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A Clinical Trial of Aminoglutethimide in Advanced Postmenopausal Breast Carcinoma: Low Response in Patients Previously Treated with Medroxyprogesterone

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Abstract—*In an attempt to define the influence of prior hormonal treatments upon aminoglutethimide activity in advanced cancer of the breast, 42 heavily pretreated postmenopausal patients received aminoglutethimide, 4 × 250 mg daily, with hydrocortisone or cortisone. Twenty-six received high doses of medroxyprogesterone before entering this study. There was no significant difference in patients' characteristics with or without medroxyprogesterone pretreatment. A comparison of patients with and without prior medroxyprogesterone shows a significant difference in the response rate to aminoglutethimide-hydrocortisone (4 vs 32%, P = 0.02). In patients pretreated with tamoxifen but not with medroxyprogesterone the response rate to aminoglutethimide was 36%. These results suggest that aminoglutethimide has a low activity in breast cancer patients previously exposed to medroxyprogesterone, an agent with glucocorticoid-like activity inducing adrenal suppression.*

INTRODUCTION

AMINOGLUTETHIMIDE, an anticonvulsant, blocks cytochrome P-450-mediated hydroxylations required for steroid hormone synthesis, including 20α-hydroxylase in the adrenocortical tissue and aromatase in extra-adrenal and breast cancer tissues [1–4]. This agent was introduced in the palliative treatment of advanced breast cancer in 1967 [5]. Generally administered with hydrocortisone to prevent a reflex rise in pituitary ACTH, aminoglutethimide produces approximately 30% tumor regressions in postmenopausal patients [6–8]. Higher response rates may be achieved in the presence of predictive factors such as skin or soft tissue metastases, a long disease-free interval from surgery to tumor reappearance and positive tumor estrogen receptor. Response to prior tamoxifen has been shown to correlate with an improved probability of activity of aminoglutethimide [9, 10]. On the contrary, low response rates have been observed with tamoxifen in patients previously treated with aminoglutethimide [9, 11]. The prognostic value of other prior hormonal treatments in the activity of aminoglutethimide in breast cancer has not yet been completely investigated.

The subject of this report is a study initiated in 1980 by the Swiss Group SAKK to evaluate the antitumor effect of aminoglutethimide in postmenopausal breast cancer patients previously treated with hormonal manipulations, particularly medroxyprogesterone.

MATERIALS AND METHODS

Post-menopausal patients with histologically proven metastatic breast cancer were eligible for

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this study, provided they had a performance status of 0–3 on the WHO scale [12], were not currently being treated with corticosteroids and had no chemotherapy in the last 4 weeks and no hormonotherapy in the last 8 weeks. The disease status included one or more progressive lesions either measurable (in two diameters) or evaluable (in one diameter). Malignant effusions, brain lesions and previously irradiated tumors were not considered evaluable. All prior hormonal treatments and the response to them were registered. The determination of steroid hormone receptors was an optional requirement. Results of 10 fmol/mg cytosol protein were classified as positive.

Aminoglutethimide was supplied by Ciba-Geigy, Basle, Switzerland in 250-mg tablets. The oral daily dose was increased from 2 × 125 to 4 × 250 mg in 13 days and maintained at this level for the duration of the treatment. All patients also received a daily dose of 3 × 20 mg hydrocortisone or an equivalent dose of cortisone or another glucocorticoid. The treatment was administered for at least 4 weeks or until documented tumor progression. Physical status and tumor measurements were repeated every second week. Hemoglobin concentration, leukocyte and platelet counts, serum creatinine, calcium, sodium, potassium, chloride, protein, alkaline phosphatase and transaminase were recorded monthly. Patients treated for 3 weeks or more were considered evaluable for tumor response and treatment toxicity, provided there was no major protocol violation or incomplete study documentation. Response categories were defined according to the WHO formulation [12]. The drug toxicity was evaluated according to a 5-level scale ranging from 0 (no toxicity) to 4 (toxicity requiring discontinuation of treatment). In this report mild toxicity refers to grades 1 and 2 and severe toxicity to grades 3 and 4. Survival time and duration of response were determined from day 1 of aminoglutethimide treatment. Survival curves were established according to Kaplan and Meyer. Fisher's exact test was used for the comparison of response rates. Steroid receptor determinations were performed according to the dextran-coated charcoal separation technique as standardized by the EORTC Breast Cancer Cooperative Group [13].

RESULTS

Fifty-nine patients were entered into the study. Five patients were ineligible: three were found to have received hormonal treatment and two chemotherapy in the 4 weeks preceding aminoglutethimide. In 12 of the remaining 54 patients the tumor response could not be evaluated. In six the initial tumor criteria (four in bone, two in lymph nodes) were judged insufficient at the time of the study evaluation. One patient with a measurable lung lesion developed a pleural effusion early in the treatment. Five patients were treated for less than 3 weeks, including two early non-toxic deaths. Forty-two patients were evaluable for tumor response and 45 patients for toxicity. Three evaluable patients received no glucocorticoids during aminoglutethimide treatment. They were not excluded from the overall evaluation of treatment. One received 15 mg prednisone daily. All others received either hydrocortisone (median daily dose 60 mg) or cortisone (median daily dose 50 mg). Table 1 summarizes the characteristics of the evaluable patients. Two had no prior chemotherapy and five had no prior tamoxifen. Twenty-six patients

Table 1. Characteristics of evaluable patients

No. of evaluable patients	42
Mean age (range) in years	59 (32–74)
Prior treatments:	
surgery	41
radiotherapy	28
chemotherapy:	40
adjuvant	6
palliative	26
adjuvant + palliative	8
ovariectomy	13
tamoxifen	37
estrogens	0
medroxyprogesterone	26
glucocorticoids	25
Median interval between surgery and first relapse (range) in months	26 (0–240)
Tumor sites at onset of study treatment:	
locoregional	21
soft tissue	17
bone	32
visceral	20

Table 2. Response to prior treatments

Palliative chemotherapy	13/34 (38%)
Ovariectomy*	5/9 (56%)
Tamoxifen*	11/34 (32%)
Medroxyprogesterone	10/26 (39%)

*Not available in four patients with ovariectomy and three patients with tamoxifen.

Table 3. Results of treatment according to tumor sites

	Response/evaluable	(%)
Local recurrence	4/21	(19)
Soft tissues	1/17	(6)
Bone	0/32	
Visceral lesions	2/20	(10)
Overall response rate	6/42	(14)

Table 4. Results of treatment according to prior chemo- and hormonotherapy

Prior treatments	Response/evaluable* (%) With	Without
Mastectomy	6/41 (15)	0/1
Radiotherapy	5/28 (18)	1/14 (7)
Chemotherapy	6/40 (15)	0/2
Ovariectomy	3/13 (23)	3/28 (11)
Tamoxifen	6/37 (16)	0/5
Medroxyprogesterone	1/26 (4)†	5/16 (31)†
Medroxyprogesterone in tamoxifen-treated patients	1/23 (4)‡	5/14 (36)‡
Glucocorticoids	4/25 (16)	2/17 (12)

*Treatment result known in 41 patients.
†$P = 0.02$ between these two values.
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had received medroxyprogesterone. Eighteen of them had been treated in a randomized trial with either 1000 or 5000 mg medroxyprogesterone i.m. weekly shortly before becoming eligible for this study [14]. The responses to prior palliative treatments are shown in Table 2. As prior glucocorticoids have mainly been part or combined chemotherapy programs, the response rate to this steroid could not be defined. The steroid receptor status was known in seven evaluable patients only. Six were positive for estrogen receptors and four for progesterone receptors.

Fourteen per cent of evaluable patients responded to the aminoglutethimide-glucocorticoid combination. Table 3 shows the response rates observed by tumor site. No response of bone lesions could be measured in 32 patients with skeletal metastases. The correlation of the response rate with prior tumor treatments is shown in Table 4. Only 1/26 patients with prior medroxyprogesterone had an objective response, whereas 5/16 patients (31%) without prior medroxyprogesterone responded. This difference is significant ($P = 0.02$). The response rate was 16% in patients with prior tamoxifen. However, in the subgroup with tamoxifen and medroxyprogesterone the response rate was 4%, and 36% in the subgroup without prior medroxyprogesterone. This difference is also significant ($P = 0.02$). Of 11 patients who responded to prior tamoxifen, ten had also received medroxyprogesterone and none responded to aminoglutethimide. One of seven patients without prior exposure to either medroxyprogesterone or glucocorticoids showed a tumor response. Only one patient with prior medroxyprogesterone responded to aminoglutethimide-hydrocortisone (in subcutaneous tumor lesions). This patient had received, 1 yr earlier, 200 mg oral medroxyprogesterone daily during 8 weeks. This treatment was discontinued because of tumor progression. Table 5 compares

Table 5. Characteristics of patients with and without prior medroxyprogesterone

	With	Without
Tumor sites in %:		
local recurrence	42	63
soft tissue	42	38
bone	85	63
visceral	42	56
Other prior treatments in %:		
mastectomy	100	94
radiotherapy	65	69
chemotherapy	100	88
ovariectomy	28	38
tamoxifen	88	88
glucocorticoids	62	56
mean age in years (range)	61 (40-74)	55 (32-72)
Median interval between surgery and first relapse in months	26.0	17.5
(95% confidence limits)	(12.2-34.3)	(12.1-34.6)

the characteristics which could have influenced the response rate in patients with and without prior medroxyprogesterone. No significant difference was detected.

The median survival was 23.0 months for the 42 evaluable patients, with a 95% confidence interval of 12.6–34.2 months. For responders and non-responders the corresponding values were 36.0 (16.8–41.5) and 14.5 (12.1–30.3) months. In four of the six responders the remission terminated in tumor relapse after 6.5, 8.5, 13 and 17 months respectively. One patient died of lung infection after 6 months whilst in remission. One patient was lost to follow-up after 18 months in remission.

overall response rate of only 19% [17]. In this latter study, as in ours, the minimum period of treatment required before a first evaluation was 4 weeks, and patients could be withdrawn in case of non-response. It is probable that many bone lesions would have required a longer treatment before a response could be shown. Nevertheless, the subgroup of patients without prior medroxyprogesterone, although sharing the same poor characteristics, had the generally observed 30% response to aminoglutethimide, even if no objective improvement could be detected in bone lesions. On the contrary, in 26 patients previously treated with medroxyprogesterone the response rate was below 10%, the difference being

Table 6. Toxicity of the aminoglutethimide-glucocorticoid treatment

	No. of patients with:		
	no toxicity	mild toxicity	severe toxicity
Somnolence	29	11	5
Anorexia, nausea	33	9	3
Dizziness	37	7	1
Skin rash	40	4	1
Hypotension	42	3	0
Diarrhea	43	2	0
Ataxia, tremor	43	2	0
Hypercorticism	43	2	0

The overall tolerance to aminoglutethimide and to hydrocortisone or cortisone was good. Table 6 summarizes the observed toxic reactions. Somnolence was frequently reported but was generally mild and well-tolerated. The same is true for dizziness or arterial hypotension. Anorexia, nausea and vomiting were tolerable, with the exception of three patients, including the only one for whom toxic reactions were responsible for the discontinuation of the treatment. Signs of hypercorticism were seen in two patients, one with cushingoid facies and one with hyperglycemia.

DISCUSSION

The overall 14% response rate observed in this study is low when compared with other published series [6–8]. Although the majority of our patients were heavily pretreated and had no determination of tumor steroid receptors, these factors could not explain the low level of responsiveness.

The absence of objective response in bone lesions may be a partial explanation of the poor results. Other authors have observed improvement in bone metastases in as high as 35 or 53% of patients for overall response rates of 37 and 37.5% [15, 16]. On the other hand, Kaye *et al.* had no response in 30 patients with bone lesions and an

statistically significant. Thus the poor response in this study might be related to the large proportion of patients with a prior exposure to medroxyprogesterone. The low response in this group of patients could be either related to the detrimental effect of medroxyprogesterone on the responsiveness to aminoglutethimide or to a negative selection of patients with more intensive prior treatments. The analysis of characteristics of patients with and without prior medroxyprogesterone shows nothing that could explain the difference of significant pronostic factors in terms of responsiveness to hormonal treatment. This strongly suggests that pretreatment with medroxyprogesterone is the only difference in the two groups and that medroxyprogesterone plays a major part in the low responsiveness to aminoglutethimide.

To our knowledge the negative value of prior medroxyprogesterone treatment in the responsiveness of breast cancer to aminoglutethimide-hydrocortisone has not been previously described.

High-dose progestins, particularly medroxyprogesterone, inhibit ACTH secretion and produce adrenal suppression [18, 19]. This may be due to a glucocorticoid-like activity. Medroxyprogesterone may interact with a cytosolic

glucocorticoid receptor, as observed in the MtTW15 rat somatotropic pituitary tumor [20]. In adrenalectomized patients symptoms of adrenal insufficiency may be reversed with 100 mg of medroxyprogesterone daily [21]. In patients with endometrial cancer treated with medroxyprogesterone a decreased glucose tolerance and adrenal response to ACTH has been observed [22]. In postmenopausal breast cancer patients medroxyprogesterone reduces the serum ACTH and cortisol concentrations to subnormal levels [23].

Our results suggest that the adrenal cortex suppression produced by medroxyprogesterone has a long duration after discontinuation of the treatment, and that this adrenal suppression is not compatible with a subsequent tumor response to the adrenal blockade produced by aminoglutethimide. Indirectly, this also suggests that the antitumor activity of medroxyprogesterone in breast cancer patients is, at least partially, due to a suppression of the adrenal steroid secretion.

A large proportion of breast cancer patients selected for treatment with aminoglutethimide-hydrocortisone will probably not be in their first tumor recurrence. Many of them will have already received other hormonal treatments. The influence of these previous treatments upon the probability of response to aminoglutethimide must be defined. A previous response to tamoxifen is linked with a high probability of response to aminoglutethimide. The results of this study show, on the contrary, that a prior exposure to medroxyprogesterone reduces the chance of response to aminoglutethimide.

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