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Evaluation of Estrogen Dependency of Human Breast Cancers

II. Clinical evaluation of tamoxifen in advanced primary and recurrent breast cancer*)

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ABSTRACT

An antiestrogen (tamoxifen) was given to 17 patients with advanced breast cancer (both recurrent and primary cancers) during a period from June 1981 to September 1983. The response rate to the antiestrogen was 47.8% (8/17). Sixty percent (6/10) of patients with estrogen receptor positive (ER +) responded, compared with 16.7% (1/6) of patients with estrogen receptor negative (ER −). Fourty percent of patients with soft tissue/lymph nodes involvement responded, compared with 27.2% in patients with bone metastasis, and 25.0% in patients with visceral involvement. Postmenopausal patients responded more than premenopausal ones. In recurrent cases, the response rate increased with the prolongation of disease free interval.

Eight out of 17 patients are still alive, and the longest survival case has been in a condition of partial response for 23 months so far. The mean survival period in 9 deaths was 13±9 months, with longest 32 months.

As shown here, some patients with advanced breast cancer respond very well to the therapy. From these results, we think the tamoxifen-containing endocrinotherapy in combination with chemotherapy is effective in treatment of advanced cancer and its active application may enable patients to live longer in the rehabilitated situation.

INTRODUCTION

Surgical castration and androgens had predominated in the treatment of advanced breast cancer but androgens' adverse reactions including liver function disorders and masculinization interrupeted the long-term use of these drugs. Since 1963, tamoxifen (Nolvadex®) which is a non-steroidal antiestrogen origionally developed by ICI Limited (UK) has been replacing extirpation of endocrine organs and androgens in the USA and European countries, being appraised as a drug with a few side effects for a long-term use.

The purpose of this study is to evaluate tamoxifen mainly on the basis of clinical results in 17 cases treated with the drug.

MATERIALS AND METHOD

We administered tamoxifen to 17 out of all patients with advanced breast cancer (including both primary and recurrent cancers) whom we treated during a period from June 1981 to September 1983. To 15 of them, tamoxifen was given in combination with other adjuvant therapies: chemotherapies to 13 (76.5%) cases; radiotherapy to 4 (29.4%); and further combined with other endocrinotherapy and immunotherapy to 3 of each group.

The response was rated at complete response

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(CR), partial response (PR), no change (NC), and progressive disease (PD) according to UICC criteria, and CR and PR were judged responsive. The 17 cases consisted of 16 female and 1 male, and 8 primary breast cancers and 9 recurrent breast cancers.

The metastasis/recurrence involved soft tissue and lymph nodes in 10 cases, bone in 11 cases, and the viscera in 8 cases.

Seven were premenopausal, 4 were postmenopausal for less than 5 years (perimenopausal), and 5 were postmenopausal for 5 years or longer.

Ten were ER+, 6 were ER−, and 1 was unknown (Table 1).

Table 1. Background Factor in Patients Studied

No. of Patients	17
Tumor	
Primary	8
Recurrent	9
Involved Sites	
Soft tissue/Nodal	10
Osseous	11
Visceral	8
Menopausal Status	
Premenopausal	7
Perimenopausal	4
Postmenopausal	5
Estrogen Receptor	
Positive	10
Negative	6
Unknown	1
Prior Therapy	
Yes	10
No	7

RESULT

CR was seen in 2 patients, PR in 6, NC in 5, and 4 in PD. A combination of first two resulted in the response rate of 47.8% (8/16) (Table 2).

Table 2. Response Rate of Tamoxifen

Effect*	No. of Patients		Response Rate (%)
CR	2	8	47.0
PR	6		
NC	5	9	53.0
PD	4		

* CR: Complete Response
PR: Partial Response
NC: No Change
PD: Progressive Disease

Six out of 10 ER+ patients (60%) responded to the therapy, while only one of 6 ER− (16.7%) patients did (Table 3).

Table 3. Response Rate to Tamoxifen: According to Estrogen Receptor

Estrogen Receptor	No. of Patients	No. of Responder (%)
Positive	10	6 (60.0%)
Negative	6	1 (16.7%)
Unknown	1	1 (100.0%)
Total	17	8 (47.0%)

When the results were correlated with the site of involvement, the response rate was relatively high (50%) in patients with soft tissue/lymph nodes involvement, compared to 27.2% of patients with bone metastasis, and 25.0% of patients with the visceral involvement (Table 4).

Table 4. Response Rate of Tamoxifen: According to Lesions

Lesions	No. of Patients	No. of Responder (%)
Soft tissue/nodal	10	5 (50.0%)
Osseous	11	3 (27.2%)
Visceral	8	2 (25.0%)

The response rate by each menstrual status, was 42.9% in premenopausal patients, 50% in perimenopausal patients who have been postmenopausal for less than 5 years, and 60% in postmenopausal patients for 5 years or longer (Table 5).

Table 5. Response Rate of Tamoxifen: According to Menopausal Status

Menopausal status	No. of Patients	No. of Responder (%)
Premenopausal	7	3 (42.9%)
Perimenopausal	4	2 (50.0%)
Postmenopausal	5	3 (60.0%)

The response rate in patients treated with tamoxifen only was 50.0% (2/4), not significantly different from that in combination therapy group, 46.1% (6/13) (Table 6).

Table 6. Response rate of Tamoxifen: According to combined Chemotherapy (concurrent)

Combined Chemotherapy (concurrent)	No. of Patients	No. of Responder (%)
Yes	13	6 (46.1%)
No	4	2 (50.0%)

In 5 cases of recurrent breast cancer, the disease free interval was 76±7.73 months in responder group (CR+PR) compared with 11± 9.0 months in non-responder group (NC+PD). The result indicated a higher response rate with a longer disease free interval, but showed no statistically significant difference (Table 7).

Table 7. Disease free interval: Comparison between Responder & Non-Responder

	No. of Patients	Average of Dsease Free Interval
Responder	5	76±77.3 M
Non-Responder	4	11±9.0 M

DISCUSSION

It has been reported that the response rate to tamoxifen therapy is about 30%[3,9,12]. Our finding, 47.8%, was higher than that probably because our study included mostly ER+ patients and other therapies such as chemotherapy were concomitantly given. Our finding that the response rates in ER+ patients and ER− patients were respectively 60% and 16.7% was consistent with the experience of others[6,7,9,10], although the rate in ER− was slightly higher.

It has been reported that the response rate is relatively high in patients with soft tissue/lymph nodes involvement but low in those with bone metastasis or with visceral involvement[6,9,12]. We obtained a similar result.

In USA and European countries, there is a general agreement that postmenopausal patients responded to tamoxifen better than premenopausal patients[6,7]. It has been also generally accepted that oophorectomy and adrenalectomy show relatively high efficacy in premenopausal patients and patients with bone metastasis. Thus, it seems important to choose an appropriate endocrinal manipulation to site involved and menstrual status of individual case[1,4].

As for ER determination, we have used both DCC technique and FITC method, a cytochemical assay using fluorescent estradiol conjugate. Microscopic examinations of tumor tissue cells through FITC method have revealed a mosaic structure consisting of ER+ and ER− cells in

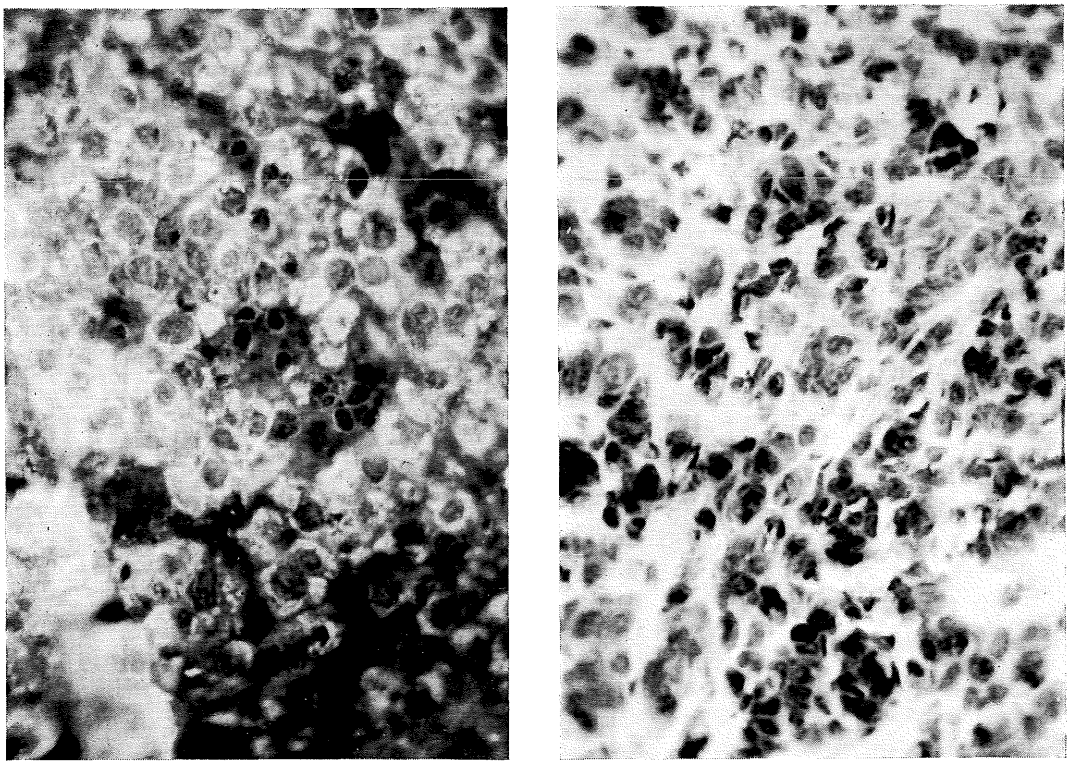

Fig. 1. The left is a fluorescent photomicrograph by FITC technique. Fluorescent uptake is noted in about 50% of carcinoma cells. (×400). The right is a photomicrograph of carcinoma cells stained by hematoxylin and eosin from the same case as the left. Carcinoma cells with irregularly sized nuclei are diffusely proliferating. (×400).

cancer tissues[5,8] (Fig. 1). It suggests that single treatment with tamoxifen is not effective enough and justifies the treatment in combination with chemotherapies for ER− cells.

Cocconi[2] and Wada[11] found that patients responded to the combination treatment with tamoxifen and chemotherapy better than to single treatment with either one of them.

Side effects of tamoxifen seen in the 17 cases included digestive symptoms (1) and amenorrhea (1). They did not require a discontinuation of the drug, indicating that tamoxifen is a drug of safety.

Eight of the 17 cases are still alive. The longest survival case has been in a condition of partial response for 23 months so far. The mean survival period in 9 deaths was 13±9 months, with longest 32 months.

As shown here, some cases of advanced breast cancer well respond to hormonal therapy and not a few patients can survive for a long time in a rehabilitated situation, when they are treated with tamoxifen in combination with other therapies which are added by ER status. On top of that, basic studies on receptors other than ER have been in progress. Thus, there is every reason to expect that the outlook for advanced breast cancer is favorable.

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