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INCREASING THE RESPONSE RATE TO CYTOTOXIC CHEMOTHERAPY BY ENDOCRINE MEANS

MARC E. LIPPMAN*‡, JANE CASSIDY*, MARGARET WESLEY† and ROBERT C. YOUNG*
*Medicine Branch and †Biometric Research Branch, 10/12N226, NCI, NIH, Bethesda, MD 20205, U.S.A.

Summary—Cloned cell lines of human breats cancer can be growth inhibited by tamoxifen and this inhibition can be reversed by estrogen. We wondered whether tamoxifen inhibition of breast cancer followed by estradiol reversal would increase the efficacy of chemotherapy by increasing the fraction of rapidly cycling cells. We describe a clinical trial in which 110 patients were prospectively randomized to chemotherapy consisting of cytoxan 750 mg/m^2 and adriamycin 30 mg/m^2 on Day 1 plus 5-FU 500 mg/m^2 and methotrexate 40 mg/m^2 on Day 8 vs the same chemotherapy plus tamoxifen 20 mg/m^2 Days 2–6 and premarin 0.625 mg Q 12-H × 3 on Day 7. Chemotherapy was given in 21-day cycles. 108 patients were evaluable. No difference exist for any important prognostic variables. The first 55 patients were randomized to a regimen in which 5-FU preceded methotrexate by 24 h; thereafter, all patients received methotrexate followed in 1 h by 5-FU. No difference in any response parameter was seen between these two 5-FU methotrexate schedules. No differences in percent of protocol chemotherapy administered or observed toxicity was seen between the 2 regimens. Objective response rate was nearly identical—57% without and 64% with additional hormones. Prior adjuvant chemotherapy with L-PAM had no observable effect on response rate, response duration or survival. In a limited number of patients with inflammatory breast cancer we saw a significantly higher response rate (93 vs 61%; $P = 0.03$) than in patients with recurrent metastatic disease. Time to progression (13 vs 17 months) and survival (17 vs 23 months) of responders significantly favored the treatment arm including tamoxifen and premarin. Greater benefits of additional tamoxifen and premarin were seen in partial vs complete responders. This may have resulted from lower doses of chemotherapy given to patients achieving a complete remission. An additive effect of hormones plus chemotherapy cannot be entirely excluded as the explanation for the improved results seen with the addition of tamoxifen for 4 days plus 1 day of premarin. We believe that our results suggest that further efforts to increase the efficacy of chemotherapy by perturbing tumor growth rates may be worthwhile.

INTRODUCTION

Several reviews of numerous published trials in metastatic breast cancer [1, 2] suggest that an apparent plateauing of response rates (in the range of 55–65%) and of median duration of response (generally less than a year) has occurred. Multiple proposals have been made in the past few years to increase the efficacy of chemotherapy. Most efforts to improve therapeutic effectiveness by increasing dose intensity [3], by using "noncross-resistant" drugs [4] or by using more drugs [1] have been unsuccessful. While a small minority of patients treated with cytotoxic chemotherapy may achieve a complete remission with a longer associated response duration, the eventual relapse and demise of virtually all of these patients suggests that drugs alone have not yet been able to eradicate sufficient numbers of tumor cells to result in cure of more than a very occasional patient.

Given the general safety and palliative potential of endocrine therapies, many have attempted to combine hormonal and drug treatment as a means of improving clinical outcome. Detailed considerations of these approaches have appeared [2, 5–7] all coming to the same conclusions: at the present time, there is no convincing evidence that combining endocrine and chemotherapy offers any substantial benefit to patients with breast cancer. Numerous studies have achieved somewhat higher initial response rates with combined therapy; however, these improvements have not translated into survival benefit. There are, additionally, both theoretical and pragmatic reasons to eschew combined therapy [2].

As an alternative approach, we considered using endocrine therapy to temporarily perturb DNA synthesis in hormonally responsive breast cancer cells so as to increase the effectiveness of chemotherapy. In prior laboratory studies [8–10] we have demonstrated that antiestrogen-induced inhibition of breast cancer cell growth can be reversed by estrogen rescue. Weichselbaum and colleagues showed that this technique could increase the sensitivity of breast cancer cells to cytotoxic drug treatment [11]. Using flow cytometry, Sutherland and collaborators demonstrated that tamoxifen induced a G_1 arrest in MCF-7 human breast cancer cells in culture [12]. Using alternative technique, we have confirmed this observation and shown that estrogen treatment can induce a synchronous wave of DNA synthesis in human breast cancer cells [13]. Allegra and colleagues managed a small group of breast cancer patients with a strategy aimed at capitalizing on these observations and have reported promising early results [14].

‡To whom correspondence should be addressed

In this report, we describe our results in a randomized comparison of 2 chemotherapy programs differing only by brief utilization of antiestrogen treatment followed by physiologic doses of estrogen just prior to cytotoxic chemotherapy.

EXPERIMENTAL

Between June 1977 and July 1982, 110 women with metastatic breast cancer were entered on study. To be eligible for this treatment protocol all patients were required to have a histologically documented diagnosis of mammay cancer with evidence of measurable progressive disease. No previous cytotoxic chemotherapy was permissible except for adjuvant 1-phenylalanine mustard. All patients were required to have a Karnofsky performance index in excess of 30. Patients were excluded who gave a past history of malignant neoplasms aside from curatively treated basal cell or squamous cell carcinoma of the skin or surgically cured carcinoma of the cervix *in situ*. Patients were also excluded who were felt to have nonmalignant systemic disease which would have prevented their receiving any part of the planned treatment. Patients were required to have a leukocyte count greater than 4,000/mm^3 and a platelet count greater than 100,000/mm^3 unless the depression of counts was due to marrow involvement by tumor. Similarly, renal and hepatic function were required to be within normal limits unless the abnormality was due to metastatic disease. All patients were required to give written informed consent prior to entry into the trial.

Prior to treatment all patients had a complete history and physical examination including calculation of body surface area. A complete blood count, urinalysis, chemistry profile, electrocardiogram, radionuclide scans of bone and liver, radiographic examinations of chest, breast and skeleton were obtained in all patients. In addition, computerized tomography, echosonography and other ancillary studies were obtained as indicated by clinical or laboratory findings. Measurements were recorded for all indicator lesions; skin disease was commonly followed by serial photography.

As part of follow-up, blood counts were obtained weekly; chemistry profiles were repeated every 3 weeks at the institution of each new chemotherapy cycle. At the beginning of each cycle, physical examination with remeasurement of visible tumours was repeated. Follow-up chest X-rays were also repeated (if previously abnormal) at the start of each therapy cycle. Other scans and X-rays were repeated every 12 weeks if previously abnormal; otherwise, patients were completely restaged every 6 months.

Patients were randomized to 1 of 2 treatment arms using an updated balanced cell procedure. Prior to randomization patients were stratified by estrogen receptor status (positive, negative or unknown), previous hormonal therapy (yes or no), menopausal status (pre or post), dominant disease site (CNS, hepatic and lymphangitic versus all others), Karnofsky performance index (≥ 60 or < 60), and previous 1-phenylalanine mustard (yes or no).

The treatment regimens employed are shown in Table 1. The first 55 patients were randomized to 1 to 2 treatments shown in Table 1 on a protocol termed 160A. In either arm of this randomization 5-fluorouracil was given in the doses shown on Day 8 of each cycle and methotrexate given on Day 9. A subsequent group of 55 consecutive patients was randomized to 1 of 2 treatment arms also shown in Table 1 on a protocol termed 160B. In either arm of this randomization methotrexate was administered on Day 8, 1 h before 5-fluorouracil. Otherwise the treatment plans in 160A and 160B were exactly identical. Thus, a nonrandomized comparison between 160A and 160B may permit exploration of the impact of two alternative methotrexate and 5-fluorouracil sequences; whereas, a nonrandomized

Table 1. Treatment regimens

160A (First 55 patients)				
C cyclophosphamide	750 mg/m^2 i.v. Day 1		C cyclophosphamide	750 mg/m^2 i.v. Day 1
A doxorubicin	30 mg/m^2 i.v. Day 1		A doxorubicin	30 mg/m^2 i.v. Day 1
		vs		
M methotrexate	40 mg/m^2 i.v. Day 8		M methotrexate	40 mg/m^2 i.v. Day 8
F 5-fluorouracil	500 mg/m^2 i.v. Day 9		F 5-fluorouracil	500 mg/m^2 i.v. Day 9
			T tamoxifen	10 mg/m^2 p.o. Days 2–6
			P premarin	0.625 mg/m^2 p.o. Q12H × 3 Day 7
160B (Subsequent 55 patients)				
C cyclophosphamide	750 mg/m^2 i.v. Day 1		C cyclophosphamide	750 mg/m^2 i.v. Day 1
A doxorubicin	30 mg/m^2 i.v. Day 1		A doxorubicin	30 mg/m^2 i.v. Day 1
		vs		
M methotrexate	40 mg/m^2 i.v. Day 8		M methotrexate	40 mg/m^2 i.v. Day 8
F 5-fluorouracil	500 mg/m^2 i.v. Day 8 (1 h later)		F 5-fluorouracil	500 mg/m^2 i.v. Day 8 (1 hr later)
			T tamoxifen	10 mg/m^2 p.o. Days 2–6
			P premarin	0.625 mg/m^2 p.o. Q12H × 3 Day 7

All drugs given in 21-day cycles.
Doxorubicin given every other cycle after documentation of an objective complete remission.
Doxorubicin discontinued after a total cumulative dose of 525 mg/m^2 was achieved.
All chemotherapy discontinued 1 year after documentation of an objective complete response.

Table 2. Distribution of prognostic factors by treatment group

Variable	CAMF	CAMFTP	Total
Number of patients	53	55	108
Estogen receptor status			
Positive	11 (20.0%)	8 (14.5%)	19 (17.6%)
Negative	22 (41.5%)	23 (41.8%)	45 (41.7%)
Previous hormonal therapy	19 (35.8%)	20 (36.4%)	39 (36.1%)
Premenopausal	15 (28.3%)	17 (30.9%)	32 (29.6%)
Dire site of disease (CNS, hepatic, lymphangitic-pulmonary	13 (24.5%)	12 (21.8%)	25 (23.1%)
Karnofsky performance index ≥ 60	45 (84.9%)	49 (89.1%)	94 (87.0%)
Previous L-PAM	11 (20.8%)	10 (18.2%)	21 (19.4%)
Inflammatory	5 (9.4%)	9 (16.4%)	14 13.0%)

comparison between CAMF and CAMFTP allows examination of the effect on clinical parameters of short courses of antiestrogen therapy followed by physiologic doses of estrogen in the form of premarin. In all treatment regimens patients were treated to a cumulative total dose of 525 mg/m^2 of doxorubicin. Patients achieving an objective complete remission received doxorubicin on an every-other-cycle basis. All patients achieving an objective complete remission had all cytotoxic therapy discontinued after 1 additional year of chemotherapy.

Dose modification for individual treatment cycles was as follows. Cyclosphosphamide and doxorubicin were reduced 25, 50 or 75% for a white blood cell count $<4{,}000$, $<3{,}000$ or $<2{,}000$ but $>1{,}500$ respectively at the start of the therapy cycle *or* for a platelet count $<100{,}000$, $<75{,}000$ or $<50{,}000$ but $>25{,}000$ respectively. Therapy was withheld for a week for greater degrees of myelosuppression. Usual dose modification criteria for hepatic or renal dysfunction were instituted. Doxorubicin was discontinued if any evidence of cardiotoxicity supravened. If hemorrhagic cystitis attributed to cyclophosphamide occurred, nitrogen mustard (8 mg/m^2 i.v. on Day 1) was substituted.

Detailed response criteria employed in these studies have been published as have objective standards for coding toxicity at various sites [15]. These response criteria do not differ importantly from UICC criteria [16]. The duration of response was calculated from the first day of treatment until progression or last date of follow-up. Statistical comparisons of patient characteristics were performed utilizing either Fisher's exact or the chi-square test. All comparisons are two tailed. Response and survival distributions were estimated using the Kaplan–Meier procedure [17]. The differences between the groups were tested by Wilcoxon and Gehan [18].

Of 110 patients randomized, 2 were not eligible for the protocol and are deleted from the data set; 3 patients were not evaluable for response but are included in the evaluation of time to progression and survival (2 patients died of drug-related toxicity during initial therapy cycles and 1 left the program); finally, 2 recently randomized patients are too early for response evaluation but are included in time to progression and survival data. Thus, 108 of 110 patients (98%) are evaluable for time to progression and survival; 103 patients (94%) are evaluable for all parameters.

Pretreatment distribution of prognostic variables by the 2 treatment groups (CAMF vs CAMFTP) is shown in Table 2. None of the prognostic variables shown in distributed significantly differently between either of the 2 treatment regimes.

The pretreatment distribution of prognostic variables between the two treatment protocols [160A vs 160B] (Table 3) shows that there was a greater likelihood for patients accrued more recently to the trial (and therefore randomized on the 160B protocol) to be estrogen receptor positive or to have inflammatory breast cancer and a lesser likelihood of having received single agent l-phenylalanine mustard as an adjuvant following mastectomy.

Table 3. Distribution of prognostic factors by protocol

Variable	160A	160B	*P* Value
Number of patients	53	55	
Estrogen receptor status			
Estrogen receptor status			
Positive	5 (9.4%)	14 (25.5%)	0.05
Negative	27 (50.9%)	18 (32.7%)	0.08
Previous hormonal therapy	20 (37.7%)	19 (34.5%)	0.88
Premenopausal	13 (24.5%)	19 (34.5%)	0.35
Dire site of disease (CNS, hepatic, lymphangitic)	15 (28.3%)	10 (18.1%)	0.31
Karnofsky performance index ≥ 60	43 (81.1%)	51 (92.7%)	0.13
Previous L-PAM	14 (26.4%)	7 (12.7%)	0.12
Inflammatory	3 (5.7%)	11 (20.0%)	0.05

Table 4. Toxicity by treatment arm

Toxicity	Code*	CAMF	CAMFTP	P Value†
WBC	0	2	2	
	1	6	3	
	2	14	25	
	3	22	19	
	4	6	6	0.81
Platelets	0	35	43	
	1	2	6	
	2	7	2	
	3	3	0	
	4	3	4	0.25
Hepatic	0	10	12	
	1	24	29	
	2	11	8	
	3	4	5	0.67
Renal	0	44	50	
	1	3	3	
	2	2	1	0.53
GI	0	2	5	
	1	12	13	
	2	27	23	
	3	9	14	0.89
Cardiac	0	49	50	
	1	0	1	
	2	0	3	
	3	1	1	0.24
GU	0	45	52	
	1	2	1	
	2	3	2	0.44

*Toxicity coding for various organ sites is outlined in detail in ref. 15.
†χ^2 test for trend.

RESULTS

An initial premise of this trial was that short-term antiestrogen therapy followed by estrogen rescue would have no substantial impact on toxicity. As shown in Table 4, there was no significant difference between CAMF and CAMFTP with respect to toxicity at any organ site examined. Furthermore, in data not shown, there was no significant difference or tendency for the quantity of drug administered to be different between the 2 treatment arms. Two patients died early in the trial at outside hospitals while myelosuppressed, presumably of sepsis. Postmortem examinations were not obtained. There were no other drug-related deaths. Five instances of presumed doxorubicin-induced cardiac disease were seen. Four were in the CAMFTP arm. All were successfully managed medically and none resulted in hospitalization or death.

An overall summary of response data is shown in Table 5. CAMF with or without tamoxifen plus premarin was effective chemotherapy. Both achieved an overall objective response rate of 65% with no difference seen in the subset achieving a complete remission. The overall median time to progression in the study was 14 months, and the survival 18.6 months. Analysis of time to progression yielded surprising results. Objective responders to CAMFTP had a significantly longer time to progression than patients treated with CAMF (17.4 vs 14 months; $P = 0.009$). Surprisingly, all of this advantage was seen in the subset of patients achieving an objective partial response (17.5 months for CAMFTP vs 11.1 months for CAMF; $P = 0.001$). There was no significant difference in time to progression for patients achieving a complete response. Data on survival for the 2 treatment regimens is also shown in Table 5 and parallels the results described for time to progression. Survival for patients treated with CAMFTP was longer than for patients treated with CAMF by 5 months (23.0 vs 18.1; $P = 0.079$). This advantage was restricted to patients achieving a partial response (22.7 months vs 16.6 months; $P = 0.021$). There was no significant difference in survival amongst complete responders on either regimen. These data are shown in Fig. 1. Unfortunately, as with all reported cytotoxic trials in breast cancer, virtually no patients enter prolonged unmaintained remission.

Overwhelmingly, the most significant variable influencing response duration was the quality of response achieved on chemotherapy. Data are shown in Fig. 2. Time to progression for complete responders was 19.4 months, partial responders 14 months, objective no change 5.5 months, and for patients with progressive disease 2 months ($P < .001$).

The influence of several other potentially important prognostic variables on response parameters are summarized in Table 6. Prospectively performed

Table 5. Response data

	CAMF	CAMFTP	P Value
Response rates			
CR	9 (18%)	12 (22%)	
PR	23 (47%)	23 (43%)	
CR + PR	32 (65%)	35 (65%)	1.0*
Time to progression (Months)			
CR	20.4	17.0	0.358†
PR	11.1	17.5	0.001†
CR + PR	14.0	17.4	0.009†
All	12.0	16.0	0.256†
Survival (Months)			
CR	28.0	24.8	0.685†
PR	16.6	22.7	0.021†
CR + PR	18.1	23.0	0.079†
All	17.0	19.0	0.291†

*Fisher exact test.
†Wilcoxon.

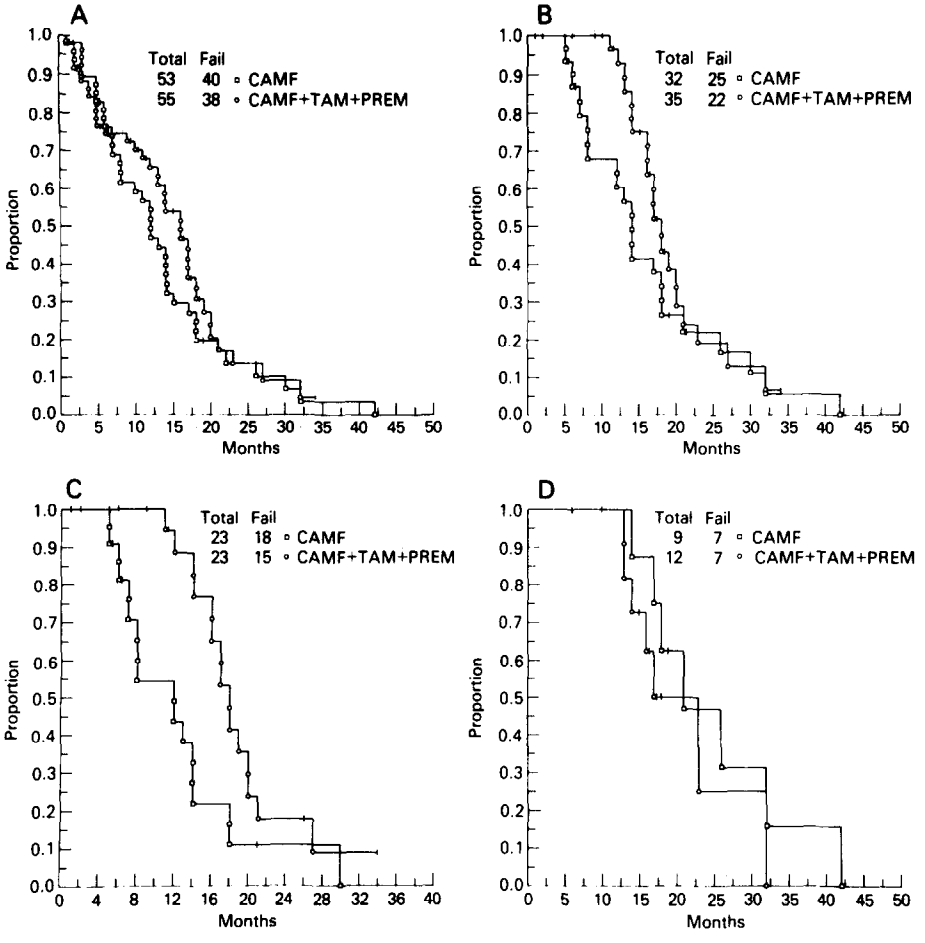

Fig. 1. Kaplan Meier plots of time to progression for various subsets of patients treated with either chemotherapy alone (CAMF) or chemotherapy plus hormonal synchronization (CAMFTP). Panel A, all patients; Panel B, all responders; Panel C, partial responders; Panel D, complete responders.

estrogen receptor analyses obtained on biopsy material immediately prior to entry on study was available on 62 of 103 patients (60%) evaluable for response and 62 of 108 patients (57%) evaluable for time to progression and survival. There were no significant differences between ER positive and negative patients with respect to response rate, time to progression or survival. Furthermore, as shown in Table 7, when the effects of either protocol regimen–CAMF vs CAMFTP—were compared separately, no difference was seen between ER positive and ER negative patients. As shown in Table 6, prior endocrine therapy had no influence on response parameters of patients to chemotherapy in this trial. Similarly,

Table 6. Response by prognostic factors

Variable	No. eval.	Response rate	2-Sided *P* value[a]	Time to progression (months)	2-Sided *P* value[b]	Survival (months)	2-Sided *P* value[b]
ER positive	19	68%	0.76	12.0	0.462	17.0	0.381
ER negative	43	60%		12.6		17.7	
Prev. horm. Rx	37	68%	0.86	14.8	0.195	19.7	0.879
No prev. horm. Rx	66	64%		13.0		17.0	
Premenopausal	31	55%	0.23	12.0	0.173	14.0	0.331
Postmenopausal	72	69%		14.0		19.9	
Dire mets.	23	57%	0.46	12.2	0.071	15.0	0.017
Other mets.	80	68%		14.0		20.0	
Perf. index ≥ 60	89	69%	0.12	14.0	<0.001	20.0	<0.001
Perf. index < 60	14	43%		5.0		9.8	
Prev. L-PAM	21	52%	0.27	14.0	0.95	20.0	0.436
No prev. L-PAM	82	68%		14.0		17.0	
Inflammatory	14	93%	0.03	13.7	0.12	19.2	0.187
Other	89	61%		14.0		18.0	

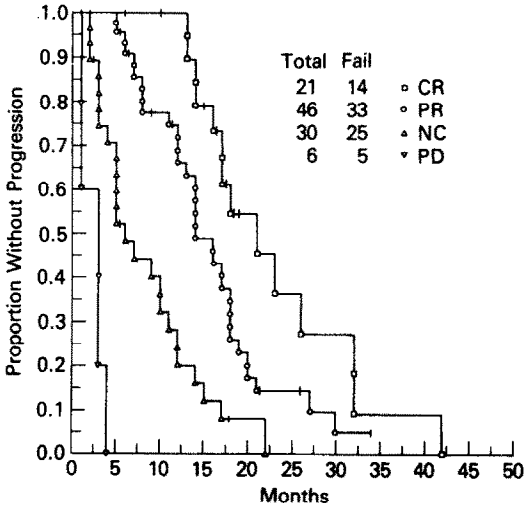

Fig. 2. Influence of quality of response on time to progression for all evaluable patients (108 of 110).

menopausal status also had no effect on response using the chemotherapy we employed.

Interestingly, adjuvant therapy with l-phenylalanine mustard had no effect on either response rate, response duration or survival.

The two most important prognostic variables in this trial were performance status and the presence of dire metastases (CNS, hepatic or lymphangitic–pulmonary). While response rates were only modestly influenced by these prognostic categories, time to progression and survival were adversely affected to a very considerable degree.

Finally, as shown in Table 6, 13 of 14 patients with inflammatory breast cancer showed an objective response to chemotherapy; a response rate which was significantly higher than that seen in patients with overt metastatic disease. This improved response rate may reflect the greater number of rapidly cycling cells. These patients have response durations and survival which are similar to patients with advanced disease.

Each member of the above prognostic categories (e.g. pre- and post-menopausal) was examined individually by treatment (CAMF vs CAMFTP) to search for an impact of therapy on an individual prognostic subset; for example, were postmenopausal patients benefitted by hormonal synchronization? None of these subset analyses were positive for response rate, time to progression or survival.

The impact of 2 different methotrexate 5-FU schedules was evaluated in consecutively accrued cohorts of 55 patients. Results are shown in Table 8. 160A (5-FU followed in 24 h by methotrexate) and 160B (methotrexate followed in 1 h by 5-FU) were not significantly different with respect to response rate, response duration or survival. Furthermore, there were no significant differences between results achieved with CAMF vs CAMFTP on either 160A or 160B.

DISCUSSION

In this trial an attempt was made to increase the efficacy of cytotoxic chemotherapy by stimulating cell proliferation by hormonal means. Modest improvements in time to progression and survival were seen in some but not all subsets of patients; however, no effect was seen on response rate. There was no apparent alteration in toxicity when 5 days of tamoxifen plus 1 day of estrogen were interdigitated with the cytotoxic chemotherapy. Several important issues require discussion. First, is the improvement seen in the combined arm of this trial a result of synchronization of tumor cells or are we simply observing and additive effect of cytotoxic plus endocrine therapy? When this trial was instituted, pharma-

Table 7. Time to progression and survival as a function of treatment protocol and ER status

	Time to progression		Survival	
	Time (months)	*P* Value*	Time (months)	*P* Value*
ER positive				
CAMF	12.0	0.953	17.0	0.725
CAMFTP	12.1		14.0	
ER negative				
CAMF	11.0	0.596	16.0	0.895
CAMFTP	14.6		19.1	

*Wilcoxon.

Table 8. Influence of 5-FU methotrexate scheduling on response parameters

	Response rates				
	CR	PR	CR + PR	Time to progression	Survival
160A	11 (22%)	21 (41%)	32 (63%)	14.0	17.0
160B	10 (19%)	25 (38%)	35 (67%)	13.4	19.3
P Value			0.78*	0.264†	0.208†

*Fisher exact (2-sided).
†Wilcoxon.

cologic data on the prolonged plasma half life of 10–14 days and metabolism of tamoxifen to more active polar metabolites were not available [19, 20]. Human breast cancer cell lines do not form 4-OH tamoxifen *in vitro* which has at least 10 times greater potency than tamoxifen. In recent work with MCF-7 breast cancer cells in culture we have shown that the ability of estradiol to reverse more potent anti-estrogens is less complete [21]. Thus, a model for estrogen rescue of tamoxifen inhibition *in vitro* [8–10] may not apply *in vivo*. Unfortunately, we have neither blood levels of tamoxifen and its metabolites nor specific measures of effects of hormonal treatment on *in vivo* cell kinetics. Furthermore, a 3-armed trial in which the third arm would have been 5 days of tamoxifen followed by a day of estrogen rescue every cycle (the "endocrine therapy" used in the trial) clearly could not be justified. We believe, however, that the modest benefits seen in this trial are not due to such an additive effect of endocrine therapy. Reviews of numerous combined chemohormonal trials for advanced breast cancer [2,5–7] reveal that the usual pattern of benefit (if any) is on an increase in response rate, not response duration or survival. It is difficult for us to explain why the benefit of CAMFTP was apparently restricted to partial responders. A conceivable posibility lies in the observation that complete responders were paradoxically treated less intensively; that is, following documentation of a complete remission complete responders received doxorubicin on an every-other-cycle basis. Furthermore, after a year all therapy was stopped. This appeared to correspond closely with the time at which many of these patients relapsed although this may simply be coincidental. Alternatively, the differences seen may reflect chance alone.

Allegra and colleagues used similar reasoning to perform a small uncontrolled trial of antiestrogen therapy followed by estrogen rescue and methotrexate and 5-fluorouracil [14]. They achieved an unusually high complete remission rate of 56%.

We believe that the results achieved in this trial are interesting and merit further exploration particularly in the context of appropriate simultaneous measures of biologic effect on tumor kinetics. This approach may have even greater promise in prostatic cancer given the far greater degree of hormone dependency in previously untreated patients.

A second important observation in this trial is the failure of single agent adjuvant therapy with l—henylalanine mustard to have any impact on response rate, time to progression or survival. While these results are obviously not applicable to other adjuvant regimens, they help to dispel the notion that patients failing adjuvant regimens have a substantially shortened survival versus other patients.

A third issue of interest is the optimal scheduling of methotrexate and 5-fluorouracil. When this protocol was initiated, evidence had been presented suggesting that 5-fluorouracil prior to methotrexate would provide optimal scheduling [22]. Thus, the initial 55 patients (160A) received 5-fluorouracil on Day 8 followed by methotrexate on Day 9. Subsequent studies in several systems [23, 24], as well as laboratory investigations in human breast cancer cells [9], led us to try an alternative drug sequence (160B) in which methotrexate preceded 5-fluorouracil by 1 h on Day 8. While 160A and 160B are not as comparable as a concurrently randomized trial, they do represent a sequential experience in a single institution in which absolutely identical accrual, treatment and evaluation criteria were employed. In addition, when prognostic variables were examined for these 2 groups of patients (Table 3), the 2 groups of patients (Table 3), the 2 groups were generally comparable. The slightly higher proportion of ER positive patients and smaller proportion of patients who had received prior adjuvant l-phenylalanine mustard is unlikely to be important, since, as shown in Table 6, these factors had no influence on response parameters. With these caveats in mind, we found absolutely no difference of any significance in response parameters between 160A and 160B. Furthermore, there was no overall difference in the response to CAMF versus CAMFTP for either 160A and 160B nor was any difference apparent when various prognostic subsets were analyzed on 160A or 160B.

We continue to believe that trials designed on strictly empirical grounds in breast cancer are unlikely to lead to significant advances in the therapy of breast cancer. A more effective means of briefly perturbing the growth of a larger cohort of breast cancer cells needs to be identified.

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