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TREATMENT OF BREAST CARCINOMA WITH AMINOGLUTETHIMIDE

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Abstract

During the past three years 52 patients (51 females and 1 male) have been treated for advanced carcinoma of the breast with aminoglutethimide (AG) with addition of a glucocorticoid. More than half of the patients had received three or more systemic treatments and at least two different endocrine regimens before the start of the AG therapy. All patients had previously been treated with tamoxifen. The treatment had to be discontinued after less than six weeks in 2 patients due to acute toxicity and in 4 patients due to intercurrent disease. Fifteen out of the 52 patients had an objective response; 4 complete responders were noted. In addition, the disease remained stable for 2 to 19 months in 16 patients. Aminoglutethimide in combination with a glucocorticoid seems to be an efficient treatment as a late endocrine alternative in a sequence of different endocrine regimens.

Adrenalectomy is a well-established treatment for metastatic carcinoma of the breast (4, 5). Aminoglutethimide (AG) in combination with a glucocorticoid has been used as an alternative to surgical adrenalectomy, with similar response rates (14). AG is known to suppress the adrenal steroid synthesis (3), and it has more recently been shown to inhibit the peripheral, non-glandular conversion of androgens to estrogens (13). AG as the primary treatment in 929 patients with advanced breast carcinoma resulted in objective responses in 32 per cent, while 52 per cent of estrogen receptor (ER) positive patients responded (11).

In randomized trials where AG was compared with tamoxifen, similar response rates were obtained with the two treatments (15). AG induced remissions in 31 per cent in tamoxifen failures and tamoxifen resistant patients (11).

It was considered of interest to elucidate the therapeutic potential of AG as a late endocrine alternative in a sequence of different endocrine regimens in advanced breast malignancy. The results from treatment of the first 22 patients have been published previously (9). The present report describes treatment with AG in 52 patients.

Material and Methods

Between April 1980 and November 1983, 52 patients (51 postmenopauseal females and 1 male) with advanced, progressive breast malignancy were submitted for treatment. In 6 patients treatment had to be discontinued after less than six weeks, due to acute toxicity (2 cases) or to intercurrent disease (apoplexy in 2, sepsis in 1, and senility in 1 case), and these patients were not considered evaluable. The data concerning the remaining 46 patients appear in Table 1.

The UICC criteria for response were used (7). The criteria for inclusion of the patients were: Previous response to endocrine treatment; previous failure of endocrine therapy if the patient had clinical characteristics and/or receptor status (estrogen-, progesteron-receptor positivity $\geq$10 pmol/g protein) predicting a response; previous adjuvant endocrine therapy with tamoxifen in patients with clinical characteristics as mentioned. All patients had progressive disease at the time when the AG treatment was started.

The medan number of different systemic treat-

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ments before the start of AG treatment was 3 (range 1–6). Twenty-nine patients had previously received at least 2 different kinds of endocrine therapy, and all had received tamoxifen either as an adjuvant or in the advanced situation. Twenty-eight patients had previously received combination chemotherapy.

In 26 patients the receptor status was known either from primary tumours (n=15), recurrences (n=8) or both (n=3). All these receptor values predicted response to endocrine therapy. The dose schedule used in this investigation was aminoglutethimide (Orimeten—formerly known as Elipten; Ciba-Geigy) 250 mg 4 times a day, and dexamethasone (Decadron) 0.75 mg 4 times a day or cortisone acetate (Cortone) 25 mg twice a day. Half of the patients received a full dose of AG from the start of treatment, while the others received AG 250 mg twice a day together with cortisone acetate 50 mg twice a day for the first two weeks.

Results

The 46 evaluable patients received AG treatment for 8 weeks or more. Patients with stable disease were not included among responders.

The treatment results are shown in Table 2. The median duration of response so far is 8 months, with 6 patients still in remission. One patient had liver metastases in combination with other manifestations, in one patient this was the only manifestation; both patients achieved a partial response.

In 38 patients, data concerning the objective response to previous tamoxifen treatment were available (Table 3). Seven of 14 previous responders had another objective response to AG therapy, while 6 of 24 previous failures to tamoxifen obtained an objective response on the AG regimen.

Comparing responders with non-responders to AG treatment, no differences could be found as regards age at primary diagnosis, disease-free interval, time from first recurrence to start of AG treatment, or number of previous different endocrine treatments.

In 26 patients a receptor status predicting a positive response to endocrine treatment was available. Among these, 9 patients obtained an objective response (35%).

Acute and chronic toxicities are shown in Table 4. These were more frequently observed when AG was administered at full dose from the start of the treatment. After 6 to 8 weeks however, most of the side effects had passed off and the treatment was well tolerated. In one patient, the treatment had to be discontinued due to agranulocytosis. This condition had receded one week after the cessation of therapy, with normalization of peripheral blood values and bone marrow morphology.

Table 1

Patient data. Stages (I–IV) are used as defined by UICC (16). Recurrence defined as new appearance and/or progression of known tumours

Number of patients	46
Age at diagnosis	Mean 58.5 years
Clincal stage at diagnosis	I n=14
	II n=21
	III n=8
	IV n=3
Disease-free interval (I–III)	Median 26.5 months
	Range 3–204 months
Previous recurrences	1–6 (median 2)

Table 2

Results of AG treatment

Response	
Complete responders	4/46 (9%)
Partial responders	11/46 (24%)
Stable disease	16/46 (35%)
Progressive disease	15/46 (33%)
Duration of response	
Complete + partial responders	Median 8+ months (2–27)
Stable disease	Median 7 months (2–19)
Response (complete + partial) by site of location	
Locorregional	10/22
Skeletal	1/4
Pulmonary	0/5
Pleural	0/1
Hepatic	1/1
Combined	3/13

Table 3

Response to AG in relation to previous response to tamoxifen

Previous response to tamoxifen	Response to AG	
	Responders (complete + partial response)	Non-responders (stable + progressive disease)
Responders	7	7
Non-responders	6	18

Table 4

Acute and chronic toxicities with AG treatment (per cent in parentheses)

	Leth-argy	Ver-tigo	Other CNS*	Skin rash	Pruri-tus	Other symptoms
Full dose from start of therapy						
Acute	19/24 (79)	9/24 (37)	8/24 (33)	10/24** (42)	7/24 (29)	4/24*** (17)
Chronic	1/24 (4)	0/24	0/24	1/24 (4)	1/24 (4)	0/24
Reduced amount of AG during first 2 weeks						
Acute	9/28 (32)	1/28 (4)	0/28	2/28** (7)	2/28 (7)	4/28*** (14)
Chronic	–	–	–	–	–	–

*Ataxia, mental depression, insomnia, nystagmus.

** Accompanying fever in 7/12.

*** Nausea, diarrhoea, fever without accompanying skin rash, agranulocytosis.

Discussion

The response rate obtained was the same as that reported previously for AG treatment after tamoxifen (10, 11) but somewhat higher than was reported for similar groups of patients receiving AG treatment late in a sequence of systemic therapies (1, 2, 6). The slightly higher response rate reported initially from this department (9) may have been due to a more selected recruitment of patients.

The estrogen-receptor analyses were to a large extent performed on primary tumours. A somewhat lower frequency of receptor positivity in metastases, compared with primary tumours, and possibly the influence of prior endocrine therapy, might explain why the response rate was slightly lower in the receptor-positive group than was found for other endocrine regimens used earlier in the sequence.

Dexamethasone was chosen for glucocorticoid replacement in the first 24 patients in this investigation, in order to monitor adrenal suppression by means of serum cortisol measurements, as an assay for dehydroepiandrosterone-sulphate (DHEA-S) was not available. A significant reduction of serum cortisol was obtained in all patients. However, since AG may induce an increase in the metabolism of dexamethasone but not cortisol (12) we now prefer cortisone-acetate as a substitute, which may be administered in fixed doses twice a day. The clinical results from 929 patients treated with AG have not given support for the advantages of one glucocorticoid regimen over the other (11).

The frequency of side effects among patients receiving a full dose from the beginning was about the same as has been reported by others. However, the frequency of these effects was significantly reduced by administration of half the amount of AG together with twice the amount of cortisone-acetate for the first two weeks (Table 4), confirming the report of SANTEN (11). The reduction of CNS symptoms may be related to the initial AG dosage, while the skin rash and pruritus may have been modified by the increase in corticosteroid administration.

Sixteen of the evaluable patients achieved stability of their disease. This is of clinical importance, as the survival for patients with stable disease on endocrine treatment seems to approach the survival for responders (8).

AG is a new, efficient endocrine therapy for the treatment of breast carcinoma. Its place in the treatment of advanced disease is not clear. At present, AG would not seem to be suitable as a first-line treatment, but the investigation confirms its potential as a late alternative in a sequence of different endocrine regimens. It would be of interest to compare AG with other regimens as second-line alternatives.

AG seems to be efficient also in male breast malignancy, as a complete response was observed in the male patient in this series.

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