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Phase-II Trial of Tamoxifen in Advanced Breast Cancer

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Summary. *Seventy-eight advanced breast cancer patients, most of whom had had prior treatment, were treated with the synthetic antiestogen tamoxifen. The overall objective response rate was 27% (21/78). An additional 19% (15/78) showed disease stabilization. Sixty-seven percent (14/21) of the responses were in soft tissue sites, 24% (5/21) on bony sites and one each occurred in liver and nodular lung disease. Forty percent of patients with soft-tissue disease alone responded, while < 10% of patients with visceral disease showed responses in visceral sites. The response rate was 28% among patients with a known positive estrogen receptor (ER) assay. It was 21% among patients who had previously received cytotoxic drugs. Toxicity was mild and was seen in nausea and vomiting, hot flushes and vaginal bleeding, and occasional myelosuppression. One patient was withdrawn from the study because of a rash. In two patients the disease flared, once with concomitant hypercalcemia. Tamoxifen is a useful agent for advanced breast cancer even in some patients with visceral disease.*

Introduction

Antiestrogenic compounds, such as nafoxidine, tamoxifen and clomiphene, have been used in Europe for advanced breast cancer with good results [1, 2, 10]. Evaluation of tamoxifen in the United States has shown objective response rates in the range of 28%–53% [6, 8]. We report the response rate in a series of postmenopausal patients with advanced followable breast cancer, most of whom had received previous therapy. The data are analyzed for factors useful in predicting the likelihood of response. Some of these patients were presented at the Tamoxifen Workshop, Key Biscayne, Florida, April 1976 [7].

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Patients and Methods

Women selected for the study had histologically proven breast adenocarcinoma with either a local recurrence or distant metastatic disease that could be objectively measured. Prior cytotoxic or hormonal therapy did not disqualify a patient. Tamoxifen was obtained from ICI United States and patients gave informed consent for inclusion on the study. Initially patients started at a dosage of 10 mg PO bid, with escalation to 20 mg bid as tolerated. Subsequently the treatment dosage was fixed at 10 mg bid.

Pretreatment CBC, liver chemistry, and serum calcium, in addition to accurate measurement of the indicator lesions, were obtained. Patients were evaluated at intervals of 2 weeks to 1 month with physical examination, repeat blood studies, and X-rays and scans as needed. Complete response (CR) was defined as the disappearance of all objective evidence of disease, without the appearance of new lesions and with the recalcification of osteolytic bone lesions. Partial response (PR) was defined as a 50% or greater decrease in the product of the two largest perpendicular diameters of measurable lesions, partial recalcification of osteolytic lesions, or resolution of lesions on bone scan, with no progression in other sites or appearance of new lesions. 'No change' indicated a decrease of less than 50% of the measurable lesions, or symptomatic improvement in bone pain. 'Progression' indicated an evident increase in the size of the original lesion, or the appearance of new lesions. Patients who had progressive disease were given alternate forms of therapy.

Results

Ninety-five patients were treated with tamoxifen, and 78 were considered evaluable. The 17 nonevaluable cases were patients who received concurrent chemotherapy [6], who were treated for less than one month [4], who were lost to follow-up, or who on careful review did not have measurable disease [3]. The remaining four were excluded for a variety of reasons. The median age of the evaluable patients was 55 years, with a range of 33–81. Only three patients (4%) had received no therapy other than primary surgery (Table 1); 53% had received at least two therapeutic modalities and 57% had undergone prior hormonal manipulation. Sixty-seven percent of the patients had a performance status (ECOG 0–4)

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Table 1. Number of evaluable patients, distributed by prior therapy[a]

Previous treatment	No. (%)
No prior therapy	3 (4%)
Chemotherapy only	4 (5%)
Hormonal therapy only	10 (13%)
Radiation therapy only	8 (10%)
Chemo and hormonal	4 (5%)
Chemo and radiation	6 (8%)
Hormonal and radiation	24 (31%)
Chemo, hormonal, and radiation	19 (24%)

[a] Hormonal therapy includes abblative procedures. All categories include therapy given in the surgical adjuvant situation

Table 2. Relation of onset of menopause to TAM response

	Partial response	No change	Prog. dis.
Natural (43)	13/43 (30%)	8/43 (19%)	22/43 (51%)
Surgery- (35) or radiation-induced	8/35 (23%)	7/35 (20%)	20/35 (57%)
Years after menopause			
0–5 (39)	9/39 (23%)	9/39 (23%)	21/39 (54%)
> 5 (39)	12/39 (31%)	6/39 (15%)	21/39 (54%)

Table 3. Correlation of TAM response with ER assay

	Partial response	No change	Prog. dis.
ER-positive	8/29 (28%)	5/29 (17%)	16/29 (55%)
ER-negative	0	0	3/3 (100%)
ER not done	13/46 (28%)	10/46 (22%)	23/46 (50%)

of 0 or 1 at the onset of therapy, while the remaining 33% were at a performance level of 2 or 3. Sixty patients were treated with 20 mg bid and the remaining 18 with 10 mg bid. The objective response rate of evaluable cases was 27% (21/78), with one CR and 20 PRs; the median duration of response is in excess of 4 months (range 1+ to 16+), with 16 patients still in remission. Fifteen patients (19%) had either symptomatic relief of bone pain or disease stabilization for a minimum of 2 months, and the remaining 42 cases (54) showed progressive disease.

All evaluable patients were postmenopausal upon entry into the study (Table 2), and no significant response differences existed between patients who had a natural (30% response) and those who had a surgical or radiation-induced menopause (23%). The differences in response rate between intramenopausal (0–5 years) and postmenopausal (> 5 years) patients were also not significant. The sites of objective response in the 21 responding patients were 14/21 (67%) in soft-tissue sites, 5/21 (24%) in bone, and one each in liver and lung. Among the 14 patients showing soft-tissue responses, a total of six occurred in the 15 patients who had only soft-tissue disease, six were in the 15 patients who had soft tissue plus bone disease (40%), and two occurred in a group of nine patients with associated visceral disease (22%). Thus the response rate for patients with disease confined to soft tissue was high (40%). By contrast there were < 10% responses in visceral sites (2/23) in patients with disease involving visceral organs. In the patient with responding hepatic metastases, the response duration was 4 months, measured from the documentation of significant decrease in hepatomegaly.

Results of estrogen receptor (ER) assays, performed by the dextran-coated charcoal method, were available for 32 patients. The assays had been performed on a metastatic lesion in approximately two-thirds of cases and on the primary tumor in approximately one-third. The correlation of the ER assay with tamoxifen response is shown in Table 3. Twenty-nine of the 32 patients demonstrated estrogen-binding protein at levels greater than 10 fmol/mg protein, and only eight of these 29 (28%) patients experienced objective regression of their disease. No patient with a negative ER assay (ER-) responded to tamoxifen. In the patients in whom an ER assay was not performed, 28% responded, 22% remained stable, and 50% demonstrated progressive disease.

Nineteen of the 21 responding patients had been previously treated with one or more forms of hormonal manipulation (i.e., ovariectomy, adrenalectomy, estrogens, or testosterone), and in 14 of these patients it was possible to determine their response to that therapy (Table 4): 4/14 (29%) had responded, 6/14 (43%) had progressed, and 4/14 (29%) had exhibited no change or only a symptomatic response. Conversely, there were 14 patients in the overall group of 78 who had responded to prior hormonal therapy. Of these 14 patients, four (29%) responded to tamoxifen, six (43%) progressed, and four (29%) showed stabilization. Seven of the 21 responding patients had previously been treated with some combination of cytotoxic drugs, and of these seven, three had responded to chemotherapy, three had progressed and one result could not be determined. Of the 33 patients out of the entire group of 78 who had received prior chemotherapy, seven (21%) responded to tamoxifen.

Table 4. Tamoxifen response in patients who responded to previous hormone manipulation

Partial response	No change	Progression
4/14 (19%)	4/14 (29%)	6/14 (43%)

Table 5. Side effects of tamoxifen

Side effect	No. affected
Nausea and vomiting	12
Myelosuppressive effect	5
Transient leukopenia	3
Decreased hematocrit and platelet count	1
Thrombocytopenia	1
Hot flushes	7
Vaginal bleeding	2
Disease flare	2
Erythematous rash	2

In general, the toxicity of tamoxifen was mild (Table 5). Nausea and vomiting occurred in 12/78 (15%) patients, and in only one did it necessitate withdrawal from the study. Three patients exhibited transient mild leukopenia associated with tamoxifen administration. In each case the fall was from a baseline of 4000–6000 WBC/mm^3 to a nadir of 3000–3500/mm^3. The nadirs occurred 4–8 weeks after initiation of the therapy and resolved over the subsequent 12 weeks. Two patients with extensive disease at the initiation of therapy showed falls in the hematocrit and platelet count while in tamoxifen. One had 7 days of the drug, during which time she experienced rapid disease progression and a concomitant fall in the platelet count from 200,000/mm^3 to 20,000/mm^3. There was not a clear relation between her disease progression and thrombocytopenia and tamoxifen administration, and she died 13 days after the drug was started. The second patient showed advancing disease over a 5-week course of tamoxifen, with a progressive fall in hematocrit from 31% to 22% and in platelet count from 180,000/mm^3 to 46,000/mm^3. After four weeks of therapy she also manifested moderate vaginal bleeding. No patient with stable or responding disease showed thrombocytopenia that could be clearly ascribed to tamoxifen administration.

Five patients had not flushes and two patients had vaginal bleeding. One patient had marked acceleration of skin disease and hypercalcemia (18 mg/100 ml) associated with tamoxifen administration and two patients developed an erythematous rash. In one of these two, therapy was discontinued. In the other it was interrupted for 2 weeks and the rash resolved.

Discussion

In this series of 78 evaluable postmenopausal patients with metastatic breast cancer, treatment with tamoxifen produced a 27% objective response rate. Other investigators have reported objective response rates varying from 22% to 52% [2, 4, 5, 7–10]. In different studies, response to tamoxifen has been variably correlated with the presence of estrogen-binding protein in the tumor [5, 6]. Lerner et al. [6] reported 13 patients with positive ER assays, nine of whom (69%) responded to tamoxifen, while Tormey et al. [8] reported only 2/10 responses to tamoxifen alone in patients with positive ER assays and Heuson [3] noted 8/25 (32%) responses in ER+ cases. In the present series, a positive ER assay (29 cases) predicted tamoxifen responsiveness in 28% (8 cases). The differeing response rates obtained in patients with positive ER assays may be related to different definitions of ER positivity. In addition, a mixed population of tumor cells, with or without ER, and different areas in the same tumor showing high or low estrogen-binding capacity could account for lower response rates in ER+ patients [1]. Other factors thought to be prognostic for tamoxifen responsiveness were also not confirmed in our series. The response rate in patients with prior chemotherapy was almost equivalent to the rate in those who had had none previously, and prior hormone responsiveness did not appear to be of prognostic significance. It should be noted, however, that this population of patients had been treated rather extensively prior to entry to the study. In addition, the number of patients in each prognostic category was rather small for a significant effect to be seen.

Objective response was observed most frequently in soft tissue, with 14/21 (67%) responses occurring in these sites and 40% of patients with only soft-tissue disease responding. Patients with dominant bone disease demonstrated a 25% response rate. Patients with visceral disease responded less frequently. However, of four patients in the group with hepatic metastases, one showed a response, indicating that the presence of liver disease need not necessarily rule out a therapeutic trial of tamoxifen.

Tamoxifen is a relatively nontoxic and effective addition to the range of agents that are useful in breast cancer. Its efficacy compares with that of additive therapy with diethylstilbestrol (DES). Furthermore, its side effects are less severe than those of high doses of DES. Ongoing and future studies will define its effectiveness relative to that of DES in postmenopausal patients and as an adjunct to ovariectomy in premenopausal patients.

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