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Tamoxifen and Oophorectomy in the Treatment of Recurrent Breast Cancer[1]

A Southwest Oncology Group Study

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ABSTRACT

The relatively short survival following chemotherapy in patients with metastatic carcinoma of the breast and the introduction of antiestrogens has led to renewed interest in the hormonal therapy of breast cancer. Pritchard *et al.* (Cancer Treat. Rep., *64:* 787–796, 1980) have recently stated that response to the antiestrogen tamoxifen (TAM) strongly predicts a subsequent response to oophorectomy in premenopausal patients. The Southwest Oncology Group administered TAM to pre- and postmenopausal women with first recurrence of breast cancer. Following response and subsequent relapse, or after no response, patients underwent an oophorectomy while continuing on TAM. None of 14 premenopausal patients who responded to TAM had a response to oophorectomy plus TAM, while 5 of 22 had a remission with oophorectomy plus TAM after initially failing with TAM alone. The reverse was seen in postmenopausal women; 4 of 18 responders to TAM subsequently responded to oophorectomy plus TAM, but none of 18 TAM failures responded to oophorectomy plus TAM. These results suggest that in the premenopausal women the TAM dose may be insufficient to block all estrogen action and that oophorectomy, by removing the major source of estrogen, can result in a more effective antiestrogen action of TAM leading to a response. No explanation is readily available for the results in postmenopausal patients.

INTRODUCTION

Before the 1970's, it was usual for a recurrence of breast cancer to be treated first with endocrine therapy. Chemotherapy has changed this; *i.e.*, only one-third of 281 patients with metastatic breast cancer from 21 institutions of SWOG[3] had been on estrogen or androgen therapy before they were started on a chemotherapeutic trial (2). The introduction of antiestrogens and the relatively short survival following chemotherapy is beginning to direct oncologists back to endocrine manipulation as the first line of treatment. The importance of estrogen and progesterone receptor proteins in predicting the outcome of hormonal therapy is well known (4), but unfortunately, in most patients with metastatic disease, the status of tumor markers is unknown. Since ovarian ablation, adrenalectomy, and hypophysectomy are of potential benefit in some patients, it is important to find ways of predicting such benefit. Pritchard *et al.* (9) have recently stated that response to the antiestrogen TAM strongly predicts a subsequent response to oophorectomy in premenopausal patients.

Members of SWOG have studied the efficacy of TAM and of ablative surgery in patients with recurrent breast cancer, all of whom were previously untreated for their recurrence.

Both pre- and postmenopausal patients were initially treated with TAM. After response and subsequent recurrence or after failure to respond, the patients underwent an oophorectomy, and the TAM was continued. It was hoped that by removing the ovaries as the major source of estrogen the antiestrogen would be more effective. The biological effects of TAM in the postmenopausal women are not yet clearly understood; therefore, SWOG wished to reopen the question of oophorectomy in postmenopausal patients under these new circumstances. This report gives the outcome of part of that study and discusses the results in relation to those reported by other investigators.

MATERIALS AND METHODS

The eligibility criteria were as follows: (*a*) first recurrence of breast cancer; (*b*) no treatment of the recurrence other than a biopsy to confirm the diagnosis, not even radiotherapy; (*c*) treatment of the primary breast cancer with radical or modified radical mastectomy; (*d*) pre- or postmenopausal status with intact ovaries (For the purpose of this study, premenopause is defined as active menses and postmenopause as cessation of menses for 1 year or longer.); (*e*) eligibility despite any use of birth control pills or estrogens to alleviate symptoms of menopause prior to discovery of the recurrence; (*f*) patients with ER-unknown or ER-positive tumors (patients with ER-negative tumors were ineligible); (*g*) no extensive liver or pulmonary involvement which in the opinion of the investigators could preclude surgical intervention.

The entire treatment plan, including the surgery, was explained to the patient before an informed consent could be obtained. All patients were started on TAM (10 mg twice a day). Patients who clearly had progressive disease after 3 to 6 weeks underwent an oophorectomy. The other patients were treated for 10 weeks and continued thereafter if they had acceptable stable disease or response, until the disease progressed or a relapse took place, at which time the oophorectomy was performed. It is important to note that TAM was continued after the oophorectomy. Ovarian ablation by radiation was not permissible. Surgical guidelines for oophorectomy were included in the protocol. The criteria for response and for toxicity were those formulated by the Breast Cancer Task Force (3).

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[3] The abbreviations used are: SWOG, Southwest Oncology Group; TAM, tamoxifen; ER, estrogen receptor.

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The study parameters before entering the study included: histopathological review of the original tumor and new biopsy by the Pathology Committee of SWOG; biopsy of accessible tumor for ER assay; tumor measurements according to the Breast Cancer Task Force guidelines; bone marrow biopsy, complete blood count, blood urea nitrogen, creatinine, calcium, aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase, and chest X-ray; bone scan and X-ray of suspicious areas on the bone scan; and liver scan if physical examination or liver chemistries were abnormal.

Characterization of the patients with respect to prognostic discriminants is shown in Table 1. At the time of entry into the study, nearly one-half of the patients had either a normal or near-normal performance status; but at time of oophorectomy, only 24% of pre- and 33% of postmenopausal women had a normal performance. A little over one-half of the patients had a disease-free interval of 2 years or less; very few were disease free for longer than 5 years.

Table 1
Characteristics of the 2 groups of patients

Characteristic	Premenopausal (%)		Postmenopausal (%)	
	TAM	Oophorectomy	TAM	Oophorectomy
Performance (10)				
0	45	24	49	33
1	47	58	46	51
2	8	18	5	15
Sites of metastases				
Bone	60.5	63	61.5	61.5
Local-regional	71	66	49	51
Lung	13	13	20.5	23
Pleura	10.5	18	15	11
Liver		13	11	11
Disease-free interval				
≤12 mos.	16		31	
13–24 mos.	37		23	
25–60 mos.	34		33	
>60 mos.	13		13	
ER				
Positive	21		10	
Unknown	79		90	
Postmenopause				
13–60 mos.			36	
61–120 mos.			23	
>120 mos.			41	

RESULTS

Of 43 eligible premenopausal women, 40 (93%) had an oophorectomy. One patient refused surgery, one was lost to follow-up, and the physician advised against the operation in one patient. Two patients were declared nonevaluable, one because no TAM was given after oophorectomy and one because the physician added chemotherapy to the TAM. Of 61 eligible postmenopausal patients, 40 (66%) had ovarian ablation. In 7 who did not the investigator decided against the surgery; 6 patients refused, 3 were lost to follow-up, and no reason was given for 5 patients. One patient who had a total hysterectomy for endometrial cancer while still in remission from TAM was declared nonevaluable.

The average elapsed time between discovery of the recurrence and the registration on the protocol was 0.89 month for premenopausal patients and 1.83 months for postmenopausal patients. For only 4% of all patients was the delay longer than 4 months.

The response to TAM is shown in Table 2. Each site of involvement was evaluated for the individual patient. Overall, there were 37% responding premenopausal patients and 46% postmenopausal patients. Visceral involvement responded just as frequently as did soft tissue disease, while response of skeletal tumor, which is difficult to judge at best, occurred in only 18% of patients. None of the premenopausal women had liver metastasis, while this was present in 4 postmenopausal women, of whom 3 responded. The median duration of response was 274 days for premenopausal women (range, 102 to 1037 days) and 444 days for postmenopausal patients (range, 101 to 970 days). The 5 patients with stable disease were on TAM for 127 to 343 days (median, 203 days). There were 10 patients with no response, and these were on TAM for a median of 112 days (range, 49 to 186 days). The range for patients with increasing disease was 22 to 147 days (median, 65 days). Only 4 patients (5%) were started on the second phase of the study after 3 to 6 weeks because of progressive disease.

The results of the oophorectomy plus TAM are shown in Table 3. None of the premenopausal women who had responded previously to TAM subsequently had a beneficial effect from ovarian ablation plus TAM. However, 5 of 22 patients who had not responded to TAM or who had increasing disease, had a complete response or a partial response subsequently. The ages of these 5 patients were 33, 36, 37, 46, and 49 years, and they had been on TAM for 85, 88, 147, 54 and 42 days, respectively. In the postmenopausal patients, the opposite was found; namely, responses to oophorectomy plus TAM were only seen in women who had previously responded to TAM alone. Their time on TAM alone was 101, 217, 262, and 675 days, and they were 81, 85, 64, and 194 months postmenopausal, respectively. The median duration of response of the 9 patients was 290 days, lasting up to 1595 days, while the median duration of stable disease was 255 days (range, 122 to 854 days). The sites of involvement in these responding patients did not differ significantly from those of the nonresponding patients.

ER assays were positive in 13 patients. Only 3 responded to TAM, and a fourth had a partial response with oophorectomy plus TAM. Only one of 4 patients with an assay value over 100 fmol/mg had a response to either type of hormonal therapy. The survival while on TAM and oophorectomy plus TAM is slightly longer for the postmenopausal women than for the premenopausal patient with the median times of 32 and 48 weeks, respectively (Chart 1). A bias has been introduced, since 21 postmenopausal women who were potential oophorectomy candidates were not included in the survival curves, as were 3 eligible premenopausal patients.

DISCUSSION

The treatment of advanced breast cancer with TAM has been reported by several investigators, but never in a study of patients with a first recurrence which had not been treated previously with radiotherapy, other hormones, or chemotherapy. Our results may therefore have some significance for comparison with future studies.

This is the third study which reports the effects of ovarian ablation following TAM. Pritchard *et al.* (9) studied only premenopausal patients. They report no response following oo-

Table 2
Metastatic involvement and response to TAM by menopausal status

Site	Patients		Involved sites/patient		Response			CR[a] + PR (%)
	No.	%	No.	Mean	CR	PR	Stable	
Soft tissue								
Premenopausal	27	71	34	1.26	4	8	3	44
Postmenopausal	20	51	25	1.25	6	4		50
Visceral								
Premenopausal	7	18	9	1.29	1	2		43
Postmenopausal	15	38	18	1.20	4	5	1	60
Skeleton								
Premenopausal	23	61	23	1.00		3	3	13
Postmenopausal	22	56	22	1.00	2	3	5	23
Total								
Premenopausal	38	100	66	1.72	4	10	2	37
Postmenopausal	39	100	65	1.67	7	11	3	46

[a] CR, complete response; PR, partial response.

Table 3
Response to oophorectomy plus TAM in relation to response to TAM

TAM	No. of patients	Oophorectomy + TAM		
		CR[a] + PR	Stable	NR + ID
Premenopausal				
CR + PR	14		2	12
Stable	2			2
NR + ID	22	5	2	15
Postmenopausal				
CR + PR	18	4	3	11
Stable	3			3
NR + ID	18		3	15

[a] CR, complete response; PR, partial response; NR, no response; ID, increasing disease.

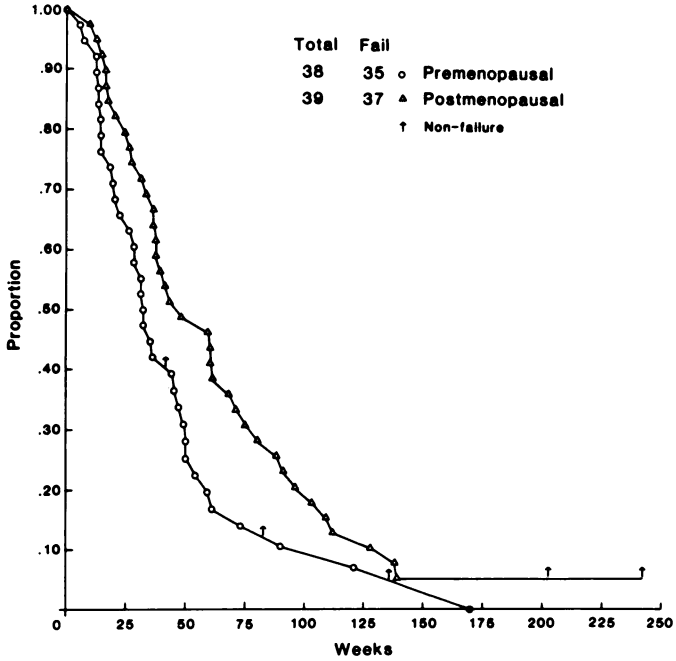

Chart 1. Survival while on TAM and oophorectomy plus TAM.

phorectomy in 13 patients who had failed on TAM and 6 responses after ovarian ablation among 8 patients who had responded to TAM initially. A review of the report reveals that a total of 19 patients had ovarian ablation, without the addition of prednisone or chemotherapy. The result of TAM treatment was not assessable in 3 of these 19, and in one patient it was too early to evaluate the result of the ablation. Of the remaining 15 patients, all were considered to have failed on TAM, 6 of whom were on that drug from 9 to 35 days. None of the 11 responded to the ablation. Four patients had a response to ovarian ablation. Of these, 2 had a previous response while on TAM, one was considered to have stable disease after only 28 days on the drug, and the best responder to ablation was not assessable, as far as response is concerned, after 43 days on TAM.

Fabian *et al.* (1) have shown that a dose of 10 mg/sq m twice daily leads to peak TAM blood levels for responders in 4 to 6 weeks, although 75% of the patients have by Day 7 reached the lowest value observed in a responder (70 ng/ml). The use of 10 mg twice a day in our study may in part explain the discrepancy between our results and those already in the literature. At least one-half of the patients have a TAM level ≥70 ng/ml 3 weeks later, a level which is still associated with response. It is therefore possible that the response attributed to oophorectomy in these last 2 patients may have been induced partly by the continued influence of TAM.

In the study by Pritchard *et al.* were 2 patients who had a partial response to TAM and subsequently had a response to the ablation, whereas none of our 14 responding premenopausal women had a subsequent response to oophorectomy plus TAM. Continuation of the TAM is the difference between 2 studies. We do not have a good explanation as to why we saw no results with oophorectomy plus TAM in patients who previously had responded to TAM and had 5 responses in 22 women who had failed on TAM. Manni and Pearson (7) performed an oophorectomy on 5 patients, and in 4 of these the TAM was continued. Two women who had failed on the drug alone also failed after ovarian ablation plus continued TAM, while one of 2 TAM responders had a response to oophorectomy. The authors suggest that in this last patient the dose of TAM was insufficient to block all estrogen action and that oophorectomy, by removing the major endogenous source of estrogens, permitted more effective antiestrogen action of TAM, and that this resulted in tumor regression. If this were the explanation for that patient, one must wonder why the patient had responded to the drug alone for 10 months. During the design of our study, we postulated that in premenopausal

women who did respond to TAM all estrogen action was blocked by the drug and that after relapse an oophorectomy plus continued TAM would have no effect, whereas in patients who did not respond to TAM the oophorectomy might allow TAM to become effective. The results appear to support this postulate.

Regression of tumor following castration in postmenopausal women has been reported, but for most of these patients it had been less than 2 years since the last menstrual period, and castration alone is regarded as of no real value in the truly postmenopausal women (5). TAM has no effect on serum estrogens and gonadotropins in postmenopausal women (8), and we are at a loss to explain the responses following oophorectomy plus TAM in 4 of our patients. Kiang *et al.* (6) followed the TAM therapy with a hypophysectomy. Two of 7 responding patients to TAM also had a remission following hypophysectomy, but 2 who failed on TAM also failed after hypophysectomy. One of the responders was 68 years old. The authors could not explain the results of their study.

The results with TAM in our study are not peculiar as far as response rates and response duration are concerned, since similar results have been reported by other investigators. The results do raise several questions about the biology of breast cancer and ovarian function in relation to antiestrogen therapy. No answers are readily available to such questions at the present time, either from us or from several other investigators with whom we have discussed the results.

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