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Aminoglutethimide for the Treatment of Advanced Postmenopausal Breast Cancer

A. L. HARRIS,* T. J. POWLES, I. E. SMITH, R. C. COOMBES, H. T. FORD, J. C. GAZET, C. L. HARMER, M. MORGAN, H. WHITE, C. A. PARSONS and J. A. MCKINNA

Breast Unit, Royal Marsden Hospital, Fulham Road, London & Downs Road, Sutton, U.K.

Abstract—*Two hundred and thirteen unselected postmenopausal women with advanced breast cancer were treated with aminoglutethimide and hydrocortisone. There were 6 complete responses (CR), 47 partial responses (PR), 25 stable disease (SD) and 3 mixed response. Overall objective response rate was 28%, and with SD 41%. Median duration of objective response was 14 months. Years after menopause, age and tumour-free interval did not affect response rates. Main side-effects were drowsiness and lethargy (33%), rash (23%) and nausea (15%). Eleven patients (5%) stopped treatment because of toxicity. Median survival from start of treatment was 28 months and was the same for CRs, PRs and SD, compared with 10 months for progressive disease ($P < 0.001$). Median survival from first metastasis was 43 months for PR/CR, 40 months for SD (not significantly different) and 22 months for progressive disease ($P < 0.001$). Aminoglutethimide is an effective endocrine therapy in advanced postmenopausal breast cancer, particularly for bone deposits. Disease stabilization is associated with symptomatic and survival benefit similar to CR/PR.*

INTRODUCTION

AMINOGLUTETHIMIDE was initially introduced as an anticonvulsant in 1960 but withdrawn after it was found to produce adrenal insufficiency [1]. Aminoglutethimide 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 effect.

The main source of oestrogens in postmenopausal women is the peripheral conversion of adrenal androgens (Δ^4 androstenedione) to oestrone by aromatase enzymes [4]. This conversion is inhibited by 95–98% with aminoglutethimide [5]. The combination of aminoglutethimide with hydrocortisone is referred to as 'medical adrenalectomy'. Initial reports show that it is an effective treatment in postmenopausal breast cancer [6, 7]. This study describes the long-term results of a large phase II study of aminoglutethimide to define its role in the treatment of advanced postmenopausal breast cancer.

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*To whom requests for reprints should be addressed at: University Department of Radiotherapy and Clinical Oncology, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne NE4 6BE, U.K.

MATERIALS AND METHODS

Between August 1977 and October 1980, 213 unselected postmenopausal patients with advanced breast cancer were treated at the Royal Marsden Hospital (Sutton and Fulham Road branches) with aminoglutethimide and hydrocortisone in a phase II study. All patients had progressive disease before treatment. The study included patients with lymphangitis and liver secondaries who had already had tamoxifen or adriamycin-containing combination chemotherapy regimens, but not patients with known CNS metastases. Patients of poor performance status were not excluded if they were thought to have a life expectancy of 1 month, since one possible advantage of 'medical adrenalectomy' is the ability to offer it to patients not fit for surgery. Aminoglutethimide was initially given as 250 mg orally three times a day and the dose was increased to 250 mg four times a day after two weeks if well tolerated or if side-effects present in the initial 1–2 weeks were decreasing. The hydrocortisone dose was 20 mg twice a day. In the first 41 patients fluorocortisone 0.1 mg daily was given because of

evidence that aldosterone production is decreased by aminoglutethimide [8], but it was found to be unnecessary and subsequent patients were not given it.

All patients have been followed up to death or until August 1981. Age ranged from 23 to 84 yr.

Response was defined by standard UICC criteria [9]. Complete response (CR) was defined as the disappearance of all detectable soft tissue disease and of all lytic disease in bone with normal bone texture for 3 months. Partial response was a 50% decrease in the sum of the products of all measurable lesions and recalcifications of lytic bone disease. Stable disease (SD, no change) was less than 50% reduction in the sum of products of measurable lesions and less than a 25% increase in the sum of the products for 3 months, with no new lesions. If there was no change in bone lesions but pain was not relieved this was considered progressive disease.

An adequate trial of therapy was considered to be a minimum of 1 month, and if no progression occurred therapy was continued.

Survival curves were analysed by the Peto log rank test [10] and tables by the χ^2 test.

RESULTS

Early deaths

Twenty-three patients died within 1 month of starting treatment. Their median survival from first metastasis was 14 months. Age ranged from 30 to 84 yr, median 55 yr, and years postmenopause ranged from 2 to 36 yrs, median 3 yrs. Fifteen had previous endocrine therapy, 12 had previous chemotherapy and only 2 had no previous treatment. Eleven died from progressive liver secondaries, 7 died from progressive lung secondaries and 1 from central nervous system metastases. Three elderly patients (ages 72, 76 and 84) died at home with extensive bone- and soft tissue disease. These patients were assessable for toxicity. They have not been included in assessment of response or survival.

Response rates

Out of 190 patients assessable for response there were 6 CR (5 alive by August 1981), 47 PR (25 alive by August 1981), 25 stable disease (10 alive by August 1981) and 3 mixed responders. The latter had PR in soft tissues, relief of bone pain but progression of lytic bone disease. The response of 41 patients taking fluorocortisone did not differ significantly (11 PR, 2 CR, 2 stable disease). Thus objective response rate was 28% and overall response including stable disease was 41%.

Response duration

Median response duration for the objective responders was 14 months (Fig. 1). Median response duration for patients with stable disease was 14 months ($P>0.5$, log rank test).

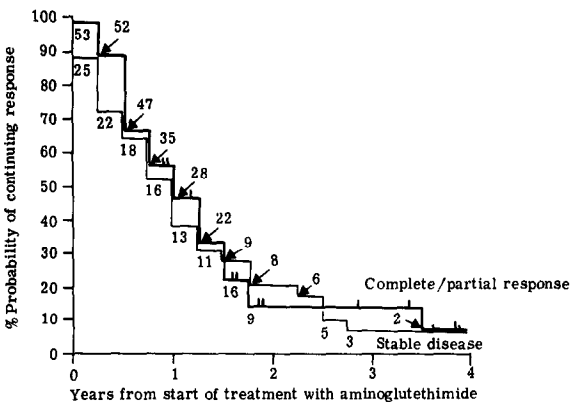

Fig. 1. Response duration to aminoglutethimide. Numbers at the beginning of each time period are the number of patients alive and responding at that time. Vertical bars on the curves represent patients still responding.

Survival

The median survival from start of treatment for the responders was 28 months and for non-responders 10 months ($P<0.001$; Fig. 2). There were no significant differences in survival between objective responders and stable disease patients ($P>0.5$, log rank test; Fig. 2).

Median survival from first metastasis was 22 months in patients with progressive disease and 43 months in responders ($P>0.001$; Fig. 3). There was no difference between stable disease patients (median survival 40 months) and objective responders (median 43 months, $P>0.5$, log rank test; Fig. 3).

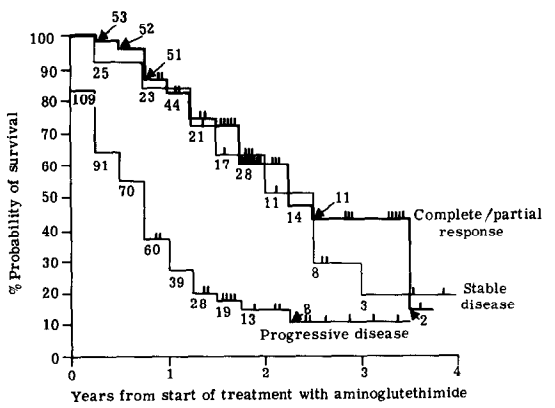

Fig. 2. Actuarial survival curve for 190 patients from start of treatment with aminoglutethimide. Numbers at the beginning of each time period are numbers of patients alive at that time. Vertical bars are patients who are still alive.

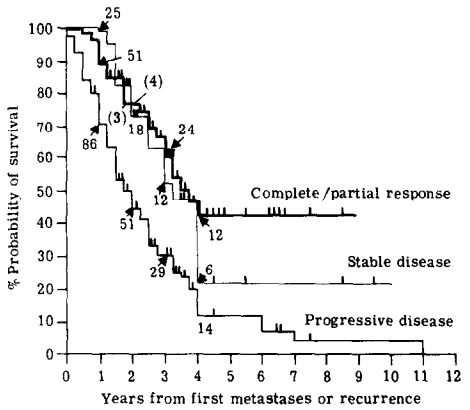

Fig. 3. Actuarial survival curves from first metastasis for 190 patients treated with aminoglutethimide. Numbers at the beginning of each time period are numbers of patients alive at that time. Vertical bars and numbers in brackets are patients who are still alive.

Table 1. Response by site: 190 patients treated with aminoglutethimide

Site	Total	CR	PR	SD	PD	Objective %	Stable %
Soft tissue	86	5	22	11	48	31	13
Nodes	37	4	6	10	17	27	27
Pleura	30	0	6	8	16	20	26
Lung	44	1	6	12	25	16	27
Liver	32	2	5	-	25	22	-
Bone	132	3	27	42	60	23	32

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Prognostic factors for response

Response by site. The highest objective response rate was in soft tissues and the lowest was in lung (Table 1). There was a high response rate in bone, with 23% objective responses, 32% stable disease and 19 out of the 60 patients whose bone disease continued to progress while receiving aminoglutethimide had relief of bone pain.

Nine out of the 25 patients with stable disease had bone as the only site of metastasis, compared with 14 out of 53 patients with objective response (not significantly different). Other sites of disease stabilisation in the stable disease patients included soft tissue (6), lymph nodes (6), pleura (3) and parenchymal lung deposits (3).

Four patients had bone as the only assessable site, stable disease on X-ray at 3 months, but progressive bone pain. They were classified as progressive disease.

The other patients with bone pain, whose pain was not relieved by aminoglutethimide, had progressive disease on X-ray or progression at other sites. Thus, overall, 91 out of 132 patients (69%) had objective responses or pain relief with aminoglutethimide. In some patients relief occurred within 24 hr of starting therapy.

Response to previous endocrine therapy. The pretreatment characteristics of patients with objective response, stable disease and progressive disease were similar with regard to previous endocrine therapy, chemotherapy and no previous treatment (Table 2). Objective responders to aminoglutethimide had a higher objective response rate to previous endocrine therapy than those with progressive disease ($0.05 > P > 0.02$, χ^2). The high rate of patients nonassessable for previous endocrine therapy was due to simultaneous treatment with chemotherapy or radiotherapy.

Five patients had previously had an adrenalectomy (not assessable) and none responded to aminoglutethimide. One patient relapsed after PR to aminoglutethimide and did not respond to adrenalectomy. One patient had responded to hypophysectomy and had stable disease on aminoglutethimide (16 m). Ten out of 26 patients who had previously responded to other endocrine therapy responded objectively to aminoglutethimide (38%) and 4 had stable disease. Ten out of 53 patients who had previously progressed on other endocrine therapy responded objectively to

Table 2. Pretreatment characteristics of 190 patients treated with AG: classification by response to AG

	CR/PR to AG	%	SD on AG	%	PD on AG	%
Total	53		25		109	
Previous ET	31	58	14	56	67	61
Previous CT	13	25	5	20	35	32
No previous treatment	19	36	9	36	34	31
PR/CR to ET	10	19	4	16	12	11
Not assessable for response to ET	11	21	3	12	19	17
Response to ET	10/20	50	4/11	36	12/48	25
Oophorectomy	7	13	4	16	25	23

ET, endocrine therapy; CT, chemotherapy. The 3 patients with mixed response are omitted from this table.

aminoglutethimide (19%) and 7 had stable disease. Previous therapy in the 10 objective responders was tamoxifen (7), stilboestrol (2) and oophorectomy (1).

There were 33 patients not assessable for previous endocrine therapy and their objective response rate was 11/33 (33%), with 3 additional patients showing disease stabilisation.

Menopausal status

There was no significant effect of years after the menopause on response rate (Table 3: $\chi^2 = 6.46$, $P > 0.1$). Women within 2 yr of the menopause had similar response rates to those 10 yr afterwards. Menopausal status in 2 of the patients was unknown because of premenopausal hysterectomy.

Table 3. Menopausal status and response to aminoglutethimide

Time from LMP	Responders (PR/CR/SD) No.	% of group responding	Non-responders No.
<2 yr	17	37	29
2 yr, 1 month–5 yr	13	39	20
5 yr, 1 month–10 yr	19	59	13
10 yr, 1 month–15 yr	11	32	23
15 yr, 1 month–20 yr	10	50	10
>20 yr, 1 month	11	48	12
Total	81		107

Two patients had a hysterectomy before the menopause and thus their menopausal status is unknown.

Tumour-free interval (disease-free interval)

Curves of cumulative probability of remaining disease-free in responders and non-responders are shown in Fig. 4. There is no significant difference ($0.5 > P > 0.1$, log rank tests). Reanalysing including the 23 early deaths did not change the significance.

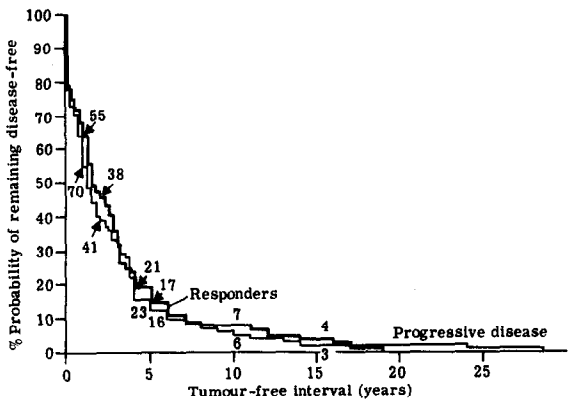

Fig. 4. The tumour-free interval in responders and non-responders to aminoglutethimide. CR/PR and SD are included as responders. The numbers are the number of patients alive after the treatment of their primary disease who have not yet relapsed.

Age

Response by age is shown in Table 4. Although response rate for women under age 45 was less than in the other age groups, this was not significant. Analysis of the whole table shows no significant effect of age on response ($\chi^2 = 7.46$, $P > 0.1$).

Table 4. Age and response to aminoglutethimide

Age (yr)	Responders No.	% of group responding	Non-responders
<45	6	27.2	16
45–50	10	52.6	9
51–55	21	51.2	20
56–60	13	38.2	21
61–65	11	35.5	20
66–70	8	38.1	13
71–75	5	55.5	4
>76	7	53.8	6

PR/CR and SD are included as responders.

Toxicity

All patients were assessable for toxicity. The commonest side-effects were drowsiness, rash and nausea (Table 5). The drowsiness and nausea settled within 3 weeks in most patients, although in 18 patients dosage of aminoglutethimide was not increased above 250 mg three times a day.

The rash was macular, erythematous, symmetrical and occasionally accompanied by fever. It usually started about the 10th day after starting aminoglutethimide and started to show improvement over the following 5 days. Dosage reduction was not necessary in most cases, but in patients with severe rash hydrocortisone dosage was doubled to 40 mg twice daily for a week.

In 10 of the 190 patients assessable for response the drug had to be discontinued and in 1 of the early deaths. Aminoglutethimide was stopped for the following reasons: nausea and headaches, 1; severe drowsiness, 4; exacerbation of Meniere's

Table 5. Toxicity of aminoglutethimide in 213 patients

	No.	%
Drowsiness	80	33
Rash	48	23
Nausea	32	15
Ataxia	9	4
Depression	9	4
Cramps	8	4
Visual disturbance	2	
Flu syndrome/diarrhoea	2	
Headache	2	
Sore mouth	2	
Electrolyte disturbance	1	
Tinnitus	1	
Transient agranulocytosis	1	
Stevens-Johnson syndrome	1	

Eleven patients stopped treatment because of toxicity.

disease, 1; Stevens-Johnson syndrome, 1; flu-like syndrome with vomiting and diarrhoea, 1; severe rash, 1; visual blurring, 1; electrolyte disturbance (hyponatraemia), 1. One of these patients had achieved a PR but had to stop because of drowsiness. The only patient with electrolyte disturbance (hyponatraemia) was taking fluorocortisone. The overall withdrawal rate was 5%.

Seventeen patients had mild persistent side-effects after 6-weeks, mainly lethargy or depression. It was difficult to separate these effects from those of the disease.

The patient who had agranulocytosis developed this 4 weeks after starting treatment and had complete absence of neutrophils on her blood film. Aminoglutethimide was continued and within 2 weeks neutrophil count was back to normal. She has had stable disease for 2.5 yr and continues on aminoglutethimide.

The response rate of the 18 patients who took 750 mg/day aminoglutethimide was the same as for those taking 1000 mg/day (6 PR, 2 stable disease).

Toxicity, apart from the rash, was age-related since the incidence of one or more of the following side-effects: nausea, drowsiness, lethargy and ataxia, was 32% in those aged 46–55 (19/60), 45% of those aged 56–65 (29/65) and 60% of those over age 66 (26/43).

DISCUSSION

This study shows that aminglutethimide in combination with hydrocortisone is an effective endocrine therapy in postmenopausal women with breast cancer. The data on early deaths shows a clear subgroup of patients with rapidly progressing lung and liver secondaries for whom this treatment is not suitable.

The response rates (CR + PR) are similar to those reported for tamoxifen, stilboestrol and adrenalectomy [11–16]. Others have reported objective response rates to aminoglutethimide varying from 16 to 50% [6, 17–19], similar to our rate of 28%. The differences are probably partly related to patient selection, since Savaraj and Troner [17] selected patients who were oestrogen receptor (ER) positive, and in the series of Wells *et al.* [6] 46% of their responders had previously had a CR or PR to endocrine therapy, compared to 19% of our responders.

Median survival from start of treatment was 28 months for objective responders and 10 months for non-responders. Patients with stable disease also had a median survival of 28 months. Survival data are not available from other series.

The survival from first metastasis has been suggested as a more suitable method of assessing the benefits of therapy rather than survival from start of treatment [20]. The median for objective responders is 43 months, stable disease 40 months (not significantly different) and non-responders 22 months. The achievement of disease stabilisation with aminoglutethimide is thus associated with similar time to progression and survival from start of treatment and from first metastasis, as is found with CR/PR. This provides justification for including stable disease with responders. The important therapeutic implication is that aminoglutethimide should not be discontinued prematurely if there is no objective regression and a trial of up to 3 months is warranted. If there is no progression therapy should be continued.

Although after 4 yr from first metastasis the survival curves of CR/PR stable disease diverge (Fig. 5), the curves are not significantly different, and from 4 to 9 yr 11/51 (21.5%) of CR/PR patients are alive and 4/25 (16%) stable disease patients. Compared with tamoxifen, stilboestrol and adrenalectomy, there is a similar distribution of favourable sites for response, soft tissue and nodes being best and liver or lung the worst sites. Aminoglutethimide had a particularly marked effect on patients with bone secondaries, the overall response rate including objective responses, stable disease and bone pain relief being 69%, similar to adrenalectomy or hypophysectomy [21, 22]. This effect on bone secondaries has been confirmed in a randomised trial of tamoxifen vs aminoglutethimide, where amino-gluethimide, was superior for bone secondaries [23].

Patients who had previously progressed on other endocrine therapy, particularly tamoxifen, responded to aminoglutethimide. However, none of the patients who had had adrenalectomies responded, and the responder who had an

adrenalectomy after relapse did not respond. These results suggest that adrenalectomy and aminoglutethimide therapy are cross-resistant, but numbers are small. Aminoglutethimide has recently been compared to adrenalectomy in a randomised trial and found to produce results not significantly different [24].

Women within 2 yr of their menopause respond as well as those many years later, and there is no effect of tumour-free interval on response, in contrast to treatment with stilboestrol [11].

Although there is an initial high rate of side-effects, most are transient. The withdrawal rate of 5% is higher than that for tamoxifen found in a randomised trial of tamoxifen vs aminoglutethimide [23], but less than that for stilboestrol [25]. Aminoglutethimide induces its own metabolism within 1 week of administration and this may explain increasing tolerance after 2–3 weeks [26]. It is for this reason that we increased aminoglutethimide dose after 2 weeks, rather than giving 250 mg 4 times a day initially. Nevertheless, 9.5% of patients could not tolerate the full dose. However, tolerance is also noted for a variety of anticonvulsant drugs and this may be a central nervous adaptation.

It is possible that a lower dose of aminoglutethimide could be used, with less side-effects, since the response rate of patients taking 750 mg/day was similar to those taking 1000 mg/day. We have found similar suppression of adrenal androgens (dehydroepiandrosterone sulphate), oestrone and oestradiol in patients taking 250, 750 and 1000 mg/day [27]. The increased toxicity observed with age may be secondary to decreased renal clearance since aminoglutethimide is cleared predominantly unchanged in the urine [28].

This study shows that aminoglutethimide may be considered for first-line treatment of bone secondaries in postmenopausal women and second-line treatment for women who fail to respond or who relapse after responding to other endocrine therapy. Adrenalectomy should no longer be necessary.

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