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Phase II Study of Low Dose Aminoglutethimide 250 mg/day Plus Hydrocortisone in Advanced Postmenopausal Breast Cancer

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Abstract—*Low dose aminoglutethimide* 125 mg *twice daily plus hydrocortisone* 20 mg *twice daily was shown to produce oestrogen and androgen suppression in postmenopausal women. A phase II study was carried out in* 101 *patients with advanced postmenopausal breast cancer. Objective response rates were* 4% *CR and* 21% *PR. Fourteen per cent had disease stabilization for more than* 6 *months (SD). Soft tissue sites showed the best response. Responses occurred in previous tamoxifen failures* (28%) *including SD. Toxicity was less than reported for higher dose regimens or low dose aminoglutethimide without hydrocortisone, particularly nausea and drowsiness. Survival from first relapse and start of therapy was not significantly different between PR and SD. This dosage regimen appears of comparable efficacy to previously reported higher dosage regimens with reduced toxicity compared to low dose regimens without hydrocortisone.*

INTRODUCTION

AMINOGLUTETHIMIDE was initially introduced as an anticonvulsant in 1960 but withdrawn after it was found to produce adrenal insufficiency [1]. It inhibits an early step in adrenal steroid synthesis, the conversion of cholesterol to pregnenolone [2]. This inhibition can be overcome by ACTH [3], so replacement doses of hydrocortisone are also given to block the feedback effects.

Another major site of action of aminoglutethimide is the inhibition of the periperhal conversion of adrenal (and ovarian) androgens to oestrogens by aromatase [4]. This peripheral conversion is the major source of oestrogens in postmenopausal women [5]. Yet another mechanism recently described is the increased clearance of oestrone sulphate [6].

Because *in vitro* studies showed that aromatase was more sensitive than the adrenal to the inhibitory effects of aminoglutethimide [7, 8], there have been several dose ranging studies of the amounts of aminoglutethimide required to inhibit aromatase *in vivo* [9–11]. These short-term studies have shown that doses as low as 62.5 mg twice daily inhibit aromatase, and doses of 125 mg twice daily produce similar inhibition to 500 mg twice daily [9–12].

However, addition of hydrocortisone to low dose aminoglutethimide 125 mg twice daily was associated with lower oestrogen levels than aminoglutethimide alone [13]. This effect was mainly due to reduction of adrenal androstenedione by hydrocortisone. In effect, a dual endocrine approach was produced, depletion of substrate as well as inhibition of the target enzyme.

There has been only one randomized trial of different aminoglutethimide dosage regimens, with 1 g vs. 500 mg daily, and hydrocortisone in both trial arms. This showed therapeutic equivalence with less toxicity for the lower dose [14].

The interest in lower dosage regimens is related to the toxicity of aminoglutethimide in conventional dosage, which includes drowsiness, ataxia, nausea, vomiting, skin rash and occasional agranulocytosis [15].

We showed that doses as low as 125 mg twice daily with hydrocortisone were equally effective at hormone suppression as the higher doses and more effective at oestrogen and androgen suppression than low dose aminoglutethimide without hydrocortisone [10, 13]. We have therefore carried out a phase II study in advanced postmenopausal breast

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cancer to assess the efficacy and toxicity of low dose aminoglutethimide 125 mg twice daily with hydrocortisone.

MATERIALS AND METHODS

One hundred and one consecutive patients with progressive breast cancer were entered into this study. Patients with known CNS metastases were not included. Minimum follow-up is 7 months.

Aminoglutethimide was given as 125 mg twice daily with hydrocortisone 20 mg twice daily, 8 a.m. and 8 p.m. Patients were assessed monthly.

Response was defined by standard UICC criteria [16] and categorized initially at 3 months. For analysis, the best response achieved was used. Patients with no change in disease for 6 months or longer were assessed as stable disease. Because of the potential contribution of stable disease to symptomatic and survival benefit, patients who had stable disease at 3 months but progressed at 6 months were separately analysed as 'stable disease 3–6 months'. For analysis of prognostic factors and overall response, they are classified with progressive disease patients.

RESULTS

Response rates

There were four complete responders, CR (4%), and 21 patients with partial response, PR (21%). Fourteen patients had stable disease, SD, for more than 6 months (14%). Thirteen progressed by 6 months, after initial assessment as stable disease at 3 months (Table 1).

Response duration

The median response duration for the objective responders was 50 weeks for PR, 200 weeks for CR and 40 weeks for SD. The response duration was significantly longer for PR vs. SD ($P < 0.025$ log-rank) (Fig. 1).

Survival from start of treatment

The groups of patients with PR, SD and stable disease for less than 6 months each showed significantly longer survival than those with PD ($P < 0.01$ log-rank for each comparison) (Fig. 2). Survivals were respectively 30, 17.5, 16 and 7 months. There was no significant difference between PR, SD or SD less than 6 months and the survival curves were superimposable in the first year of follow up.

Thus any type of response was associated with better survival than PD, with a trend for longer surival with better category of response.

Survival from first relapse after treatment of primary tumours

Because patients were treated at different times from first relapse, at earlier or later stages of their disease, survival was calculated from first relapse in each category.

Median survival of patients with PR was significantly longer than for PD (50 vs. 24 months $P < 0.01$) and survival for SD and SD less than 6 months was 45 and 32 months respectively (Fig. 3). There was no significant difference between SD and SD less than 6 months or either of these categories and PR.

Thus survival from first relapse had an association with response category similar to survival from start of treatment. All these categories had improved survival compared to PD, and there was a trend for the better category of response to have longer median survival.

Prognostic factors for response

Response by site (Table 2). The highest objective response rates were in soft tissue and lymph nodes, the lowest in lung and bone. Although the objective response rate in bone was low, there was a substantial proportion of patients who had stable disease, and also a group who obtained significant pain relief in spite of progressive disease (58%).

Table 1. Pretreatment characteristics and response

		Response to AG (*n*)				
		CR	PR	SD	SD 3–6	PD
Total No. of patients	101	4	21	14	13	49
Previous endocrine therapy	73					
Previous chemotherapy	14					
Previous surgery	53					
Previous radiotherapy	59					
No previous treatment	16	4	5	3	2	2
No previous hormones (including group with no previous treatment)	28	4	8	6	3	7
Age,years; median (mean: range):	64 (62: 36–83)					
Time from LMP, years; median (mean: range)	11 (13: 1–43)					
Tumour-free interval, months; median (mean: range)	10 (23: 0–196)					

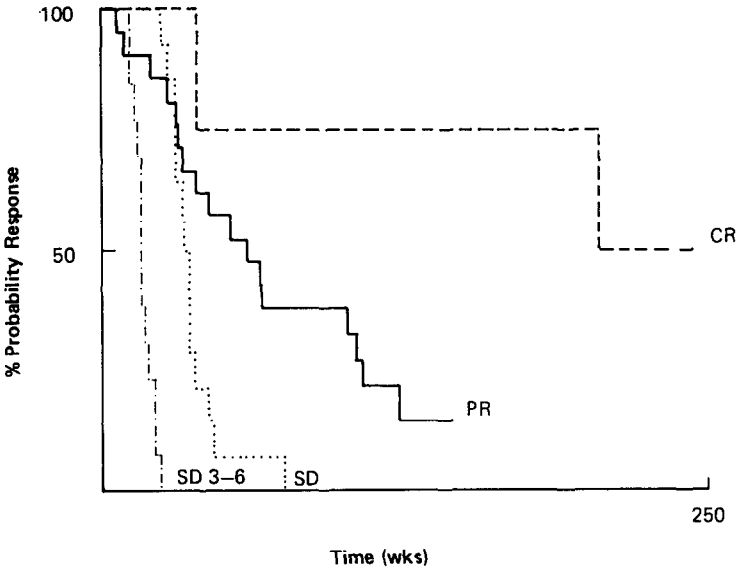

Fig. 1. Duration of response to low dose aminoglutethimide and hydrocortisone.

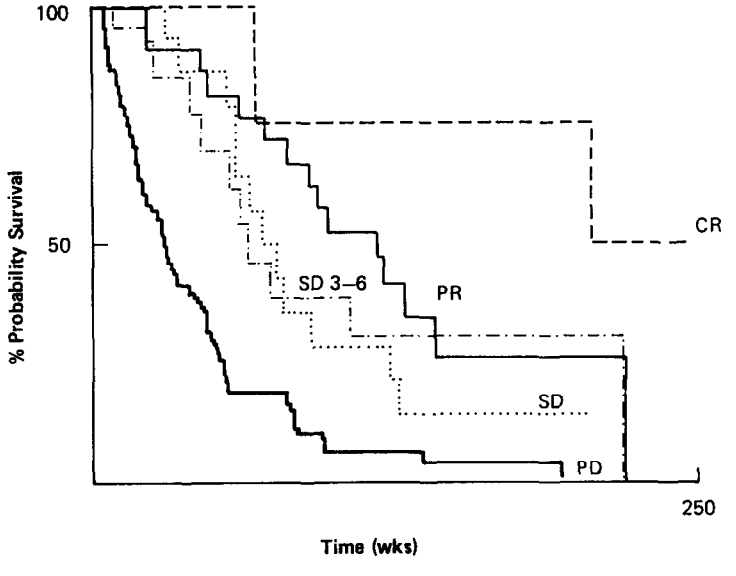

Fig. 2. Survival from start of treatment with low dose aminoglutethimide and hydrocortisone.

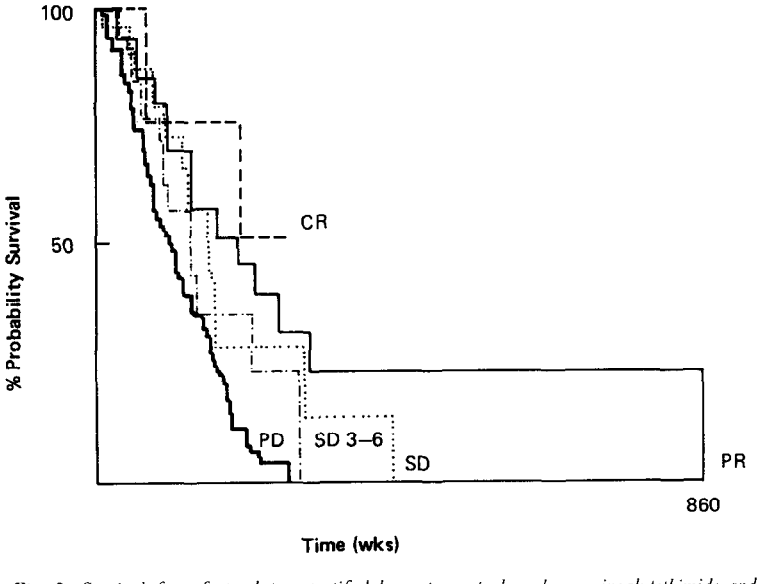

Fig. 3. Survival from first relapse stratified by response to low dose aminoglutethimide and hydrocortisone.

Table 2. Response by site

Site	Soft Tissue		Nodes		Lung		Pleura		Bone		Pain		Liver	
Total number for site	69		36		7		15		41		38		4	
Response	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
CR	4	5	3	8	0	—	2	13	0	—	5	13	0	—
PR	15	21	7	19	1	14	1	6	4	9	17	44	1	25
SD >6	12	17	6	16	0	—	1	6	8	19	3	7	0	—
SD 3–6	9	13	3	8	2	28	2	13	4	9	2	5	0	—
PD	29	42	17	47	4	57	9	60	25	61	11	29	3	75

There was no relationship of age and tumour-free interval or time from last menstrual period to response.

Response to previous endocrine therapy with tamoxifen (Table 3). Sixty patients were assessable for previous response to tamoxifen. Of those with a previous CR or PR to tamoxifen, 5/11 (45%) had a subsequent response to aminoglutethimide. Of those with previous PD on tamoxifen, 10/35 (28%) had a response to aminoglutethimide. Although response was lower, previous tamoxifen failure did not preclude a therapeutic effect of aminoglutethimide.

First line low dose aminoglutethimide

Sixteen patients with advanced local disease received aminoglutethimide as first therapy, without previous surgery or radiotherapy. A high objective response rate of 56% was observed, as may be expected because of the characteristics of this group of patients (Table 4). They were elderly, many years past the menopause and only one had metastases besides regional lymph nodes. Therapy was well tolerated in this group of patients.

Toxicity

The regimen was well tolerated with only one patient withdrawing because of toxicity (Table 5).

Table 3. Response to previous endocrine therapy and response to aminoglutethimide

		Response to AG + HC			
		CR	PR	SD>6	PD
Response to previous tamoxifen	CR	0	1	1	1
	PR	0	2	1	5
	SD >6	0	4	2	8
	PD	0	6	4	25

Table 4. First line low dose aminoglutethimide

		Median	Range	(n=16)
Age (years)		70	60–83	
Years post menopause		23	8–43	
Response duration in weeks	CR (n=4)	210	38–244	
	PR (n=5)	44	31–65	
	SD (n=3)	25	30–36	
	PD (n=4)			

Sites of disease:	Soft tissue	Nodes	Bones
(n)	16	6	1

She had severe recurrent dermatitis after rechallenge with aminoglutethimide. The incidence of rash was very similar to that on high dose regimens or low dose regimens without hydrocortisone. Other side-effects such as nausea and lethargy were rarer than in previous studies with higher dosage regimens.

Weight gain was commonly observed in responders. The mean pretreatment weight of responders was 63 kg (S.D. 10, median 64, range 40–85) and in non-responders was 62 kg (S.D. 12, median 60, range 40–97), which was not significantly different. However, at 3 month assessment, the mean weight gain in responders was 2.6 kg (S.D. 2.6, median 2.3, range −4 to +8.7), whereas in non-responders it was −0.2 kg (S.D. 2.9, median 0.3, range −7.2 to +6.6), $P < 0.001$.

DISCUSSION

The objective response rate obtained in this study falls within the range reported for other phase II studies of conventional dose (1 g) aminoglutethimide and hydrocortisone [15, 17–20]. In the only randomized trial of aminoglutethimide dosage, the response rates were 19% and 24% in the two arms [14]. Our response rate is between these values.

Table 5. Toxicity of low dose aminoglutethimide with hydrocortisone

	250 mg AG Present study	250 mg AG no HC [22, 23]		1000 mg AG no HC [24]	500 mg AG with HC [14]	1 g AG with HC [14, 15] (a)	(b)
n	101	65	57	47	78	213	83
Toxicity (%)							
Drowsiness	9	31		62	9	33	17
Rash	22	15	16	23	4	23	11
Nausea	9	12	4	26	4	15	8
Ataxia	4				3	4	10
Stopped from toxicity	1	8	1	11	5	5	7
Depression	3					4	
Cramps	2					4	
Flu syndrome	4					1	
Sore mouth	1					1	
Dermatitis	1	1					
Jaundice	1						

Clearly patient selection will affect the responses in phase II endocrine studies but we included a higher proportion of patients with previous hormone therapy and they were of similar age and menopausal status. In our study, the group of elderly patients with advanced local disease and no previous hormone therapy showed a much higher response rate. This regimen is therefore comparable to other hormone studies in the elderly [21].

Two studies have been reported with 125 mg amioglutethimide twice daily without hydrocortisone, and one study with 1000 mg daily [22–24]. The two former studies had a 19% objective response rate, but one had much higher toxicity than our current study. It is possible, therefore, that hydrocortisone may ameliorate some of the central nervous system side-effects such as drowsiness and nausea. However the other had similar toxicity to our study [3] but one death possibly due to adrenocortical insufficiency. The skin rash has been reported at a similar frequency at all doses (Table 5) and is probably an idiosyncratic rather than a toxic reaction.

The side-effects that did occur were transient except in one case of dermatitis. This transient effect is not likely to be due to induction of drug metabolism, since Miller *et al.* [25] showed no induction with 500 mg aminoglutethimide daily. A central nervous system adaptive effect is more likely. Even in the elderly it was well tolerated, a group shown previously to be at particular risk of side-effects [11].

It is interesting that in this current series, plus the two others with 125 mg bd aminoglutethimide alone, there were no cases of agranulocytosis (0/215), whereas previous reviews suggest a 1–2% incidence with conventional dose aminoglutethimide [26]. We previously suggested that this was a direct toxic effect, so lower doses would be expected to have less marrow toxicity [27].

The addition of hydrocortisone to low dose aminoglutethimide in this series of patients was previously reported to produce a lower oestrone and oestradiol level than in a similar group of patients treated with low dose aminogluethimide alone [13]. That hydrocortisone may have an additional therapeutic effect is supported by the observations of Murray and Pitt [23] that patients failing to respond to low dose aminoglutethimide (250 mg daily) alone responded to the addition of hydrocortisone and higher dose aminoglutethimide (1 g daily). Increasing aminoglutethimide alone to 1 g daily in patients not responding to 500 mg daily did not produce any responses [14]. Corticosteroids alone produce objective responses in postmenopausal breast cancer [28]. The addition of hydrocortisone suppressed the androgen rise found with aminoglutethimide used alone [10] and in our series with low dose aminoglutethimide and hydrocortisone, adrostenedione was significantly suppressed [13]. In studies with conventional dose aminoglutethimide and hydrocortisone there was no significant androstenedione suppression [29].

In some previous studies there have been reports of high objective response rates in bone [15] but this is not observed in others [14]. The results we obtained were similar to those of Bonneterre *et al.* [14]. An antiprostaglandin effect has been demonstrated with conventional aminoglutethimide and hydrocortisone dosage regimens which may account for good responses in bone [30]. It is possible that the lower doses of aminoglutethimidine had less effects on this pathway. There have been no dose ranging studies of aminoglutethimide on prosta-

glandin metabolism. Nevertheless, significant pain relief and disease stabilization was achieved in the majority of patients.

In this study, the category of stable disease was specifically examined. Our study demonstrates the importance of not discontinuing endocrine therapy prematurely and accords with results for stable disease reported both with conventional aminoglutethimide dosage [14, 15] and low dose aminoglutethimide [23], as well as tamoxifen [31].

Although SD less than 6 months had a shorter response duration than SD or PR, this group nevertheless fared better than PD, both in survival from start of the treatment and survival from first relapse.

The shorter duration of disease stabilization may still be associated with better overall survival because this is a measure of the rate of growth of tumour, and is one end of a spectrum of progressive disease. Slow progression in soft tissue may be associated with similar survival to a PR, which then relapses and progresses more rapidly.

The therapeutic implication for this group of patients may be that, although relatively unresponsive, they have a better prognosis than PD and efforts should be concentrated on mild chemotherapy and good quality palliative care rather than successive hormone therapies.

Weight gain was very common in the responders, with a median weight change of 2–6 kg, whereas the non-responders showed no weight change on average. This difference was not due to different follow-up times, since in all cases patients were compared for weight before treatment and at 3 months. In previous studies, weight gain was not as pronounced and it may be that the dose of hydrocortisone is greater than necessary to suppress adrenal androgens. Alexieva-Figusch *et al.* [29] showed that hydrocortisone alone suppressed androstenedione, and that there was loss of diurnal variation with elevated cortisol levels with 40 mg hydrocortisone/day. With higher doses of aminoglutethimide, the adrenal actions of the drug are more pronounced and this may result in a different resetting of the ACTH–adrenal–cortisol feedback loop. Bonneterre *et al.* [14] noticed a significantly higher incidence of moonface in the lower dose arm of their randomized trial. This effect is even more marked in our study.

The association of weight gain with response may be related to a balance between weight gain due to the endocrine effects vs. weight loss due to tumour effects. In those with an antitumour response, the gain in weight predominates. In those whose tumour progresses, production of factors that are associated with cachexia may counteract the effects of hydrocortisone. Tumour necrosis factor is one possible mediator, which has been shown to be markedly elevated in many breast cancer patients [32].

Although aminoglutethimide has been in use for breast cancer since 1974 [3], the optimum dosage has not yet been derived. We would suggest on endocrine data 125 mg twice daily with hydrocortisone suppresses oestrogens and androstenedione most effectively. The combination was less toxic than aminoglutethimide alone or high dose aminoglutethimide with hydrocortisone with the exception of weight gain. It has equivalent efficacy in this phase II study but only a very large randomized trial will be able to finally assess the comparison. Preliminary results suggest an advantage for the combination [33]. Several new aromatase inhibitors are being evaluated [34–36] and it will be necessary to decide the dose of aminoglutethimide for comparative purposes. Also, the question of concomitant steroids to reduce the substrate for aromatase and the optimal hydrocortisone schedule still needs to be evaluated.

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