Chemohormonal Therapy in Advanced Carcinoma of the Breast: Cancer and Leukemia Group B Protocol 8081

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In a prospective, randomized trial Cancer and Leukemia Group B (CALGB) evaluated CAF chemotherapy (cyclophosphamide + doxorubicin + 5-fluorouracil [5-FU]) *v* CAF plus tamoxifen (TCAF) in advanced breast cancer. Patients were stratified by estrogen receptor (ER) status, dominant site of metastatic disease, menopausal status, and prior adjuvant therapy. Regardless of ER status or menopausal status, the addition of tamoxifen conferred no significant advantage in response rate, response duration, time to treatment failure (TTF) or survival over CAF alone. A secondary objective was to compare the response to CAF of ER positive (ER+) and ER negative (ER−) patients to determine if there was a differential response to cytotoxic chemotherapy. Response rates of ER+ and ER− patients to CAF were identical (56%), but the response duration, time to treatment failure, and survival of ER+ patients were significantly longer than ER− patients. This lack of differential response implies that chemotherapy and hormonal therapy may compete for the same pool of ER+ cells. It also suggests that chemotherapy kills breast cancer cells indiscriminately, regardless of ER status.

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AFTER AN INITIAL WAVE of success, the treatment of advanced breast cancer has plateaued. Combination chemotherapy is capable of inducing objective responses in 60% to 70% of cases, but only 10% to 15% of these are complete responses.[1] When seen, response durations are relatively short, in the range of 10 to 12 months. Hormonal therapy produces responses in 25% to 30% of unselected patients, with median response durations in the same range.[2] However, the frequency of hormonal responses can be increased significantly by selecting patients whose tumors contain specific cytosolic receptors for estrogen or progesterone or both.[3,4] Although complete responses can be seen with both forms of therapy, there are few cures of breast cancer once metastases have been demonstrated.[5,6]

If it were assumed that breast cancers are heterogeneous in terms of their estrogen receptor (ER) content, ie, composed of ER positive (ER+) and ER negative (ER−) cells in various proportions, then they may have a differential response to endocrine and cytotoxic chemotherapy. The differential responses of ER+ and ER− cells to hormonal therapy has been well documented.[7,8] However, it is not clear that there is a differential response of ER+ and ER− cells to cytotoxic chemotherapy.[9,10] Using a monoclonal antibody specific to human breast cancer ER, King et al documented tumor heterogeneity in terms of ER content.[11] Using a similar technique Nenci was able to demonstrate that breast tumors are rarely composed of homogeneous cell types, ie, almost all breast cancers are composed of mixed receptor-positive and receptor-negative cell populations in variable proportions.[12] Nenci also found that positivity of 20% of the cells was

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sufficient to give a positive ER by cytosolic assay.

The rationale for combining hormonal therapy with cytotoxic chemotherapy is based on the assumption that breast cancers are heterogeneous in terms of ER content, and that there is a differential responsiveness of ER + and ER − cells to hormonal and chemotherapy. It is also assumed that neither chemotherapy nor hormonal therapy will interfere with action of the other form of treatment so that the response rates for the combination will be at least additive, and not antagonistic.

With this theoretical background, Cancer and Leukemia Group B (CALGB) designed protocol 8081 to determine if the addition of a hormonally active agent (tamoxifen) would enhance the response rate, response duration, and survival of women with advanced breast cancer treated with combination chemotherapy. A previous CALGB study demonstrated that the combination of cyclophosphamide, doxorubicin (Adriamycin; Adria Laboratories, Columbus, OH), 5-fluorouracil (5-FU), vincristine, and prednisone (CAFVP) or CAF were each superior to the widely used combination of cyclophosphamide, methotrexate, and 5-FU (CMF).[13] The same study also confirmed that CAF was less toxic than CAFVP.[13] CAF was therefore selected as the chemotherapy for CALGB 8081. Tamoxifen was chosen as the hormonal agent because of its demonstrated efficacy in postmenopausal women with breast cancer and its relative lack of toxicity.[14,15]

Patients were prospectively randomized after stratification by ER content, menopausal status, dominant site of metastatic disease, and prior adjuvant chemotherapy. CALGB 8081 opened for patient entry on February 1, 1980 and closed on August 1, 1982. Preliminary data have been previously reported.[16] This constitutes the final report.

MATERIALS AND METHODS

Patient Eligibility

Eligibility requirements for this study included histologically documented carcinoma of the breast that was locally recurrent, metastatic or surgically incurable (stage III or IV); measurable disease; a CALGB performance score of 3 or less; and age < 75 years. Any radiation therapy must have been completed at least 3 weeks earlier. Patients had to have a WBC count of $>4{,}000/\mu L$, platelets $> 100{,}000/\mu L$, a blood urea nitrogen level of < 20 mg/dL, serum creatinine of < 1.5 mg/dL, and normal values for SGOT and bilirubin, unless abnormal values resulted from metastatic involvement. Informed consent was required.

Patients were ineligible if they did not satisfy all the above criteria or if they had a second primary neoplasm other than cured basal cell carcinoma of the skin or carcinoma in situ of the cervix. They were also excluded if they had medical or psychiatric disease that would not permit the patient to give informed consent or undergo therapy. A history of myocardial infarction within 6 months of protocol entry, congestive heart failure requiring digitalis, or angina were all causes for exclusion. Radiation therapy to 50% or more of the bony pelvis and lumbar spine or palliative radiotherapy to more than two sites of metastatic disease also rendered a patient ineligible. Patients who had received prior ajuvant chemotherapy were eligible if it had been discontinued for at least 6 months at the time of protocol entry. Patients who relapsed while receiving adjuvant therapy or who had been previously treated with chemotherapy or tamoxifen for metastatic disease were ineligible.

Stratification and Randomization

Patients were randomized from within 13 strata based on ER status (negative, positive, or unknown), dominant site of disease (visceral or nonvisceral), prior adjuvant chemotherapy or hormonal therapy, and menopausal status (pre- or postmenopausal) as follows: the postmenopausal patients were divided into 12 strata based on the other three factors, and the premenopausal patients were a single stratum (Table 1). Randomization was accomplished by a "sealed envelope method" using a Latin square design balancing within and across institutions and stratification factors.[17]

The protocol recommended the use of the dextran-coated charcoal ER assay. Using the data of Hilf et al, values of ≥ 7 fmol/mg/protein were considered positive, and < 7 fmol/mg/protein negative.[18] When no ER assay was performed, the patient was designated ER unknown. When feasible, the ER assay was performed on tissue obtained from a metastatic site at the time of protocol entry. If this were not possible, patients were stratified according to the ER determination made on the primary tumor. The ER assays were quality controlled using reference powders provided by James Witliff, PhD of the University of Louisville.

Patients were classified as having either visceral or other (osseous or soft tissue) dominant sites of disease on study entry.

Table 1. Stratifications

ER status	
ER −	< 7 fmol/mg protein
ER +	≥ 7 fmol/mg protein
ER unknown	Test not performed
Dominant site of metastatic disease	
Visceral	
Nonvisceral (osseous or soft tissue)	
Prior therapy	
No prior adjuvant chemotherapy or hormonal therapy	
Prior adjuvant chemotherapy and/or hormonal therapy	
Menopausal status	
Premenopausal	
Postmenopausal	

Visceral metastases included disease in the liver, pulmonary parenchyma or pleura, brain, or bone marrow. Osseous disease indicated metastases in bone. Soft tissue disease was defined as local recurrence in the skin or lymph nodes or inoperable (stage IV) breast cancer. When multiple sites were involved, visceral disease was dominant over others for classification purposes. Patients were considered naturally postmenopausal if at least 6 months had elapsed since the last menstrual period.

Treatment

After appropriate stratification, patients were randomized to receive either chemotherapy or chemotherapy plus tamoxifen (Fig 1). Chemotherapy was administered in 28-day cycles—a 14-day period of drug administration followed by a 14-day rest period. Patients received cyclophosphamide, 100 mg/m^2 orally for days 1 through 14 of each cycle, plus doxorubicin, 25 mg/m^2, and 5-FU, 500 mg/m^2 intravenously (IV) on days 1 and 8 of each cycle (CAF). Patients in regimen 1 also received tamoxifen, 10 mg, twice daily continuously (TCAF). Dose calculations were based on the patient's ideal body weight or actual weight, whichever was lower. After a total cumulative dose of 450 mg/m^2 of doxorubicin had been reached, methotrexate was substituted at a dose of 40 mg/m^2 (30 mg/m^2 for patients older than 60 years).

Dose modifications for cyclophosphamide, doxorubicin, and 5-FU were based on the total WBC count and platelet count on the day of treatment. Reductions were also made for elevations of serum bilirubin and SGOT and for the occurrence of stomatitis, diarrhea, or cystitis.

Ancillary Therapy

Palliative radiation was not permitted for patients on protocol, with the exception of cranial irradiation for documented intracranial metastases. Chemotherapy was not withheld when patients required such irradiation.

Response Criteria

A complete response (CR) required disappearance of all signs and symptoms attributable to the tumor, including the disappearance of all lesions for at least 1 month. No new lesions could appear. For bony disease, CR meant recalcification of all osteolytic lesions.

A partial response (PR) indicated a $>50\%$ reduction in the sum of the products of the two largest perpendicular diameters of all measured lesions without deterioration in performance. This had to last at least 1 month without the appearance of new lesions or the enlargement of existing ones. For bony metastases, a PR meant partial recalcification of osteolytic lesions without the development of new lesions.

Stable disease (stable) was a reduction in tumor size of $<50\%$ or an increase $<25\%$ over the original measurements. For bone lesions, this meant no change. In addition, no new lesions could appear.

Progressive disease (PD) indicated the appearance of new lesions subsequently proven to be metastases. If the sum of the products of the two largest perpendicular diameters increased by 25% over that obtained at the time of maximum regression, the patient was also considered to have progressive disease. Progression of osteolytic lesions or the appearance of new osteolytic lesions on x-ray also constituted progression of disease.

Patients were evaluated after two courses (8 weeks) of therapy. If progressive disease was evident, the patient was considered a treatment failure and taken off protocol. Responding patients and those with stable disease continued on therapy until there was evidence of tumor progression or prohibitive drug toxicity.

Statistical Methods

Differences in distributions of duration of response, time to treatment failure, and survival time were evaluated using a Cox proportional hazard multivariate model[19] or, univariately, the log rank test.[20] Differences in response frequencies and patient characteristics were evaluated using a multivariate linear logistic model,[21] or, univariately, the chi square test.[22] Medians and survival curves were estimated by the Kaplan-Meier method.[23] The term "statistically significant" refers to P values $<.05$.

RESULTS

A total of 474 patients were entered on CALGB protocol 8081 between February, 1,

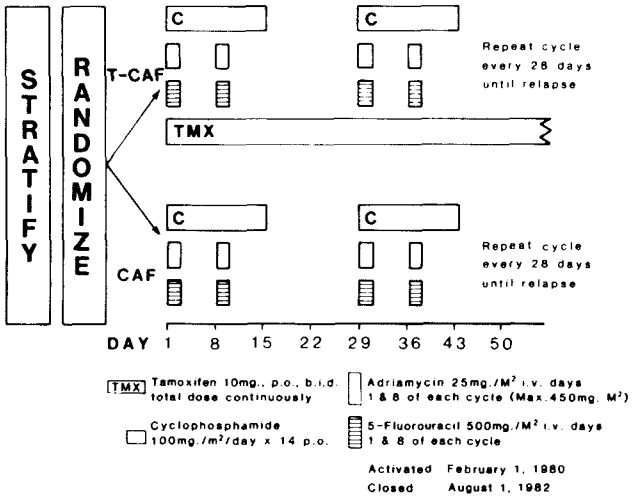


Fig 1. Schema of CALGB protocol 8081. A prospectively randomized study comparing the combination of hormonal therapy (tamoxifen) and chemotherapy (CAF) with chemotherapy alone for the treatment of advanced breast cancer in women. Patients were stratified by ER status, dominant site of metastatic disease, menopausal status, and prior adjuvant therapy.

Table 2. Patient Entries and Exclusions

	Total	Randomized Treatment	
		TCAF	CAF
Entered	474	238	236
Ineligible	11	6	5
Never treated	7	2	5
No data	5	5	—
Evaluable	451	225	226
Prior adjuvant chemotherapy*	46	21	25
Bone disease only, not measurable*	26	16	10
Cases analyzed	379	188	191

*These patients will be analyzed in a subsequent report.

1980 and August, 1, 1982 (Table 2). Originally, the protocol was open only to postmenopausal patients, but an addendum in April 1980 permitted the entry of premenopausal patients as well. Fewer than 5% (23) of the 474 patients were inevaluable: 11 were ineligible, seven were never treated on protocol, and five had incomplete data submitted, leaving 451 evaluable patients. Of the 451 evaluable cases, 46 had prior adjuvant chemotherapy (completed >6 months before protocol entry), and 26 had evaluable but nonmeasurable bone disease. The adjuvant group will be analyzed separately.

Comparability of Groups (Patient Characteristics): Measurable Disease

The treatment groups were comparable on all baseline characteristics (Table 3). Approximately three quarters of the patients on this study were postmenopausal, with a median age of 56 years. Nearly two thirds of the patients had visceral disease. Roughly one third of the patients were ER−, one third ER+, and one third ER unknown in each arm of the protocol. Seventy-seven percent of the patients on the CAF regimen and 75% of those on the TCAF regimen had a performance score of 0 or 1.

Comparability of Groups (Patient Characteristics): Nonmeasurable Disease

When compared with the 379 patients in the main analysis, the 26 patients with "bone-only" disease were more likely to have had prior radiotherapy (50% *v* 29%; $P = .03$, chi square test). They also had more pain at entry (20% pain-free *v* 46%; $P = .013$, chi square test) and were less likely to have visceral disease.

Table 3. Patient Characteristics at Entry by Treatment Regimen

	Randomized Treatment (%)	
	TCAF	CAF
No. of patients	188 (100)	191 (100)
Age (yr)		
<40	17 (9)	17 (9)
40-49	35 (19)	43 (23)
50-59	67 (36)	58 (30)
60-69	56 (30)	55 (29)
70+	13 (7)	18 (9)
Median	56	56
Range	26-76	28-75
Menopausal status		
Premenopausal	41 (22)	50 (26)
Perimenopausal	5 (3)	5 (3)
Postmenopausal	142 (76)	135 (71)
Natural	84 (45)	92 (48)
Surgical	40 (21)	32 (17)
Type unknown	18 (10)	12 (6)
Median age at menopause (yr)	48	49
Dominant site of metastases		
Visceral	120 (64)	122 (64)
Osseous	34 (18)	38 (20)
Soft tissue	34 (18)	31 (16)
Prior therapy		
Any hormonal	18 (10)	6 (3)
Any radiotherapy	56 (30)	55 (29)
Any immunotherapy	— (0)	1 (1)
ER status		
Negative	66 (35)	71 (37)
Borderline	3 (2)	1 (1)
Positive	64 (34)	61 (32)
Unknown	55 (29)	58 (30)
Performance status		
0, normal	77 (41)	83 (43)
1, ambulatory	63 (34)	65 (34)
2, <50% in bed	32 (17)	30 (16)
3, >50% in bed	9 (5)	8 (4)
Unknown	7 (4)	5 (3)
Median	1	1
Pain score		
None	94 (50)	82 (43)
Mild	46 (24)	48 (25)
Moderate	34 (18)	46 (24)
Severe	7 (4)	8 (4)
Unknown	7 (4)	7 (4)
Median	0	1

Response

Four patients were considered inevaluable for the response analysis due to error, inadequate records, or hip fracture. Among 375 patients, CRs were seen in 47 (25%) of patients treated with TCAF and 34 (18%) of patients treated with CAF (Table 4). This difference was not statistically significant ($P = .08$). PRs were seen in 71

Table 4. Best Response: All Cases

	TCAF (%)	CAF (%)
No. of patients	185	190
CR	47 (25)	34 (18)
PR	71 (38)	71 (37)
Stable	13 (19)	21 (27)
PD	19 (10)	20 (11)
Unevaluable	12 (6)	12 (7)
CR + PR	47 + 71/185 = 64% (TCAF)	
CR + PR	34 + 71/190 = 55% (CAF)	

(38%) TCAF patients and 71 (37%) patients on CAF. The difference between the total (CR and PR) response rates—TCAF, 64% *v* CAF, 55%—was also not statistically significant ($P = .09$).

The best response by selected patient characteristics is shown in Table 5. Univariately, there were no significant differences in response rates according to menopausal status or ER status. Patients with soft tissue disease had a higher response rate than those with visceral or osseous disease ($P = .05$), and patients with better performance status at entry had a higher response rate ($P = .02$).

Among postmenopausal patients, the response rates between TCAF (62%) and CAF (53%) were not significantly different ($P = .12$), nor was there a significant difference in response among ER+ patients to TCAF (67%) *v* CAF (56%); $P = .22$. However, among patients with soft tissue disease, TCAF produced a higher response rate than CAF (88%, 58%; $P = .009$). In a multivariate logistic model, only performance status was shown to be a significant prognostic factor for response. When treatment was added to the model, the P value was .15 for the significance of treatment regimen while controlling for performance status.

Table 5. Best Response by Selected Patient Characteristics

	Randomized Treatment: CR + PR/Total (%)			
	TCAF		CAF	
Menopausal status				
Pre-, perimenopausal	13 + 19/46	(70)	12 + 22/55	(62)
Postmenopausal	34 + 52/139	(62)	22 + 49/135	(53)
ER status				
Negative	19 + 25/71	(62)	9 + 33/75	(56)
Positive	15 + 26/61	(67)	15 + 17/57	(56)
Unknown	13 + 20/53	(62)	10 + 21/58	(53)
Dominant site of metastases				
Visceral	30 + 43/120	(61)	22 + 43/121	(54)
Osseous	4 + 13/33	(52)	2 + 20/38	(58)
Soft tissue	13 + 15/32	(88)	10 + 8/31	(58)
Performance status at entry				
0	24 + 26/75	(67)	22 + 33/83	(66)
1	16 + 25/62	(66)	9 + 25/64	(53)
2,3	6 + 17/41	(56)	3 + 13/38	(39)

Response rates (CR and PR) for bone-only patients were significantly lower than for other patients (35% *v* 59%; $P = .013$, chi square test). However, more of the bone-only patients achieved stable disease or subjective improvement, and none had progression as the best response. If the difficulty of assessing response for the bone-only patients was taken into account, then bone-only patients were equally responsive to therapy (Table 6).

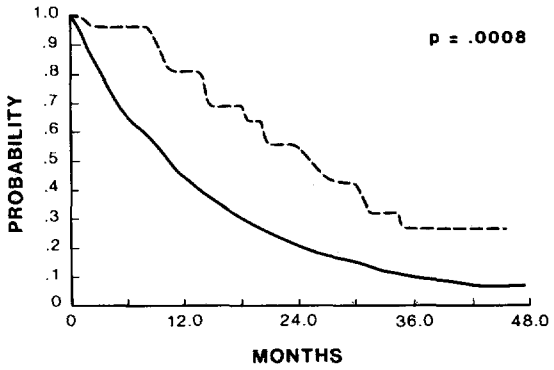
Time to treatment failure (TTF), survival, and duration of response were significantly longer for bone-only patients (Figs 2 and 3). No differences were found between the CAF and TCAF regimens, although the sample size was very small.

Duration of Response, Time to Treatment Failure, Survival

Duration of response was defined as the time from response to relapse, death, or the date the patient was last seen (if the patient was still responding). Similarly, TTF was the time from randomization to relapse, progression, or death (if the patient died without documented progression of disease) or the date last seen. Survival was measured from randomization to death or the date last seen.

Table 6. Best Response: Number (Percent) of Cases

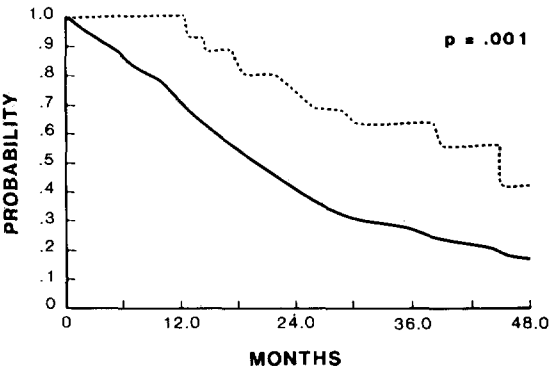
	Evaluable Bone Only	Other
CR + PR	9 (35)	223 (59)
CR	5 (19)	81 (22)
PR	4 (15)	142 (38)
Improvement	9 (35)	34 (9)
Stable	8 (31)	53 (14)
PD	—	39 (10)
Unevaluable		
Radiotherapy given	—	4 (1)
Other reason	—	22 (6)
Total	26	375



BONE EVAL ONLY?	CENSORED	FAILED	TOTAL	MEDIAN
— NO	67	358	425	10.6
--- YES	9	17	26	25.2

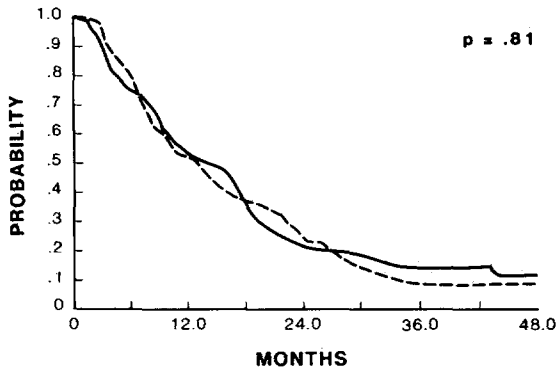
Fig 2. TTF—Bone evaluable only *v* others. Patients with nonmeasurable metastatic disease confined to bone have a significantly longer ($P = .0008$) TTF than those with metastases to other sites (viscera and soft tissue). TTF is a useful parameter in the evaluation of patients with nonmeasurable metastatic disease.

The median duration of response in this study was 12.0 months (Fig 4). The duration of response did not differ significantly between the TCAF and the CAF treatment programs. The median durations of response were 12.3 (TCAF) and 11.3 (CAF) months, respectively ($P = .81$). Univariately, regardless of treatment (TCAF *v* CAF), ER positivity was significantly related to the duration of response, with ER + and ER unknown patients responding longer than ER − patients (Fig 5). Median durations of response were 16.5, 15.8, and 8.5 months, respectively, with a P value of .004. There were no significant differences in durations of response according to dominant site of metastases or menopausal status. There was no significant difference in duration of response by treatment (TCAF *v* CAF) in ER + patients. Thus, the addition of tamoxifen failed to increase response duration of ER + patients treated with CAF chemotherapy. Response rate and response duration of ER − patients treated with CAF or TCAF were not significantly different, ie, there was no detrimental effect of tamoxifen in ER − patients.



BONE EVAL ONLY?	ALIVE	DEAD	TOTAL	MEDIAN
— NO	115	310	425	19.4
--- YES	15	11	26	44.5

Fig 3. Survival–bone evaluable only *v* others. Patients with metastases confined to bone have a significantly longer ($P = .001$) survival than those whose dominant site of metastatic disease is in other sites (visceral and soft tissue).

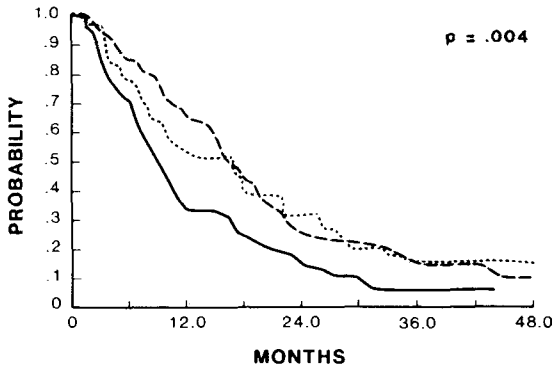


REGIMEN	CENSORED	FAILED	TOTAL	MEDIAN
— T CAF	22	96	118	12.3
--- CAF	21	84	105	11.3

Fig 4. Duration of response by treatment (TCAF *v* CAF). One hundred eighteen of 185 (64%) TCAF treated patients achieved a CR or PR as compared with 105 of 190 (55%) patients treated with CAF (see also Table 4). There was no significant difference in response duration by treatment ($P = .81$). Censored, failure-free at last follow-up.

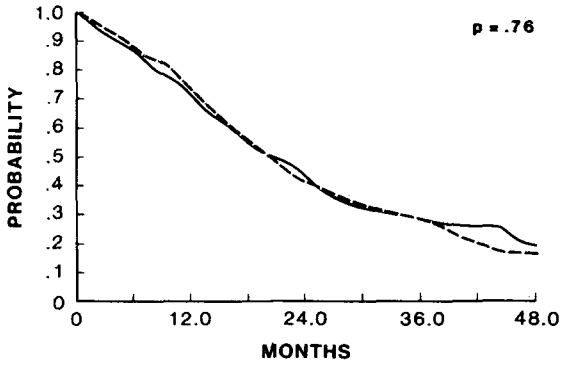
The overall median TTF was 10.6 months. TTF did not differ significantly between the two treatment groups, with medians of 11.4 and 9.5 months; $P = .25$.

Among ER + patients, TTF by treatment (TCAF *v* CAF) did not differ significantly ($P = .71$). In a multivariate Cox proportional hazards model, the following significant prognostic factors relating to TTF were identified: performance status (0 better than 1,2,3: $P = .02$), number of disease sites (one better



ER STATUS	CENSORED	FAILED	TOTAL	MEDIAN
— NEGATIVE	12	74	86	8.5
- - - POSITIVE	16	57	73	16.5
····· UNKNOWN	15	49	64	15.8

Fig 5. Duration of response by ER status regardless of treatment. Since there was no significant difference in response duration by treatment, TCAF and CAF treated cases were pooled and analyzed for response duration with ER being the only variable. ER+ cases, regardless of treatment, had a significantly longer duration of response than ER− with ER unknown falling in between: ER+, 16.5 months; ER−, 8.5 months; $P = .004$. Censored, failure-free at last follow-up.



REGIMEN	ALIVE	DEAD	TOTAL	MEDIAN
— TCAF	68	157	225	20.6
- - - CAF	62	164	226	19.9

Fig 6. Survival of patients by treatment (includes patients with only bone disease). Survival in the two treatment groups (TCAF *v* CAF) was identical.

than two or more; $P = .037$), and ER status (negative worse than positive or unknown; $P = .00006$). In a model that controlled for these factors, the P value for the comparison of treatment groups was .56.

The overall median survival was 19.6 months (Fig 6). Survival distributions did not differ significantly between the two treatment groups (medians, 20.6 and 19.9 months; $P = .76$). Two factors were prognostic for survival in a univariate analysis: dominant site of disease with visceral worse than osseous or soft tissue (medians, 18.3, 22.8, 22.0 months; $P = .05$), and ER status with negative worse than positive or unknown (medians, 15.8, 24.9, 23.1 months; $P < .0001$). There were no significant differences according to menopausal status ($P = .75$). Among ER+ patients, the treatments did not differ significantly ($P = .45$).

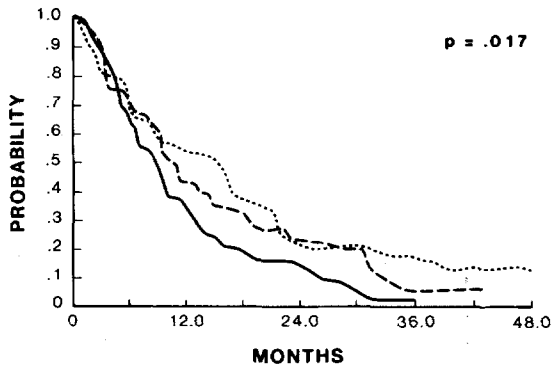
A secondary objective of this study was to evaluate prospectively the response of ER+ *v* ER− tumors to CAF chemotherapy. When the 190 evaluable patients receiving CAF were analyzed by ER status (Table 7), there was no significant difference in response rate between ER+ and ER− tumors (56%). However, TTF, response duration, and survival of ER+ patients were significantly longer than those of ER− patients ($P = .017$, .0074, and .0057, respectively) (Fig 7).

Toxicity

Toxicity data were available on 375 of 379 cases (98.9% of cases entered) and are displayed in Table 8. There were three early deaths and one patient had treatment withheld after a hip fracture. Both programs produced equivalent incidences of leukopenia, thrombocytopenia, nausea and vomiting, and infection. Tamoxifen appeared to add little in the way of toxicity to CAF. There were seven toxic deaths (1.8%), four on CAF and three on TCAF. All but one of these patients died of infection while neutropenic. The other lethal toxicity was congestive heart failure.

Table 7. Results of CAF-Treated Patients by ER Status

	Response Rate: CR+PR/Total (%)	Median (mo)		
		TTF	Response Duration	Survival
ER+	16+17/60 (55)	14.5	17.0	21.2
ER−	8+33/72 (57)	8.3	8.1	15.6
ER unknown	10+21/58 (53)	9.8	8.8	19.8
P value	.92	.017	.0074	.0057



ER STATUS	CENSORED	FAILED	TOTAL	MEDIAN
— NEGATIVE	5	67	72	8.3
- - - POSITIVE	13	48	61	14.5
····· UNKNOWN	10	48	58	9.8

Fig 7. TTF in CAF treated patients by ER status. ER+ patients have significantly longer time to treatment failure (19.1 months) than ER− patients ($P = .0015$). ER+ and ER− patients have identical response frequencies to CAF (56%). See also Table 6.

DISCUSSION

Our data demonstrate that there is no significant benefit to adding tamoxifen to CAF chemotherapy in the treatment of advanced breast cancer. The lack of advantage to the addition of tamoxifen was unanticipated. Tamoxifen did not enhance the response rate, response duration or survival in ER+ patients over CAF alone. Obviously, one or more of the initial assumptions on which the protocol was based was not correct.

Monoclonal antibody studies have demonstrated that breast cancers are heterogeneous in ER content; ie, breast cancers are composed of ER+ and ER− cells.[11,12] This assumption appears to be correct. Clearly, there is a differential response of ER+ *v* ER− cells to hormonal therapy with at least some ER+ cells responsive and ER− cells resistant. In terms of cytotoxic chemotherapy ER− cells are sensitive, but are they more or less sensitive than ER+ cells? Do cytotoxic chemotherapy and hormonal therapy compete for the same pool of ER+ cells?

The secondary question asked by this study was whether there is a differential response of ER+ *v* ER− tumors to chemotherapy. The retrospective data on this topic have been conflicting. Lippman et al retrospectively analyzed 70 patients with metastatic breast cancer treated with chemotherapy.[24] Objective responses were seen in 34 of 45 (75%) ER− (<10 fmol/mg) patients, but only three of 25 (12%) of ER+ (≥10 fmol/mg) cases responded ($P < .0001$).

Table 8. Toxicity*

	Treatment Received					
	TCAF (n=182) (%)			CAF (n=193) (%)		
	Severe	Life Threatening	Lethal	Severe	Life Threatening	Lethal
Leukopenia	23	13	—	23	10	—
Thrombocytopenia	9	3	—	8	2	—
Anemia	8	2	—	6	2	—
Neurological	1	—	—	1	—	—
Hepatic	1	—	—	1	—	—
Renal	1	—	—	—	—	—
Bladder	1	—	—	—	—	—
Oral	1	—	—	3	—	—
Gastrointestinal	12	—	—	8	1	—
Infection	13	—	1	5	2	2
Cardiac	2	—	1	1	—	—
Alopecia	9	—	—	6	—	—
Hot flashes	1	—	—	—	—	—
Thrombophlebitis, phlebitis	2	—	—	—	—	—
Allergy	1	—	—	—	—	—
Extravasation†	—	—	—	1	—	—
Ulcer	—	—	—	—	1	—

*Four patients were not evaluable for toxicity.
†Adriamycin.

Kiang et al reported just the opposite; 24 of 28 ER + patients (86%) responded to chemotherapy, but only 13 of 36 (36%) ER − patients responded ($P < .0001$).[25] Other retrospective reports have also yielded inconsistent data.[26,27] A retrospective review of ER and response among patients on a prior CALGB study failed to show any impact of ER on response frequency.[13] This study is the only prospectively randomized study analyzing the response of ER + *v* ER − patients to chemotherapy (Table 6). Our ER + and ER − cases had identical response rates (56%) to chemotherapy (CAF), but ER + patients had significantly longer response durations ($P = .00015$), TTF ($P = .0061$), and survival ($P = .0058$) than ER − patients (Fig 5).

Clearly, the assumption that there is a differential response of ER + *v* ER − patients to chemotherapy is not correct. Therefore, it appears that cytotoxic chemotherapy and hormonal therapy may compete for the same pool of ER + cells. A lack of differential response of ER + cells to chemotherapy may explain the lack of additive effect in ER + patients when chemotherapy and hormonal therapy are used concurrently.

The assumption that neither therapy will interfere with the action of the other may also not be valid. Osborne et al and Sutherland et al have demonstrated that tamoxifen arrests cells in G_0/G_1 phases of the cell cycle.[28,29] This arrest of cell division renders cells resistant to cycle-specific agents such as 5-FU and methotrexate, and less susceptible to other drugs such as doxorubicin and cyclophosphamide. Hug et al have confirmed that tamoxifen attenuates the cytotoxic potential of 5-FU and doxorubicin in human breast cancer cell lines.[30]

Combining chemotherapy with hormonal therapy is not a new idea; the first clinical trials were reported over 15 years ago. However, to date, there have been no convincing data that the addition of hormonal therapy has enhanced the response rate, response duration, or survival over chemotherapy alone. The postoophorectomy studies of VanDyke and Falkson did show an enhanced response rate to combination treatment, but response rates were not greater than that reported for chemotherapy alone.[31] The Cooperative Breast Cancer Group was unable to demonstrate benefit from the addition of androgens to 5-FU.[32] The use of short-term cyclophosphamide with estrogen also did not prolong response duration or survival.[33]

More recent trials such as that reported by Cocconi et al and Viladiu et al seemed to show some benefit in response rate to combined chemohormonal therapy, but in neither trial was a survival advantage confirmed.[34,35] Cocconi et al evaluated CMF (cyclophosphamide + methotrexate + 5-FU) with or without tamoxifen. Viladiu et al evaluated CMF *v* CMF + tamoxifen *v* CMF + medroxyprogesterone acetate. Neither of these trials stratified patients by receptor status. Krook et al were unable to demonstrate that the addition of tamoxifen to CFP (cyclophosphamide + 5-FU + prednisone) improved time to disease progression or survival over treatment with CFP alone.[36]

There have been three clinical trials reported of chemohormonal therapy in which the patients have been stratified by ER status.[37-39] However, each of these trials was designed to evaluate hormonal therapy with or without chemotherapy, rather than chemotherapy with or without hormonal therapy. In the first of these trials, Glick et al randomized 89 ER + or ER? postmenopausal women to tamoxifen with CMF or to tamoxifen (with CMF on progression), and were unable to document benefit of the combined therapy over tamoxifen alone.[27] Bezwoda et al randomized 52 ER + patients to tamoxifen ± CMF and were also unable to confirm a benefit of combined therapy over tamoxifen alone.[38] Lastly, Kiang et al randomized 40 ER + postmenopausal women with advanced breast cancer to estrogen therapy with diethylstilbesterol (DES) or DES + chemotherapy with cyclophosphamide and 5-FU (CF).[39] The survival of 21 ER + patients treated with combined DES + CF was significantly longer than 19 ER + treated with DES followed by chemotherapy after relapse or treatment failure. They also randomized 31 ER − patients to CF ± DES, but were unable to demonstrate any advantage to combined treatment.

Despite the fact that bone is a frequent site of metastases from breast cancer, patients with metastases only to bone are often excluded from treatment protocols because of difficulties in assessing objective response. Segaloff[40] included sclerosis and eventual disappearance of pure osteolytic lesions as an objective response in the

response criteria for the Cooperative Breast Group. The healing of osteolytic lesions also constitutes a response as defined by the UICC.[41] However, bone lesions are frequently sclerotic, or mixed lytic and blastic, making objective evaluation of response by standard radiologic criteria difficult. Serial bone scans may be helpful, but bone scans improve slowly, thus rendering this technique of greater value in documenting treatment failure rather than response.[42,43] Scans also may appear "worse" as healing occurs. Pain "flares" are sometimes seen with successful hormonal or chemotherapy but Coombes et al[44] found that pain relief was the most consistent index of response to treatment, since nearly all responding patients with bone metastases eventually became pain free.

As confirmed in this study, patients with only bone metastases frequently have a prolonged chronic course, and have a significantly longer survival than patients with visceral metastases.[45] Therefore, the exclusion of those with only bone disease from survival analyses will skew the data in an unfavorable manner. Although the criteria for objective response in patients with bone only metastases are frequently lacking, the criteria for treatment failure are quite good. If new lesions develop on a bone scan or if there is greater intensity of uptake on a bone scan, the patient is usually considered a treatment failure. If there is an increase in pain, or pain in a new site, the patient is probably a treatment failure, and objective criteria should be sought. The same is true for a deterioration in performance status.

As documented in this study, TTF is an excellent and probably the only means of evaluating response in bone only patients. TTF is not dependent on objective response criteria such as the healing of a lytic lesion. TTF, as its name implies, is dependent only upon treatment failure. TTF inherently incorporates deterioration of performance status and increased pain as well as more objective criteria such as progression on the bone scan.

It must therefore be concluded that the addition of tamoxifen to CAF confers no advantage over chemotherapy alone, except perhaps in soft tissue metastases. This failure to confer an advantage to the combined treatment is independent of menopausal status, and more importantly, independent of ER status. Regardless of ER status, the use of combined chemohormonal therapy with tamoxifen and CAF cannot be recommended over the use of CAF alone for the treatment of advanced breast cancer in premenopausal or postmenopausal women.

APPENDIX

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