Breast Cancer Research and Treatment, 3, 365–372 (1983)

Report

Chemoendocrine therapy vs chemotherapy alone for advanced breast cancer in postmenopausal women: preliminary report of a randomized study

Cancer and Leukemia Group B Study 8081

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Keywords: advanced breast cancer, CAF, chemoendocrine therapy, chemotherapy, tamoxifen

Summary

From January 1980 to August 1982 the Cancer and Leukemia Group B conducted a prospective randomized trial comparing chemoendocrine therapy with T-CAF (cyclophosphamide, adriamycin, and 5-fluorouracil plus tamoxifen) to CAF alone in postmenopausal women with advanced breast cancer. The patients were stratified by estrogen receptor (ER) status into three groups: ER-negative, ER-positive, ER-unknown. They were also stratified by dominant site of metastatic disease: visceral and other (osseous and/or soft tissue). A total of 246 eligible patients were enrolled in the study; 232 were evaluable and constitute the basis for this report. The study revealed that there was no difference in overall response frequency or response duration between T-CAF and CAF; there was no difference in response between T-CAF and CAF in ER-positive or in ER-negative patients; and there was no difference in response between T-CAF and CAF by dominant site of metastatic disease. The expected advantage of T-CAF over CAF, especially for ER-positive patients, was not observed.

Introduction

Metastatic breast cancer is responsive to a variety of cytotoxic drugs with differing mechanisms of action (1). This makes breast cancer the prototype solid tumor for the study of combination chemotherapy. Greenspan (2) introduced the use of combination chemotherapy in advanced breast cancer almost twenty years ago. This was modified by Cooper (3), and then further modified following the introduction of adriamycin (1). Multiple attempts have been made to combine and recombine the various active agents into 2-drug, 3-drug, 4-drug, 5-drug, and even 6-drug combinations. However, the results have plateaued. It appears that by using currently available drugs, an objective response rate of 50% to 65% can be obtained, with about 10% to 15% of the responses being complete. The median response durations are from 9 to 16 months.

It has been recognized for many years that 20% to 25% of unselected breast cancers are hormonally responsive (4). By restricting endocrine manipulation to tumors containing estrogen receptor (ER) protein, the response rate can be increased to 55%.

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Again most of these responses are incomplete and of relatively short duration.

Greene and Jensen (5), using fluorescent staining techniques with monoclonal antibody for estrogen receptor, have recently noted that many breast cancers are heterogeneous in terms of their ER content. That is, breast cancers are composed of both ER-positive cells as well as ER-negative cells. A tumor's ER positivity or ER negativity appears to depend upon the relative concentration of receptor activity in the various cells present. Using immunocytochemical techniques, Mercer et al. (6) have demonstrated that 71% of human breast cancers are heterogeneous for estradiol binding.

Since the results of treatment of advanced breast cancer have plateaued, new approaches to therapy are needed. Based upon the observation that the majority of breast cancers are heterogeneous in terms of ER content (5, 6), and the recognition that endocrine therapy and cytotoxic chemotherapy have different mechanisms of action, the Cancer and Leukemia Group B (CALGB) performed a study evaluating the relative effectiveness of chemoendocrine therapy as compared to chemotherapy alone in postmenopausal women with advanced breast cancer. Although chemoendocrine therapy had a theoretical advantage over chemotherapy alone, it was felt that a prospectively randomized controlled study was necessary to truly answer the question. Also, a controlled study was felt to be necessary since the endocrine therapy could compromise the effectiveness of the cytotoxic drugs by altering the cycling characteristics of the tumor cells. This constitutes the report of the first major data analysis of CALGB Study 8081.

Methods

Cancer and Leukemia Group B Study 8081, a randomized trial comparing chemoendocrine therapy with T-CAF (cyclophosphamide, adriamycin, 5-fluorouracil plus tamoxifen) to chemotherapy alone (CAF) in postmenopausal women with advanced breast cancer, was open to patient entry from January 1980 to August 1982. Postmenopausal women with histologically documented carcinoma of the breast were eligible if they had measurable metastatic, locally recurrent, or surgically incurable (stage IV) disease. Only patients with their first recurrence were eligible. Patients were not eligible if they had a performance status of greater than 3, or a second primary malignant neoplasm or a malignant neoplasm of the breast other than carcinoma. A history of recent myocardial infarction, congestive heart failure, or documented angina also rendered the patient ineligible. Patients who had completed adjuvant chemotherapy greater than six months prior to entry were eligible provided it was their first documented recurrence. Prior therapy with tamoxifen rendered the patient ineligible. Informed consent was obtained from all patients.

Stratifications

The patients were stratified on the basis of ER status, dominant site of metastatic disease, and by no prior therapy versus prior adjuvant chemotherapy (Table 1). The estrogen receptor assays were quality controlled by internal monitoring utilizing reference powders provided by James Wittliff, PhD, of the University of Louisville. Detailed results of the quality control program will be the subject of a subsequent publication. There was good agreement for all laboratories analyzing reference powders which were negative, and only one of fourteen laboratories tested reported a negative result on an ER-positive reference powder. Patients were stratified into three groups on the basis of ER: ER-positive ≥ 7 femtomoles/mg protein; ER-negative

Table 1. Stratifications.

1.	*Estrogen receptor (ER) status*	
	A. ER-negative	<7 femtomoles/mg protein
	B. ER-positive	≥ 7 femtomoles/mg protein
	C. ER-unknown	– test not performed
2.	*Dominant site of metastatic disease*	
	A. Visceral	
	B. Osseous	
	C. Soft tissue	
3.	*Prior therapy*	
	A. No prior therapy	
	B. Prior adjuvant chemotherapy	

< 7 femtomoles/mg protein; ER-unknown (test not performed).

The cut-off value of 7 femtomoles/mg was selected based upon the data of Hilf et al. (7). Stratification by site of metastatic disease was into two groups: visceral dominant or other (osseous and/or soft tissue). An attempt was made to separate osseous and soft tissue dominant during the data analysis. This did result in a stratification imbalance which will be pointed out.

Randomization

Based upon the appropriate stratifications, patients were randomized to receive CAF chemotherapy alone (cyclophosphamide, adriamycin, 5-fluorouracil) or T-CAF chemoendocrine therapy (CAF + tamoxifen). The schema for CALGB Study 8081 is illustrated in Fig. 1.

Treatment schedule

Patients randomized to receive T-CAF received the tamoxifen continuously in a dose of 10 mg twice daily. The chemotherapy was the same in each treatment arm and was given in intermittent cycles over a 28-day period with 14 days of cytotoxic drug administration followed by a 14-day rest as follows (see Fig. 1): cyclophosphamide 100 mg/m^2/day p.o. days 1–14; adriamycin 25 mg/m^2 i.v. days 1 and 8; and 5-fluorouracil 500 mg/m^2 i.v. days 1 and 8. Treatment cycles were repeated on day 29, 57, 85, etc. After a total cumulative dose of adriamycin of 450 mg/m^2 had been administered, methotrexate was substituted. The methotrexate dose was 40 mg/m^2 i.v. on days 1 and 8 unless the patient was over age 60 in which case it was reduced to 30 mg/m^2.

Response criteria

A complete response (CR) was defined as complete disappearance of all signs and symptoms attributable to the tumor including the disappearance of all measurable lesions for at least one month and the appearance of no new lesions. For osseous disease a CR required recalcification of all osteolytic lesions. A partial response (PR) was defined as greater than 50% reduction in the sum of the products of the two largest perpendicular diameters of all measured lesions with no deterioration in performance status,

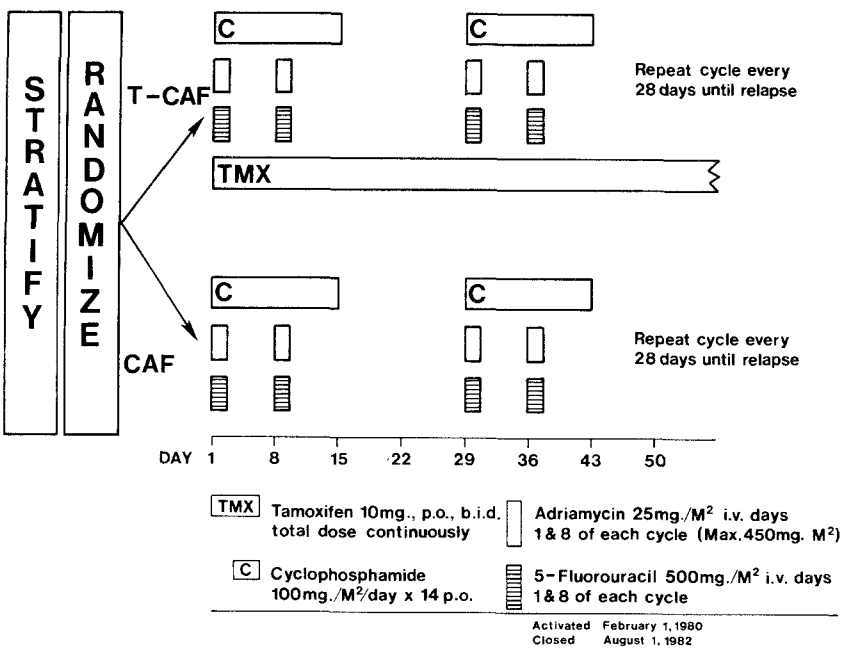

Fig. 1. Schema of Cancer and Leukemia Group B Study 8081. Treatment of metastatic breast cancer in postmenopausal women.

and without the appearance of any new lesions.

There was no provision in the study for ER-positive or ER-unknown patients randomized to CAF alone who did not respond, or who responded and then failed, to automatically receive tamoxifen alone as secondary treatment.

Statistical aspects

This interim analysis was performed primarily using the chi-square test for contingency tables and Breslow's modification of the Kruskal-Wallis test. Multivariate analyses using Cox's linear logistic model were also used to assess the importance of prognostic variables on response.

Results

A total of 246 eligible patients were enrolled in the study. Of these, 232 were evaluable for response. Fourteen cases were too early to evaluate. An additional 21 cases were disqualified (11 T-CAF and 10 CAF) because of a major protocol violation, inadequate records or improper randomization. The comparability of the treatment groups is outlined in Table 2. The two treatment groups are comparable with one notable exception, i.e., there was an imbalance in the stratification for dominant site of disease ($p = 0.02$). The reason for this imbalance is explained in the section entitled *Stratifications*. This imbalance probably accounts for the difference in response between T-CAF and CAF in the ER-unknown group. The ER-unknown group treated with T-CAF contained twice as many visceral dominant patients as the ER-unknown group treated with CAF.

The *overall response frequency* for all patients is outlined in Table 3. There is no difference in overall response rate (CR + PR) between T-CAF (56%) and CAF (51%). The *overall response durations* are outlined in Table 4. Response duration is defined as the period that a patient achieved a documented CR or PR to the time of documented disease progression. Since this is the first major data analysis for this study, the maximum follow-up is only 22 months. However, at this time, there is no difference in projected median response duration for T-CAF (17.3 months) as compared to CAF (14.6 months). Also there is no difference in the percent of responders remaining in remission at 12 months for the T-CAF-treated group (59%) compared to the CAF group (56%).

When the data were analyzed for *response by ER*

Table 2. Comparability of treatment groups.

	T-CAF	CAF
Total eligible	120	126
Number evaluable	116	116
Dominant site of metastases		
Visceral	71%	59%
Osseous	17%	32%
Soft tissue	12%	9%
Estrogen receptor status		
ER-negative	33%	32.5%
ER-positive	29%	35%
ER-unknown	38%	32.5%
Prior therapy		
Adjuvant chemotherapy	11%	14%
No prior therapy	89%	86%
Performance status		
0–1	71%	79%
2–3	29%	21%

Table 3. Overall frequency of response.

Therapy	*N*	CR	PR	%CR + PR
T-CAF	116	18(15.5%)	47(40.5%)	56
CAF	116	16(14%)	43(37%)	51

N = number of evaluable cases; CR = complete response; PR = partial response.

Table 4. Duration of response – preliminary data (follow-up up to 22 months).

	Projected median	% responders in remission at 12 months
T-CAF	17.3 months	59%
CAF	14.6 months	56%

status, there were also no differences in response between T-CAF and CAF for either ER-negative or ER-positive patients (Table 5). The responses in the ER-positive patients were identical whether they were treated with T-CAF (47%) or with CAF (50%). Response in the ER-negative patients was greater with CAF alone (70%) than for T-CAF (54%), but this did not achieve statistical significance ($p = 0.14$). The difference in response observed for ER-unknown patients treated with T-CAF (65%) vs CAF (33%) seems to be due to a decreased response to CAF rather than an increased response to T-CAF. This difference is difficult to reconcile. Perhaps the stratification imbalance for dominant site of disease may account for it at least partially. Obviously, ER-unknown patients must consist of ER-positive and ER-negative cases and there were no differences in response in the latter two groups.

A secondary objective of this study was to evaluate differences in responses to CAF chemotherapy in ER-positive patients as compared to ER-negative. These data are also displayed in Table 5. There appears to be an advantage in response to CAF for ER-negative patients (70% as compared to 50% for ER-positive). Despite the fact that there is a 20% difference, the data do not achieve statistical significance ($p = 0.07$). These data will be carefully re-evaluated in subsequent analyses of this study. From a theoretical point of view, one would anticipate a higher response rate to cytotoxic chemotherapy in ER-negative tumors since they tend to have a higher thymidine labeling index and growth rate as well as a shorter disease-free interval (8).

Response by dominant site of metastatic disease is outlined in Table 6. There are no differences in response between T-CAF and CAF in visceral dominant, osseous dominant, or soft tissue dominant metastatic disease.

Lastly, the data were analyzed in terms of no prior chemotherapy versus prior adjuvant chemotherapy completed greater than six months prior to protocol entry (Table 7). This was restricted to those patients who would be receiving their first systemic treatment for metastatic disease. Although the protocol was open to patients who had received any type of adjuvant chemotherapy, almost all of the previously treated group had received adjuvant CMF (cyclophosphamide, methotrexate, 5-fluorouracil). No patient had received adjuvant hormonal therapy. Most of these had been treated in accordance with a previous CALGB protocol evaluating adjuvant chemotherapy with CMF vs CMF + MER vs CMFVP (vincristine, prednisone). There was no difference between T-CAF and CAF in those pa-

Table 5. Response by ER status.

	T-CAF	CAF	*p*
	(CR + PR/total)	(CR + PR/total)	
ER-negative	9 + 12/39 = 54%	4 + 22/37 = 70%[a]	0.14
ER-positive	2 + 14/34 = 47%	7 + 13/40 = 50%[a]	0.80
ER-unknown	7 + 21/43 = 65%	5 + 8/39 = 33%	0.004

[a] $p = 0.07$

Table 6. Response by dominant site of metastatic disease.

	T-CAF	CAF	*p*
	(CR + PR/total)	(CR + PR/total)	
Visceral	15 + 27/82 = 51%	9 + 26/69 = 51%	0.95
Osseous	1 + 10/20 = 55%	4 + 15/38 = 50%	0.72
Soft tissue	2 + 10/14 = 86%	3 + 2/ 9 = 56%	0.11

Table 7. Response by prior adjuvant chemotherapy (adjuvant chemotherapy completed greater than six months prior to protocol entry).

	T-CAF	CAF	*p*
	(CR + PR/total)	(CR + PR/total)	
No prior chemotherapy	17 + 43/103 = 58%	13 + 38/99 = 51%	0.34
Prior adjuvant chemotherapy	1 + 4/ 13 = 38%	3 + 5/17 = 47%	0.26

tients who had no prior chemotherapy nor was there difference between T-CAF and CAF in those patients who had prior adjuvant chemotherapy. *But* what is of more interest is that those patients who received prior adjuvant chemotherapy responded to CAF with the same frequency as those who had no prior chemotherapy (47% vs 51%).

The *toxicity* observed during this study is what would have been expected for CAF alone, i.e., mild to moderate myelosuppression, mild to moderate nausea and vomiting, and alopecia. None of the patients developed severe or life-threatening complications. There was no additional toxicity observed in those patients treated with tamoxifen. Specifically, none of the patients treated with tamoxifen were observed to have developed hypercalcemia or a tumor flare.

Discussion

The expected theoretical advantage for T-CAF chemoendocrine therapy over standard CAF chemotherapy alone was not observed even in the subset of patients who were ER-positive. This is in contrast to the data of Cocconi et al. (9) who conducted a similar but smaller study, evaluating CMF ± tamoxifen in 133 postmenopausal women with metastatic breast cancer. In their series the group treated with tamoxifen + CMF had a greater response rate, but response duration and survival were equivalent. The results reported by Mouridsen et al. (10) also evaluating CMF ± tamoxifen were similar to those of Coconni et al. These two studies utilized the cycle active drug methotrexate rather than the more active but cycle nonspecific drug adriamycin. The differences observed in response using CMF + tamoxifen may have been masked in our study by a kinetic effect of the adriamycin.

There are two reported series evaluating chemoendocrine therapy utilizing an adriamycin-containing drug combination with tamoxifen. The first of these was reported by Ahmann et al. (11). They treated a group of 65 evaluable patients with adriamycin and cyclophosphamide (AC) plus tamoxifen and compared this to a historical control group of patients treated with AC alone between 1973 and 1975. They concluded that AC plus tamoxifen was superior to AC alone. The other reported series utilizing an adriamycin combination is that of Tormey et al. (12). They reported a group of 135 patients with advanced breast cancer who had been previously treated with chemotherapy who were randomized to adriamycin plus dibromodulcitol ± tamoxifen. They did note an advantage to the tamoxifen-treated group. However, the response to chemotherapy alone in their series was quite low, probably reflecting the fact that the patients had been heavily previously treated.

Perhaps one of the most interesting observations of the present study is that patients who received prior adjuvant chemotherapy completed more than six months prior to protocol entry, responded well to CAF chemotherapy. This is despite the fact that almost all of this group of patients had received prior CMF, i.e., they had previously received at least two of the agents. Moreover, the response rate of these patients to CAF was essentially the same as those patients who had not been previously treated (47% vs 51%). This response rate is markedly better than the 20% to 25% expected for adriamycin alone in previously treated patients (1). This implies that patients who fail after completion of adjuvant chemotherapy are not inherently resistant to further

treatment with similar chemotherapeutic regimens.

The rationale for the combined use of endocrine therapy and chemotherapy appears sound especially since breast cancers have been shown to be heterogeneous tumors composed of ER-positive and ER-negative cells (5, 6). According to Osborne (13), a simple additive effect on tumor cell kill would be observed only if the endocrine therapy and chemotherapy did not interact with each other biochemically, biologically, or pharmacologically. The effects of hormonal manipulation on breast cancer cell kinetics suggest that traditional endocrine therapy may serve to antagonize the effects of certain cytotoxic drugs by blocking tumor cells in an unfavorable position in the cell cycle. With tamoxifen a progressively larger fraction of tumor cells is found accumulating in the G_1 phase of the cell cycle (13).

It must therefore be concluded that the addition of tamoxifen to CAF chemotherapy offers no therapeutic advantage regardless of estrogen receptor status. It must also be concluded that simultaneous chemoendocrine therapy utilizing cytotoxic drugs plus tamoxifen cannot be recommended.

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