Eur J Cancer Clin Oncol, Vol. 21, No. 1, pp. 19-22, 1985.
Printed in Great Britain.

0277-5379/85$3.00+0.00

Low-dose Aminoglutethimide without Steroid Replacement in the Treatment of Postmenopausal Women with Advanced Breast Cancer

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Abstract—*Fifty-seven patients with actively progressing advanced breast cancer have been assessed for their response to low-dose aminoglutethimide* (125 mg *bd*) *without steroid replacement. Eleven women* (19%) *had an objective response while a further eight had stabilization of disease. However, one patient died with apparent adrenal insufficiency and another developed low plasma cortisol and serum sodium. Furthermore, 4/17 patients who had failed to respond to low-dose A/G subsequently responded when changed to conventional-dose A/G + steroid replacement, while three patients had stabilization of previously progressing disease. These results indicate that low-dose A/G without steriod replacement is potentially hazardous and that low-dose and conventional-dose A/G + steroids do not produce identical results.*

INTRODUCTION

AMINOGLUTETHIMIDE (A/G), in combination with physiological replacement of glucocorticoids, ± mineralocorticoids has now been shown to be effective treatment for patients with advanced breast cancer, with a similar remission rate and duration of response to other hormonal treatments [1-4]. However, the minimum effective dose of A/G and whether steroid replacement is essential is not yet known. It has been demonstrated that the aromatase enzyme system (which is involved in conversion of androgens to oestrogen) is much more sensitive than the desmolase one (which converts cholesterol to pregnenolone) to inhibition by A/G when tested *in vitro* [5], and low-dose (LD) A/G without steroid supplementation has been reported to produce a similar fall in plasma oestrogens to that seen with conventional dose (CD) [6]. These findings suggest that treatment with smaller doses of A/G than are conventionally given, without replacement steroids, might be as effective as conventional dose A/G + steroids.

In this paper we present results of treatment using low-dose A/G (125 mg bd) without glucocorticoid or mineralocorticoid replacement in patients with advanced breast cancer. Some patients who failed to respond to LD A/G were subsequently changed to CD A/G + steroid replacement and their response was again assessed.

Accepted 26 July 1984.

MATERIALS AND METHODS

All patients were either postmenopausal or postoophorectomy and had actively progressing advanced (stage III or IV) breast cancer. They were referred by other clinicians who had judged them as suitable for hormonal treatment.

Prior to starting treatment each patient had a complete history and examination and the following investigations were carried out: full blood examination, estimation of urea and electolytes, liver function tests, calcium, CEA, DHEA-SO_4, testosterone and cortisol.

Each patient had a full skeletal survey and liver scan, while CT scanning was carried out if indicated. The haematological, biochemical and hormonal estimations were repeated at least monthly while the patient was on treatment and the skeletal survey and liver scan were repeated at three-monthly intervals. Classification of response was by two observers according to standard UICC criteria.

Treatment was started with aminoglutethimide 125 mg bd and no steroid replacement was given. Therapy was continued on this regimen until there was clear evidence of response. Those

patients whose disease remitted to treatment or in whom the previously progressing disease had become static continued on the same dose of A/G. In those patients in whom there was no response the A/G was either stopped and alternative therapy was started or the dose of A/G was increased to 250 mg tds and replacement therapy with cortisone acetate 25 mg AM, 12.5 mg PM and fludrocortisone 0.1 mg mane was added.

RESULTS

At the time of writing 57 patients (median age 66 yr, range 43–90 yr) have been assessed. Of these 11 (19%) have had an objective response, while another eight have had stabilization of their disease. Thus 19 of the 57 assessable patients (or 33%) appeared to have been helped by the treatment. Median durations of remission and stabilization have not yet been reached but 81% of remitters are still in remission at 8 months while all of the static group still currently have stabilization of disease (range 3+ to 15+ months). All remitters are currently alive at a time ranging from 8 to 18 months since starting A/G but median survival in the non-remitters is only 7.8 months.

The clinical characteristics of all the patients and of the remitting, static and non-remitting groups are shown in Table 1. There are no significant differences in age, time since the menopause or free interval between the groups. The non-remitters had received slightly more treatment prior to commencing A/G than the static and remitting patients, but the average number of sites of involvement was the same for all three groups. All patients had previously received tamoxifen but in many instances the response to this could not be determined because of poor documentation, concurrent other treatment or no assessable lesion being present. Nevertheless a higher percentage of the remitting and static patients had a previous classifiable response to tamoxifen than had the non-remitters.

Results of measurement of DHEA-SO, testosterone and cortisol measurement are currently being analysed and will be presented elsewhere.

Twenty-seven of the patients who failed to respond to LD A/G have been changed to conventional dose A/G + steroid replacement. Six of these patients are on treatment but have not yet been assessed and four were given concurrent other treatment and cannot therefore be assessed, leaving 17 patients whose response to CD A/G could be determined. Four patients who failed on LD A/G have had unequivocal regression of disease on CD A/G and a further three have had stabilization of previously progressing disease. Brief summaries of the clinical course of two patients who had a remission and a third who had stabilization of disease after changing to CD A/G + steroids are presented below.

1. (SM) This 52-yr-old woman started treatment with LD A/G following progression of bony, pulmonary and soft tissue metastases after a 2-yr remission to tamoxifen. Three months later there had been a slight increase in her soft tissue lesion and a skeletal survey showed progression of both bone and pulmonary lesions. The patient was changed to CD A/G and steroid replacement. One month later the soft tissue lesion was noted to be smaller while at 3 and 6 months later X-rays showed a decrease in the pulmonary lesions and sclerosis of previously lytic bone lesions.

2. (EM) This patient was a 45-yr-old woman who presented with stage IV cancer of the breast in 1980. This breast mass was treated with radiotherapy and she was started on tamoxifen 20 mg bd. Two and a half years later she relapsed with bony metastases which incapacitated her and confined her to bed. Low-dose A/G was substituted for the tamoxifen but she remained restricted in activity and her CEA did not alter. Skeletal

Table 1. Clinical characteristics of all patients and of them sub-divided into groups by response

	All patients (57)	Remitters (11)	Static (8)	Non-remitters (38)
Age (yr)*	65.3 ± 1.2	67.9 ± 12.7	65.6 ± 9.5	64.5 ± 12.6
Time since menopause (yr)*	17.3 ± 11.2	17.5 ± 10.9	16.4 ± 8.1	17.6 ± 12.1
Free interval (yr)*	4.0 ± 4.9	4.9 ± 5.0	4.7 ± 4.8	3.6 ± 5.1
No. with a classifiable response to tamoxifen and % responding to it	39 48.77%	10 70%	5 60%	26 35%
Average No. of previous treatments	1.5	1.3	1.5	1.8
Average No. of sites of disease involvement	1.3	1.3	1.3	1.3

*Mean ± S.D.

survey after 3 months of LD A/G showed further progression and lysis so she was changed to CD A/G + steroids. After a further 3 months she was walking with the aid of a stick, her CEA had fallen from 15 to 5 mg/ml and X-rays showed sclerosis of previously lytic lesions. Eight months later she remains in remission and pain-free.

3. (HW) This 74-yr-old woman who had previously responded to tamoxifen started on LD A/G following relapse with bony metastases. Over the following 3 months she had increasing pain and gradually became more incapacitated. Her analgesic intake increased from II codral 4-hourly until she required regular injections of narcotics. X-rays showed no evidence of healing with an increase in size of lytic lesions in the skull. She was changed to CD A/G + steroid replacement and subsequently experienced a marked clinical improvement. Three months later she was pain-free and taking no analgesics. Her weight increased by 10 kg and her CEA fell from greater than 20 to normal (iess than 5 μg/ml). X-rays 6 months after changing to CD A/G did not show any healing, but no further progression had occurred. Twelve months later the patient remains in excellent health with no evidence of active disease.

Three patients treated with LD A/G died unexpectedly within a month of starting treatment. One of these was admitted to a peripheral hospital complaining of anorexia, lethargy and tiredness increasing over a 10-day period. Twenty-four hours before her death she was noted to have a blood pressure of only 80/50 and a plasma aminoglutethimide level taken at that time was 33 μmol/l. This level is similar to that found in many patients taking conventional doses of 750 or 1000 mg of A/G per day. Unfortunately, although measurement of plasma cortisol was requested this was not carried out. She was treated with intravenous hydrocortisone but failed to improve and died some hours later. It is not certain whether her death was due to adrenal inhibition but this must be considered a possibility. The cause of death in the other two patients is not known, but may have been due to unrelated factors. Another patient who had normal urea and electrolytes prior to starting A/G developed low serum sodium and low plasma cortisol on treatment. She was then given routine steroid replacement. Although we have found it necessary to routinely use fludrocortisone to prevent postural hypotension in patients receiving CD A/G [4] this was not a problem in patients on LD A/G, suggesting that aldosterone synthesis was not inhibited except in this one instance.

Other side-effects consisted of the typical generalized erythematous rash (16% of patients) seen in some patients treated with CD A/G, nausea in two patients and severe exfoliative dermatitis in one instance which necessitated discontinuation of treatment.

DISCUSSION

Aminoglutethimide has now been accepted as a useful and effective treatment for advanced breast cancer, with a response rate of around 30% and a mean duration of response of between 12 and 18 months [1-4]. Most workers have used 1 g of A/G per day, although in some instances 750 mg has been given [2]. Steroid replacement has usually been hydrocortisone 20 mg bd or cortisone acetate 25 mg AM, 12.5 mg PM ± fludrocortisone when indicated [4]. These regimens have the drawbacks of (1) multiple medication; (2) the dose of A/G must be slowly built up in order to prevent a high incidence of side-effects; (3) careful monitoring of fluid and electrolyte status is necessary particularly when diuretics are being used; and (4) in times of intercurrent illness or infection increased doses of glucocorticoids are required.

The concept that a lower dose of A/G without steroid replacement might inhibit conversion of androgens to oestrogen by the aromatase enzyme system without inhibiting production of steroids by the adenal glands [5, 6] therefore presents an attractive therapeutic alternative.

The results presented here show clearly that A/G in a dose of 125 mg bd without steroid replacement can produce regression of disease in patients with advanced breast cancer. However, whether the actual remission rate is the same as that when CD A/G + steroids are given is not clear, as the true response rate for these 57 patients estimated with 95% confidence limits could be anywhere between 10 and 30%. The finding that four patients had progressive disease on LD A/G but then had unequivocal regression of disease on CD A/G, and that three patients who failed to respond to LD A/G had stabilization of disease on CD A/G, indicates that the two treatments are not identical. While falls in plasma oestrone and oestradiol has been reported to be similar in patients treated with 125 mg of A/G bd to those seen in patients treated with 500 mg of A/G + steroid replacement [6], levels of DHA-S (the principal adrenal androgen and precursor of other androgens) have been shown to fall in the latter but not the former group [6]. It is possible that these changes in androgen levels are

responsible for the remission seen in patients who respond to CD A/G + steroid but not to LD A/G. It is not clear whether it is the combination of the increased dose of A/G and the steroid replacement that causes the remission or whether the same response could be obtained if steroid replacement was given in association with LD A/G, or, indeed, by the same dose of steroids in the absence of A/G.

The finding of a low plasma cortisol in one patient and the death of another with hypotension and a plasma A/G level similar to that found in patients given conventional doses of A/G raise serious questions about the safety of LD A/G administration in the absence of steroid replacement. Routine measurement of plasma cortisol may not predict those patients whose adrenal function is adequate under basal conditions but cannot respond to increased stress, while ACTH stimulation will test adrenal reserve but not the integrity of the pituitary-adrenal axis. It should be recalled also that when A/G was originally withdrawn as an anticonvulsant it was because only a small minority of patients showed signs of adrenal insufficiency. In the opinion of the authors considerable caution needs to be exercised in using A/G without steroid replacement.

The findings reported here show that LD A/G without steroid replacement is not a safe or satisfactory alternative to conventional treatment with higher dose A/G and steroid replacement. Further studies are needed to accurately define the limits of safety of A/G without steroid replacement and to determine whether the remission rate and duration of remission are the same for LD A/G as they are for CD A/G + replacement steroids.

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