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Combined Cytotoxic and Endocrine Therapy in Postmenopausal Patients with Advanced Breast Cancer. A Randomized Study of CMF vs CMF plus Tamoxifen*

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Abstract—*In this study* 263 *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 have been assessed by external review for the* 220 *evaluable patients and were the following for the CMF and CMF + T groups, respectively: PD:* 24 *and* 10%; *NC:* 27 *and* 15%; *PR:* 29 *and* 44%; *and CR:* 20 *and* 31%. *The difference between response (CR + PR) rates is highly significant* (P = 0.0001). *The median duration of remission was* 12 months *in the CMF-treated group and* 18 months *in patients treated with CMF + T* (P = 0.09). *The median duration of survival was* 19 months *and* 24 months *respectively* (P = 0.07). *However, in the group of responders patients receiving CMF + T survived significantly longer than those who received CMF alone* (32 months *vs* 21 months, P = 0.005). *The addition of T appeared to be of benefit in all subgroups. The largest differences were seen in patients with the dominant site of disease in the viscera, in patients with a Karnofsky index of* 100, *and in patients of more than* 60 yr *of age. The amount of CMF given was identical in the two treatment groups and there was a trend toward a decrease in dose with increasing age. No relationship between response and dose given was observed. In conclusion, the simultaneous use of T and CMF improves the therapeutic results in patients with advanced breast cancer.*

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INTRODUCTION

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

The anti-estrogen 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 30-45% [1, 2]. A large number of cytotoxic drug combinations, most of which include cyclophosphamide, methotrexate and either 5-fluorouracil or adriamycin, have also been used for treatment of advanced disease and objective remissions are seen in about 50-60% of the patients [3].

Experimental, histopathological and biochemical 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.

Goldie *et al.* [4] have analyzed the repetitive use of non-cross-resistant cytotoxic therapy by a mathematical model. Through development of this model they could substantiate the claim that use of concurrent cytotoxic and endocrine therapies achieved the greatest probability of cure when used as adjuvant therapy in the treatment of breast cancer [5]. Basic assumptions in this model are that cytotoxic and endocrine therapies act independently and that the two modalities are non-cross resistant. Rose and Mouridsen recently reviewed the clinical literature to analyze the validity of these assumptions [6]. Pooled clinical data show that the response to cytotoxic therapy is identical in estrogen receptor-positive (ER+) and -negative (ER-) patients, whereas response rates of 50% in ER+ and 10% in ER- patients following treatment with tamoxifen indicate that endocrine therapy is related to the receptor status. Moreover, cross-sensitivity and non-cross-resistance between sequential cytotoxic and endocrine therapy is only partial. From a clinical point of view, endocrine and cytotoxic therapies therefore appear to act independently and to be non-cross-resistant.

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

MATERIALS AND METHODS

Two hundred and sixty-three patients admitted consecutively to the participating centers from March 1977 to March 1979 entered this trial.

Criteria of eligibility: (1) histological evidence of breast cancer; (2) postmenopausal status which is defined as at least 1 yr after spontaneous or artificial menopause; (3) the individual institutions were allowed to use either 68 or 75 yr as upper age limit; (4) progressive disease with measurable and/or evaluable lesions according to UICC criteria [7]; (5) Karnofsky index ≥ 50; (6) normal hematological values and normal serum-creatinine and serum-calcium levels.

Criteria of ineligibility: (1) previous treatment with the agents used in the study either as an adjuvant or for advanced disease; (2) treatment for the present disease by endocrine ablative procedures; (3) less than 4 weeks of cessation of additive endocrine treatment. A longer delay was required when long acting or depot hormones had been used; (4) previous or concomitant malignancies with the exception of excisional biopsy of *in situ* carcinoma of the cervix uteri or 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 were the sole manifestation of the disease.

Trial design

Patients were stratified according to institution, age and dominant site of the disease and were randomly allocated by the EORTC Data Center to one of the following two treatment groups: CMF (cyclophosphamide, methotrexate and 5-fluorouracil) and CMF plus tamoxifen (T).

Therapeutic regimens

Cycles of CMF (cyclophosphamide 100 mg/m^2 p.o. days 1-14, methotrexate 40 mg/m^2 i.v. bolus days 1 + 8 and 5-fluorouracil 600 mg/m^2 i.v. bolus days 1 + 8) were repeated every 4 weeks. Tamoxifen was given continuously, 20 mg twice daily.

Dose modification

The relative dose of CMF was adjusted according to platelets and white blood cell counts (WBC) 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% dose; platelets 50-100 and/or WBC 2-3: 25% of dose; platelets < 50 and/or WBC < 2: 0%.

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

Treatment duration

It was aimed to give a minimum of 8 weeks of treatment which then was continued until progression of the disease. In the event of a complete remission that had lasted for 1 yr, therapy could be discontinued at the discretion of the individual investigator.

Pretreatment and follow-up investigations

Pretreatment examinations included physical examination, chest X-rays, bone X-rays or bone scintigraphy, and clinical chemical tests (serum-creatinine, serum-calcium, serum-alkaline phosphatase, serum-transaminase, serum-bilirubin).

At the time the study started, hormone receptor studies were not routinely performed in the

participating centers and quality control studies had not yet been established by the group. Hormone receptors are therefore not included in this presentation.

Definition of response

Patients were assessed 8 weeks after initiation of therapy and at 1- to 3-month intervals thereafter. Assessment of response, duration of response, time to treatment failure and duration of survival were defined according to the UICC criteria [7].

All cases were reviewed by an extramural review committee for both patient eligibility and for response to treatment. The only exception to this procedure was the 131 evaluable patients from a single center. In a random sample of 20 of these patients complete agreement between the local coordinator and the review committee was observed.

Definition of toxicity

Toxicities were graded according to WHO criteria [8].

Statistical techniques

Two different chi-square tests were used to compare the response rates. P_0 gives the significance level based on a comparison of the percentage of responders (CR + PR) in the two treatment groups using the chi-square test for the comparison of two proportions. P_1 is the significance level resulting from a comparison of the degree of response, or equivalently the average response, using a chi-square test for linear trend [9]. All P values correspond to a two-tailed test. The 95% confidence limits (95% C.L.) of the difference in response rates ($d \pm 2$ S.E.D. are given according to Wulff [10].

Survival curves and time to progression curves were calculated according to the Kaplan-Meier product-limit method, and were compared using the log-rank test and the Breslow-Gehan test [11].

RESULTS

From March 1977 to March 1979 a total of 10 institutions entered 263 patients in the trial, of whom 127 were randomized to CMF and 136 to CMF + T. This analysis is based on all data available as of June 1983.

As shown in Table 1, 220 patients were evaluable for response after 8 weeks of therapy. In 30 of the 43 patients who could not be evaluated for response the data were incomplete, either due to loss to follow-up, treatment refusal prior to the evaluation at 8 weeks or because the data required for the evaluation were missing or incomplete. Another seven patients were not evaluable for response, five of whom went off-study due to early death (<8 weeks of treatment), four of these dying of malignant disease. Three of these were on CMF and one was on CMF + T. The remaining patient was on CMF + T and died from severe myelosuppression and septicemia. One patient left the study after two courses of treatment because of toxicity (allergic reaction considered to be due to tamoxifen) and one was taken off-study due to major protocol violations. Six other patients, three in each group, were ineligible for the following reasons: Karnofsky <50: 1; previous treatment with cyclophosphamide and 5-fluorouracil: 2; CNS metastases: 1; persistant

Table 1. Patient material

	CMF	CMF + T	Total
Evaluable	105	115	220
Non-evaluable:	19	18	37
incomplete data*	16	14	30
early death	3	2	5
toxicity	0	1	1
violation	0	1	1
Ineligible	3	3	6
Total	127	136	263

*Includes lost to follow-up or treatment refusal prior to the first evaluation.

Table 2. Distribution of evaluable patients by institution and treatment

Institution	CMF	CMF + T	Total
Finsen Institute, Copenhagen	62	69	131
A.V. Leeuwenhoek, Amsterdam	19	22	41
R.R.T.I., Rotterdam	6	9	15
St. Radboud Zieken., Nijmegen	5	4	9
Inst. J. Bordet, Brussels	4	4	8
Olv. Gasthuis, Amsterdam	3	4	7
C.H. Tivoli, La Louvière	3	1	4
Univers. Klinik, Ulm	2	1	3
Hôp. D'Ixelles, Brussels	1	0	1
Binnengasthuis, Amsterdam	0	1	1
Total	105	115	220

leucopenia before start of treatment: 1; and presence of osteoblastic lesions only: 1.

The distribution of the 220 evaluable patients according to institution is given in Table 2 and the characteristics of these patients are given in Table 3. Except for the fact that there are more patients above 65 yr of age on CMF + T, the two treatment groups are well balanced with respect to the distribution of patient characteristics.

The overall response data in the 220 evaluable patients are shown in Table 4. The rate of response (CR + PR) was 49% in the group receiving CMF and 75% in the group receiving CMF + T($P = 0.0001$). Thus the difference in rates of response was 26%, with 95% confidence limits of 14 and 38%. Even if the 37 non-evaluable patients are included in the analysis as treatment failures, the rate of response is 41% in the patients treated with CMF as compared to 65% in the patients who received CMF + T, which is also significant ($P = 0.003$). In the following analyses only the 220 evaluable patients are included.

The duration of remission in each treatment group is presented in Fig. 1. The median duration of remission as measured from the beginning of the treatment was 12 months on CMF and 18 months on CMF + T. This difference in the duration of remission is significant at $P = 0.04$ when using the Breslow-Gehan test and $P = 0.09$ when applying the log-rank test.

Table 3. Patient characteristics

Total number	CMF ($n = 105$)	CMF + T ($n = 115$)
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		
<80	16 (18%)	13 (12%)
80	21 (23%)	25 (24%)
90	24 (27%)	31 (29%)
100	29 (32%)	37 (35%)
median	90	90
range	50-100	60-100
Dominant site		
soft tissue	41 (39%)	45 (39%)
bone	26 (25%)	26 (25%)
viscera	38 (36%)	41 (36%)
Prior therapy		
cytotoxic	4 (4%)	2 (2%)
endocrine	3 (3%)	0 (0%)
local RX	77 (73%)	87 (76%)

Table 4. Response in 220 evaluable patients

Response	CMF n (%)	CMF + T n (%)
PD*	25 (24)	12 (10)
NC†	69 (27)	17 (15)
PR‡	30 (29)	50 (44)
CR§	21 (20)	36 (31)
CR + PR	51 (49)	86 (75)
Total	105 (100)	115 (100)

$P_0 = 0.0001$ (χ^2, % responders); $P_1 = 0.0002$ (χ^2 for trend).
*Progressive disease.
†No change.
‡Partial response.
§Complete response.

Figure 2 gives the time to progression for all evaluable patients in each treatment group. In the CMF group the median time to progression is 7 months, as opposed to 14 months in the CMF + T group. This difference is significant at less than the 1% level.

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 ($P = 0.07$). However, if one considers the median duration of survival in the group of responders only, Fig. 4 shows that a significantly longer survival is seen on CMF + T than on CMF, with median values of 32 and 21 months respectively ($P = 0.005$). Approximately 40% of the responders in the combined treatment group are alive after 4 yr, which is in contrast to 20% in the CMF treated group.

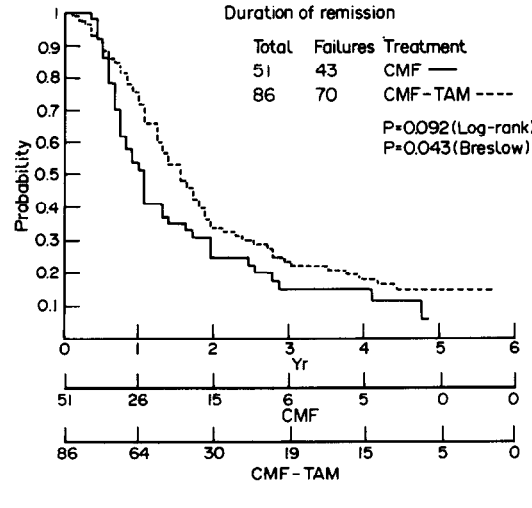

Fig. 1. CMF vs CMF + T. Duration of remission in each treatment group. No. of patients at risk is given below the abscissa.

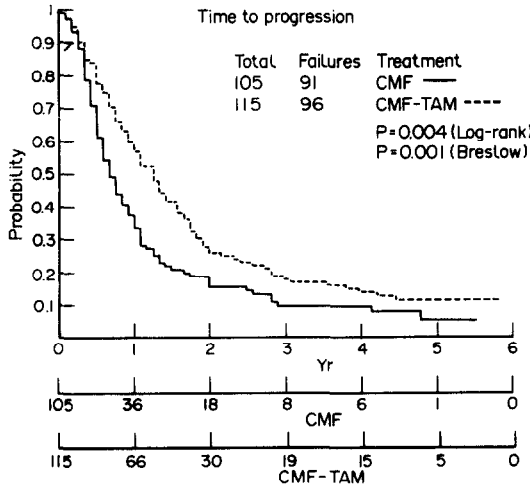

Fig. 2. CMF vs CMF + T. Time to progression in each treatment group. No. of patients at risk is given below the abscissa.

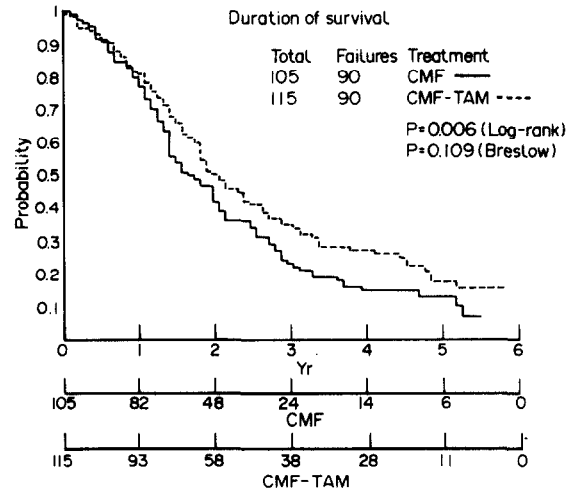

Fig. 3. CMF vs CMF + T. Duration of survival in each treatment group. No. of patients at risk is given below the abscissa.

The cause of death was breast carcinoma in 92% of the cases, with an equal distribution in the two treatment groups. Three patients died due to treatment toxicity, two of these with infection: one died after eight courses due to a bilateral pneumonia (CMF) and another died after only one course due to septicemia and severe myelosuppression (CMF + T). The third patient died after three courses of treatment due to bone marrow toxicity as manifested by infection and bleeding (CMF + T). Cardiovascular death was reported in four patients, three in the CMF group and one in the CMF + T group.

The patients response to treatment was further related to a number of prognostic factors.

Table 5 shows the response rates for each dominant site of the disease in the two treatment groups. The addition of tamoxifen appears to be of therapeutic benefit in all three sites of the dominant disease. The largest difference occurred in patients with visceral involvement, who achieved an 83% response rate on the combined treatment compared to 42% on CMF alone.

The response rates according to the Karnofsky index and the treatment received are given in Table 6. A higher response rate is achieved with CMF + T in each performance category, and it is also apparent that the response rates increase with increasing Karnofsky index.

The response rates for the different age and treatment groups are presented in Table 7. The response rate for CMF alone appears to decrease with increasing age whereas the response rate on CMF + T increases with age. While there is no apparent difference in the overall response rates between CMF and CMF + T among patients less than 55 yr of age, the difference is significant in patients over 60 yr of age, with an 85% response rate in patients 60-64 yr old treated with CMF + T. The rate of complete response appears to be consistently higher on CMF + T independently of the patient's age, but an analysis of the patient's disease-free interval demonstrated that this is of no prognostic significance.

Adjustment of the comparisons of treatment for dominant site, Karnofsky index and age did not change the overall conclusions.

The amounts of drugs administered in the two treatment groups are shown in Table 8. The percentage of drug dose received was calculated

Table 5. Response according to 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_0 (χ^2, % responders)	0.32		0.08		0.0004	
P_1 (χ^2 for trend)	0.02		0.32		0.002	

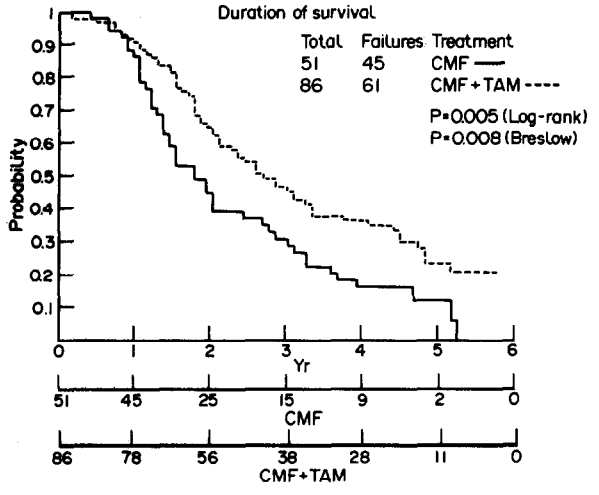

Fig. 4. CMF vs CMF + T. Duration of survival in responders (PR + CR) in each treatment group. No. of patients at risk are given below the abscissa.

for each patient by two different methods. In the first method the theoretical amount of drugs the patient should have received between the beginning and the end of treatment was calculated and compared to the actual amount received. Using this method, postponement of the treatment because of toxicity reduces the percentage of drug given. In the second method the theoretical amount of drugs the patient should have received was based only upon the number of treatment cycles the patient actually received. In this case postponement has no effect on the percentage of drug received. Analyzed by both methods, the amount of CMF received is identical in the two treatment groups as seen in Table 8.

The response rate was further analyzed both in relation to whether the drug dose received was 60% or more of the scheduled drug dose and for the patient's age. The results are given in Tables 9 and 10. While it appears that the more elderly patients receive less drug per unit time, no statistically significant correlation was observed.

The toxicities observed during treatment are summarized in Table 11. Nearly all the side-effects recorded were mild or moderate and only 1-2% were graded as severe or life-threatening. It is evident from the table, which includes all eligible patients ($n = 245$) for whom follow-up data are available, that the two treatments produced similar rates of toxicity. In addition to the three cases of toxic death and the one allergic reaction previously reported, four other patients went off-study due to bone marrow toxicity.

DISCUSSION

The addition of tamoxifen to CMF significantly increased the response rate from 49% in the CMF treated group to 75% in the CMF + T group. Time to progression was also significantly prolonged in patients receiving the combined treatment. The median duration of survival was 19 months in the

Table 6. Response according to Karnofsky index and treatment

	Karnofsky index					
	<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_0 (χ^2, % responders)	0.13		0.10		0.008	
P_1 (χ^2 for trend)	0.21		0.01		0.006	

Table 7. Response according to age and treatment

	Age (yr)							
	≤54		55-59		60-64		≥65	
	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_0 (χ^2, % responders)	0.82		0.17		0.001		0.02	
P_1 (χ^2 for trend)	0.80		0.09		0.002		0.008	

Table 8. Percentage drug dose given per unit time and per cycle in the CMF and CMF + T groups

Drug	Per unit time CMF (%)	Per unit time CMF + T (%)	Per cycle CMF (%)	Per cycle CMF + T (%)
C	53	52	59	59
M	55	53	61	59
F	57	55	64	62
CMF	55	53	62	60

Table 9. Relationship between patient age and percentage drug dose given per unit time; CMF patients only

Drug dose	<60 yr *n*	<60 yr (%)	≥60 yr *n*	≥60 yr (%)	Total
≤60%	24	56	32	70	56
>60%	19	44	14	30	33
Total	43	100	46	100	89*

*Missing information in 16 patients.
$P = 0.26$.

Table 10. Relationship between patient age and percentage drug dose given per cycle; CMF patients only

Drug dose	<60 yr *n*	<60 yr (%)	≥60 yr *n*	≥60 yr (%)	Total
≤60%	18	40	24	49	42
>60%	27	60	25	51	52
Total	45	100	49	100	94*

*Missing information in 11 patients.
$P = 0.50$.

Table 11. 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

CMF group as compared to 24 months in the CMF + T group. In those patients who responded to treatment, the median duration of survival was significantly increased from 21 to 32 months; and at 6 yr 20% of the responding patients treated with CMF + T were alive whereas all of those who responded to CMF had died after 5¼ yr.

CMF + T was superior to CMF in all subgroups of patients where the therapeutic results were analyzed. The difference in response to treatment was greatest in patients with viscera as the dominant site of disease, in those with a Karnofsky index of 100 and in those of more than 60 yr of age. The Karnofsky index was found to be the most important prognostic factor. In patients with the highest index the overall response rate of CMF + T was 92% and there were 42% complete responders.

As has been the case with other endocrine therapies, tamoxifen has been given in combination with cytotoxic therapy in simultaneous, sequential or alternating modes, and the results have been analyzed in several randomized trials. Simultaneous use of tamoxifen and non-adriamycin-containing regimens has been evaluated in three studies [12-14]. In two of these [13, 14] a higher rate of response was observed in the combined treatment group. The first trial [14] did not include data on duration of response, time to progression or survival. In the second trial [12] duration of response was significantly longer in the combined treatment group, but this difference did not lead to any difference in survival. In the third study Cocconi *et al.* [13] compared the same treatments as those in the present investigation and found that time to progression was significantly longer in patients receiving CMF + T. No difference in survival was observed. However, more than half of the patients who initially received CMF only were later treated with both CMF and tamoxifen. A direct comparison of the survival data is therefore difficult.

When tamoxifen is also part of an adriamycin-containing regimen [15-18], combined cytotoxic and endocrine therapy seems superior. The demonstrated differences in response rates are only significant, however, in two of the four studies [17, 18] and although the survival data are in favour of the combined therapy, the differences observed are not significant.

The question of sequential therapy with cytotoxic drugs and tamoxifen has been addressed in four trials [13, 19-21]. Glick and co-workers [21] found equal rates of remission of about 85% among 88 patients, all of whom were first treated with tamoxifen for 12 weeks, and thereafter randomized to continue either with tamoxifen alone or with a combination of tamoxifen and CMF. All patients had either estrogen receptor-

positive or estrogen receptor-unknown tumors, which explains the relatively high rate of response of 44% during the first 12 weeks of therapy. In a study by Bezwoda *et al.* [19], 52 receptor-positive patients were treated with either tamoxifen or tamoxifen plus CMF. The addition of cytotoxic therapy to tamoxifen treatment in this selected group of patients did not increase either the rate of remission or median time of survival above that obtained with tamoxifen alone. In a large trial performed by the Swiss Group [20], 297 patients were randomized to treatment with tamoxifen or to tamoxifen in combination with one of three different cytotoxic regimens depending on the cooperative group's own definition of the aggressiveness of the disease. The group of patients initially treated with tamoxifen alone was subsequently treated with cytotoxic therapy, and the cumulative response rate and the survival in these patients were similar to those observed with the combined therapy. Treatment was given irrespectively of estrogen receptor status; but even so, a remission rate of 17% in the patients first treated with tamoxifen alone is rather low and is difficult to interpret.

Alternating or repetitive use of cytotoxic and endocrine therapy has been proposed [22, 23] as an approach by which non-dividing cells could be recruited and thereby optimize the effect of the cytotoxic drugs. Lippman and co-workers [22] have tried to recruit cells into the S-phase by a short pulse of the estrogen premarin subsequent to treatment with tamoxifen on days 2-6. Cyclophosphamide and adriamycin are administered on day 1, and in order to exploit possible synchronization, 5-FU and methotrexate are given immediately following the premarin stimulation. The data from this trial reveal no differences in rate of response or time to progression. Survival was only extended in the group of responders treated with cytotoxic and endocrine therapy. In a phase II trial [24], 35 patients were treated with tamoxifen for 10 days followed by primarin for 4 days. Methotrexate and 5-FU were then given on day 14 in order to utilize the presumed cell cycle-specific effect of these two drugs. A remarkably high rate of remission of 69% was obtained by this rather non-toxic regimen. The EORTC Breast Cancer Cooperative Group is currently evaluating the same type of estrogen recruitment in a randomized trial based upon a phase II trial [25] where 55 patients were treated continuously with aminoglutethimide and hydrocortisone (plus oophorectomy in premenopausal patients) with courses of FAC given every 3 weeks. Each course was preceded by oral administration of ethinyl estradiol. A response rate of 71% has been achieved.

Lippman [26] recently questioned whether the simultaneous use of cytotoxic and endocrine therapies should be continued. Based upon figures of response rates to multiple drug cytotoxic therapy and endocrine therapy of 66 and 33% respectively, he concluded that little could be achieved by the combined therapy. However, figures of response rates for these therapies of 50 and 33% may be more realistic. If these figures are employed in an additive model, the response rate of combined therapy should theoretically increase from 51 to 67%. These figures are very close to those achieved both in the study by Cocconi *et al.* [13] and the present study, where the response rate increased from 49 to 75% when tamoxifen was added to CMF.

Thus the available clinical data concerning the simultaneous use of cytotoxic drugs and tamoxifen suggest that the effect is additive in terms of response rates whereas the data regarding survival is conflicting.

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