Aminoglutethimide in the Treatment of Advanced Postmenopausal Breast Cancer

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Abstract

A group of 213 unselected postmenopausal women with advanced breast cancer were treated with aminoglutethimide, 250 mg 4 times a day, and hydrocortisone, 20 mg 2 times a day. Follow-up is 10 months to 4 years from the start of treatment. In 190 assessable patients, there were 6 complete responses (CR), 47 partial responses (PR), 25 stable disease (SD), and 3 mixed responses. Overall objective response rate was 28% and with SD was 41%. Median duration of objective response was 14 months. Objective response by site was: soft tissue, 31%; nodes, 27%; bone 23%; liver, 22%; and lung, 16%. A further 32% of patients with bone deposits had SD, and 19 of 60 patients with progressive disease had pain relief.

Years after menopause, age and tumor-free interval did not affect response rates. Thirty-eight % of patients responding to previous endocrine therapy responded to aminoglutethimide compared with 19% of patients who had progressed on previous endocrine therapy.

A group of 213 patients were assessable for toxicity. Main side effects were drowsiness (33%), rash (23%), and nausea (15%). Eleven patients stopped treatment because of toxicity.

Median survival from start of treatment was 28 months for PR-CR and for SD and 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 inhibits an early step in adrenal steroid synthesis, the conversion of cholesterol to pregnenolone (3). This inhibition can be overcome by adrenocorticotropic hormone (14) so replacement doses of hydrocortisone are also given to block the feedback effect.

The main source of estrogens in postmenopausal women is the peripheral conversion of adrenal androgens ($\Delta^4$-androstenedione) to estrone by aromatase enzymes (5), and this conversion is also inhibited by aminoglutethimide (15). The use of the combination of aminoglutethimide with hydrocortisone to produce adrenal suppression is referred to as medical adrenalectomy. Initial reports show that it is an effective treatment in postmenopausal breast cancer (19, 22).

Patients, Materials, and Methods

Between August 1977 and October 1980, 213 unselected postmenopausal patients with advanced breast cancer were treated with aminoglutethimide and hydrocortisone in a Phase II study. Aminoglutethimide was initially given as 250 mg p.o. 3 times a day, and dose was increased to 250 mg 4 times a day after 2 weeks if well tolerated or if side effects present in initial 1 to 2 weeks were decreasing. The hydrocortisone dose was 20 mg twice a day. In the first 41 patients, fludrocortisone, 0.1 mg daily, was given, but it was found not to be necessary, 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 years.

Response was defined by standard UICC criteria (7). CR$^2$ 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. PR was a 50% decrease in the sum of the products of all measurable lesions and recalcification of lytic bone disease. Stable disease (no change) was less than 50% reduction in the sum of products of measurable lesions and less than 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 analyzed by the Peto log-rank test (12) and tables by the $\chi^2$ test.

Response Rates

Out of 190 patients assessable for response, there were 6 CR (5 alive in August 1981), 47 PR (25 alive in August 1981), 25 stable disease (10 alive in August 1981), and 3 mixed responders. The latter had PR in soft tissues and relief of bone pain but progression of lytic bone disease. The response of 41 patients taking fludrocortisone 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%. The 23 nonassessable patients died within 1 month of treatment from progressive liver or lung secondaries, and all but 2 had received previous therapy.

Response by Site

The highest response rate was in soft tissues, and the lowest was in lung (Table 1). In 60 patients with progressive bone disease, 31.7% had reduction in bone pain. This often started within 24 hr of initiation of therapy.

Response Duration

Median response duration for the objective responders was 22 months for PR-CR and for SD and 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 $(p < 0.001)$.


2 The abbreviations used are: CR, complete response; PR, partial response; SD, stable disease.
Response to Previous Endocrine Therapy

A group of 112 patients had previously received endocrine therapy, 53 had previously received chemotherapy, and 62 had no previous treatment. There were no significant differences between objective responders, patients with stable disease, and those with progressive disease with regard to previous treatments.

Ten of 26 patients who had responded previously to other endocrine therapy responded objectively to aminoglutethimide (38%), and 4 had stable disease. Ten of 53 patients who had previously progressed on other endocrine therapy responded objectively to aminoglutethimide (19%), and 7 had stable disease. Previous therapy in the 10 patients whose disease had progressed included tamoxifen, stilbestrol, and oophorectomy. There were 33 patients not assessable for previous endocrine therapy, and their objective response rate was 11 of 33 (33%) with 3 additional patients showing disease stabilization.

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 months).

Menopausal Status

There was no significant effect of years after the menopause on response rate. Women within 2 years of the menopause had similar response rates (17 of 46 patients) to those 10 to 15 years afterward (11 of 34 patients).

Tumor-free Interval

There was no significant difference in response rates between those who developed recurrence within 2 years of their primary treatment [41 of 111 patients (37%)] and those who developed recurrences more than 2 years later [37 of 79 patients (47%)].

Age

Women under age 45 had a lower response rate (6 of 22 patients) than did those over 45 (75 of 168 patients), although this is not significant (p < 0.1).

Toxicity

All 213 patients were assessable for toxicity. The most common side effects were drowsiness, rash, and nausea (Table 2). The drowsiness and nausea settled within 3 weeks in most patients, although in 18 patients dosage of aminoglutethimide was not increased above 250 mg 3 times a day.

In 10 of the 190 patients assessable for response and in 1 of the early deaths, the drug had to be discontinued. Aminoglutethimide was stopped for the following reasons: nausea and headaches, 1 patient; severe drowsiness, 4 patients; exacerbation of Ménière's disease, 1 patient; Stevens-Johnson syndrome, 1 patient; flu-like syndrome with vomiting and diarrhea, 1 patient; severe rash, 1 patient; visual blurring, 1 patient; electrolyte disturbance, 1 patient. One of these patients had achieved a PR but had to stop because of drowsiness. The only patient with electrolyte disturbance (hyponatremia) was taking fludrocortisone. Thus, overall withdrawal rate was 5%.

The patient who had agranulocytosis developed this 4 weeks after starting treatment. Aminoglutethimide was continued and, within 2 weeks, neutrophil count was back to normal. She has...
had stable disease for 2.5 years and continues on aminoglutethimide.

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

**Survival**

The median survival from start of treatment was 28 months for the responders and 10 months for nonresponders (p < 0.001; Chart 2). There was no significant difference in survival between objective responders and stable disease patients (p > 0.5, log-rank test; Chart 2).

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

**Discussion**

This study shows that aminoglutethimide in combination with hydrocortisone is an effective endocrine therapy in postmenopausal women with breast cancer. Women within 2 years of their menopause respond as well as those many years later, and there is no effect of tumor-free interval on response, in contrast to treatment with stilbestrol (21). The data on early deaths show a clear subgroup of patients with rapidly progressive lung and liver secondaries for whom this treatment is not suitable.

The response rates (CR plus PR) are similar to those reported for tamoxifen (9, 11), stilbestrol (21), and adrenalectomy (2, 4, 18). There is a similar distribution of favorable sites for response, soft tissue and nodes being the best and liver or lung being the worst site. 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 70%.

Others have reported objective response rates varying from 16 to 50% (1, 10, 17, 22) in contrast to our rate of 28%. These differences are probably partly related to patient selection, since Savaraj and Troner (17) selected patients who were estrogen receptor positive and in the series of Wells et al. (22) 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 nonresponders. 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 (13). The median is 43 months for objective responders, 40 months for stable disease (not significantly different), and 22 months for nonresponders. The achievement of disease stabilization with aminoglutethimide is thus associated with similar time to progression, 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.

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 randomized trial and was found to produce results not significantly different (16).

Although there is an initial high incidence of side effects, these are usually transient and they appear age related. Tolerance develops after 2 to 3 weeks, and it is for this reason...
that we increased aminoglutethimide dose after 2 weeks rather than giving 250 mg 4 times a day initially.

The withdrawal rate of 5% is higher than that for tamoxifen found in a randomized trial of tamoxifen versus aminoglutethimide (20) but less than that for stilbestrol (8).

It is possible that a lower dose of aminoglutethimide could be used with fewer 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 sulfate), estrone, and estradiol in patients taking 500, 750, and 1000 mg/day.

Thus, 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 relapse after responding to other endocrine therapy.

References
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