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Aminoglutethimide in Advanced Breast Cancer: Clinical Results of a French Multicenter Randomized Trial Comparing 500 mg and 1 g/day

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Abstract—*We have conducted a multicenter randomized clinical trial comparing in advanced post-menopausal breast cancer patients* 500 mg *vs* 1 g *AG/day. The hydrocortisone dose was* 40 mg/day *in both groups. One hundred and seventy patients have been randomized;* 161 *were evaluable for tolerability,* 149 *for effectiveness. Response rates were similar in both groups,* 19 *and* 24% *respectively for the* 500 mg *and* 1 g *groups. No difference was observed according to tumor site. Duration of response was the same in both groups* (14 months), *as was mean time to response* (about 3 months). *Survival* (*studies in* 125 *patients*) *was similar in both groups* (*responders and non-responders*). *No response could be obtained with* 1 g *after relapse or failure with* 500 mg (n = 17). *Tolerability was good in* 91% *of the* 500 mg *group patients and* 78% *of the* 1 g *group patients* ($P < 0.03$). *It was poor in* 4 *and* 15% *respectively* ($P < 0.03$). *Side-effects were the same in both groups but less frequent and less severe in the* 500 mg *group; however, these patients more frequently had 'moon face'.*

INTRODUCTION

AMINOGLUTETHIMIDE (AG) has been widely used as a treatment for advanced breast cancer in post-menopausal women [1, 2]. Its use has also been proposed as an adjuvant treatment [3]. The AG dosage was previously 1 g/day with 40 mg hydrocortisone. In 1980 it was shown that, *in vivo*, lower concentrations of AG had the same activity as 1 g on estrone and estradiol plasma levels [4]; these results were in agreement with those obtained in *in vitro* studies [5] which have shown aromatase to be ten times more sensitive to AG than desmolase; the preliminary results of *in vivo* hormonal studies have been largely confirmed [6, 7]. These studies suggested that objective clinical responses could be obtained with lower doses of AG.

We conducted a multicenter randomized clinical trial comparing the effectiveness and tolerability of 500 mg AG vs 1 g AG plus 40 mg hydrocortisone. The last patient was taken into this trial in August 1983.

MATERIALS AND METHODS

Patient selection

One hundred and seventy spontaneously or radiation-induced menopausal women with proven metastatic breast carcinoma and measurable progressive disease were selected for study. Patients with central nervous system involvement or hepatic metastasis were excluded from the study. Chemotherapy and/or other additive hormone therapy had to be discontinued at least 1 month prior to entry into this trial. Among these 170 patients, one was found to be ineligible (pulmonary cancer), eight were not evaluable

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(neither for tolerability nor for effectiveness), 161 were evaluable for tolerability and 149 were evaluable for effectiveness. The reasons for not being evaluable were: treatment of too short a duration, non-evaluable lesions, patients dropping out and treatment discontinuation because of toxicity. Most of these patients had been heavily pretreated: 68% of the 149 evaluable patients had already received at least one hormone therapy and/or chemotherapy.

Patients were stratified according to the receptor status. All patients were either receptor-positive (R+) (estradiol and/or progesterone) or receptor-unknown (R?). Receptor-negative patients were not eligible. Receptor assays were performed by the dextran-coated charcoal method. Positivity criteria were those accepted in each participating center.

No patient received simultaneous radiotherapy at an evaluable site.

Patient evaluation and response criteria

Patients were evaluated after 15, 45 and 90 days, and then every 3 months. Response criteria were those of the UICC. Objective responses (whether complete or partial) and stable disease had to persist at least 3 months to be taken into consideration. Complete response (CR) means disappearance of all lesions. Partial response (PR) means regression of more than 50% of the product of two perpendicular diameters of all measurable lesions; stable disease (SD) was defined as a decrease of less than 50% or an increase of less than 25% in all the lesions, and progressive disease (PD) as a progression of more than 25% in the lesions and/or appearance of new lesions. Responses in bone metastases were considered only in the case of clear-cut radiological evidence of bone healing: regression of more than 50% in sclerosing metastases and evidence of calcification of more than 50% of the area of lytic lesions. Regression of bone pain, without evidence of bone healing, as defined, or with exaggerated calcification were not considered as a response, even in the case of regression of other metastatic sites.

The duration of PR and SD was the interval between the beginning of the treatment and evidence of relapse. Duration of CR was the interval between the time that disappearance of the lesions was first observed and the first evidence of relapse.

Subjective effectiveness (regression of pain, dyspnea) was classified as S0 in the case of worsening or no change in symptoms, S1 in the case of great improvement and S2 in the case of complete disappearance of all symptoms.

The patient's performance status (PS) was evaluated according to the WHO criteria (PS 0/1 refers to patients in good general condition, able to work, PS 2 to patients unable to work but able to take care of themselves and PS 3/4 to patients confined to bed more than 50% of the daytime).

Treatment protocol

Patients were randomly allocated to treatment with either 500 mg or 1 g AG/day. All patients took 500 mg for the first 2 weeks (250 mg twice a day); from day 15 the patients of the 1 g group received 250 mg in the morning, 250 mg in the afternoon and 500 mg at bedtime. Hydrocortisone dosage was constant at 40 mg/day throughout the treatment, 10 mg at 8 a.m., 10 mg at 4 p.m. and 20 mg at bedtime in both groups.

Statistical analysis

All survival curves were calculated by the method of actuarial survival analysis and the difference between pairs of curves was tested for statistical significance using the log rank test.

RESULTS

One hundred and sixty-one patients were evaluated for tolerability and 149 for effectiveness; clinical characteristics of these patients appear in Table 1.

Table 1. Clinical characteristics of the evaluable patients in the two groups

	500 mg	1000 mg
No. of patients	73	76
Age (yr)*	59.8 ± 10.2	59.7 ± 10.6
Relapse-free interval (months)*	51.4 ± 57.4	45.9 ± 35
Previous hormone therapy	44%	56%
R+†	25	29
R?†	48	47
Metastatic sites:		
lymph nodes	15	22
bone	39	38
skin	26	34
lungs	21	14

*m ± 1 S.D.

†R+, steroid receptor (oestradiol and/or progesterone)-positive; R?, steroid receptor (oestradiol and progesterone) unknown.

Clinical response according to AG dosage and metastatic site (Table 2)

The overall response rates were 19% in the 500 mg group and 24% in the 1 g group. If stabilization was included, the response rates were the same (58%) for both groups.

Table 2. Response rates according to AG dosage, metastatic site and receptor status

	AG regimen	CR - PR	CR - PR - SD
Overall response	500 mg	(14) 19%	(42) 58%
	1000 mg	(18) 24%	(44) 58%
Bone	500 mg	(4) 10%	(29) 74%*
	1000 mg	(3) 8%	(20) 53%
Skin	500 mg	(8) 31%	(14) 54%
	1000 mg	(5) 15%	(19) 56%
Lymph-node	500 mg	(5) 33%	(10) 67%
	1000 mg	(8) 36%	(16) 73%
Lung	500 mg	(4) 19%	(13) 62%
	1000 mg	(7) 50%	(10) 71%
R+	500 mg	(7) 28%	(15) 60%
	1000 mg	(8) 28%	(19) 66%
R?	500 mg	(7) 15%	(27) 56%
	1000 mg	(10) 21%	(25) 53%

* $P < 0.05$.

Table 3. Response rates according to previous hormone therapy

Patients	*n*	Response to AG PR - CR
With previous hormone therapy	101	(15) 15%
Responders	28	(8) 29%
Non-responders	58	(6) 10%
Not evaluable	15	(1) 7%
Without previous hormone therapy	48	(12) 25%

Table 4. Response rates according to the No. of previous different hormone therapies and to AG dosage

No. of different hormone therapies	No. of responders (%) 500 mg ($n = 48$)	1 g ($n = 53$)
1	4/18 (22%)	3/20 (15%)
2	5/22 (23%)	6/25 (24%)
≥3	1/8 (12%)	0/8 (0%)

The difference in the response rates between the two groups was not statistically significant. When stable disease was included, the response rate for bone metastases was better in the 500 mg group.

Clinical response according to AG dosage and receptor status (Table 2)

Response rates were not different in R+ and R? patients, irrespective of whether they received 500 mg or 1 g. Similarly, response rates were not different in group I and group II patients, irrespective of whether they were R+ or R?

Mean time to response according to AG dosage

The mean time before a response was observed was 3 months for both groups (2.8 ± 1.2 months in the 500 mg group and 3.4 ± 1.4 months in the 1 g group). In all cases the response was observed within 6 months of the start of the study.

Response rate according to performance status (PS)

The response rate was similar, whatever the performance status of the patients at entry into the trial. Responses rates were 25% ($n = 55$), 14% ($n = 49$) and 22% ($n = 18$), respectively, for PS 0/1, PS 2 and PS 3/4.

Response rate according to previous hormone therapy (Tables 3 and 4)

Most of the patients had previously received hormone therapy or simultaneous hormone and chemotherapy which had most frequently been ineffective. The response rate was higher in patients who had never received previous hormone therapy (25%) and in patients who had responded to a previous hormone therapy with at least a minor response (29%). Response rates according to the number of different previous hormone therapies appear in Table 4. When the 500 mg and the 1 g group patients are taken together, the response rates are 18% after one hormone therapy ($n = 38$), 23% after two ($n = 47$) and 6% after three or more different hormone therapies ($n = 16$).

Subjective response

Disappearance or improvement of subjective symptoms was noted in 68% of patients in both groups.

Response to 1g after failure with 500 mg AG

In 17 patients randomly allocated to the 500 mg group and who failed to respond, a trial with 1 g was initiated; no response was observed.

Duration of response according to AG dosage

Median duration of response was 14 months in both groups. Median duration of stabilization was 16 months in the 500 mg group and 10 months in the 1 g group.

Survival according to type of response and AG dosage

Survival was studied according to the type of response in 125 patients, whatever the AG dosage (Fig. 1). Considering both groups together, no difference was noted between patients who responded and those who were stabilized.

However, a highly significant difference was found between these two groups and the non-responders ($P < 0.001$).

As no difference in survival was noted between responders and patients who were only stabilized, they were considered together to compare survival in the 500 mg and 1 g groups. No difference was seen between the two groups (Fig. 2).

Tolerability

Tolerability was evaluated by the patient as good, fair or poor (Table 5). Tolerability was poor in 4% of the patients in the 500 mg group and 15% in the 1 g group ($P < 0.03$); it was good in 91 and 78% ($P < 0.03$) of the two groups respectively. Tolerability was thus better in the 500 mg group.

The side-effects are listed in Table 6. Although lethargy and skin rash were much less frequent in the 500 mg group, the difference did not reach statistical significance. Conversely, 'moon face' was more frequent in the patients of 500 mg group ($P < 0.02$). Four percent of the patients in the 500 mg group and 7% in the 1 g group had to have AG stopped because of toxicity.

DISCUSSION

Our results show that 500 mg AG has the same therapeutic activity with a better tolerance than 1 g/day. No difference was observed between the two groups in response rate, duration of response, mean time to complete or partial response, or survival. Furthermore, no response was seen with

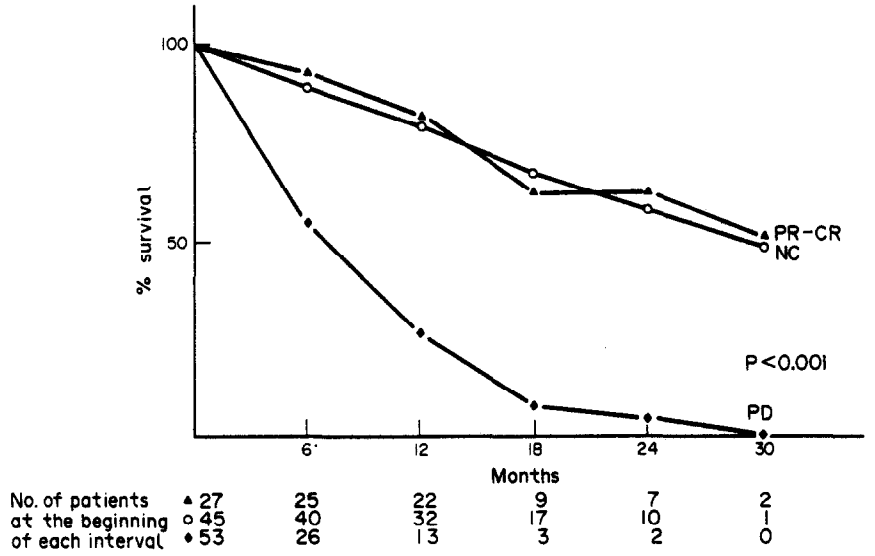

Fig. 1. Survival of all patients (whatever the AG dose) according to the type of response. Patients experiencing no change survived for as long as those who responded to the treatment.

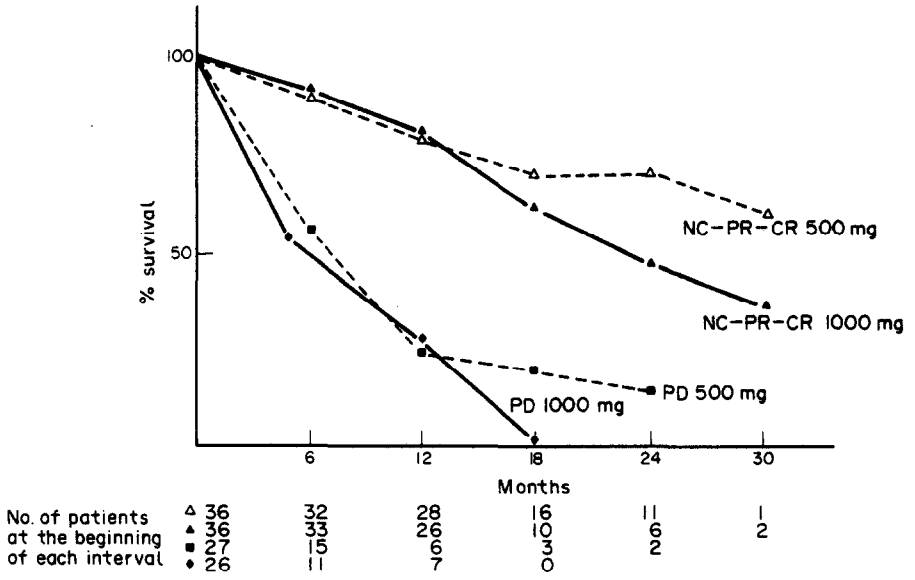

Fig. 2. Survival of patients according to the type of response (CR, PR and NC or PD) and AG dose. No difference in survival was noted between the 1 g and the 500 mg groups.

Table 5. Tolerability

	Good	Fair	Poor
500 mg ($n = 78$)	(71) 91%	(4) 5%	(3) 4%
	*		*
1000 mg ($n = 83$)	(65) 78%	(6) 7%	(12) 15%

* $P < 0.03$.

Table 6. Side-effects

	500 mg ($n = 78$)		1000 mg ($n = 83$)
Drowsiness	(7) 9%		(14) 17%
Skin rash	(3) 4%		(9) 11%
Vertigo	(2) 3%		(3) 4%
Ataxia	(2) 3%		(5) 6%
Moon face	(9) 12%	*	(1) 1%
Cramps	(2) 3%		(0) 0%
Weight increase	(1) 1%		(1) 1%
Hyperthermia	(2) 3%		(3) 4%
Hypotension	(2) 3%		(2) 2%
Hypertension	(1) 1%		(1) 1%
Digestive symptoms	(3) 4%		(7) 8%

*$P < 0.02$.

1 g when 500 mg was ineffective or after relapse with 500 mg.

In this study, response rates in both the 500 mg and the 1 g groups were low compared with the published results [1, 2]. This is probably due to the fact that most of the patients had been heavily pretreated, especially with hormone therapy (most of the patients had received several types of hormone therapy and chemotherapy). Furthermore, the first hormone therapy was not evaluable or was ineffective in 72% of the cases; the likelihood of response to AG was therefore very low in these patients. The response rates in women who had already responded to hormone therapy and then relapsed and the response rates of those without any previous hormonal treatment are in keeping with published reports [8, 9].

Our results in bone metastases were very disappointing, since Smith *et al.* [10] and Lipton *et al.* [11] had published objective response rates in 35% of 31 patients and in 33% of 27 patients. These results were much better than those obtained with tamoxifen. Response criteria are very difficult to assess and ours were strictly defined. The poor results that we obtained could be due to the fact that half of our patients had sclerosing or lytic and sclerosing metastases, the regression of which was particularly difficult to study. However, this cannot be the only explanation since the response rate of lytic lesions (eventually associated with sclerosing metastases but separately evaluated) was poor, too. Another explanation could be that bone healing may only be observed after a long-term treatment [2]. However, the response rate for bone metastases, including stable disease, was 74% in the 500 mg group and 53% in the 1 g group.

The response rates were not dependent on patients' performance status. This had already been reported by Gale [12]. As it is well tolerated, this drug may safely be given to patients in a poor general condition, in contrast to chemotherapy. To our knowledge, such results have not been reported for other hormone therapies.

Tolerability was better in patients receiving 500 mg. Drowsiness, skin rash and ataxia were more frequent in patients treated with 1 g AG, but the difference was not statistically significant. However, patients treated with 500 mg felt much better. It should be emphasized that in the patients of our 1 g group tolerability was better than that reported in previous studies. In Santen and Brodie's experience [1], skin rash was observed in 30% of the cases and drowsiness in 33%. The incidence of 'moon face' in the patients of the 500 mg group in our study might be due to an overcompensation with hydrocortisone. It seems possible that with 500 mg AG/day desmolase is moderately inhibited; 20–30 mg hydrocortisone would probably be enough in patients receiving 500 mg AG/day. The 'moon face' regressed after reduction of the hydrocortisone dosage.

To our knowledge, this study is the first which compares two dosages of AG in a randomized trial. Harris *et al.* [6] has shown that estrone and estradiol plasma levels were suppressed by 125 mg AG given twice a day and that a further increase in the dosage did not result in a greater suppression of these plasma levels. Vermeulen *et al.* [7] showed that 125 mg AG caused a slight but significant decrease in estrone and estradiol plasma levels; 1 g AG did not produce a greater decrease in estrone and estradiol levels than 250 mg AG (20–40%). According to Vermeulen *et al.* [7], treatment with 150 mg, 250 mg and 1 g AG reduced aromatase activity to 33%, 20% and 5% of the basal values respectively. These hormonal studies could explain why no response was obtained with 1 g AG after failure with 500 mg; the lowering of the estrone and estradiol plasma levels was probably sufficient with 500 mg AG to allow a response. Cantwell *et al.* [13], using 250 mg AG and 40 mg hydrocortisone, obtained 6 objective responses in 20 patients. An alternative to the combined treatment is a lower AG dosage without hydrocortisone. Stuart-Harris *et al.* [14] treated 65 patients with low-dosage AG alone (62.5 and 125 mg twice daily); these dosages were as effective in lowering plasma estrone and estradiol levels as the standard 1 g dose, with minimal adrenal

inhibition. The response rate was 19%; surprisingly, side-effects were numerous in that study (lethargy 31%; skin rash 15%). Eight percent of these patients had to discontinue their treatment because of side-effects; Stuart-Harris *et al.* [14] suggest that hydrocortisone might diminish AG-induced side-effects.

From the statistical point of view, it is not easy to show that two treatment arms give similar results; the number of patients to be included is so high that such trials are very difficult to conduct. However, these results together with our failure to obtain a response with 1 g after relapse with 500 mg and together with the results of clinical non-comparative studies of low AG dosages [14] suggest that 500 mg is as effective — and better tolerated — as 1 g.

REFERENCES

1. Santen RJ, Brodie AMH. Suppression of estrogen production as treatment of breast carcinoma: pharmacological and clinical studies with aromatase inhibitors. *Clin Oncol* 1982, 1, 77-130.
2. Santen RJ, Henderson IC. *A Comprehensive Guide to the Therapeutic Use of Aminoglutethimide.* Basel, Karger, 1982.
3. Coombes RC, Chilvers C, Dowsett M *et al.* Aminoglutethimide as an adjuvant to surgery in poor-risk post-menopausal patients with breast cancer. The Royal Society of Medicine. International Congress and Symposium Series, 1982, No. 53, 37-39.
4. Paridaens R, Vermeulen A, Heuson JC. The inhibiting influence of increasing doses of aminoglutethimide on adrenal function and oestrogen production. Preliminary data. In: Paesi FJA, ed. *Aminoglutethimide. Mechanism of Action and Clinical Results in Breast Cancer.* Basel, Ciba Geigy, 1982, 72-82.
5. Graves PE, Salhanick HA. Stereo-selective inhibition of aromatase by enantiomers of amino-glutethimide. *Endocrinology* 1979, **105**, 52-57.
6. Harris AL, Dowsett M, Smith IE, Jeffcoate SL. Endocrine effects of low dose aminoglutethimide alone in advanced postmenopausal breast cancer. *Br J Cancer* 1983, **47**, 621-627.
7. Vermeulen A, Paridaens R, Heuson JC. Effects of aminoglutethimide on adrenal steroid secretion. *Clin Endocrinol* 1983, **19**, 673-682.
8. Harris AL, Powles TJ, Smith IE *et al.* Aminoglutethimide for the treatment of advanced postmenopausal breast cancer. *Eur J Cancer Clin Oncol* 1983, **19**, 11-17.
9. Powles TJ. The role of aromatase inhibitors in breast cancer. *Semin Oncol* 1983, **10**, 20-24.
10. Smith IE, Harris AL, Morgan M, Gazet JC, McKinna JA. Tamoxifen versus aminoglutethimide versus combined tamoxifen and aminoglutethimide in the treatment of advanced breast cancer. *Cancer Res* 1982, **42**, 3430s-3433s.
11. Lipton A, Harvey HA, Santen RJ *et al.* Randomized trial of aminoglutethimide versus tamoxifen in metastatic breast cancer. *Cancer Res* 1982, **42**, 3434s-3436s.
12. Gale KE. Treatment of advanced breast cancer with aminoglutethimide: a 14 year experience. *Cancer Res* 1982, **42**, 3389s-3396s.
13. Cantwell BMJ, Sainsbury JRC, Harris AL *et al.* Low-dose aminoglutethimide (AG); phase II study in advanced post-menopausal breast cancer. 2nd European Conference on Clinical Oncology, Amsterdam, November 1983, No. 17-09, 185.
14. Stuart-Harris R, Dowsett M, Bozek T *et al.* Low dose aminoglutethimide in treatment of advanced breast cancer. *Lancet* 1984, ii, 604-607.