Eur J Cancer Clin Oncol, Vol. 25, No. 2, pp. 369–376, 1989.
Printed in Great Britain

0277-5379/89$3.00 + 0.00

Low Dose Aminoglutethimide Without Hydrocortisone for the Treatment of Advanced Postmenopausal Breast Cancer

P.F. BRUNING,*‡ J.M.G. BONFRER,* A.A.M. HART,* E. VAN DER LINDEN,* M. DE JONG-BAKKER,* A.J. MOOLENAAR† and W.J. NOOIJEN*

**Department of Clinical Oncology, The Netherlands Cancer Institute (Antoni van Leeuwenhoekhuis), 121 Plesmanlaan, 1066 CX Amsterdam, The Netherlands and †Department of Chemical Pathology, University Hospital, 10 Rijnsburgerweg, 2333 AA Leiden, The Netherlands*

Abstract—*One hundred and one postmenopausal patients with advanced breast cancer were enrolled in a randomized phase II clinical trial to investigate the clinical and hormonal response to aminoglutethimide administered at daily doses of* 2 × 125 mg, 3 × 125 mg *or* 2 × 250 mg, *with no addition of hydrocortisone. Among* 71 *evaluable patients* 25% *showed objective tumor response (three complete,* 15 *partial), at all three dose levels and irrespective of the major tumor site. Previous treatment with Tamoxifen had been successful in* 75%. *Out of the* 18 *responding patients* 10 *had estrogen receptor positive, four had estrogen receptor negative tumors; the receptor status was unknown in four other patients. Progression-free interval was more than* 700 *days in* 50% *of the responders. Drowsiness caused early drug withdrawal in one patient. Side-effects were very mild, comparing favorably with standard therapy of* 250 mg *aminoglutethimide q.i.d. plus hydrocortisone. Plasma estrogen levels were reduced by all doses to the same* 50% *or less as in patients on standard treatment. In nine out of* 27 *patients a further decrease of estrone levels could be monitored with clinically improved results in five. Plasma cortisol and mineralocorticoids remained normal throughout more than* 6 *months.*

The original role of hydrocortisone administration to suppress a reflex rise of ATH in 'medical adrenalectomy' with standard dose aminoglutethimide is no longer tenable. Further phase III comparative clinical results pending, low dose aminoglutethimide as an aromatase inhibitor may at present be considered as an appropriate second-line endocrine treatment with low toxicity and expense.

INTRODUCTION

THE PROSPECTS for women presenting with primary breast cancer have improved through earlier diagnosis and better primary treatment. However, most patients still face metastatic disease, for which endocrine treatment often constitutes optimal palliation.

Since the original application of aminoglutethimide (AG) for 'medical adrenalectomy' as an adequate endocrine treatment of advanced postmenopausal breast cancer [1–4], the insight has been developed that AG exerts its lowering effect on plasma estrogens by inhibition of aromatase activity in peripheral tissues, rather than by interference with the adrenal production of estrogen precursors [5, 6]. Developing 'medical adrenalectomy' Santen *et al.* [7] originally added hydrocortisone (HC) 40 mg daily to a dose of 250 mg AG q.i.d. to prevent an increase of the adrenal estrogen precursor Δ_4-steroids, which was presumed to result from the corticotrophin (ACTH) feed-back reaction to diminished cortisol secretion when AG alone was given. Subsequent studies provided evidence that AG could also cause elevated androstenedione levels by acceleration of the enzymatic conversion of Δ_5- to Δ_4-steroids [8]. From *in vitro* studies it has been learned that aromatase activity is inhibited by AG concentrations, which are many-fold lower than those required for the inhibition of various adrenocortical hydroxylation steps [9]. Recently, Dowsett *et al.* [10] reported 92% inhibition of peripheral

Accepted 10 October 1988.
‡Author to whom correspondence and reprint requests should be addressed.
Presented in part at the 14th International Cancer Congress, Budapest, Hungary, 21–27 August 1986, and the fifth NCI-EORTC symposium on New Drugs in Cancer Therapy, Amsterdam, The Netherlands, 22–24 October 1986.

aromatase activity *in vivo* in five postmenopausal breast cancer patients treated with 125 mg AG b.d. With low dose AG therapy aiming at aromatase inhibition the original rationale for the administration of HC seems no longer tenable.

Short-term endocrine studies in limited numbers of postmenopausal women [11–13] have shown that low dose AG without HC can cause a decrease of plasma estrone levels similar to those obtained with AG + HC. On the other hand, Vermeulen *et al.* demonstrated that administration of HC alone caused a smaller decrease of plasma estrone concentration than 500–1000 mg AG plus HC [11]. Whether HC adds to the tumor response to AG therapy is still questionable.

The purpose of the present study has been to investigate the clinical and hormonal effects of three different low dose levels of AG, with no additional HC, in postmenopausal women with advanced breast cancer.

Data are presented to show that low dose AG alone effectively decreases plasma estrogen levels and produces satisfactory tumor response rates. By its low toxicity and financial cost, low dose AG therapy compares favorably with the standard treatment using high dose AG plus HC.

MATERIALS AND METHODS

Study population

Postmenopausal women (n = 101) with advanced breast cancer, previously treated with Tamoxifen, were randomly assigned to one of three AG low dose schedules: group A receiving orally 125 mg AG b.i.d., group B 125 mg AG t.i.d. and group C 250 mg b.i.d.

Criteria for entry into the study included the presence of measurable or evaluable progressive lesions and a WHO performance score less than 3. In 27 women showing stable disease or progression on treatment with low dose, the AG dose was escalated to the conventional dose of 250 mg AG q.i.d., in combination with HC 10 mg at 8 a.m., 10 mg at 1 p.m. and 20 mg at 10 p.m., according to Santen *et al.* [14].

All patients had given their informed consent.

Clinical evaluation

Clinical tumor response was measured after 3 months according to UICC response criteria [15]. Patients should be treated for at least 4 weeks to become evaluable. The duration of remission was calculated from the start of treatment and until renewed progression.

Clinical toxicity was monitored at 2, 4, 8, 12 and 24 weeks using WHO criteria [16].

Laboratory evaluation

Blood sampling was done before therapy and after 4, 8 and 24 weeks of treatment. Serum concentrations of AG, various steroid hormones and parameters of thyroid function were measured according to methods described earlier [17, 18]. Estradiol assays were kindly performed by CIBA-Geigy Research Division, Basle, Switzerland using a modification of the [^{125}I]estradiol RIA kit from EIR (Würenlinger, Switzerland); the lower detection limit of this assay was 7.3 pM.

Data analysis

For all parameters normal probability plots were made of the differences between the serial measurements both on the linear and the logarithmic scale in order to validate the use of analysis of variance and to check for outliers. Changes in time were tested using analysis of variance (repeated measurements) as implemented in the P_2V program of the BMDP package (version 1981 for PDP-11). The basis analysis was done on direct results or on log values, as indicated by the normal plots.

RESULTS

Clinical response to low dose aminogluethimide treatment

Among the 101 patients entered into the study, eight women were ineligible because AG was never taken by two, one had a second cancer, four did not have previous treatment with Tamoxifen, and follow-up data were missing in one patient. Among the remaining 95 patients, 15 were inevaluable since they did not complete the first 4 weeks of treatment for the following reasons: early drug withdrawal because of disease progression in 11 patients (three in group A, four in group B, four in group C), early death in four patients (two in group A, one in group B, one in group C). Drug withdrawal because of serious drowsiness in one patient (group A), protocol violations in four, and loss to follow-up in four patients made nine more patients inevaluable. Of the 71 evaluable patients 18 (25%) showed an objective tumor response (three complete and 15 partial); 37 (53%) had stabilization of their disease; 16 patients (22%) showed progressive disease. Table 1 demonstrates that objective responses were obtained at all three dose levels, irrespective of the major tumor site.

The estrogen receptor (ER) content of the tumor cytosol was known to be positive (i.e. more than 15 pmole estradiol per mg protein) in 52%, negative in 23%, and unknown in 25% of the evaluable patients, the numbers being evenly distributed over the treatment groups. Out of 18 objective responders 10 patients had ER positive, four had ER negative tumors. The ER status was unknown in four other patients. Among the 38 patients with stable disease 18 were ER positive, 11 were ER negative. Ten patients with ER positive tumors had progressive disease.

Response to previous Tamoxifen therapy had been positive in 75% of the patients, again evenly

Table 1. *Tumor response and major tumor site*

	Group A $n = 25$	Group B $n = 19$	Group C $n = 27$	All $n = 71$	Response rate(%)
Progressive disease	7	6	3	16	22
Stable disease	14	8	15	37	53
Objective response					
Complete	1	1	1	3	4 } 25
Partial	3	4	8	15	21 }
Major tumor site					
Bone	1/6	1/4	5/12	7/22	
Soft tissue	1/9	1/4	2/6	4/19	
Visceral	2/10	3/11	2/9	7/30	

distributed over group A, B and C. Among the 54 patients who head a positive tumor response to previous Tamoxifen 18 (33%) showed an objective tumor response to low dose AG therapy. One of the 17 patients who had not responded to previous Tamoxifen therapy did respond to AG.

As shown in Fig. 1, the progression-free interval was longer than 700 days in 50% of the responders, and longer than 180 days in 50% of the patients with stable disease.

Table 2 shows that clinical toxicity due to low dose AG was minimal, and definitely much less than observed earlier with the conventional dose of 250 mg AG q.i.d. plus hydrocortisone (HC) [18]. This was also true for the effect on thyroid function. The free thyroxine index decreased by 10%, but became subnormal at 4 and 8 weeks in only one out of 11 patients in group A, 0 out of 10 in group B and one out of 17 in group C. All patients showed an increase of thyrotropin (TSH) at 1 and 2 months of treatment. A rise to abnormal serum levels of TSH was observed only in those patients, who had a subnormal free thyroxine index, and in three additional patients in group C in whom thyroid function remained compensated.

Clinical response to dose escalation

After at least 3 months of treatment the low AG dose was escalated to the standard dose of 250 mg AG q.i.d. plus 40 mg HC daily in 27 patients. Among the six patients who progressed on low dose AG treatment four showed further progression; the tumor growth stabilized in two. Out of 18 patients with stable disease on low dose AG during at least 3 months, four obtained an objective tumor response after dose escalation, eight remained stable and six showed progressive disease. In one out of three patients relapsing from an objective response to low dose AG a second objective response was observed with standard AG plus HC; the two other patients

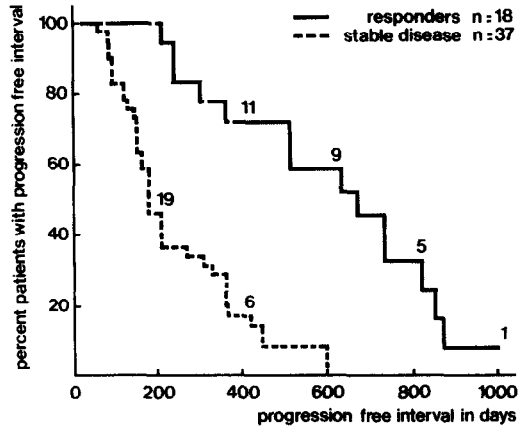

Fig. 1. *Kaplan–Meier plot of the progression-free interval in* 71 *postmenopausal patients with advanced breast cancer treated with low dose aminoglutethimide* (125 mg *b.d.*, 125 mg *t.i.d. or* 250 mg *b.d.*).

Table 2. *Clinical toxicity scored according to WHO grading criteria* [16] *at* 4 *and* 8 *weeks of treatment*

	Group A				Group B				Group C			
Week	4		8		4		8		4		8	
Grade*	1	2	1	2	1	2	1	2	1	2	1	2
Nausea	6	1	2	—	2	—	1	—	4	—	1	—
Fever	—	—	—	1	—	—	—	—	—	1	—	—
Skin rash	1	—	—	1	1	—	—	—	—	1	—	—
Somnolence	2	1	1	1	5	—	—	—	4	—	—	1
Patients with toxicity	10		4		7		1		6		2	

*Grade 3 and 4 toxicity were not observed.

showed stable disease. Therefore seven out of 27 patients (26%) had a benefit from dose escalation (five objective response, two stable disease), with no noticeable preference for any of the low dose groups.

Very minor toxicity was seen after dose escalation in nine of the 27 patients: six showed somnolence grade I, four had nausea grade I. Skin rash or fever did not occur.

Hormonal response to low dose aminoglutethimide treatment

As shown in Table 3, the plasma levels of the estrogen precursor Δ_4-steroid androstenedione significantly increased within 1 month, with no further rise thereafter. Androstenedione levels were higher in group C than either in group A or B ($P = 0.0001$). This difference disappeared when plasma AG concentration was controlled for. The Δ_4-steroid 17-α-hydroxyprogesterone also rose, the increase being statistically significant in group C but not in group A. Nevertheless, an equal and significant ($P < 0.0001$) decrease of plasma estrone and estradiol of more than 50% was obtained at all three dose levels. This effect was observed after 1 month, with no further decrease of estrogen levels after 2 and 6 months of treatment, as shown in Table 4.

Plasma cortisol levels remained normal in all groups. Only with the 2 × 250 mg AG dose a just significant decrease of plasma cortisol was observed after 6 months (Table 5). The plasma concentration of another exclusive adrenal corticosteroid, dehydroepiandrosterone sulfate did not significantly change in either of the dose groups (data not shown).

The levels of the mineralocorticosteroid precursor desoxycorticosterone did not change significantly. These findings were in accordance with the clinical observation that no patient showed any symptom or sign of adrenocortical insufficiency, such as orthostatic hypotension, shock or hyponatremia with hyperkalemia. A decrease of corticosterone levels was observed with 125 mg AG b.d. (from 39.7 ± 32.0 nM before treatment to 17.7 ± 5.3 nM after 6 months; $n = 7$), but was significant only at a dose of 250 mg AG b.d. (from 29.6 ± 13.6 nM to 18.6 ± 7.6 nM; $n = 9$; $P = 0.05$).

As a result the desoxycorticosterone/corticosterone ratio increased in 5/7 patients at the lowest, and in 8/9 patients at the highest dose. The mean rise of this ratio in the latter dose group was significant (0.9 ± 0.3 to 1.5 ± 0.5; $P < 0.01$).

The amounts of plasma available were not sufficient for measurements of aldosterone.

Hormonal response to dose escalation

Interestingly, dose esclation to 1000 mg AG with addition to 40 mg HC daily resulted in a further decrease of plasma estrone levels, which could be monitored in nine out of 27 patients (Fig. 2).

There was no clear relationship between this phenomenon and the clinical response to dose increase. Plasma androstenedione decreased to pretreatment levels as expected. The dehydroepiandrosterone sulfate concentrations, which did not sig-

*Table 3. Low dose AG and plasma Δ_4-steroid levels**

	Treatment duration (months)				
	0	1	2	6	*P* value
Androstenedione					
Group A	1.98 ±0.93 $n = 12$	5.53 ±4.00 $n = 12$	4.93 ±3.30 $n = 12$	4.77 ±4.64 $n = 12$	n.s.
Group B	2.35 ±1.30 $n = 10$	4.37 ±2.14 $n = 10$	6.26 ±2.75 $n = 10$	4.51 ±2.11 $n = 10$	<0.01
Group C	1.90 ±0.81 $n = 16$	6.99 ±3.05 $n = 16$	6.70 ±3.50 $n = 16$	6.10 ±4.58 $n = 16$	<0.01
17-α-Hydroxyprogesterone					
Group A	1.01 ±0.70 $n = 6$			1.89 ±1.05 $n = 6$	n.s.
Group C	0.72 ±0.40 $n = 9$			5.74 ±4.20 $n = 9$	<0.01

*nM; mean ± S.D.

*Table 4. Low dose AG and plasma estrogen levels**

	Treatment duration (months) 0	1	2	6	*P* value
Estrone					
Group A	128 ±48 $n = 12$	55 ±21 $n = 12$	51 ±24 $n = 12$	46 ±22 $n = 12$	<0.01
Group B	127 ±52 $n = 10$	58 ±33 $n = 10$	55 ±12 $n = 10$	56 ±15 $n = 10$	<0.01
Group C	126 ±57 $n = 16$	51 ±18 $n = 16$	66 ±37 $n = 16$	48 ±25 $n = 16$	<0.01
Estradiol					
Group A	39.6 ±17.2 $n = 23$		22.8 ±6.2 $n = 23$	24.6 7.0 $n = 8$	<0.01
Group B	38.9 ±16.1 $n = 15$		22.0 ±5.1 $n = 14$	16.5 ±4.0 $n = 8$	<0.01
Group C	37.1 ±11.7 $n = 21$		22.4 ±3.7 $n = 22$	21.3 ±4.8 $n = 9$	<0.01

*pM; mean ± S.D.

*Table 5. Low dose AG and plasma cortisol levels**

	Treatment duration (months) 0	1	2	6	*P* value
Group A	0.51 ±0.30 $n = 12$	0.50 ±0.18 $n = 12$	0.44 ±0.16 $n = 12$	0.43 ±0.22 $n = 12$	n.s.
Group B	0.57 ±0.21 $n = 10$	0.54 ±0.19 $n = 10$	0.47 ±0.23 $n = 10$	0.50 ±0.14 $n = 10$	n.s.
Group C	0.37 ±0.17 $n = 16$	0.53 ±0.18 $n = 16$	0.43 ±0.15 $n = 16$	0.38 ±0.14 $n = 16$	0.03

*μM; mean ± S.D.

nificantly change during low dose AG therapy, invariably dropped to low values.

DISCUSSION

Blockade of estrogen action by administration of the anti-estrogen Tamoxifen is widely accepted as the first-line endocrine treatment of advanced postmenopausal breast cancer, since Tamoxifen is effective with very little toxicity. Although no such general agreement exists on second-line endocrine treatment, inhibition of estrogen biosynthesis by AG in combination with HC has been demonstrated to yield response rates similar to those obtained with Tamoxifen [19, 20], hypophysectomy [21] or adrenalectomy [14]. The principal source of estrogen in postmenopausal women is the enzymatic conversion of androstenedione to estrone. Androstenedione is mainly produced by the adrenal cortex [5]. The conversion to estrone is mediated by aromatase, which is mainly present in body fat, muscle and liver, and to some extent also in breast cancer tissue itself [22–24]. Estrone is further metabolized to the more active estradiol by 17-β-hydroxysteroid dehydrogenase, or to the biologically inactive estrone sulfate. Since AG was known to interfere with the adrenal synthesis of cortisol and various

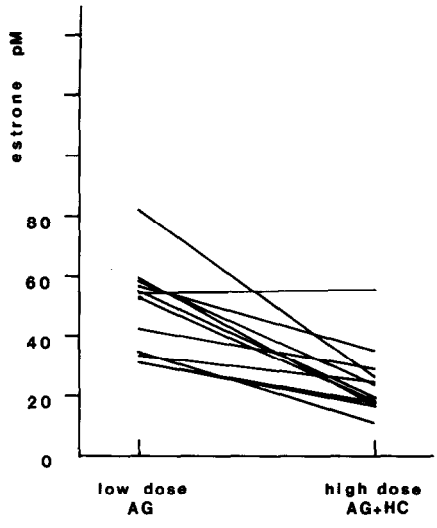

Fig. 2. The effect of aminoglutethimide dose escalation from low dose to 250 mg *q.i.d., in combination with hydrocortisone* 20 mg *b.d. on plasma estrone concentration in* 12 *patients (after* 2 *months of high dose treatment).*

other steroids, the original application of AG in breast cancer treatment was to cause 'medical adrenalectomy' with the purpose of diminishing the production of estrogen precursor steroids. To overcome an adrenal escape by increased ACTH as a feed-back reaction to impaired cortisol secretion, first dexamethasone and later hydrocortisone was added to a daily dose of 1000 mg AG [7]. It was successively found that AG inhibited aromatase *in vitro* at much lower concentrations than required for the impairment of adrenal steroid synthesis [9]. Moreover, the plasma concentrations of androstenedione were not lowered, but rather increased by AG therapy [17, 25, 26]. So, it appeared that it is the inhibition of aromatase as the rate-limiting step in estrogen biosynthesis that matters, rather than 'medical adrenalectomy'.

Various observations have also shown that daily AG doses as low as 125 mg could cause a decrease of plasma estrone similar to the effect from 1000 mg AG or adrenalectomy [11–13].

In a randomized phase II clinical trial, Bonneterre *et al.* [27] found no significant difference between the responses to daily doses of 500 mg AG with 40 mg HC and 1000 mg AG with 40 mg, respectively.

The results of the present study show that low doses of AG without HC ranging from 125 to 250 mg b.d. yield a response rate, which can also be expected from the standard AG dose in combination with HC. Toxicity was very small, comparing favorably with the side-effects from the conventional schedule. In the present study first line endocrine treatment with Tamoxifen was a major eligibility criterion. As has been demonstrated in various other studies, objective tumor response was more likely if the patient had responded to previous Tamoxifen treatment, or had a positive estrogen receptor. However, we did observe objective responses and stabilization of disease with low dose AG in ER negative tumors, as has been reported for standard dose AG with HC. Tumor responses were observed irrespective of the major tumor site.

Since the present study was carried out as a randomized phase II clinical trial, allocation bias has been ruled out as much as possible, but the small numbers involved do not provide sufficient statistical power for comparisons of clinical response between the dose groups. The impression given that the response rate in group C seems somewhat better than in groups B and A respectively should therefore be regarded with caution. However, from the hormonal data it is clear that at all dose levels a similar reduction of plasma estrogens is seen. This decrease is similar to what is obtained with conventional AG in combination with HC [17, 28]. Still, in a number of the patients in which the AG dose was escalated a further decrease of estrone was observed, indicating that at the low doses used in this study the suppression of plasma estrogens is not always maximal. It is uncertain to which extent the addition of HC has played a role here. Harris *et al.* [12] did not observe further reduction of plasma estrogen when HC was added to AG alone. Dowsett *et al.* [26] compared the reduction of estrogen levels in two geographically separate populations of postmenopausal breast cancer patients. They found a significantly greater reduction of estrone and less markedly of estradiol by AG 125 mg b.d. combined with HC 20 mg b.d. compared to AG 125 mg b.d. alone.

Androstenedione levels were increased in the AG alone group, but decreased in the AG with HC patients. In some of our patients dose escalation also meant improvement of the clinical result, i.e. further tumor regression or stabilization, even after tumor relapse on low dose therapy.

From these findings we conclude that individual differences in endocrine and tumor responses are to be expected, justifying low dose AG treatment with a dose increment to 1000 mg AG plus 40 mg HC in individual cases if the tumor response after 2–3 months is unsatisfactory.

Hoeffken *et al.* [29] reported recently that patients treated with 1000 mg AG daily showed stable cortisol plasma levels without hydrocortisone substitution. Our clinical and endocrine data demonstrate that low dose AG caused no impairment of cortisol secretion. The moderate increase of 17-α-hydroxyprogesterone suggests that the interference of AG with the hydroxylation steps required for cortisol formation is easily overcome by feed-back regulation stimulating the adrenal with some extra ACTH. Theoretically, adrenal crisis may occur in rare cases of unexpected hydroxylase deficiency or metabolic accumulation of AG. To our knowledge,

no well-documented reports of such conditions have been published. For the elevation of androstenedione levels a reflex increase of ACTH forms a very unlikely explanation, since the plasma concentrations of the sulfated form of its precursor dehydroepiandrosterone are not increased. The inhibition of aromatase can account for only a small part of the rise of androstenedione from an average of 2–6 nM, whereas estrone falls from 125 to 50 pM. An increased conversion from dehydroepiandrosterone to androstenedione due to AG has been demonstrated by Samojlik and Santen [8]. A diminished conversion to its major metabolite, 11-hydroxy-androstenedione, may be another important factor producing elevated androstenedione plasma levels. Vermeulen *et al.* [11] have shown that a dose as low as 125 mg AG b.d. without HC can inhibit 11-hydroxylase. Our observation of decreasing corticosterone with unchanged deoxycorticosterone levels also indicates that low dose AG can inhibit 11-hydroxylase to some extent.

Since a similar decrease of plasma estrogens occurs in practically all patients studied, two main conclusions can be drawn. Firstly, the lowest dose used, 125 mg b.d. is effective in reducing plasma estrogens. Secondly, there is no clear relationship between estrogen plasma level and tumor response. Apparently, most estrogen-receptor positive, postmenopausal breast cancers respond to this degree of estrogen deprivation, be it due to hypophysectomy, adrenalectomy, high or low dose AG with or without HC.

It is known that AG may interfere with thyroid hormone synthesis. In previous studies we have found that Dutch postmenopausal breast cancer patients who had been postoperatively irradiated at the supraclavicular lymph nodes developed primary hypothyroidism as often as 25% when treated with AG 250 mg q.i.d. and HC [18, 30]. The characteristics of the population treated with low dose AG in the present study did not differ from the groups studied in the past concerning age or postoperative radiotherapy. However, with low dose AG only a subclinical decrease of thyroid function (approximating 10% free thyroxine index at 1 and 2 months of treatment) was observed. Apparently, the increase of TSH (37% at 1 and 50% at 2 months; $P > 0.0001$) provided adequate compensation. Differences between the dose groups were not significant. It can be concluded that low dose AG has also little thyroid toxicity, compared to conventional AG dose. This is of clinical importance since hypothyroidism may easily remain undetected in this patient category if not specifically looked for.

Low dose AG as second-line endocrine therapy of advanced postmenopausal breast cancer appears at present as a fair option because of its low toxicity, its simplicity and relatively low cost. Whether HC should be added is still a matter of debate. Further phase III clinical trials should be performed to compare conventional dose AG plus HC with low dose AG with and without HC for tumor response and toxicity.

Acknowledgements—We are indebted to Dorothe Linders and Jan van Loon for excellent technical assistance, and to Ria de Jong for skillful assistance in the preparation of the manuscript.

REFERENCES

1. Cash R, Brough AJ, Cohen MNP, Satoh PS. Aminoglutethimide (Elipten-CIBA) as an inhibitor of adrenal stereoidogenesis. Mechanism of action and therapeutic trial. *J Clin Endocrinol Metab* 1967, **27**, 1239–1248.
2. Griffiths CT, Hall TC, Saba Z, Barlow JJ, Nevinny HB. Preliminary trial of aminoglutethimide in breast cancer. *Cancer* 1973, **32**, 31–37.
3. Lipton A, Santen RJ. Medical adrenalectomy using aminoglutethimide and dexamethasone in advanced breast cancer. *Cancer* 1974, **33**, 503–512.
4. Wells SA, Santen RJ, Lipton A *et al.* Medical adrenalectomy with aminoglutethimide. Clinical studies in postmenopausal patients with metastatic breast carcinoma. *Ann Surg* 1978, **187**, 475–484.
5. Santen RJ, Santner S, Davis B, Veldhuis J, Samojlik E, Ruby E. Aminoglutethimide inhibits extraglandular estrogen production in postmenopausal women with breast carcinoma. *J Clin Endocrinol Metab* 1978, **47**, 1257–1265.
6. Santen RJ, Boucher AE, Santner SJ, Craig Henderson I, Harvey H, Lipton A. Inhibition of aromatase as treatment of breast carcinoma in postmenopausal women. *J Lab Clin Med* 1987, **109**, 278–289.
7. Santen RJ, Wells SA, Runic S *et al.* Adrenal suppression with aminoglutethimide 1. Differential effect of aminoglutethimide on plasma androstenedione and estrogen levels. *J Clin Endocrinol Metab* 1977, **45**, 469–479.
8. Samojlik E, Santen RJ. Adrenal suppression with aminoglutethimide III. Comparison of plasma Δ_4- and Δ_5-steroids in postmenopausal women treated for breast carcinoma. *J Clin Endocrinol Metab* 1978, **47**, 717–724.
9. Graves PE, Salhanick HA. Stereoselective inhibition of aromatase by enantiomers of aminoglutethimide. *Endocrinology* 1979, **105**, 52–57.

10. Dowsett M, Santner SJ, Santen RJ, Jeffcoate SL, Smith IE. Effective inhibition by low dose aminoglutethimide of peripheral aromatization in postmenopausal breast cancer patients. *Br J Cancer* 1985, **52**, 31–35.
11. Vermeulen A, Paridaens R, Heuson JC. Effects of aminoglutethimide on adrenal secretion. *Clin Endocrinol* 1983, **19**, 673–682.
12. Harris AL, Dowsett M, Smith IE, Jeffcoate SL. Endocrine effects of low dose aminoglutethimide alone in advanced postmenopausal breast cancer. *Br J Cancer* 1983, **47**, 621–627.
13. Stuart-Harris R, Bozek T, Gazet JC *et al.* Low dose aminoglutethimide in treatment of advanced breast cancer. *Lancet* 1984, **2**, 604.
14. Santen RJ, Worgul TJ, Samojlik E *et al.* A randomized trial comparing surgical adrenalectomy with aminoglutethimide plus hydrocortisone in women with advanced breast cancer. *N Engl J Med* 1981, **305**, 545–551.
15. Hayward JL, Carbone PP, Heuson JC, Kumaoka S, Segaloff A, Rubens RD. Assessment of response to therapy in advanced breast cancer. *Cancer* 1977, **39**, 1289–1294.
16. *WHO Handbook for Reporting Results of Cancer Treatment.* WHO offset publication No. 48, Geneva, 1979.
17. Bruning PF, Bonfrer JMG, de Jong-Bakker M, Nooyen W. Influence of ACTH on aminoglutethimide induced reduction of plasma steroids in postmenopausal breast cancer. *J Steroid Biochem* 1984, **21**, 293–298.
18. Bruning PF, Bonfrer JMG, Engelsman E, Hamersma-van der Linden E, de Jong-Bakker M, Nooyen W. Pros and cons of aminoglutethimide for advanced postmenopausal breast cancer. *Breast Cancer Res Treat* 1984, **4**, 289–295.
19. Smith IE, Harris AL, Morgan M, Gazet JC, McKinna JA. Tamoxifen versus aminoglutethimide versus combined Tamoxifen and aminoglutethimide in the treatment of advanced breast carcinoma. *Cancer Res* 1982, **42** Suppl, 3430s–3433s.
20. Lipton A, Harvey HA, Santen RJ *et al.* Randomized trial of aminoglutethimide versus Tamoxifen in metastatic breast cancer. *Cancer Res* 1982, **42** Suppl, 3434s–3436s.
21. Harvey HA, Santen RJ, Osterman J, Samojlik E, White DS, Lipton A. A comparative trial of transsphenoidal hypophysectomy and estrogen suppression with aminoglutethimide in advanced breast cancer. *Cancer* 1979, **43**, 2207–2214.
22. Miller WR, Forrest APM. Oestradiol synthesis from C_{19} steroids by human breast cancers. *Br J Cancer* 1976, **33**, 116–118.
23. Tilson-Mallett N, Santner SJ, Feil PD, Santen RJ. Biological significance of aromatase activity in human breast tumors. *J Clin Endocrinol Metab* 1983, **57**, 1125–1128.
24. Lipton A, Santner SJ, Santen RJ *et al.* Aromatase activity in primary and metastatic human breast cancer. *Cancer* 1987, **59**, 779–782.
25. Samojlik E, Santen RJ, Kirschner MA, Ertel NH. Steroid hormone profiles in women treated with aminoglutethimide for metastatic carcinoma of the breast. *Cancer Res Suppl* 1982, **42**, 3349s–3352s.
26. Dowsett M, Harris AL, Stuart-Harris R *et al.* A comparison of the endocrine effects of low dose aminoglutethimide with and without hydrocortisone in postmenopausal breast cancer patients. *Br J Cancer* 1985, **52**, 525–529.
27. Bonneterre J, Coppens H, Mauriac L *et al.* Aminoglutethimide in advanced breast cancer: clinical results of a French multicenter randomized trial comparing 500 mg and 1 g/day. *Eur J Cancer Clin Oncol* 1985, **21**, 1153–1158.
28. Stuart-Harris RC, Smith IE. Aminoglutethimide in the treatment of advanced breast cancer. *Cancer Treat Rev* 1984, **11**, 189–204.
29. Hoeffken K, Miller AA, Miller B, Becher R, Schmidt CG. New aspects of hormonal treatment of metastatic breast cancer. *Dtsch Med Wschr* 1985, **110**, 1799–1802.
30. Bruning P, Bonfrer J, De Jong-Bakker M, Nooyen W, Burgers M. Primary hypothyroidism in breast cancer patients with irradiated supraclavicular lymph nodes. *Br J Cancer* 1985, **51**, 659–663.