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Adjuvant Aminoglutethimide Therapy for Postmenopausal Patients with Primary Breast Cancer[1]

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ABSTRACT

Three hundred and twenty-two postmenopausal patients with primary breast cancer and ipsilateral axillary node involvement were randomized to receive aminoglutethimide and hydrocortisone or placebo for 2 years in a double blind randomized trial between April 1980 and March 1985. Two hundred and eighty-six patients were eligible for the study of whom 145 received active drug and 141 received placebo. At the present time significantly fewer patients have relapsed or died without previous relapse in the treatment arm ($P = 0.002$); 43 of 145 (30%) patients receiving aminoglutethimide have relapsed or died compared with 63 of 141 (40%) of those receiving placebo. Local recurrence is also significantly reduced ($P = 0.002$) since only 6 patients receiving active treatment developed local recurrence compared to 21 receiving placebo. Side effects were severe enough to necessitate complete withdrawal or reduction of therapy in 27 of 145 (19%) in the treatment arm of the study compared with 21 of 141 (15%) in the placebo arm. A single treatment-related death occurred, due to agranulocytosis.

Aminoglutethimide and hydrocortisone therefore delay relapse after surgery for primary breast cancer in postmenopausal women. It is too early to assess any effect on overall survival.

INTRODUCTION

Aminoglutethimide (Orimeten; CIBA) is an effective agent in the treatment of postmenopausal patients with advanced breast cancer (1, 2). Approximately 30% of patients respond to therapy, similar to the results obtained using tamoxifen. Tamoxifen has been shown to delay recurrence when given to primary breast cancer patients following surgery (3, 4).

Studies using other adjuvant endocrine therapies have indicated that they too cause a delay in recurrence. These include ovarian ablation (5) and ovarian ablation with prednisone (6).

In view of the effectiveness of aminoglutethimide in advanced breast cancer, we decided to evaluate this agent in postmenopausal patients with primary node-positive breast cancer. A preliminary report outlining the nature of the study has been published (7). This report is the first to outline results of this therapy.

PATIENTS AND METHODS

Patients. Three hundred and twenty-two postmenopausal patients with breast cancer aged 75 years or less were entered into a double-blind randomized trial from 9 hospitals in the South West Thames Region and the Royal Marsden Hospital, Sutton and Fulham Road. All hospital Ethical Committees had approved the protocol and all patients agreed to participate in the study. Each surgeon was permitted to carry out his usual surgical procedure, provided that this was consistent and considered to be adequate surgery, *i.e.* radical mastectomy, total mastectomy with lower third axillary sampling, or wide excision with lower third axillary sampling. The latter operation had to be followed by postoperative irradiation. To be eligible for this study patients had to have histologically proven resectable primary breast cancer, with at least one axillary node involved by breast cancer but no evidence of distant metastasis as shown by clinical examination, chest X-ray, liver function tests, limited skeletal survey, or isotopic bone scanning. Patients with T3 and T4 tumors were only included if they were considered operable. Patients were not considered for this study if they had significant renal (urea > 15 mmol/liter) or hepatic (bilirubin > 20 μmol/liter) dysfunction or gastrointestinal ulceration. Any patient who had a previous history of malignant disease of either breast or any other organ (except basal cell carcinoma of the skin) was also excluded from the study. All patients were postmenopausal (at least 1 year since their last menstrual period or aged >55 if they had had a hysterectomy).

Trial Design. Patients were randomized centrally. The respective hospital pharmacist telephoned the trial office which held the randomization list for each surgeon. Randomization was carried out separately for each surgeon. Treatment was started within 8 weeks in all patients; recruitment began in April 1980 and ended in July 1985.

Thirteen of the patients randomized to receive aminoglutethimide and hydrocortisone and 23 of those randomized to receive placebo were found, on review of the original patient records by trial staff, to be ineligible leaving 286 eligible patients in the trial. Reasons for ineligibility are shown in Table 1.

Those randomized to receive active treatment received aminoglutethimide 250 mg twice daily and hydrocortisone 20 mg twice daily for the first month and aminoglutethimide 250 mg 3× daily and hydrocortisone 20 mg twice daily for the second month. Thereafter patients received 250 mg 4× daily and hydrocortisone 20 mg twice daily for 22 months. Control patients took placebo aminoglutethimide and placebo hydrocortisone, both of which had an appearance identical to the active compound. Neither the patients nor the attending physician knew the nature of the tablets taken. All patients carried cards indicating the nature of the trial and the possibility that they might be taking steroids.

Follow-up. Patients were seen 2 weeks after the start of treatment and then monthly for 2 months and every three months thereafter. At each visit chest X-ray, γ-glutamyl transpeptidase, alkaline phosphatase (Autoanalyser; Technicon), and carcinoembryonic antigen (radioimmunoassay) were measured. Clinical examination was undertaken, and a standard questionnaire designed to detect any toxicity was completed. Any abnormality in the metastatic screen was then followed by liver and bone scans and limited skeletal survey, and development of metastatic disease was confirmed histologically except in the case of multiple pulmonary or radiologically defined bone metastases and reported to the trial office. Adjuvant aminoglutethimide was then discontinued and hydrocortisone tailed off over a 3-week period. If treatment was discontinued for any other reason, patients were followed up in an identical fashion and included in the analysis.

Local recurrence was recorded only in patients attending the Royal Marsden Hospital (117 patients in the treated and 108 in the placebo group). When patients relapsed, those in the placebo arm of the study received active aminoglutethimide wherever possible, but essentially treatment on relapse was left to the discretion of the collaborators.

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Table 1 *Reasons for withdrawing patients from the study*

All patients withdrawn failed to fulfill entry critera for the study.

	Active	Placebo
Randomized more than 3 months from surgery	3	3
Previous malignancy	1	5
Hysterectomy and under 55 years of age	3	4
Pre- or perimenopausal	4	5
Metastases present at entry	1	0
Over 75 years of age	0	3
Current endocrine therapy	1	2
No nodes involved	0	1
Total	13	23

Histology and Steroid Receptor Content. All histological sections of primary tumor and lymph nodes were reviewed by one histopathologist (R. B.). Steroid receptors were measured in 171 samples at the Ludwig Institute for Cancer Research (London Branch) using a modification of the method of McGuire *et al.* (8) which has been previously described (9).

Hormonal Assays. Blood samples were taken from patients at 3 monthly intervals during therapy and the serum was stored at −70°C until analysis. Ten samples were taken randomly from a group of patients receiving aminoglutethimide who had remained disease free for 4 years and from 10 patients who had relapsed within 2 years of starting treatment. Methods for the analysis of DHA-S[3] (10), estrone (11), and estradiol (12) have been previously described.

Statistical Analysis. Between April 1980 and March 1985, 286 eligible patients were randomized of whom 145 were randomized to receive the active drug and 141 to receive placebo. The principal end point was first distant recurrence of breast cancer or death.

Local recurrence prior to metastasis was also considered. The treatment effect on each of these events was assessed using the logrank test. Cox regression analysis (13) was used to estimate the effect of treatment on the event rate and to test for interaction between treatment effect and various prognostic factors. An initial analysis was planned when 100 relapses had occurred.

An external review of patient eligibility and protocol adherence was carried out by Dr. H. Stewart, Royal Infirmary, Edinburgh, United Kingdom.

RESULTS

Comparison between the Two Groups in the Study. Table 2 shows that there is excellent comparability between the two arms of the study in terms of age, primary treatment, clinical and histological staging, and ER.

Results of Treatment. Table 3 and Fig. 1 show that significantly fewer patients receiving aminoglutethimide have relapsed at the present time at a median follow-up of 26 months (P = 0.004); 43 of 145 (29%) of the patients receiving aminoglutethimide have relapsed or died compared with 63 of 141 (38%) of the patients receiving placebo. The estimated reduction in first event rate, using Cox regression, is 36% (95% confidence limits; 6 to 57%). With 106 relapses or deaths the study has a 93% power to detect a 50% reduction in relapse rate and a 55% power to detect a 30% reduction.

The difference in disease-free survival remains significant if the analysis is stratified by T stage (T_0–T_2 and T_3–T_4) or by N stage (N_0 and N_1–N_2) (P = 0.002 and 0.007, respectively); thus the difference cannot be explained by differences in staging distributions.

There is a significant reduction in local recurrence in the treated arm (P = 0.002); 6 patients receiving active treatment and 21 receiving placebo developed local recurrence.

[3] The abbreviations used are: DHA-S, dehydroepiandrosterone-sulfate; ER, estrogen receptor.

Table 2 *Clinical features of patients entered into the trial*

Shown is the distribution of relevant clinical and pathological features in each arm of the study.

	Active no. (%)	Placebo no. (%)
No. of patients	145	141
Age		
45–59	55	58
60–79	90	83
Mean age (SD)	62.1 (6.41)	61.2 (6.35)
Type of primary treatment		
Radical mastectomy + radiotherapy	26	24
Radical mastectomy	11 (57)	5 (57)
Total mastectomy + radiotherapy	28	36
Total mastectomy	18	16
Local excision + radiotherapy	55 (38)	51 (36)
Other	7	9
Clinical staging		
T_0–T_2	107 (74)	110 (78)
T_3–T_4	38 (26)	31 (22)
N stage		
N_0	68 (47)	53 (38)
N_1–N_2	77 (53)	88 (62)
Histology		
Infiltrating ductal carcinoma	121 (83)	117 (83)
Other	24 (17)	24 (17)
Lymph nodes		
1–3 involved	84 (58)	77 (55)
>3 involved	61 (42)	64 (45)
Estrogen receptor		
0–15 fmols/mg cytosol protein (negative)	22 (25)	26 (31)
>15 fmols/mg cytosol protein (positive)	65 (75)	58 (69)
Not done	58	57

Table 3 *Logrank analysis of total events by allocated treatment and prognostic factors*

Disease-free survival was significantly improved by treatment with aminoglutethimide. This improvement is not significantly related to T or N stage or ER status, although a greater benefit was seen in patients with ER-positive tumors.

	Events (distant recurrences, or deaths)				
Group	No.	Observed	Expected	Observed/expected	P
All patients					
Aminoglutethimide	145	43	57.8	0.74	0.004[a]
Placebo	141	63	48.2	1.31	
T staging					
T_0–T_2, aminoglutethimide	107	25	38.4	0.65	
Placebo	110	47	33.6	1.40	>0.10[b]
T3–T4, aminoglutethimide	38	18	20	0.89	
Placebo	31	16	13.8	1.16	
N staging					
N_0, aminoglutethimide	63	16	22	0.72	
Placebo	53	23	16.8	1.37	>0.10[b]
N_1–N_2 aminoglutethimide	77	27	34.7	0.78	
Placebo	88	40	32.3	1.24	
Estrogen receptor					
≤15 fmol/mg aminoglutethimide	22	11	10.4	1.06	
Placebo	26	11	11.6	0.95	>0.10[b]
>15 fmol/mg aminoglutethimide	65	16	24.4	0.66	
Placebo	58	26	17.6	1.48	
Unknown aminoglutethimide	58	16	22.6	0.71	
Placebo	57	26	19.4	1.34	

[a] Logrank test for treatment effect.

[b] Test of interaction between treatment effect and prognostic factor, using Cox regression.

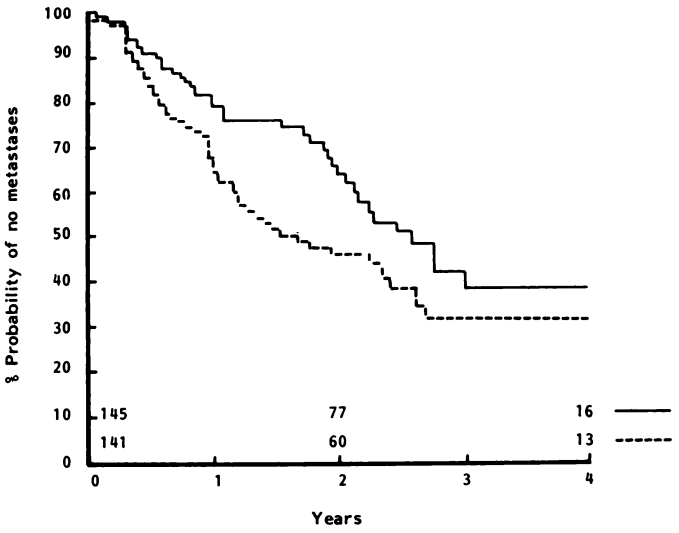

Fig. 1. Overall disease-free survival by allocated treatment (logrank test, $P = 0.004$). ——, aminoglutethimide; - - - - placebo. *Numbers along X-axis,* numbers of patients at risk.

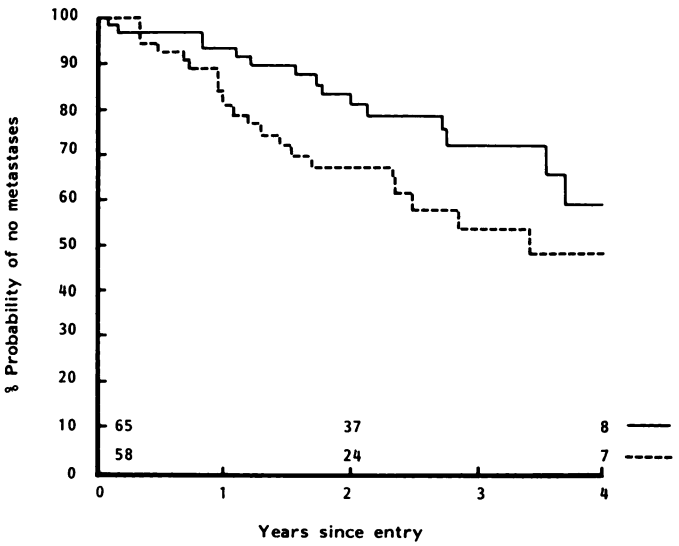

Fig. 3. Disease-free survival by allocated treatment for patients with positive estrogen receptor (see text). *Numbers along X-axis,* numbers of patients at risk. ——, aminoglutethimide; - - - -, placebo.

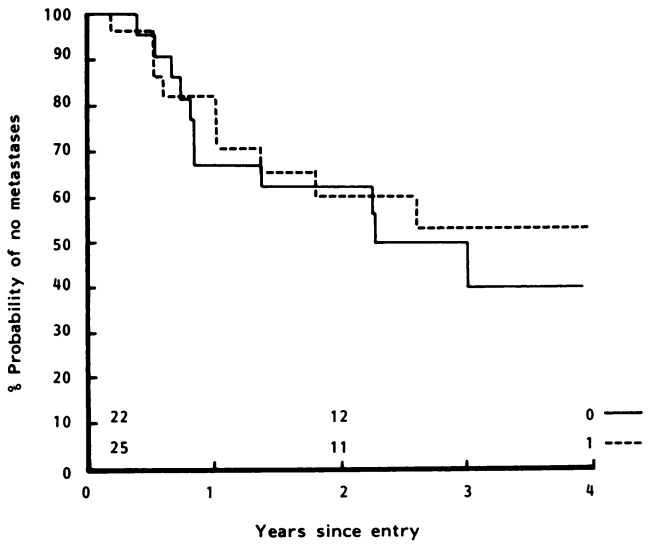

Fig. 2. Disease-free survival by allocated treatment for patients with negative estrogen receptor (see text). *Numbers along X-axis,* numbers of patients at risk. ——, aminoglutethimide; - - - -, placebo.

Table 4 *Side effects of treatment*

Among major side effects considered were lethargy, skin rash, ataxia, and bone marrow failure. Of patients receiving active therapy, 88% had side effects when compared to 52% of those receiving placebo.

Side effect	Active no. (%)	Placebo no. (%)
Lethargy	88 (61)	45 (32)
Skin rash	69 (48)	15 (11)
Nausea and vomiting	47 (32)	29 (21)
Ataxia	27 (19)	5 (4)
Bone marrow failure	3 (2)	0
Other	61 (42)	39 (28)
None	17 (12)	65 (48)

The data shown in Table 3 suggest that the treatment effect is greater in, or perhaps entirely restricted to, patients with ER-positive tumors; however, this interaction is not statistically significant at present (Figs. 2 and 3).

There is no evidence that treatment affected sites of first metastasis. Thus, the proportion of relapses in the treated and control arms, respectively, are bone, 16 of 44 (36%), 25 of 62 (40%)); liver, 11 of 44 (25%), 11 of 62 (18%); lung, 7 of 44 (16%), 16 of 62 (26%); and soft tissue, 4 of 44 (9%), 9 of 62 (15%).

We consider that it is too early for an analysis of overall survival. However, of 63 deaths to date, 27 have been in the treatment and 36 in the placebo arm, respectively. All except 7 deaths have been due to metastatic disease. The deaths due to other causes were, in the treated group, agranulocytosis (one case), malignant hypertension (one case), and congestive cardiac failure (2 patients); and in the placebo group, acute myocardial infarction (2 cases) and cerebrovascular accident (one case).

Effect of Therapy on Hormone Levels. Our previous publication (14) showed that significant suppression of both estradiol and DHA-S occurred throughout the 2-year period of active treatment. We have now compared mean levels of estrone, estradiol, and DHA-S after 3 months in 9 randomly chosen patients who have remained disease free on active therapy for at least 4 years with levels in 9 patients who have relapsed within 2 years on active treatment. The mean estrone, estradiol, and DHA-S levels (with 95% confidence limits) were 37.0 pmol/liter (14.5, 44.0), 1.5 pmol/liter (1.5, 10.00), and 0.30 μmol/liter (0.13, 1.1), respectively, in the disease-free group compared to 14.5 pmol/liter (14.5, 47.0), 6.0 pmol/liter (1.5, 10.0), and 0.43 μmol/liter (0.35, 1.2) in the relapsed group. None of the levels differs significantly between the 2 groups and thus there is no evidence of any difference in degree of suppression between those who relapse on therapy and those who remain disease free.

Side Effects. Table 4 lists side effects in each arm of the study. One hundred and twenty-eight (88%) patients in the active arm had some toxicity mentioned compared to 76 (54%) on the placebo arm ($P < 0.003$). These side effects were severe enough to necessitate complete withdrawal of treatment in 27 patients (19%) in the treatment arm and in 21 patients (15%) in the placebo arm. In addition, there were 11 further treatment reductions in the active arm (9 to 750 and 2 to 500 mg/day) and 3 treatment reductions in the placebo arm of the study.

The most severe side effect was granulocytopenia, which has been previously reported (15). This occurred in 3 patients in the group receiving active treatment, and one patient died as a result of this. The other 2 patients subsequently recovered on withdrawal of the drug.

DISCUSSION

This study demonstrates that aminoglutethimide significantly increases the interval to first "event" (*i.e.*, distant metastasis or death) after primary treatment of breast cancer in postmenopausal women ($P = 0.004$). Although this report is preliminary, the duration of follow-up is comparable to that in reports of other studied such as the National Surgical Adjuvant Breast Project (16) and other trials (17). Furthermore, the total number of patients reported here is similar to the number of patients in the node positive, postmenopausal subgroup in other published trials (17, 18). At similar time of follow-up it seems that the delay in relapse due to aminoglutethimide and hydrocortisone is similar to that seen for tamoxifen (4).

The major drawback of this type of adjuvant therapy is toxicity. Thus, 19% of patients in the active arm of the study had to discontinue therapy compared to around 4% of patients receiving tamoxifen (4). However, comparison of reported toxicity levels in different trials can be misleading. In this trial a substantial number of patients in the placebo arm also reported side effects and 15% stopped treatment with placebo. This result suggests either that some side effects were more disease than treatment related, or that toxicity was over emphasized in explanations of the treatment given to patients. Side effects were generally reversible although there was one treatment-related death, caused by a side effect that had not been reported at the time the study was initiated.

Unlike tamoxifen therapy in which the activity of the drug is difficult to measure, we have been able to confirm and monitor treatment by measuring circulating steroids such as estrone, estradiol, and dehydroepiandrosterone sulfate. We have previously reported a significant reduction of these steroid hormones in treated patients compared to controls maintained throughout the 2 years of therapy (7). There does not seem to be any lack of suppression in patients who relapse within 2 years of treatment, indicating that this is not the reason for the therapy being ineffective in this group.

The antitumor activity of aminoglutethimide is now thought to work by inhibition of aromatase (estrogen synthetase). Unfortunately this agent will inhibit desmolase and thereby cortisol synthesis with the consequent need for steroid replacement. A more specific aromatase inhibitor, 4-hydroxyandrostenedione, has now been shown to be an effective agent for treatment of advanced breast cancer (12). It is possible that this agent may be a more suitable candidate for adjuvant therapy, since we have not yet observed any serious side effects in more than 100 patients that we have treated during the past 18 months. Studies carried out by our group in patients with advanced disease suggest that aromatase inhibitors complement antiestrogens such as tamoxifen in 2 ways: (*a*) they are effective in some patients after they have relapsed on tamoxifen therapy; and (*b*) there is a subgroup of patients with ER-rich tumors who fail to respond to tamoxifen but who respond to aromatase inhibitors (14).

At present, therefore, our results suggest that aminoglutethimide can reduce the risk of relapse in postmenopausal patients, but at the expense of unwanted side effects. Retrospective subgroup analysis does not yet reveal any subgroup that benefits especially from treatment, although this may emerge later as more events occur, particularly for those patients whose primary carcinomas contain significant ER who seem to benefit to a greater extent than do those with ER-negative tumors.

Further follow-up will be carried out to assess any effect of aminoglutethimide on overall survival.

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