriamycin, have been used in advanced disease, leading to response in about 50–60% of the patients [2].

The present study was undertaken to compare in a randomized trial the combination of cyclophosphamide, methotrexate and 5-fluoruracil with the same combination plus tamoxifen with respect to rate and duration of response, toxicity and survival.

EXPERIMENTAL

The study includes patients admitted consecutively to the participating centers from March 1977 to March 1979.

Eligibility requirements for the study were as follows:

1. Histological evidence of breast cancer.
2. Postmenopausal status (at least 1 year after spontaneous or artificial menopause). The individual institutions were allowed to use either 68 or 75 years as the upper age limit.
3. Progressive disease with measurable and/or evaluable lesions according to UICC criteria [3].

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4. Karnofsky index $\geqslant 50$.
5. Normal hematological values and normal serum-creatinine and serum-calcium levels.

Criteria of ineligibility were as follows:

1. Previous treatment, adjuvant or for advanced disease, with the agents used in the study.
2. Treatment for the present disease by endocrine ablative procedures.
3. Less than 4 weeks of cessation of additive endocrine treatment. This delay must be increased accordingly for long-acting or depot hormones.
4. Previous or concomitant malignancies with the exception of excisional biopsy of *in situ* carcinoma of the cervix uteri and adequately treated basal or squamous cell carcinoma of the skin.
5. Sarcoma of the breast.
6. Patients in whom pleural effusion, ascites, metastases in the central nervous system or osteoblastic bone lesions are the sole manifestation of the disease.

Patients were stratified by institution and dominant site of the disease and were randomly allocated by the EORTC Data Center to one of the following two treatment groups: Group A, CMF (cyclophosphamide 100 mg/m^2 days 1–14 p.o., methotrexate 40 mg/m^2 days 1 and 8 i.v., 5-fluorouracil 600 mg/m^2 days 1 and 8 i.v., cycles repeated every 4 weeks) and Group B, CMF as in Group A plus tamoxifen (T), 20 mg twice daily.

The relative dose of CMF was adjusted according to platelet and white blood-cell counts as follows: platelets ($\times 10^3/\mu$l) > 100 and WBC ($\times 10^3/\mu$l) > 4; 100%, platelets > 100 and WBC 3–4; 50% of dose, platelets 50–100 and/or WBC 2–3; 25% of dose, platelets < 50 and/or WBC < 2; no drug.

If at the beginning of a 28-day cycle the platelet count was < 100 and/or WBC was < 4 the cycle was delayed 1 or 2 weeks.

Required pretreatment examination included physical examination, X-rays of chest, X-rays of bones or bone-scintigraphy, and clinical chemical studies (serum creatinine, serum calcium, serum alkaline phosphatase, serum transaminase, serum bilirubin).

Patients were assessed 8 weeks after initiation of therapy and thereafter at 1- to 3-month intervals. Assessment of response, response duration, time to treatment failure and survival duration was defined according to the UICC criteria [3]. Side effects were graded according to the WHO criteria [4].

All cases were reviewed by an extramural review committee, both for patient eligibility and for the response to treatment, except the patients from one center which entered a total of 131 evaluable patients. Among these patients, however, complete agreement between the local coordinator and the review committee was observed in a random sample of 20 patients who were reviewed.

At the time the study started hormone receptor studies were not done routinely in the participating centers and quality-control studies had not yet been established by the group. For this reason hormone receptors are not included in this presentation.

Two different χ^2-tests were used to compare the response rates. P gives the significance level based on a comparison of the percentage of responders (CR + PR) in the two treatment groups using the χ^2-test for the comparison of two proportions. P_T is the significance level resulting from a comparison of the degree of response, or equivalently the average response, using a χ^2-test for linear trends [5]. All P-values correspond to a two-tailed test.

Survival curves and time-to-progression curves were calculated according to the Kaplan–Meier product-limit procedure and compared using the log-rank test and the Breslow–Gehan test [6].

RESULTS

From 1977 to 1979 a total of 263 patients entered the trial, of whom 127 were randomized to CMF and 136 to CMF + T. This analyses is based on all data available as of June 1983.

As shown in Table 1, 220 were evaluable for response after 8 weeks of therapy. In 30 out of 43 patients who could not be evaluated for response the data were incomplete, either due to loss to follow-up or treatment refusal prior to the evaluation at 8 weeks, or because the data required for the evaluation were missing or incomplete. Another 7 patients were nonevaluable for response, 5 of which were removed from the study due to early death (< 8 weeks of treatment): 3 early deaths due to malignant disease on CMF, 1 early death due to malignant disease on CMF + T and 1 early death due to severe myelosuppression and septicemia on CMF + T One left the study due to toxicity (allergic reaction considered to be due to tamoxifen) and one was taken off study due to major protocol violations. Six patients, 3 in each group were ineligible: 1 due to renal dysfunction, 2 due to previous treatment with cyclophosphamide and 5-fluorouracil, 1 due to CNS metastases, 1 due to persistant leucopenia before start

Table 1. Patient material

	CMF	CMF + T	Total
Evaluable	105	115	220
Nonevaluable	19	18	37
Incomplete data[a]	16	14	30
Early death	3	2	5
Toxicity	0	1	1
Violation	0	1	1
Ineligible	3	3	6
Total	127	136	263

[a]Includes lost to follow-up or treatment refusal prior to the first evaluation.

Table 2. Patient characteristics

	CMF	CMF + T
Total number	105	115
Age		
≤54	21 (20%)	17 (15%)
55–59	26 (25%)	32 (29%)
60–64	47 (45%)	33 (29%)
≥65	11 (10%)	30 (27%)
Median	60	61
Range	46–75	47–75
DFI (months)		
none	7 (7%)	5 (5%)
1–12	13 (14%)	22 (22%)
13–120	67 (71%)	68 (68%)
>120	8 (8%)	5 (5%)
Median	32	30
Range	0–296	0–175
Karnofsky index		
<80	16 (18%)	13 (12%)
80	21 (23%)	25 (24%)
90	24 (27%)	31 (29%)
100	29 (32%)	37 (35%)
Median	88	90
Range	50–100	60–100
Dominant site		
Soft tissue	41 (39%)	45 (39%)
Bone	26 (25%)	29 (25%)
Viscera	38 (36%)	41 (36%)
Prior therapy		
Cytotoxic	4 (4%)	2 (2%)
Endocrine	3 (3%)	0 (0%)
Local X-ray	77 (73%)	87 (76%)

of treatment and 1 due to the presence of osteoblastic lesions only.

The characteristics of the 220 evaluable patients are given in Table 2. Except for the fact that there are more patients in the 65 years age and older age group on CMF + T, the two treatment groups are well-balanced with respect to the distribution of patient characteristics.

The treatment results in the 220 evaluable patients are shown in Table 3. Rate of response (PR + CR) was 49% in the group receiving CMF as compared to 75% in the group receiving CMF + T. This

Table 3. Response rates in 220 evaluable patients

	CMF		CMF + T	
Response	*N*	(%)	*N*	(%)
PD	25	(24)	12	(10)
NC	29	(27)	17	(15)
PR	30	(29)	50	(44)
CR	21	(20)	36	(31)
CR + PR	51	(49)	86	(75)
Total	105	(100)	115	(100)

$P = 0.001$, (χ^2-test for comparison of the percentage of responders).

difference is highly significant. This group of 220 evaluable patients is included in the following analyses.

The duration of remission by treatment group is presented in Fig. 1. The median duration of remission as measured from start of treatment is 12 months on CMF as compared to 18 months on CMF + T. The difference in the duration of remission is significant at $P = 0.04$ when using the Breslow–Gehan generalized Wilcoxon test and at $P = 0.09$ when applying the log–rank test.

Figure 2 gives the time to progression by treatment group for all evaluable patients. In the CMF group the median time to progression is 7 months as opposed to 14 months in the CMF + T group. The difference between the curves is highly significant.

Figure 3 presents the duration of survival in the 220 evaluable patients. The median duration of survival is 19 months on CMF and 24 months on CMF + T. This difference is not statistically significant. If one considers the duration of survival in the group of responders only, Fig. 4 shows that the duration of the survival is significantly longer on CMF + T than on CMF alone with a median duration of survival of 21 months on CMF and 32 months on CMF + T.

The cause of death was breast carcinoma in 92% of the cases with an equal distribution in the two

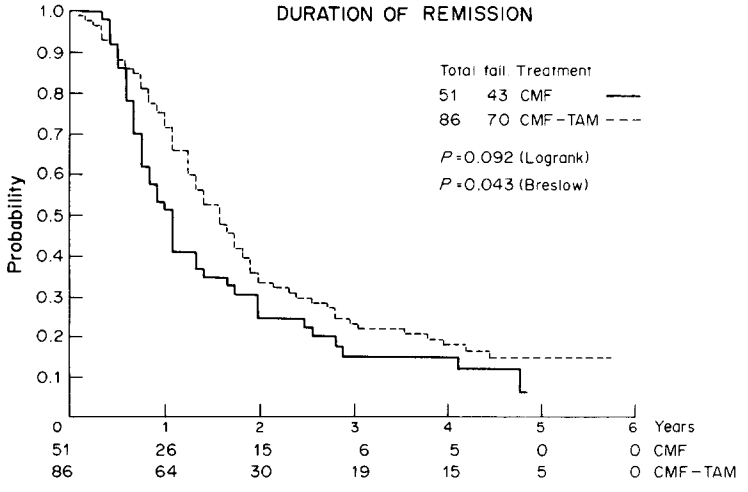

Fig. 1. CMF vs CMF + T. Duration of remission by treatment group.

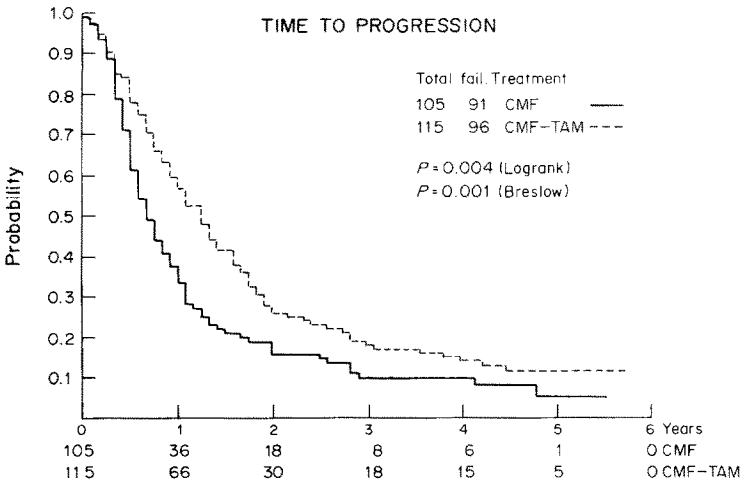

Fig. 2. CMF vs CMF + T. Time to progression by treatment group.

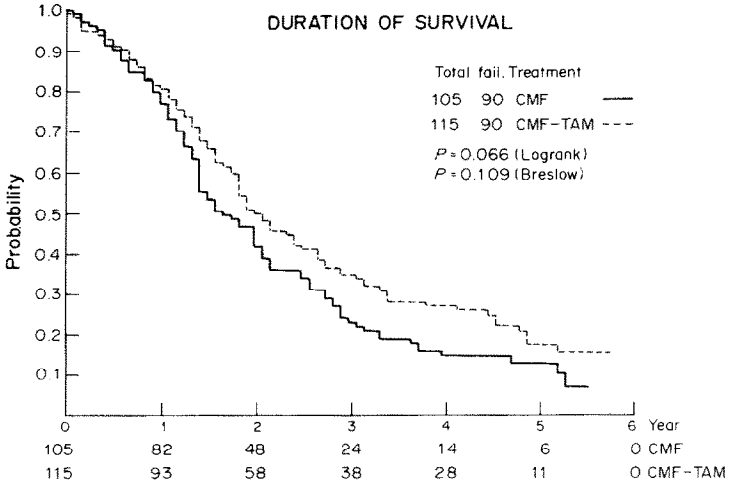

Fig. 3. CMF vs CMF + T. Duration of survival by treatment group.

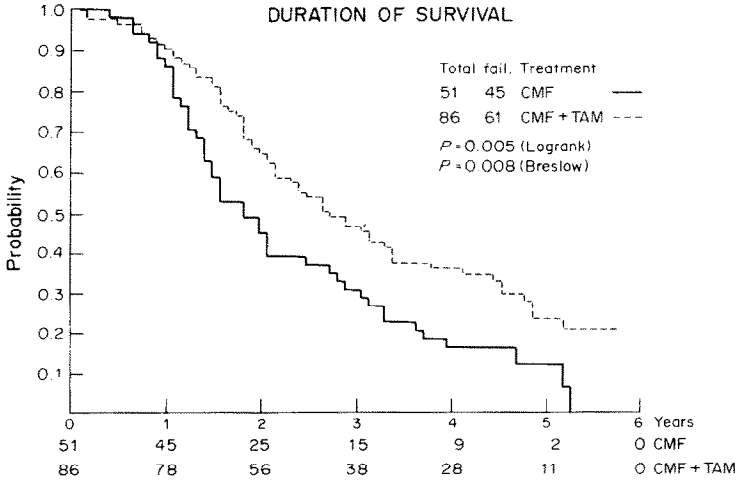

Fig. 4. Duration of survival in responders (PR + CR) by treatment group.

Table 4. Response by dominant site of disease and treatment

	Soft tissue		Bone		Viscera	
	CMF	CMF + T	CMF	CMF + T	CMF	CMF + T
PD	6	0	10	8	9	4
NC	10	12	6	2	13	3
PR	15	12	5	16	10	22
CR	10	21	5	3	6	12
CR + PR (%)	25 (61)	33 (73)	10 (38)	19 (66)	16 (42)	34 (83)
Total	41	45	26	29	38	41
P (χ^2, % responders):	0.32		0.08		0.0004	
P_T (χ^2 for trend):	0.02		0.32		0.002	

treatment groups. Three patients died due to treatment toxicity, 2 patients with infection, 1 after eight courses due to a bilateral pneumonia, (CMF) and another after only one course due to septicemia and severe myelosuppression (CMF + T). A third patient died after three courses of treatment due to bone marrow toxicity as manifested by infection and bleeding (CMF + T). Cardiovascular disease was reported as the cause of death in 4 patients, 3 in the CMF group and 1 in the CMF + T group.

In the following sections the treatment results in the 220 evaluable patients will be related to a number of prognostic factors.

Table 4 relates the response rate for each dominant site of disease to the treatment group. The addition of tamoxifen appears to be of therapeutic benefit in all three dominant disease sites. The largest difference occurred in patients with visceral involvement who achieved a 83% response rate on the combined treatment as compared to 42% on CMF alone.

The response rate according to the Karnofsky index and the treatment received is seen in Table 5. A higher response rate is achieved with CMF + T in each performance category and patients with a Karnofsky index of 100 who received CMF + T had a complete response rate of 47% and an overall response rate of 92%.

The response rate by age and treatment group is presented in Table 6. The response rate on CMF alone appears to decrease with increasing age but the response rate on CMF + T increases with age up to about 65 years. Thus while there is no apparent significant difference in overall response rate between CMF and CMF + T among patients less than 55 years of age, the difference is highly significant in patients over 60 years of age with an 85% response

Table 5. Response by Karnofsky index and treatment

	<90		90		100	
	CMF	CMF + T	CMF	CMF + T	CMF	CMF + T
PD	13	10	7	2	1	0
NC	8	4	7	8	10	3
PR	11	18	7	11	10	16
CR	5	6	3	10	8	18
CR + PR (%)	16 (43)	24 (63)	10 (42)	21 (68)	18 (62)	34 (92)
Total	37	38	24	31	29	37
P (χ^2, % responders):	0.13		0.10		0.008	
P_T (χ^2 for trend):	0.21		0.01		0.006	

Table 6. Response by age and treatment

	≤54 years		55–59 years		60–64 years		≥65 years	
	CMF	CMF + T	CMF	CMF + T	CMF	CMF + T	CMF	CMF + T
PD	3	4	4	1	12	2	6	5
NC	6	3	7	6	13	3	3	5
PR	8	4	9	15	12	16	1	13
CR	4	6	6	10	10	12	1	7
CR + PR (%)	12 (57)	10 (59)	15 (58)	25 (78)	22 (47)	28 (85)	2 (18)	20 (67)
Total	21	17	26	32	47	33	11	30
P (χ^2, % responders):	0.82		0.17		0.001		0.02	
P_T (χ^2 for trend):	0.80		0.09		0.002		0.008	

Table 7. Toxicities or side effects observed during treatment

Toxicity	CMF (120 patients)	CMF + T (125 patients)
Anorexia	66	72
Nausea	83	81
Vomiting	58	59
Alopecia	70	69
Weakness	38	44
Infection	17	28
Pain	20	27
Mucous membrane	28	37
Lung disfunction	9	15
Genito-urinary	5	10
Skin	7	13
Diarrhea	10	12
Bleeding	5	5
Dizziness	10	10

All values expressed as a percentage.

rate being found on CMF + T in patients 60–64 years of age. However, the rate of complete response appears to be consistently higher on CMF + T, independent of the patients age.

An analysis of the response rate by treatment and the number of years postmenopause provided similar results. The difference between the two treatment groups is the most significant in patients who are a minimum of 10 years postmenopause. The response rate on CMF decreases as the number of years postmenopause increases while the reverse appears to be true on CMF + T, at least up to 20 years postmenopause.

The amount of drug dose whether calculated per cycle or per unit time was identical in the two treatment groups, as described in detail elsewhere [8]. It was further evident that the more elderly patients received less drug per unit time but no statistically correlation was observed.

The toxicities observed during treatment are summarized in Table 7. Nearly all the side effects being recorded were mild or moderate and only 1–2% were graded severe or life threatening. It is evident from the table that the two treatments produced similar rates of toxicity.

DISCUSSION

Over the past few years a number of randomized trials have been published analyzing the efficacy of cytotoxic therapy alone vs the combination of cytotoxic and endocrine therapy with tamoxifen [7–10]. All these studies have obtained a higher response rate with the combined therapy as compared with the cytotoxic therapy alone. Three of the studies [8–10] present sufficient data on survival and in two of these [8, 9] a nonsignificant improvement in survival was achieved with the combination.

In agreement with these studies we observed a significant difference in response rate in the two groups, being 71% in the CMF + T group as compared to 49% in the CMF group. Time to progression was significantly longer in the CMF + T group (14 months) as compared to the CMF group (7 months), but as in the other studies [8, 9] the prolongation of survival with CMF + T was not statistically significant. It is noteworthy to mention that the rate of complete response was significantly increased with the combined therapy and that the duration of response (CR + PR) was significantly longer in the CMF + T group than in the CMF group.

The response rates were further analyzed in relation to a number of known prognostic factors. In all subgroups, CMF + T was superior to CMF alone but the difference only reached significance in patients with viscera as the dominant site of disease, in patients with a Karnofsky index of 100 and in patients more than 60 years of age. This age/response relation could not be correlated to the dose of drug given although it was obvious that the more elderly patients received less drug per unit time.

In conclusion the addition of T to CMF improves the therapeutic results in postmenopausal patients with advanced breast cancer, although the superiority of the combined treatment is statistically significant only in some subsets of patients.

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