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Aminoglutethimide in the Treatment of Premenopausal Patients with Metastatic Breast Cancer

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Abstract—*Eighteen premenopausal patients with progressive metastastic breast cancer were treated with aminoglutethimide (AG)/cortisone. All patients received* 1000 mg *AG per day in combination with* 2 × 25 mg *cortisone acetate. Complete (CR) and partial remissions (PR) were achieved in* 27.8%, *a no change (NC) in* 16.7% *and progressive disease (PD) in* 55.5% *of all cases. The clinical results show that AG/cortisone acetate is effective in the therapy of premenopausal as well as postmenopausal patients with metastatic breast cancer. One hormone receptor negative tumour completely responded. Contrary to postmenopausal patients whose low oestradiol levels continuously decrease, oestradiol levels in premenopausal patients were not influenced by treatment. A distinct suppression of the ovarian activity does not occur. Thus concluding, a mechanism—at least partially different from those in the postmenopause and not necessarily of endocrine nature—must exist in the premenopause. We, therefore, no longer think it justified to assert that the therapeutic effect of AG is merely based on medical adrenalectomy.*

INTRODUCTION

AMINOGLUTETHIMIDE (AG) has been shown to be effective in the treatment of postmenopausal patients with metastatic breast cancer [1–7]. Response rates range from < 10 to 60% and depend on pretreatment, site of involvement and hormone receptor status [1, 2, 4, 6, 7]. AG has a particularly significant effect on patients with bone metastases and relieves bone pain in more than 50% of all cases [1, 3, 8, 9].

The mechanism of action has been described as medical adrenalectomy [3, 4, 5, 7]. The blockage of oestrogen synthesis occurs in two different ways, AG inhibits both the adrenal conversion of cholesterol to pregnenolone and, moreover, the peripheral aromatization of androstendione to oestrone [6, 10, 11]. In the regimen used for the treatment of metastatic breast cancer, cortisone is given together with AG to compensate for the impaired cortisol synthesis and to prevent the reflex ACTH increment observed when AG is given alone [3, 6].

The effect of AG on premenopausal patients with breast cancer has only been investigated so far in a small number of patients with contradictory results [10, 12].

The aim of the present study was to ascertain the therapeutic effect of AG (1000 mg) in the treatment of premenopausal patients with various hormone receptor status whilst monitoring the endocrine and haematologic parameters.

MATERIALS AND METHODS

Eighteen still premenopausal patients with measurable tumour parameters and evident progressive disease entered the study. Thirteen patients had no prior systemic therapy, two hormonal treatment (tamoxifen) and three chemotherapy. Patient characteristics are shown in Table 1. All patients received 2 × 25 mg cortisone acetate* daily. An initial dose of 125 mg AG twice daily was administered for 3 consecutive days and gradually increased to 1000 mg daily within 12 days.

The hormone receptor status was known from the primary tumour and/or metastases. The cut-off point for receptor positivity was > 10 fmol/mg protein for oestrogen and > 20 fmol/mg for progesterone. The criteria used for response evaluation were those described by Hayward *et al.* [13].

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Table 1. *Characteristics of patients* (n = 18)

Age (range)	41 (32–52)
Disease free interval (months)	19 (0–59)
Oestrogen receptor status	
Positive (ER > 10 fmol and/or PR > 20 fmol)	9
Negative	6
Unknown	3
Sites of metastases	
Bone	8
Soft tissue	3
Lung	1
2 sites (bone + soft tissue)	3
3 sites	2
> 4 sites	1
Prior treatment	
None	13
Tamoxifen	2
Chemotherapy	3

On days 0, 2, 4, 8, 16, 30 and thereafter at monthly intervals, the following parameters were determined: oestradiol, testosterone, androstendione, adrenocorticotrophic hormone (ACTH), aldosterone, cortisol, thyroxine-binding index (TBI), thyroxine (T_4), triiodothyronine (T_3), thyroid stimulating hormone (TSH) basal and 30 min after stimulation, prolactin basal and 30 min after stimulation, cholesterol, triglycerides, electrolytes, liver specific enzymes, pancreatic amylase, glucose and blood count (haemoglobin, leucocytes, platelets).

The following hormones were determined using commercial radioimmunoassays: ACTH and aldosterone from Isotopendienst West (Germany), prolactin from Serono, T_3 and T_4 from Corning, TBI from Byk-Mallinckrodt (with the T_3-up-take-test) and TSH by the immuno-radiometric assay (IRMA) from Rio-Rad. Plasma cortisol was measured by a protein binding method [14]. Oestradiol and androstendione were determined by radioimmunoassay (Steranti), kindly carried out by the Department of Gynaecology, Division of Clinical and Experimental Endocrinology, University Goettingen.

Table 3. *Side-effects*

CNS	8
Increase of liver specific enzymes	12
Weakness	9
Increase in weight (mean 6 kg (3–10))	7
Loss in weight (> 6 kg)	2
Gastroenteric	6
Exanthem within 2 weeks	4
Psychic	3
Ataxia	2
Hypotonia	1
Reduction in pain	10

RESULTS

A synopsis of the results evaluated according to the hormone receptor, remission rate, and duration of remission is presented in Table 2. Complete remission (CR) was achieved in one, partial remissions (PR) in four, no change (NC) in three and progressive disease (PD) in 10 of 18 patients. Thus, objective remissions were observed in 27.8% (metastatic sites: CR: soft tissue, PR: 2 × osseous, 2 × soft tissue + osseous).

Besides objective measurable remissions, combined AG/cortisone acetate induced an evident, sometimes even dramatic relief from bone pain (10 patients), frequently occuring within 24 hr but not always corresponding to an objective tumour regression.

Side-effects of the treatment are shown in Table 3. Several may appear simultaneously but are individually specified. It must be stated, however, that most side-effects, including those affecting the mental functions, general discomfort, fatigue and weakness as well as skin rashes and increase of liver-specific enzymes, predominantly occur in the first few weeks of treatment, tend to diminish thereafter and disappear in the majority of cases after 6 weeks

Table 2. *Results*

	R+	R−	R?	total %	Duration of remission (months)
CR	–	1	–	5.6	9.5
PR	3	–	1	22.2	13 (7–28)
NC	2	–	1	16.7	9 (2–14)
PD	4	5	1	55.5	–

R+ Positive hormone receptor (ER > 10 fmol and/or PR > 20 fmol).
R− Negative hormone receptor.
R? Hormone receptor unknown.
CR Complete remission.
PR Partial remission.
NC No change.
PD Progressive disease.

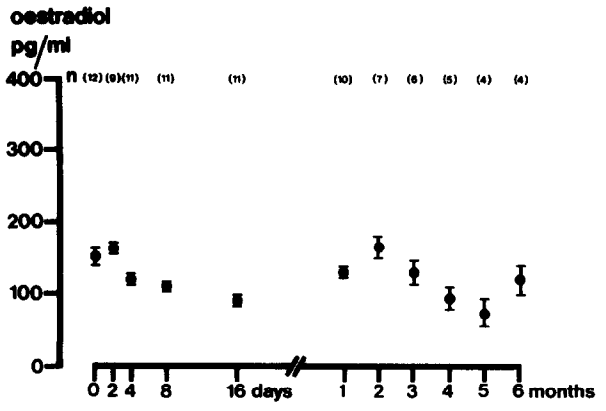

Fig. 1. Mean oestradiol in premenopausal patients treated with 1000 mg *AG (SEM).*

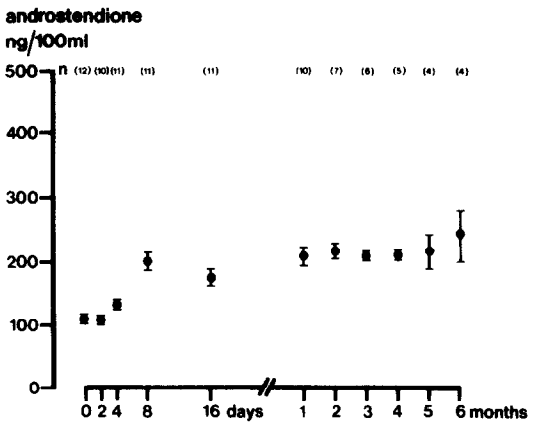

Fig. 2. Mean androstendione in premenopausal patients treated with 1000 mg *AG (SEM).*

of therapy.

Of the parameters determined on days 0, 2, 4, 8, 16, 30 and then monthly, plasma cortisol, ACTH, aldosterone, prolactin basal and 30 min after stimulation, TBI, T_3, T_4, cholesterol, triglycerides, pancreatic amylase, haemoglobin, leucocytes and platelets did not demonstrate any significant alteration. Decreased potassium occurred without exception due to diuretic therapy.

Three temporary increases in glucose were measured (maximum 172 mg %). Twelve patients developed an increase in liver-specific enzymes (gamma-glutamyltransferase, glutamate-pyruvate transaminase, glutamated oxalo-acetate transaminase). This increase could continue for up to 3 months but was obviously of no prognostic value.

The plasma level of oestradiol seemed to be essentially unchanged (Fig. 1). Also testosterone was not significantly influenced.

However, androstendione increased within 2 days of treatment and remained on a higher level during AG-therapy (Fig. 2).

DISCUSSION

The clinical results show that AG/cortisone acetate is effective in the therapy of premenopausal patients with metastatic breast cancer. The objective response rate of 27.8% and the duration of remissions corresponds to the described data of postmenopausal women [1–4, 6, 9, 11, 15].

During treatment with AG, no influence was detected on ACTH, cortisol, aldosterone and prolactin. Also, neither TBI, T_3, T_4 nor TSH basal and after stimulation significantly altered. According to the present experience of AG tolerance, the frequency and pattern of side-effects are similar to those previously described [1, 2, 7, 8].

The efficacy of AG on tumours with negative hormone receptors is described to be less than 10% [1, 4]. In this study one of six receptor negative tumours responded (CR, soft tissue) compared with five non-responders (PD). The receptor status of the single responder was determined in the primary tumour. In addition to a false measurement, a change of receptor status is therefore not out of the question. Troner [17] noticed three responders and one stable disease status among premenopausal patients with oestrogen receptor positive tumours.

The number of menstruating patients with metastatic disease previously treated with AG is rather small, and the therapeutic results contradictory. Harris *et al.* [10] did not see any response in 14 patients, but Santen *et al.* [12] described two remissions in four patients. We observed one complete remission, four partial remissions and three cases of no change in status among 18 women. This demonstrates that premenopausal patients may benefit from therapy with aminoglutethimide/cortisone acetate.

Contrary to postmenopausal patients, whose low estradiol levels continuously decrease [12], oestradiol levels in premenopausal patients were not influenced by therapy. Thus a marked suppression of the ovarian activity does not occur.

This agrees with the description of Santen *et al.* [12] (without substitution of cortisone) and Harris *et al.* [10]. Santen *et al.* [12] found the LH and FSH levels to be only slightly increased in the follicle phase but significantly higher in the luteal phase. Apparently, a reduction of the plasma oestrogen caused by inhibition of the aromatase in the ovary is compensated by the increase of gonadotrophic hormones.

Menstruation was not influenced in eight patients, completely inhibited in five, and an irregular cycle occured in five additional cases. No correlation of menstrual irregulation and response was noticed. Harris *et al.* observed irregular cycles and interpreted this as a partial blockage of the ovarian

aromatase. The indicated significant and continual increase of androstendione (Fig. 2)—also observed by Harris *et al.* [10]—would be an alternative explanation for the cycle irregularities. Santen *et al.* [12] believe that the ovarian aromatase differs in its sensitivity from those of other tissues. He concludes that the failure to suppress oestrogens is not the only explanation for the progression, since a decrease of oestradiol occurs in both responders and non-responders in postmenopausal patients.

It is possible to achieve remissions in premenopausal patients, even though the ovary appears to be resistant to AG. Therefore, AG must show other mechanisms of action, which are at least partially different from those in the postmenopause.

These modes of action are not necessarily of endocrine nature, since hormone receptor negative tumours also responded to AG. A direct effect on the tumour is quite imaginable. For example, Miller [16] showed that breast cancer cells are able to synthesize oestradiol and that, accordingly, aromatase must be available. Only the growth of those tumours under AG therapy could be suppressed, in which cases aromatase was also found. In our opinion, these results account for the fact that the mode of action of AG cannot be solely accounted for by the change in the adrenocortical steriod secretion or the decrease in the plasma oestrogens [3–5, 7].

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