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Randomized Trial of Aminoglutethimide *versus* Tamoxifen in Metastatic Breast Cancer[1]

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Abstract

We compared antiestrogen therapy (tamoxifen) with an estrogen suppression regimen (aminoglutethimide-hydrocortisone) in postmenopausal women with metastatic breast carcinoma. Fifteen of 39 patients (38%) who received tamoxifen experienced an objective tumor regression (3 complete, 12 partial remissions), whereas 13 of 36 women (36%) receiving aminoglutethimide responded (one complete remission, 12 partial remissions). The median duration of response was similar. The site of tumor involvement appears to be important in choosing between these hormonal treatments. Aminoglutethimide appears to offer a greater chance of response in patients with bone involvement.

Aminoglutethimide blocks estrogen biosynthesis at 2 separate sites, the adrenal cortex and extraglandular tissue. In the adrenal, aminoglutethimide interrupts the conversion of cholesterol to pregnenolone and thus reduces the level of the major estrogen precursor androstenedione (1–3, 6). In peripheral tissues, aminoglutethimide blocks the formation of estrogens by inhibiting the aromatizing enzymes responsible for conversion of androstenedione to estrone (10, 11, 15, 17). Estrogen suppression therapy with aminoglutethimide has been shown to be an effective chemical ablative form of therapy for metastatic breast cancer in postmenopausal women (4, 5, 8, 9, 12, 13, 16, 18). ER[3] status is useful in predicting response to this form of treatment (7).

Antiestrogen therapy with tamoxifen (Nolvadex) is the hormonal treatment most widely used to treat recurrent breast carcinoma. The present report compares the efficacy of estrogen inhibition with aminoglutethimide to that of antiestrogen therapy with tamoxifen for the treatment of women with advanced breast cancer.

Materials and Methods

Patient Selection. Ninety-seven spontaneously menopausal or surgically castrated women with proven metastatic breast carcinoma and measurable disease were selected for study. Patients with documented central nervous system involvement or with disease estimated to involve greater than one-third of the liver were excluded. Patients were entered into this protocol when their disease progressed following mastectomy (first recurrence) or upon failure of usually no more than one prior endocrine therapy. Additive hormonal treatment was discontinued at least 1 month prior to entry into this study. A signed informed consent was obtained from each patient.

All patients were ER positive or ER unknown. Receptor assays were performed by the dextran-coated charcoal method. Results were expressed as fmol of [^{3}H]estradiol bound per mg of cytosol protein. A positive estrogen receptor assay was defined as 10 fmol or greater. Women were stratified according to the dominant site of disease at the start of therapy and then randomized to treatment with tamoxifen or aminoglutethimide (Cytadren; CIBA-GEIGY Corp.) plus hydrocortisone.

Patient Evaluation and Response Criteria. Classification of a response as an objective CR indicated that during the therapy all metastatic lesions disappeared for a period of at least 3 months. PR was defined as a decrease of 50% or greater in the sum of the products of the 2 largest perpendicular diameters in all measurable lesions, partial recalcification of osteolytic lesions for at least 3 months, or both. Stabilization of osteoblastic lesions with regression of other lesions was also considered an objective response. Stable disease was defined as a decrease of less than 50% or an increase of less than 25% in metastatic lesions with marked symptomatic improvement and well being for at least 6 months. We are including this category in our total response rate because in many of these patients stabilization represented significant palliation of the disease (*e.g.*, bone pain relief without clear-cut radiological evidence of bone healing). Progression required an increase of 25% or greater over original measurements or appearance of new metastatic lesions. Resolution of a pleural effusion alone was not considered to be adequate evidence of response.

Treatment Protocol. Patients were randomized to receive either (*a*) tamoxifen, 20 mg twice a day p.o. or (*b*) aminoglutethimide, 250 mg p.o. twice a day for 14 days and then 4 times a day thereafter plus hydrocortisone 100 mg p.o. daily for 14 days (20 mg in a.m., 20 mg at 5 p.m., and 60 mg at bedtime) and then 40 mg daily thereafter (10 mg in a.m., 10 mg at 5 p.m., and 20 mg at bedtime).

Table 1

Aminoglutethimide versus tamoxifen patients

97 selected patients
6 ineligible (1 no tissue diagnosis, 2 ER negative, 1 concomitant oophorectomy, 1 Stage IV with no evidence of disease, 1 extensive liver metastases)
16 inevaluable
TAM 1 CHF[a] Week 4
2 flare of disease
1 expired at Week 2
1 severe nausea and vomiting
1 never took pills
1 less than 3 mo. of therapy
AG - 1 MI Week 3
1 CHF Week 4
1 diabetes Week 3
2 severe dermatitis
1 wished to discontinue experimental trial at Week 2
1 never took pills
1 pancytopenia
1 less than 3 mo. of therapy
75 evaluable patients

[a] CHF, congestive heart failure; MI, myocardial infarction.

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[3] The abbreviations used are: ER, estrogen receptor; CR, complete remission; PR, partial remission.

Table 2
Characteristics of evaluable patients

	No. of patients	Median age (yr)	Median disease-free interval (mos.)	Median time from menopause to start of therapy (yr)	ER positive	ER unknown
Tamoxifen	39	60	24	8	18	21
Aminoglutethimide	36	59	25	8	17	19

Table 3
Prior hormonal therapy

	None	One	Two
Tamoxifen	23	15	1
Aminoglutethimide	21	12	3

Table 4
Site of dominant disease (viscera > bone > soft tissue)

	Tamoxifen (39 patients)	Aminoglutethimide (36 patients)
Viscera	2	2
Lung	6	4
Bone	26	26
Soft tissue	5	4

Table 5
Overall response rate to aminoglutethimide versus tamoxifen therapy

	CR	PR	Stable	Progression
Tamoxifen				
ER positive	2/18	8/18	4/18	4/18
ER unknown	1/21	4/21	7/21	9/21
Total	3/39 (8%)	12/39 (30%)	11/39 (28%)	13/39 (34%)
Aminoglutethimide				
ER positive	1/17	6/17	5/17	5/17
ER unknown	0/19	6/19	8/19	5/19
Total	1/36 (3%)	12/36 (33%)	13/36 (36%)	10/36 (28%)

Table 6
Duration of response

	Median (mos.)			
	CR	PR	Stable	CR + PR + stable
Tamoxifen	21+	10+	8+	9+
Aminoglutethimide	26	11+	6+	10+

Table 7
Responses by individual site of involvement

	No. of responses/no. of patients treated							
	Viscera		Lung		Bone		Soft tissue	
	T[a]	AG	T	AG	T	AG	T	AG
CR	1/2					1/27	4/14	2/12
PR		2/3	6/7	3/4	4/27	8/27	4/14	3/12
Stable			1/7	1/4	14/27	14/27	1/14	2/12
Progression	1/2	1/3			9/27	4/27	5/14	5/12

[a] T, tamoxifen; AG, aminoglutethimide.

Results

Ninety-seven spontaneously menopausal or surgically castrated women with proven metastatic breast carcinoma and measurable disease were selected for study. Six were soon found to be ineligible for this study (2 ER negative; 1 Stage IV, with no evidence of disease; 1 no tissue diagnosis; 1 concomitant oophorectomy; 1 extensive liver metastases). Sixteen patients are inevaluable at this time (Table 1). Thus, there were 75 randomized, evaluable patients, 36 treated with aminoglutethimide *versus* 39 treated with tamoxifen.

The 2 groups of patients are comparable with respect to median age (aminoglutethimide, 59 years, *versus* tamoxifen, 60 years), disease-free interval (aminoglutethimide, 25 months, *versus* tamoxifen, 24 months, median), prior hormonal therapy, ER-positive (aminoglutethimide, 47% of patients, versus tamoxifen, 46% of patients) and ER unknown (aminoglutethimide, 53% of patients, *versus* tamoxifen, 54% of patients) (Tables 2 and 3). The site of dominant disease is also similar in the 2 treatment groups (Table 4). All patients with bone involvement had lytic metastases.

The overall objective response rate to tamoxifen is 38% (3 CR plus 12 PR), and that to aminoglutethimide is 36% (1 CR plus 12 PR). Eleven tamoxifen and 13 aminoglutethimide patients also had a stabilization of disease lasting for at least 6 months (Table 5). The median duration of objective response is similar for aminoglutethimide and tamoxifen (Table 6). Statistical evaluation revealed that the response rate and duration of response are not statistically different for these 2 groups of patients.

Table 7 reveals the response rate for different individual sites of involvement in these 75 evaluable patients. When individual sites of involvement are assessed, there is a trend suggesting that aminoglutethimide is more effective with bone involvement [9 of 27 CR plus PR (33%)] *versus* tamoxifen [4 of 27 (15%)] ($p = 0.10$).

Twenty patients treated with aminoglutethimide experienced side effects. Three patients stopped therapy, one with severe dermatitis not relieved by high-dose hydrocortisone therapy, one with pancytopenia, and one with exacerbation of diabetes due to hydrocortisone treatment. The other side effects encountered were transient skin rash (11 patients), lethargy (2 patients), ataxia (1 patient), mild gastrointestinal bleeding (1 patient), and transient fever (2 patients). Eight patients treated who received tamoxifen encountered toxicity. Two patients had significant flare in their disease which led to termination of the trial. In both of these patients, a marked increase in bone pain and hypercalcemia occurred. One patient experienced a marked acceleration of disease at Week 2 of therapy and died shortly thereafter. Five other patients experienced minor nausea or hot flashes.

Discussion

Carcinoma of the breast regresses following a variety of

hormonal manipulations. Recently, the antiestrogen tamoxifen has received wide acceptance in the treatment of postmenopausal breast cancer patients. There have been few studies comparing this drug with other hormonal approaches.

We previously described an estrogen suppression regimen using aminoglutethimide as a potent inhibitor of steroid synthesis (12–14). This regimen was previously called "medical adrenalectomy" until the additional site of action of aminoglutethimide on extraadrenal estrogen production was recognized (aromatase inhibition). The present study compared the efficacy of this chemical method to antiestrogen therapy with tamoxifen.

In this analysis of 75 evaluable postmenopausal patients with metastatic breast cancer, we found that patients treated with aminoglutethimide had at least a similar response rate when compared with tamoxifen-treated patients. The median duration of objective response was also similar for both patient groups. For the population as a whole, there was no significant difference between therapy with aminoglutethimide and tamoxifen.

When subpopulations are studied, one potentially important difference begins to emerge. At the time of this analysis, the chance of obtaining a remission in patients with predominantly bone metastases is greater with aminoglutethimide treatment than with tamoxifen.

Both aminoglutethimide and tamoxifen have some toxic side effects. The side effects of aminoglutethimide may be annoying but are usually transient and not life threatening. Similar to surgical ablative therapy, aminoglutethimide administration is not associated with disease flare. Tamoxifen, on the other hand, as with hormone-additive therapy, occasionally produces an initial exacerbation of disease. Two patients in this study experienced a flare response while receiving tamoxifen. Therapy was stopped, but more recent evidence suggests that it may be possible to treat through this period of exacerbation of disease.

In summary, aminoglutethimide therapy appears to be at least equivalent to tamoxifen therapy of postmenopausal metastatic breast cancer. The predominant site of disease involvement (*e.g.*, bone metastases) may turn out to be most important in selection of therapy. The sequence of administration of these agents and the resulting rates of response warrant further investigation.

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