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III. Antiestrogens in Combination with Chemotherapy in Early Breast Cancer

ADJUVANT ENDOCRINE THERAPY, CYTOTOXIC CHEMOTHERAPY AND IMMUNOTHERAPY IN STAGE II BREAST CANCER: 6-YEAR RESULT

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Summary—Six-year results of a prospective, randomized clinical trial of three treatment regimes [(1) cytoxan, methotrexate and 5-fluorouracil (CMF); (2) CMF plus the antiestrogen drug, tamoxifen (CMFT); (3) CMFT plus Bacillus Calmette–Guerin (BCG) vaccinations] in 312 women with stage II breast cancer are reported. Addition of tamoxifen to CMF therapy significantly decreased the number of recurrences at 6 years in ER+ patients with $\geqslant 4$ positive axillary lymph nodes, and in those with tumor diameter in excess of 3 cm. The beneficial effect of tamoxifen appeared to be independent of the menopausal status. Addition of tamoxifen to CMF had no effect on disease-free survival in ER+ patients with 1–3 positive axillary lymph nodes or in patients with ER− tumors. Addition of BCG vaccinations had no discernible effect on disease-free survival. ER measurements in the primary tumor provide important prognostic information regardless of treatment, with ER+ patients having increased overall survival after 6 years. Further follow-up is needed to determine whether tamoxifen is delaying recurrence or preventing it in a subset of these patients.

INTRODUCTION

Over the last 9 years, we have been conducting a prospective randomized clinical trial of adjuvant therapy of stage II breast cancer. Following total mastectomy with axillary clean-out, the patients were stratified according to the estrogen receptor (ER) status (positive or negative) and the number of positive axillary nodes (1–3 or >4). After stratification, the patients were randomly assigned to receive three-drug chemotherapy, three-drug chemotherapy plus the antiestrogen tamoxifen or three-drug chemotherapy plus tamoxifen plus BCG vaccination. Preliminary reports published so far have demonstrated that the addition of antiestrogen therapy to chemotherapy significantly prolongs the disease-free survival of patients with ER+ tumors [1–4]. In addition, our data have also shown that, regardless of the treatment, ER+ patients survive significantly longer than women with ER− tumors.

This report updates the result of this study to 6 years of actuarial analysis with a median follow-up of 6.2 years. The results confirm the beneficial effect of tamoxifen when added to chemotherapy in patients with ER+ tumors. Furthermore, it identifies specific subgroups among ER+ patients who are more likely to benefit from antiestrogen therapy.

EXPERIMENTAL

Patient selection, stratification and randomization, treatment regimens, methods of follow-up and statistical evaluation have been previously reported in detail [1–4] and will only be briefly reviewed here. All patients in this study underwent radical or modified radical mastectomy for primary breast cancer and had histologic evidence of axillary node involvement. ER analysis were performed in a single laboratory by one of us (W.L. McG.) using a dextran-coated charcoal method [5]. Seventy-four percent of the tumors in this series were ER+ (>3 fmol/mg cytosol protein).

After stratification for ER status and number of positive axillary nodes, the patients were randomly assigned to one of three treatment modalities.

(1) *CMF chemotherapy*—cytoxan (60 mg/m^2) was given orally from day 1 through 14 for each of 12 monthly cycles. Methotrexate (25 mg/m^2) and 5-fluorouracil (400 mg/m^2) were given i.v. on days 1 and 8 of each cycle. No chemotherapy was given for the latter 2 weeks of the month.

(2) *CMF + tamoxifen (CMFT)*—the patients were treated with the same combination chemotherapy + tamoxifen (20 mg orally twice a day), also given for 1 year.

(3) *CMF, tamoxifen and BCG vaccination*—these patients received BCG vaccination during the second year after completion of the chemotherapy and antiestrogen treatment.

Approximately 100 patients have been entered in each of the arms of the study between September of 1974 and June of 1979. The total number of patients evaluated in this trial is 312. No major differences in the three treatment groups were observed with regard to patients' age, number of positive axillary nodes,

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average ER value, average tumor size and menopausal status. The first endpoint of the study was evidence of recurrence either locally or at distant sites. A secondary endpoint was total survival. Therapy following recurrence was left to the discretion of the physician in charge of the patient.

Statistical analysis was performed using a generalization of the Kruskal–Wallis test [6, 7] and the generalized Wilcoxon test [8]. In addition, delay in recurrence was assessed on the basis of quartile analysis [9]. Delay in onset of metastasis was obtained whenever at least 25% (first quartile) and possibly 50% (second quartile) of the patients had recurred in each of two groups being compared.

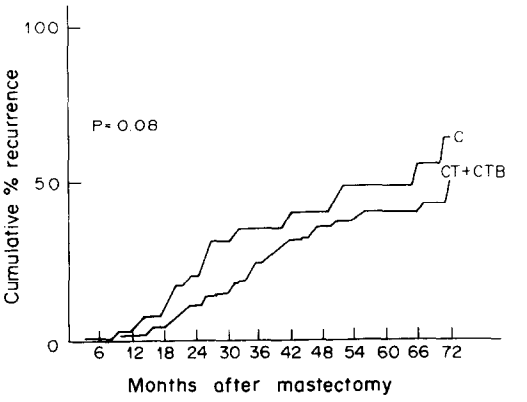

Fig. 1. Life-table plot of recurrence rate for ER+ patients divided according to treatment. C = chemotherapy; CT = chemotherapy + tamoxifen; CTB = chemotherapy + tamoxifen + BCG vaccination.

RESULTS

No significant difference in recurrence rate has been observed so far between the CMFT and the CMFT + BCG groups. Thus, the data for these two groups have been combined for comparison with patients treated with CMF alone. When all patients were included in the analysis, tamoxifen-treated women tended to recur less rapidly than those treated with CMF alone, but the difference was not statistically significant ($P = 0.11$). The beneficial effect of tamoxifen was more apparent when only ER+ patients were evaluated (Fig. 1) and reached clear statistical significance when the delay in relapse was analyzed according to the quartile system (Table 1). In contrast, no significant difference in recurrence rate between tamoxifen-treated and untreated patients was observed in women with ER− tumors ($P = 0.74$). Further analysis of the data revealed that, among ER+ patients, tamoxifen benefited those with tumor diameter in excess of 3 cm and those with $\geqslant 4$ positive nodes (Figs 2 and 3, Table 1). No benefit from tamoxifen was obtained by ER+ patients with 1–3 positive nodes (Table 1). Next, we compared the CMFT group with the CMF alone group with respect to menopausal status. Table 1 clearly indicates that both pre- and postmenopausal women benefited from tamoxifen therapy. However, when the data were evaluated according to life-table plot analysis, the beneficial effect of tamoxifen was of borderline statistical significance in postmenopausal (Fig. 4) but not premenopausal (Fig. 5) patients. It is possible that this finding may be due to the larger number of older women.

To date, no significant difference in overall survival has been observed between the three treatment groups. When total survival is evaluated with regard

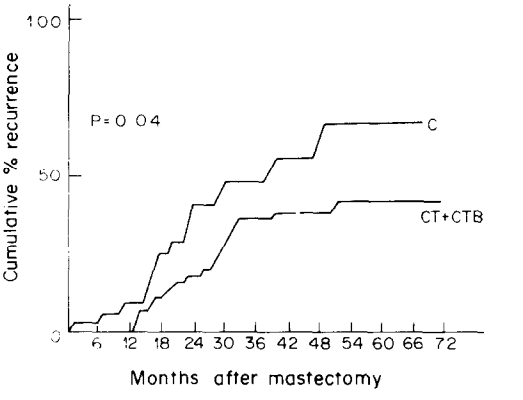

Fig. 2. Life-table plot of recurrence rate for ER+ tumors with a diameter >3 cm divided according to treatment.

Table 1

Group	Quartile	CMF (months)	CMFT (months)	Delay[a] (months)	P^b
ER+	1	25.2	35.5	10.2	0.024
	2	65.2	>72	>6.8	—
ER+: 1–3 positive nodes	1	70.0	66.2	−3.8	0.99
ER+: ⩾4 positive nodes	1	21.2	30.3	9.1	0.0034
	2	40.1	49.6	9.4	0.023
ER+: tumor diameter, 3 cm	1	21.1	30.8	9.7	0.00023
	2	40.8	>72	>31.2	—
ER+: premenopausal	1	30.5	39.1	8.6	0.0095
ER+: postmenopausal	1	24.2	35.3	11.1	0.0086
	2	50.7	71.4	20.7	<0.000001

[a]Delay in recurrence obtained with the addition of tamoxifen to chemotherapy in the groups indicated. Delay was calculated when 25% (1st quartile) and 50% (second quartile) of patients had relapsed in each group.

[b]Computed for a one-tailed test.

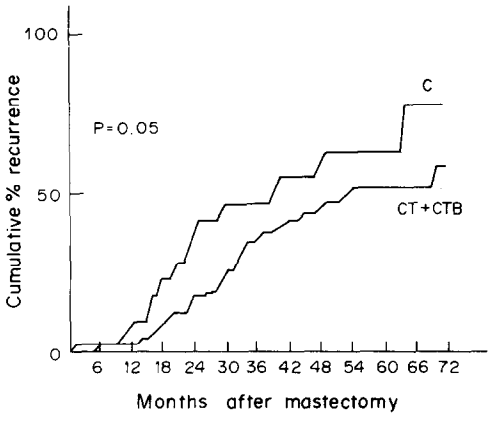

Fig. 3. Life-table plot of recurrence rate for ER+ patients with ⩾4 positive axillary nodes divided according to treatment.

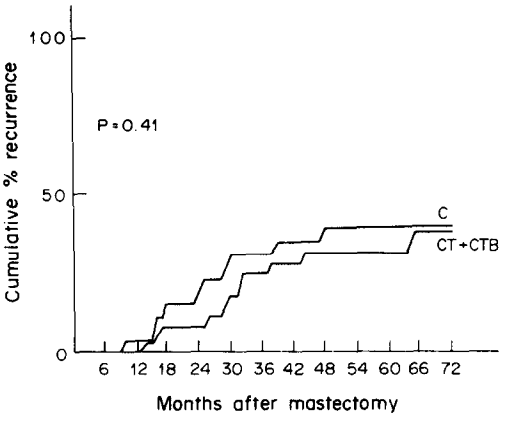

Fig. 5. Life-table plot of recurrence for ER+ premenopausal patients divided according to treatment.

to the receptor status irrespective of the treatment used, it is clear that ER+ patients lived significantly longer (Fig. 6).

DISCUSSION

Endocrine treatment was the first adjuvant systemic therapy to be used in women with primary operable breast cancer in an attempt to decrease the possibility of relapse in these patients. Castration induced by radiation or surgery has been frequently found to delay the onset of recurrence in premenopausal patients [10–12], although this beneficial effect has not been universally observed [13]. With the introduction of the antiestrogen, tamoxifen, over 10 years ago, new adjuvant trials with this antihormone have been undertaken in women with primary, operable breast cancer. Several preliminary reports have shown that this drug is capable of improving disease-free survival in a fraction of breast cancer patients [14–16]. The 6-year results of our study show that tamoxifen plus three-drug chemotherapy significantly increases disease-free survival in women with ER+ tumors as compared to three-drug chemotherapy alone. When patients were divided according to the number of axillary nodes involved with tumor, it is apparent that only ER+ patients with ⩾4 positive nodes obtained significant improvement from the addition of tamoxifen. In addition, only patients with the larger primary tumors obtained significant benefit from tamoxifen therapy. Thus, it appears that the patients with a more advanced stage of disease exhibited the most benefit from the addition of antiestrogens. It is of interest that in a recent adjuvant clinical trial where tamoxifen alone was compared to no treatment, only patients with ⩾4 positive nodes appeared to benefit from antiestrogen therapy [16]. In contrast, Fisher *et al.*[14] observed that the beneficial effect of tamoxifen added to two-drug chemotherapy was independent of the nodal status. However, close analysis of their data reveals that the effect of tamoxifen was more significant in women with ⩾4 or more positive nodes than in those with 1–3 positive nodes. It is of interest that in our trial for the first 2.5 years, tamoxifen-treated patients with 1–3 positive nodes had fewer recurrences than

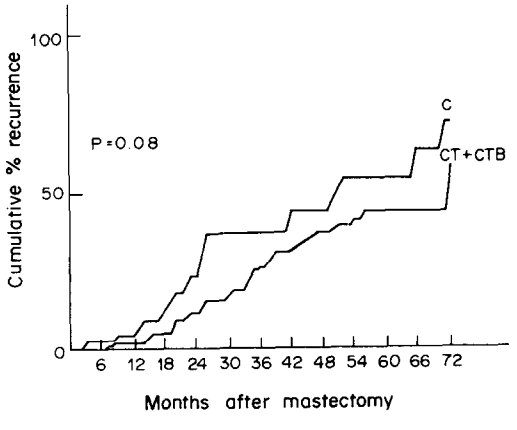

Fig. 4. Life-table plot of recurrence for ER+ postmenopausal patients divided according to treatment.

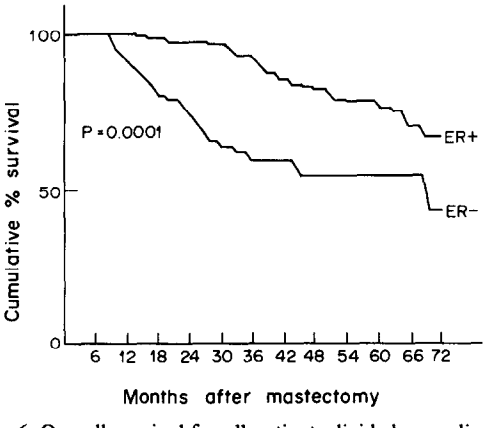

Fig. 6. Overall survival for all patients divided according to the ER status of the primary tumor, irrespective of the treatment used.

those treated with CMF alone and that only after 2.5 years, the curves crossed over [17]. Since Fisher *et al.* report their data at 2 years, it will be of interest to see their results on a longer follow-up.

Our results indicate that the beneficial effect of tamoxifen is independent of the menopausal status. Although life-table plot analysis did not show a significant difference in disease-free survival between tamoxifen-treated and untreated ER positive premenopausal patients, quartile analysis revealed that tamoxifen induced a significant delay in recurrence in this group of patients. This finding is somewhat at variance with the report by Fisher *et al.*[14] who observed no benefit from the addition of tamoxifen to two-drug chemotherapy in ER+ patients less than 49-years old. In agreement with our results, in a recent adjuvant clinical trial where tamoxifen was compared to no treatment, improvement in disease-free survival was demonstrated both for pre- and postmenopausal women [15].

Finally, our results show that ER measurements in the primary tumor continue to provide important prognostic information after 6 years of follow-up. Progesterone receptor (PgR) were also measured in a subset of the patients in this trial and Clark *et al.*[18] have recently reported an analysis of this data. PgR levels were also found to yield significant prognostic information in this group of patients which was not dependent upon the treatments used. Multivariant analysis of multiple prognostic factors showed that PgR and the number of positive nodes remained significant in predicting disease-free survival whereas ER was no longer significant. This apparent superiority of PgR over ER needs confirmation but suggests that both ER and PgR should be measured in future clinical trials.

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