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SECOND LINE HORMONAL THERAPY WITH AMINOGLUTETHIMIDE IN METASTATIC BREAST CANCER

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Abstract

One hundred and twenty patients with metastatic breast cancer, whose disease progressed on hormonal therapy with tamoxifen, were treated with aminoglutethimide. The overall response rate was 34% and the median duration of response 9.5 months. Response to aminoglutethimide was achieved in all metastatic sites except lung and brain. Even 25% of patients who had failed to respond to prior tamoxifen did respond objectively to aminoglutethimide. The actuarial survival for all patients at 30 months was 22%. Although initial toxicity was high (70%), side effects of aminoglutethimide were transient, and treatment had to be discontinued in only four patients. The results of this trial confirm that aminoglutethimide is an effective treatment in metastatic breast cancer.

Key words: Breast cancer, aminoglutethimide, tamoxifen.

Aminoglutethimide blocks estrogen synthesis at two independent sites: the adrenal cortex and peripheral tissue. In the adrenal cortex, the drug interrupts the conversion of cholesterol to pregnenolene, reducing the level of androstenedione, the major estrogen precursor (1-4). In peripheral tissue, aminoglutethimide blocks the synthesis of estrogen by inhibiting aromatases, the enzymes involved in the conversion of androstenedione to estrone (5, 6).

Estrogen suppression therapy with aminoglutethimide has been reported to be an effective treatment modality for metastatic breast cancer (7-16).

The present report summarizes our experience in 120 patients treated with aminoglutethimide during a period of 5 years.

Material and Methods

This study includes 120 consecutive patients with metastatic breast cancer treated at the Department of Clinical Oncology of the Hadassah University Hospital between November 1981 and October 1986. Most of the patients had progressive disease while on hormonal treatment with tamoxifen.

Patient characteristics are summarized in Table 1. The median age of the patients was 54 years (range 22 to 83). At the time of diagnosis, 33% of the patients were premenopausal and 67% postmenopausal, although when aminoglutethimide was started, all patients were postmenopausal. The median relapse-free survival was 27 months (range 0 to 26 years). Hormone receptor status was not routinely performed in our hospital at the time when most of these patients were diagnosed, and was available in only 53 cases (44%). Prior chemotherapy had been given to 84 patients (70%). Ninety-eight percent of the patients had previously been treated with tamoxifen.

The main sites of metastases included several combinations of bone, soft tissue, skin, liver, lung, pleura and brain.

Aminoglutethimide was started 3 to 4 weeks after evidence of failure of tamoxifen. Before entering this trial, all patients were carefully evaluated for extent of disease, including physical examination, blood chemistry, chest radiography and liver scan. Bone scan and skeletal radiography were performed in order to assess the response of patients with bone metastases. Patients were reevaluated at 6 to 8 weeks after initiation of aminoglutethimide.

Aminoglutethimide was administered orally, at an initial dose of 250 mg/day, escalating to 250 mg q.i.d. Hydrocortisone was initially given at a dose of 100 mg/day and was gradually decreased to 10 mg q.i.d. In 20 patients (17%)

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Table 1

Patient characteristics

Total number	120
Menstrual status at diagnosis	
Premenopausal	39 (33%)
Postmenopausal	81 (67%)
Median age (range)	54 (22 to 83)
Median relapse-free survival (range)	27 months (0 to 26 years)
Prior chemotherapy	84 (70%)
Prior tamoxifen	118 (98%)

the dose of aminoglutethimide could not be increased above 750 mg/day due to toxicity.

Evaluation of response was assessed according to the UICC criteria (17). Complete response (CR) meant disappearance of all evidence of disease. Partial response (PR) was defined as $\geqslant 50\%$ decrease in size of measurable lesions. The result was recorded as stabilization (S) when there was $<50\%$ decrease or $<25\%$ increase in the size of measurable disease. Progression (P) meant appearance of new lesions and/or $\geqslant 25\%$ increase in size of known measurable lesions.

Subjective improvement (SI) was defined as improvement of the general condition lasting for at least 3 months, in order to ensure that this improvement was not due to the administration of initial high doses of hydrocortisone.

Duration of response was calculated from the initiation of aminoglutethimide therapy. All patients were followed until December 1988 or until death. Analysis of survival was calculated according to the life-table method of Berkson & Gage (18). The generalized Wilcoxon's test was utilized to evaluate differences between subgroups (19). P-value was a two-tailed test.

Results

All patients were evaluable for response (Table 2). Complete response (CR) was achieved in 4 patients (3%); the median duration of response was 9 months (range 8 to 15). Partial response (PR) was observed in 37 patients (31%), the median duration being 10 months (range 6 to 36).

Table 2

Response and duration of response

Type of response	No.	(%)	Median duration (months)
Complete (CR)	4	(3)	9 (range 8 to 15)
Partial (PR)	37	(31)	10 (range 6 to 36)
Stable disease (S)	43	(36)	7 (range 4 to 20)
Progression (P)	36	(30)	
Subjective improvement (SI)	90	(75)	

Table 3

Response to aminoglutethimide according to dominant site of metastases

	No.	Responders (CR + PR)	Stable	Progression
Pleura	6	3 (50%)	0	3
Soft tissue	18	8 (44%)	3	7
Liver	8	3 (37%)	2	3
Bone	74	27 (36%)	31	16
Lung	11	0	6	5
Brain	3	0	1	2

Forty-three patients (36%) remained stable (S) for a median duration of 7 months (range 4 to 20), and the remaining 36 patients (30%) showed progression (P) of their disease. Subjective improvement was observed in 90 patients (75%).

Table 3 shows that objective responses to aminoglutethimide were achieved in all metastatic sites, except for lung and brain.

Hormone receptor status was examined in 53 patients (44%); in 28 of them, receptors were positive for estrogen. Of these patients, 16 responded to aminoglutethimide, while 12 remained stable or progressed. Thus, the response rate for estrogen receptor positive patients was 57%. Only 3 out of 25 patients with negative estrogen receptors (12%) responded to aminoglutethimide.

The response to prior tamoxifen therapy correlated well with the response to aminoglutethimide (Table 4). Of 41 patients who responded to tamoxifen, 22 (54%) responded to aminoglutethimide and, of 77 patients who failed to respond to prior tamoxifen, 19 (25%) showed a clear objective response to aminoglutethimide ($p = 0.0008$).

Eight out of 20 patients (40%) who received 750 mg aminoglutethimide daily, had objective response to treatment.

The actuarial survival of all patients at 30 months was 22% (Figure). The actuarial survival for responding patients (CR + PR) was 34%, as compared with 16% for non-responders (S + P; $p < 0.0001$).

All patients were evaluable for toxicity (Table 5). Eighty-four patients (70%) suffered initially from one or

Table 4

Correlation between response to aminoglutethimide and prior tamoxifen therapy

	Responders No.	(%)	Non-Responders No.	(%)
Response to prior tamoxifen				
Responders	22	(54)	19	(46)
Non-responders	19	(25)	58	(75)
$p = 0.0008$				

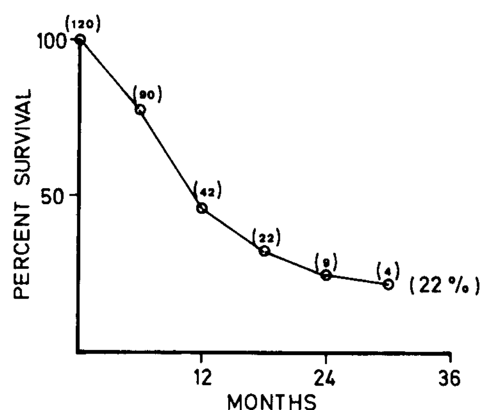

Figure. Actuarial survival of all patients.

Table 5

Side effects of aminoglutethimide

	Number	(%)
Dizziness	48	(40)
Skin rash	42	(35)
Headache	35	(29)
Electrolyte disturbances	12	(10)
Ataxia	6	(5)
Agranulocytosis	4	(3)

more toxic manifestations of aminoglutethimide, which were generally transient, and usually disapperared between the third and fourth week of treatment. Therapy had to be discontinued in four patients who manifested reversible agranulocytosis, ataxia, electrolyte disturbances and skin rash respectively. In 20 patients (17%) the dose of aminoglutethimide could not be increased above 750 mg/day because of side effects.

Discussion

The results of our trial indicate that aminoglutethimide is an effective treatment modality for metastatic breast cancer. Several reports have shown response rates ranging between 16% and 50% (7–16, 20), similar to our response rate of 34%. The highest rates were achieved when patients with positive hormone receptors were selected (20). We have found a similar pattern in our hormone receptor positive patients (15, 16).

Unlike other hormonal treatments such as estrogens and tamoxifen, where a pattern of favorable (non-visceral) and unfavorable (visceral) sites of metastases is found, with aminoglutethimide we observed objective remissions in all metastatic sites, except for lung and brain.

Since there was a subjective improvement in 75% of our patients (Table 2), it seems advisable not to discontinue aminoglutethimide, even if there is no immediate objective response, and to wait for at least 3 months. If there is no clear progression, therapy with aminoglutethimide should be continued as well.

Although initial toxicity of aminoglutethimide was high (70%), most side effects were transient, as similarly reported in other series (7–16, 20).

It may be that lower doses of aminoglutethimide are less toxic and equally effective, as suggested by Harris et al. (9), whose response rate with 750 mg/day was similar to that of patients receiving 1 g/day. We have found the same trend (15, 16), but the number of patients is small, and no definite conclusions can be made.

In conclusion, therapy with aminoglutethimide is an important addition to the management of metastatic breast cancer, especially in patients with positive hormone receptors.

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