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

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Abstract

A group of 122 postmenopausal patients with histologically proven node-positive primary breast cancer have been randomized to receive aminoglutethimide-hydrocortisone or placebo aminoglutethimide-placebo hydrocortisone for 2 years. Median follow-up is 17 months. In general, treatment was well tolerated, but 15 patients required a reduction in the dose of aminoglutethimide, and of these four patients were unable to continue therapy due to side effects. Primary staging, incidence of extensive node involvement, and estrogen receptor were similar in the treatment and control arms. Dehydroepiandrosterone sulfate (DHA-S) and estrone were measured in a subgroup of patients, and significant suppression of DHA-S levels throughout the duration of the treatment period was seen in patients receiving the active drug. No significant suppression of either DHA-S or estrone levels was seen in the controls. Patients were monitored for metastases by serial liver function tests, carcinoembryonic antigen, and chest X-rays, and of 26 relapsing patients only three patients were not detected by this screen.

We conclude that adjuvant aminoglutethimide is moderately well tolerated. It is capable of suppressing DHA-S throughout 2 years of treatment. A further 280 patients will be entered into the study to assess the survival benefit for those taking aminoglutethimide-hydrocortisone.

Introduction

Aminoglutethimide (Elipten-CIBA) is an effective agent in the treatment of patients with advanced breast cancer (5, 8) but has not yet been evaluated as an adjuvant in early breast cancer. Dao (3) reported a small series of patients who underwent adjuvant surgical adrenalectomy at the time of primary surgical treatment of breast cancer; 17 postmenopausal patients with 4 or more axillary nodes involved had adrenalectomy, and in the following 10 years only 3 of these patients died of breast cancer. Other types of endocrine therapy have been administered as adjuvant such as tamoxifen (4), and early results indicate some benefit. For these reasons, we have started a study to determine whether adjuvant aminoglutethimide given immediately after mastectomy to postmenopausal node-positive patients with primary breast cancer can significantly delay relapse and prolong survival.

The object of this preliminary report is to detail tolerance to and side effects of adjuvant aminoglutethimide and to report on the effect of prolonged adjuvant aminoglutethimide on steroid hormones.

Materials and Methods

The trial is a double-blind randomized study. To date, 129 women have been randomized to receive active aminoglutethimide and hydrocortisone or placebo aminoglutethimide and placebo hydrocortisone. These include 21 patients from the pilot trial similar in all respects to the main study except that the control arm did not receive a placebo. All patients had histologically proven primary breast cancer with at least one axillary lymph node shown to contain metastatic breast cancer. Four patients have been excluded because they were found subsequently to be premenopausal, and a further 3 patients were not included in the analysis because they were randomized more than 8 weeks after surgery (one patient) or were metastatic from the start (2 patients). The remaining 122 patients have been included in this analysis. Mean age of patients in the treatment and control arms and details of primary staging, lymph node status, and histological type of tumor are shown in Table 1. Prior to inclusion in the trial, patients were screened for metastatic disease by chest X-ray, CEA,[4] liver function tests, bone scan, and clinical examination, and evidence of metastases excluded patients from the trial (2). Patients who were considered unfit for the study due to senility or psychological reasons were also excluded as were those with significant renal, hepatic, or gastric disease. In particular, patients with serious peptic ulceration were excluded. Any patients who had had previous malignant disease of either breast or any other organ were also excluded from the study.

Outline of Trial and Drug Doses. Nine hospitals participated in this study (see Footnote 3). Patients were reported to the hospital pharmacist who then telephoned the central trial office, and the data secretary then randomized the patients. The patients were stratified according to surgeon, but there was no other stratification parameter. The treatment was started within 8 weeks of surgery in all patients.

Those randomized to receive drug treatment received aminoglutethimide, 250 mg twice daily, and hydrocortisone, 20 mg twice daily, for the first month and then aminoglutethimide, 250 mg 3 times daily, and hydrocortisone, 20 mg twice daily, for the second month. After this aminoglutethimide was given at 250 mg 4 times daily, and hydrocortisone was given at 20 mg twice daily. Control patients took placebo

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[4] The abbreviations used are: CEA, carcinoembryonic antigen; DHA-S, dehydroepiandrosterone sulfate.

Table 1
Details of patients

	Treatment	Placebo
No. of patients	54	68
Age		
Mean	62.3	62.1
Range	[a]44–76	50–75
S.D.	7.8	6.5
Clinical staging		
T_1-T_2	40	47
T_3-T_4	11	14
T unknown	3	7
Histology		
Primary infiltrating ductal carcinoma	36	52
Other	13	15
Type not recorded	5	1
Lymph nodes		
1–3 involved	25	34
>3 involved	18	27
No. not recorded	11	7
Type of operation		
Radical mastectomy	26	13
Total mastectomy	13	28
Wide excision and node dissection	11	25
Not recorded	4	2
Radiotherapy		
Given	33	54
Not given	16	12
Not recorded	5	2

[a] One 44-year-old patient had been oophorectomized 6 months previously.

aminoglutethimide and hydrocortisone in an identical way, and 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. The first 21 patients randomized to receive placebo received no tablets since placebo was not available at the start of the trial.

Primary Treatment. In view of the fact that we stratified for each surgeon, primary treatment and radiotherapy was left to the discretion of the surgeon. Primary treatment policy of individual surgeons was consistent. The type of primary surgery in treatment and control groups is detailed in Table 1, as are the details of patients receiving radiotherapy.

Follow-up. Patients were seen 2 weeks after the start of treatment and then monthly for 2 months and trimonthly thereafter. At each trimonthly visit, chest X-ray, γ-glutamyl transpeptidase, alkaline phosphatase (Autoanalyser, Technicon), and CEA (radioimmunoassay) were measured. Clinical examination was undertaken, and a standard questionnaire designed to detect any toxicity was filled in. Any abnormality in the metastatic screen was then followed by a liver scan and bone scans, and development of metastatic disease was confirmed histologically and reported to the trial office. Adjuvant therapy was then ceased. If for any reason treatment was discontinued, patients were followed up in an identical fashion.

Concerning treatment on relapse, patients in the placebo arm received active aminoglutethimide wherever possible, but essentially treatment on relapse was left to the discretion of the collaborators.

Histology and Steroid Receptor Content. All histological sections of primary tumor and lymph nodes were examined by one individual (Radka Bettelheim). Steroid receptor was measured at the Ludwig Institute for Cancer Research, Berne, Switzerland, with a single saturating dose of tritiated estradiol according to the dextran-coated charcoal method described elsewhere (7).

Hormone Measurements. DHA-S and estrone were measured on serum samples which were taken from each patient prior to treatment and at 3 monthly intervals during treatment. DHA-S was measured in serum which had been diluted 100 times, using antiserum donated by Dr. B. T. Rudd (Birmingham and Midland Hospital for Women). The antiserum cross-reacted 100% with dehydroepiandrosterone thus allowing the use of [^{3}H]dehydroepiandrosterone (Amersham International) as tracer-ligand. Estrone was assayed after ether extraction using a highly specific antiserum provided by Dr. John Moore (ICRF). Detection limits for the assay were determined as 0.05 μmol/liter for DHA-S and 30 pmol/liter for estrone.

Results

Patients. It can be seen from Table 1 that the patients in both arms of the study were comparable in most respects. The imbalance in numbers between the 2 arms of the study is to be expected at this stage of the trial. The most important factor from a prognostic point of view was the similar extent of lymph node involvement in both arms of the study. Mean ages and clinical staging of the 2 groups were also comparable, although more patients in the control arm had palpable lymph nodes.

Some patients in both treatment and control groups had elevated marker values, shown in Table 2. Similar proportions of patients in both arms had pretreatment abnormalities; none have evidence of metastases on bone or liver scintigraphy.

Estrogen Receptor Status. Estrogen receptor status was found to be comparable in both arms of the study in the patients in whom estrogen receptor has been measured to date, with 22 of 36 (61%) patients in the control group having tumor containing >15 fmol/mg cytosol protein compared with 20 of 27 (74%) patients receiving aminoglutethimide. Mean estrogen receptor content was 93.6 ± 23.3 (S.E.) fmol/mg cytosol protein and 93.3 ± 28.3 fmol/mg cytosol protein for treatment and control groups, respectively.

Side Effects. Side effects in patients receiving treatment or placebo are shown in Table 3. Lethargy was common in both groups but significantly more so in patients receiving aminoglutethimide, as were the ataxia and skin rash, although both these side effects occurred in some patients taking placebo. Other side effects in the treatment arm included 2 patients who developed severe indigestion, and one patient had a hypoadrenal episode reversible with hydrocortisone. One patient developed severe pyrexia which necessitated that therapy be discontinued. A further 2 patients discontinued therapy due to

Table 2
Biochemical tests: pretreatment abnormalities

Marker	Treatment	Control
Alkaline phosphatase > 105 IU/liter	6/42 (14)[a]	8/66 (12)
γ-Glutamyl transpeptidase > 50 IU/liter	2/35 (6)	1/54 (2)
CEA > 15 IU/liter	5/22 (23)	7/36 (19)

[a] Numbers in parentheses, percentage.

Table 3
Toxicity of aminoglutethimide/hydrocortisone compared with placebo

Side effects	No. of patients given aminoglutethimide/hydrocortisone	No. of patients given placebo
Lethargy[a]	30 (56)[b]	15 (22)
Skin rash[a]	22 (41)	7 (10)
Nausea-vomiting[a]	19 (35)	6 (9)
Ataxia[a]	15 (28)	4 (6)
Other (see text)	7 (13)	3 (4)
None	9 (17)	52 (76)
Total no. of patients	54 (100)	68 (100)

[a] $p < 0.005$; χ^2 test.
[b] Numbers in parentheses, percentage.

severe skin rashes, and one patient stopped treatment because of debilitating drowsiness.

Table 4 gives details of patients in whom therapy was reduced due to side effects. Nineteen patients required sustained reduction in aminoglutethimide treatment, including 4 receiving placebo.

Metastatic Screen and Markers. To date, 26 patients have relapsed. Twenty-three of 26 patients demonstrated an abnormality in either alkaline phosphatase, γ-glutamyl transpeptidase, CEA, or chest X-ray, or they had bone pain (Table 5). The 3 patients whose relapse was not detected by the metastatic screen all had central nervous system disease.

Hormone Measurements. Table 6 shows the results of DHA-S and estrone measurements in 9 patients receiving aminoglutethimide and 9 receiving placebo. Overall, 7 patients receiving aminoglutethimide showed significant reduction (>40%) of DHA-S whereas none of the controls did so. All patients showing suppression of DHA-S were found to have significant suppression throughout the 18 months to 2 years of treatment. Only 3 of 9 patients receiving active compound showed significant (>40%) suppression of estrone, whereas none of the controls did so. In these 3 patients, suppression lasted for the 2 years during which therapy was given.

Discussion

This is only a preliminary report on the progress of the adjuvant aminoglutethimide trial for postmenopausal patients with node-positive primary breast cancer. The results firstly demonstrate that such a study is feasible and that therapy is moderately well tolerated, since only 4 patients have had to be withdrawn because of side effects. Overall, however, 83% of patients receiving active compound complained of side effects compared to 24% of placebo-treated patients. However, side effects were severe (*i.e.*, sufficient to warrant reduction in dose) in only 28% of patients receiving active compound and in 6% of those receiving placebo. This is the first double-blind randomized-controlled clinical trial of aminoglutethimide, and the results highlight the subjective nature of some of the side effects, particularly lethargy.

Secondly, we were anxious to determine whether the current method of randomization was suitable in a multicenter trial such as this. We have demonstrated that the 2 major prognostic variables, namely, estrogen receptor and lymph node involvement, are similar in both groups of patients. Similarly, the percentage of patients who were treated by mastectomy is similar in both arms of the study.

We have also been able to assess the efficiency of the screening system for metastases. We have advocated the present screen from results found in a previous study (2). Approximately 90% of patients who relapsed did so with abnormalities in the chosen biochemical tests, chest X-ray, or clinical examination. Some patients (2) had bone pain in the absence of abnormalities in other tests.

An important aspect of this study is the effect of adjuvant aminoglutethimide on plasma hormones. It has been suggested that the effectiveness of the drug may be diminished after prolonged use due to induced metabolism of the drug (7). The present results indicate that the drug is effective, as measured by plasma DHA-S, throughout the period of treatment in the majority of patients. We have found similar results in patients receiving aminoglutethimide for advanced breast cancer (1). We have determined the acetylator status in order to investigate the reason for inadequate DHA-S suppression in the remaining patients since acetylation is an important route of metabolism of aminoglutethimide, but 2 of 3 of those demonstrating inadequate suppression were "slow" acetylators, indicating that the ability to rapidly acetylate the drug is not a major factor in hormone suppression. The effect of the drug on estrone concentrations is still uncertain, and more patients will be studied to determine whether the reduction in estrone observed in 3 patients is significant and whether lack of estrone suppression is relevant in those relapsing after taking active compound.

Table 4

Dose reduction due to side effects

Maximum dose of aminoglutethimide tolerated	Aminoglutethimide-hydrocortisone	Placebo
750 mg/day	4	3
500 mg/day	6	1
250 mg/day	1	0
Stopped	4	0
Totals	15/54 (28)[a]	4/68 (6)

[a] Numbers in parentheses, percentage.

Table 5

Adjuvant aminoglutethimide: screen for metastases

Tests	No. abnormal at first relapse
Liver function or CEA	8/26 (31)[a]
Node-skin	10/26 (38)
Chest X-ray	9/26 (35)
Bone pain	6/26 (23)
None	3/26 (12)

[a] Numbers in parentheses, percentage.

Table 6

Sequential DHA-S and estrone values in patients receiving active compound and placebo

	DHA-S (μmol/liter)			Estrone (pmol/liter)		
	Mean ± S.D.	Range	No. showing continued suppression	Mean ± S.D.	Range	No. showing continued suppression
Treatment			7/9			3/9
Pretreatment	1.51 ± 1.6	0.5-5.30		134 ± 67.7	50-260	
3-4 mos.	0.29 ± 0.45	0-1.28		82 ± 43.5	20-160	
6-9 mos.	0.30 ± 0.47	0-1.35		100 ± 54.8	30-220	
18-24 mos.	0.32 ± 0.36	0-1.07		97.8 ± 43.5	50-180	
Control			1/9			0/9
Pretreatment	1.26 ± 0.50	0.49-1.97		130 ± 42.7	80-200	
3-4 mos.	1.22 ± 0.51	0.27-1.91		146 ± 45.9	70-230	
6-9 mos.	1.21 ± 0.42	0.4-1.6		148 ± 59.5	70-270	
18-24 mos.	1.16 ± 0.47	0.15-1.73		141 ± 34.1	90-200	

[a] $p < 0.05$ compared with mean of subsequent values, (paired one-tailed t test).

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Discussion

Dr. Powles: It has been a very exciting time for us in breast cancer research to see a new drug coming through with results like this. We have had reports on about 690 patients in this session, and 325 of these had assessable metastatic disease. The consistency of responses from the different groups comes through. About 5% of patients who have metastatic disease are having complete remission, 25% of patients are having partial remission, and 11% of patients are having stabilization of disease. There is also no doubt that aminoglutethimide is good for bone and especially for bone pain. It has also been shown that we do not see the activation of tumor with AG[1] that we do see with additive hormone therapy. The toxicity is manageable. The patients who respond to AG survive much longer than do the nonresponders. It has also been shown by several groups that the patients who have stabilization of disease seem to survive as well as the patients who responded. Now let me address the unanswered questions that have been posed today. (*a*) We really do not know what dose we are supposed to be using, and we certainly do not know what hormones we are supposed to be measuring to try to find out who responds and who does not. All we do know is that patients with positive ER respond better. (*b*) When do we treat? The early results of the adjuvant program are obviously exciting, but it is much too early to draw any conclusions from them. When patients have relapsed with metastatic disease, should endocrine therapy be the first option, and if it is a first option, where does AG fit into that? I think most of us feel that TAM, because of the early results from the crossover studies, is probably the primary choice of treatment in postmenopausal women. But certainly AG must be considered as primary treatment now for patients with bone metastases. (*c*) Why do patients who respond to endocrine therapy live longer? We do not know. We do not know whether we are just selecting out a group of patients who would have lived longer anyway. I think we really must try to find out whether response to endocrine therapy is actually improving survival. (*d*) And finally, why do they relapse once they have responded? This is an unanswered question in endocrine therapy. I would like to ask Dr. Santen one question on that. It was very interesting to see that the estrogen levels fall with AG as we would anticipate from all the experimental work, but have you looked at what happens to those estrogen levels when the patients relapse? Do the estrogen levels come back up again or is there any evidence of a breakthrough?

Dr. Santen: We have really not analyzed it in the way that would be necessary to answer it definitively.

Dr. Paridaens: One should be very cautious when asked to interpret the ER assay in patients who were previously treated with TAM. If the assay has been performed within 3 months after TAM withdrawal, ER assays are generally negative, and that occurs in almost all patients in our experience. We have analyzed what happened in our patients who had never been treated previously with TAM, and in this subset of patients we had a clear-cut relationship between the ER levels and the prediction of response to treatment. More interestingly, the ER levels in patients who had stabilization of their disease were not different from the levels in patients who had remission. We also made the same observation as you, that duration of stabilization was comparable to the duration of response in this subset of patients. Thus, we might imagine that such a treatment as AG could be beneficial in many patients and mainly in ER-positive cases.

Dr. Lipton: We have previously reported a significant response rate in the ER-borderline patients (those for whom the ER is between 4 and 10). Our response rate in a modest number of patients was around 40%; it was less than in the definitely ER-positive patients. We also saw one of 7 responses in ER-negative patients, which is a category that might deserve further scrutiny in the future, although at a much lower response rate level.

Dr. Ragaz: We had 40%; of 17 patients, 40% who responded to AG with or without TAM were ER negative.

Dr. Coombes: Has anybody actually looked at the patients with stable disease to find out if in fact they are ER positive or ER negative?

Dr. Paridaens: Our experience is that patients with stable disease are ER positive.

Dr. Coombes: And so if one looks at the 60% of patients with ER-positive disease, the patients with definitely progressive disease are mostly ER negative?

Dr. Paridaens: Yes; or they have very low values.

Dr. Segaloff: How many of them were progressing unequivocally beforehand?

Dr. Paridaens: All patients. In our trial we included only patients with progressive disease. But people who reported responses in patients with negative assays should look carefully at prior treatment in these patients.

Dr. Norman Bloom (Lincoln Hospital, Bronx, New York): In answer to your question about stabilized patients, I think that progesterone receptor is more significant than ER. Contrary to what Dr. Henderson alluded to, I think that this really increases your ability to predict which patients are going to respond much better than the ER assay alone. In 40 or so patients that I treated with adrenalectomy who were estrogen and progesterone receptor positive, the response rate was about 85%. There were 3 patients who had stabilization of the disease who were both estrogen and progesterone receptor positive, and their stabilization of disease lasted the same length of time as that of the patients who had obvious regression. Of all the negative patients or the patients that were ER positive and progesterone receptor negative, there were no patients who had stabilization of disease following adrenalectomy.

[1] The abbreviations used are: AG, aminoglutethimide; ER, estrogen receptor; TAM, tamoxifen; FSH, follicle-stimulating hormone.