Aminoglutethimide and Medroxyprogesterone Acetate in the Treatment of Patients With Advanced Breast Cancer

A Phase II Study of the Association of Medical Oncology of the German Cancer Society (AIO)*

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One hundred twenty-eight women with advanced metastatic breast cancer were treated with a combination of aminoglutethimide (AG) (1000 mg orally, daily) and medroxyprogesterone acetate (MPA) (1500 mg orally, daily for six weeks and thereafter 500 mg orally, daily; omitting cortisone substitution). AG/MPA did not lead to side effects other than those described under AG or MPA monotherapy. Mental and personality changes seem to be more severe and frequent under combined therapy than under monotherapy. Impairment of mental functions, depressive syndromes, fatigue, ataxia, skin rash, and transient increase of gammaglutamyl transferase appeared and disappeared within the first 4 to 6 weeks of treatment. Objective remissions of at least 3 months duration from initiation of therapy were seen in 21 of 128 patients (21.9%) (3.9% complete remission [CR], 18% partial remission [PR]). A no change (NC) status occurred in an additional 25.8%. The remission duration (mean and range) was 19 (10.5–54) for CR, 16.5 (4.5–52+) for PR and 6 (3–27) months for NC patients. The highest response rate was registered for patients with only bone involvement (PR, 11; and NC, 11 of 26 patients). There was a distinct correlation of response to prior systemic treatment, receptor status of the primary tumor, disease-free interval, menopausal status, age and condition of the patient. PR was obtained in 4 of 20 patients with receptor-negative primary tumors. These results justify a prospective trial comparing AG/MPA with other forms of endocrine therapy in selected patient subgroups.

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AMINOGLUTETHIMIDE (AG) is as equally effective as other hormonal therapies in the treatment of postmenopausal patients with advanced breast cancer.[1–3] AG inhibits the synthesis of adrenal steroids as exemplified by cortisone depletion as well as by the aromatization of androgens to estrogens in peripheral tissues.[4,5] Glucocorticoids are administered together with AG in the treatment of breast cancer to compensate for the impaired cortisol synthesis and to prevent the reflex adrenocorticotropic hormone (ACTH) increments observed, when AG is given without the addition of cortisone.[6]

Reported response rates of metastatic breast cancer to medroxyprogesterone acetate (MPA) treatment are between 21% and 70%.[7,8] There is evidence that high-dose MPA (>1000 mg orally, daily) is superior to low-dose MPA (*i.e.*, <500 mg orally daily),[9] which is explained by different pharmacokinetics of the drug at various dose levels.[10] Investigations on the pharmacodynamics of MPA revealed a dose-dependent mechanism of action with a suppression of the pituitary adrenal axis, which is only observed in dosages of over 500 to 1000 mg orally, daily.[11]

In this phase II trial for the therapy of patients with advanced breast cancer, we combined AG with MPA, omitting cortisone, after it had been demonstrated that MPA, with its intrinsic glucocorticoid activity, is a safe cortisone substitute in combination with AG.[12] The aims of the study were to gain information on a possible syn-

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TABLE 1. Treatment Results of 128 Patients With Advanced Breast Cancer

Patient characteristics	CR/PR	NC/PD	Only patients who died within 3 mo
No.	28	100	32
Age	61 (34–75)	52 (32–78)	54 (36–74)
Menopausal status			
Premenopausal	2	13	10
Postmenopausal (<5 yr)	7	32	7
Postmenopausal (>5 yr)	19	54	14
Unknown	—	1	1
Free interval			
<2 yr	17	50	25
>2 yr	11	50	7
Karnofsky status			
<40	1	1	1
40–70	6	35	13
70–100	21	64	18
Receptor status			
R+	9	15	3
R−	4	25	12
R?	15	60	17
Metastatic type			
Bone	11	15	3
Skin	1	1	0
Lung	0	9	2
Peritoneal	0	1	1
2 organs involved	6	34	8
3 organs involved	6	18	6
4 organs involved	2	13	7
≥5 organs involved	2	9	5
Previous systemic therapy			
None	1	2	0
Hormonotherapy	11	12	3
Chemotherapy	5	18	5
Hormono-chemotherapy	11	68	24

CR: complete remission; PR: partial remission; NC: no change; PD: progressive disease.

ergistic effect and to evaluate the toxicity and pharmacodynamics of this particular drug combination. Once the preliminary data of this trial[13] suggested a considerable antitumor activity, the study population was enlarged to possibly identify patient subgroups suitable for further prospective hormonal therapy trials, including AG/MPA. The pharmacodynamic data of this trial will be reported on in a subsequent communication.

Patients and Methods

From October 1980 to August 1982, 128 patients with advanced breast cancer were recruited for the trial. Inclusion criteria were measurable and progressive metastatic disease, life expectancy of more than 6 weeks, no chemotherapy or hormonal treatment over the past 4 weeks, absence of dosage-limiting side effects of previous treatments, and the patient's consent. Patients with clinical evidence of brain metastases were excluded. Further details of the patient population are shown in Table 1. Prior to entry and in addition to history and physical examination, the following basic laboratory and staging examinations were carried out to document the extent of the metastatic disease and baseline parameters for follow-up: complete blood count; platelet count; sequential multichannel auto-analyzer 24; carcinoembryonic antigen levels (CEA); ultrasound and/or computed tomogram of the liver; x-rays of the chest, entire spine, pelvis, and of other bones expected to harbor metastatic disease after bone scanning. Blood samples for aldosterone, prolactin, luteinizing hormone, follicle-stimulating hormone, triiodothyronine, thyroxine, thyroid-stimulating hormone, and MPA determinations were taken at repeated intervals for pharmacodynamic studies. Results of the hormone investigations will be reported in a subsequent paper. Estrogen and progesterone receptor determinations were carried out in primary tumors with a dextrane-coated charcoal method. Quality control of the method was done within the national steroid receptor assay control program. Tumors were classified as receptor-positive with an estrogen receptor content of at least 10 fmol/mg protein and/or progesterone receptor content of at least 20 fmol/mg protein.

A daily dose of 1000 mg AG was given, starting with 125 mg twice daily for 3 days and escalating the dose to 1000 mg within 12 days (250 mg aminoglutethimide (Orimeten) tablets were provided by CIBA-Geigy, Wehr, West Germany). In case of severe side effects, the AG dose was temporarily reduced to 750 or 500 mg in a few patients, but increased to full dose after recovery. The MPA (250 mg medroxyprogesterone acetate (Farlutal) tablets were provided by Farmitalia Carlo Erba, Freiburg, West Germany) dose was 500 mg orally, three times a day for the initial 6 weeks of treatment and 250 mg three times a day thereafter.

Basic laboratory investigations and physical findings were documented weekly. The first treatment response evaluation was made after 3 months, followed by monthly clinical assessments and detailed lesion measurements at 3-monthly intervals or earlier, if there was clinical or laboratory evidence of a change in the status of the disease. The criteria used for response evaluation are those described by Hayward *et al.*,[14] but with the following modifications for bone metastases: complete remission (CR), disappearance of bone lesions on x-ray or bone scan; partial remission (PR), any partial recalcification of lytic lesions and decreased density of blastic lesions; no change (NC), no increase in size of existing lesions or appearance of new lesions within at least 3 months. Patients with mixed metastatic type or complete or partial remission of visceral lesions were classified as no change if bone metastases did not show recalcifications. Remission duration was calculated in weeks from onset of therapy. Pa-

TABLE 2. Side Effects of AG/MPA of 128 Patients

Side effects	Percentage of patients
Transient rise of gamma-GT	53
Adynamia	50
Weight loss 3.9 kg (1–12.5)	41
Weight increase 3.8 kg (1–7)	18
Constipation	34
Ataxia	22
Nausea/vomiting	15
Dyspnoea	12.5
Restlessness	9
Cushingoid appearance	8
Vaginal bleeding	8
Tremor	8
Mental depression	7
Erythrodermia 6–7 wk	1.5
Irritation of taste, hirsutism, mild hair loss, edema, and skin rash within first 2 wk of treatment each in 2 patients	

AG/MPA: aminoglutethimide/medroxyprogesterone acetate.

tients, whose objective response to therapy lasted less than 3 months, were classified as nonresponders.

Survival data of patients responding to therapy were compared to nonresponders by variance analysis, using the Biomedical Data Programs 2D, 2V and 6R (University of California, Los Angeles: University of California Press 1983) whereby the 33 patients taken from the protocol before the first response assessment were excluded. Treatment-unrelated prognostic factors were determined by regression analysis.

After 128 patients had been recruited, it became evident that the overall response rates were lower than anticipated from the preliminary trial and that the aim to identify subpopulations particularly sensitive to the AG/MPA combination could not be achieved. The study was therefore terminated.

Results

All 128 patients who entered the study were considered for evaluation of treatment response and side effects. The latter are listed in Table 2. Most side effects, including those affecting mental functions, personality changes, general malaise, fatigue and weakness, as well as skin rashes were seen predominantly in the first few weeks of treatment, and tended to diminish thereafter and disappeared in the majority of cases after 3 to 6 weeks of treatment. In patients presenting bedridden with a low Karnofsky status, weight loss and neuropsychiatric symptoms (mainly depressive syndromes) before the initiation of AG/MPA treatment and in old patients, the side effects were more pronounced than in ambulatory and younger women with a better performance status. Combined AG/MPA did not lead to side effects other than those described under AG or MPA monotherapy. Mental and personality changes, however, appeared to be more severe and frequent under combined therapy than under monotherapy. Contrary to the wellknown transient skin rash appearing in some patients after about 2 weeks of AG treatment, a late skin toxicity occurred in 2 patients between the sixth and eighth week of drug intake. A severe exfoliative dermatitis covering the whole body demanded withdrawal of the drug. The histologic aspect of the skin lesions was that of a severe vasculitis.

TABLE 3. Reasons to Discontinue Therapy Within the First Weeks of Treatment*

Reasons for discontinuation	No. of patients
Early death	14
Manifestation of CNS metastases	6
Insufficient patient compliance	3
Hypercalcaemia	3
Severe skin rash	3
Lost to follow-up	3
Venous thrombosis	1
Total	33

* Without progressive disease.
CNS: central nervous system.

Within the first 12 weeks of treatment, *i.e.*, until first assessment of treatment response, 33 patients were taken off the study; the reasons are listed in Table 3. As mentioned earlier, these patients were classified as nonresponders. There was no evidence that the AG/MPA treatment enhanced the tumor growth.

The overall treatment results of 128 patients are summarized in Table 4, with numbers broken down according to type of remission and hormone-receptor status. The objective response rate is 21.9% (CR, 3.9%; PR, 18.0%). One patient in PR is still under therapy.

It appears from Table 4 that there is a higher remission rate in patients with receptor-positive tumors compared

TABLE 4. Results of AG/MPA Treatment of 128 Patients According to Receptor Status

Treatment results	No. of patients			Total (no./percent)	Duration of remission in months (Mean range of remission)
	R+	R−	R?		
CR	1	2	2	5/3.9	19 (10.5–54)
PR	8	2	13	23/18.0	16.5 (4.5–52+)
NC	10	7	16	33/25.8	6 (3–27)
PD	5	18	44	67/52.3	—
Total	24	29	75	128	

AG/MPA: aminoglutethimide/medroxyprogesterone acetate; CR: complete remission; PR: partial remission; NC: no change; PD: progressive disease; R+: receptor-positive tumors; R−: receptor-negative tumors; R?: receptor status unknown.

TABLE 5. AG/MPA Treatment Results in Patients With Only One Metastatic Site

Treatment results	Bone	Lung	Skin	Peritoneal	Total
CR	—	—	1	—	1
PR	11	—	—	—	11
NC	11	3	1	—	15
PD	4	6	—	1	11
Total	26	9	2	1	38

AG/MPA: aminoglutethimide/medroxyprogesterone acetate; CR: complete remission; PR: partial remission; NC: no change; PD: progressive disease.

with those with tumors of negative or unknown receptor content. There is no correlation between the remission duration and estrogen or progesterone receptor status. Two patients had both estrogen and progesterone-positive tumors, and only one of these presented a NC status of over 12 months.

One aim of the study was the attempt to identify patient subgroups with a particularly high response rate. The only identifiable category included patients with only one organ involved with metastatic tumor. A synopsis of the treatment results of these patients is presented in Table 5. The overall response rate in patients with osseous metastases was 42.3%, with a mean response duration of 19.8 (7–51) months and 6.5 (3–15) months for patients with a NC status. This particular patient group did not differ from the rest of the patient population with regard to favorable prognostic factors, *e.g.*, disease-free interval, Karnofsky status, receptor status, and previous systemic therapy. All patients with pains secondary to bone metastases experienced partial or complete pain relief after 2 to 3 weeks of treatment, regardless of the fact whether there was a tumor response or not. In nine patients with lung metastases there was no CR or PR.

To test whether the AG/MPA treatment results showed further correlations to treatment-independent variables and/or survival prolongation, a prognostic factor subgroup analysis was carried out, based on the prognostic criteria shown in Table 1. On an average, the responders were in better condition, distinctly older and more in the postmenopausal status (>5 years). Additionally, the disease-free interval was longer and the receptor status was positive more frequently. Eleven of 28 patients with CR/PR showed bone involvement, compared to 4 of 67 with progressive disease. Contrarily, the nonresponders had experienced more intensive pretreatment and showed several specific features (more frequent familiar cancer, brain metastases *etc.*), which might indicate a poor prognosis. Using a variance analytic design it was possible to demonstrate a significant effect of the AG/MPA combination on survival prolongation of responders compared to nonresponding patients (degrees of freedom, 72; F = 20.81; $P = 0.000$).

Discussion

This and other studies confirm the previously suggested drug sensitivity of metastatic breast cancer to AG/MPA.[12,15,16] The objective response rate of 21.9% falls within the ranges reported for other forms of endocrine therapy in patients with metastatic breast cancer with comparable prognostic factors.[17,18]

It appears unlikely, from the clinical point of view of this study, that there is a synergistic effect of AG/MPA combined hormonal therapy. On the contrary, as noted elsewhere[13] (and to be reported in detail in a subsequent paper) AG and MPA appear to have an antagonistic effect on the pituitary gland.

Patients with bone metastases appeared to be particularly sensitive to AG/MPA treatment, but this observation has also been reported for either drug alone.[18–21] By comparing AG/MPA to other forms of endocrine therapy in patients with bone metastases, the data of this study suggest the following variables to be important stratification criteria: pretreatment, metastatic type, hormone receptor status, menopausal status, disease-free interval, age, and Karnofsky index.

As discussed elsewhere,[11] a particularly favorable effect of the AG/MPA in patients with both estrogen and progesterone-positive tumors (*i.e.*, estrogen-dependent and progesterone-sensitive) is to be expected. The two patients in our study with this receptor constellation, however, do not allow meaningful conclusions. In their study on the influence of the estrogen receptor status and response of metastatic breast cancer to AG therapy, Lawrence *et al.*[22] found a direct relationship between the estrogen receptor concentration and response rate, a significant response in patients with borderline receptor-positive and a 14% response rate in estrogen receptor-negative tumors. These authors performed estrogen receptor measurements on metastases prior to initiation of AG treatment in patients, who had not been heavily pretreated with chemotherapy and/or hormonotherapy. The receptor status mentioned in our study is that of the primary tumor. As no receptor determinations were carried out on metastases preceeding the AG/MPA treatment, it cannot be ruled out that the receptor status differed in metastases from the primary tumor. A difference and change in receptor status between primary tumor and metastases has been reported.[23] The clinical usefulness of receptor determinations in primary tumors to predict the treatment response to hormones in patients with advanced disease has been questioned.[24]

Combined AG/MPA did not lead to side effects other than those described under AG or MPA monotherapy. Mental and personality changes, however, seem to be more severe and frequent under combined therapy than

under monotherapy. Pretreatment impairments of the mental and psychological condition may be seriously accentuated by AG/MPA, particularly in elderly patients, and may be considered to be a contraindication of AG/MPA treatment. In these cases, a temporary dose reduction of AG by 250 to 500 mg, maintaining the full dose MPA, will help to control symptoms within days.

The increased frequency of depressive syndromes under combined AG/MPA therapy could not be attributed to the physical side effects of this combination, particularly not to the weight gain, because these mental disorders only appeared during the first weeks of treatment and the cushingoid features did not become apparent until about 6 to 8 weeks of treatment. As most side effects of the AG/MPA combination appear and disappear within the first 4 to 6 weeks of treatment, it is compulsory to closely monitor the patients during this initial phase of treatment.

In the literature, there is no report of AG toxicity being related to the chronic use of the drug. In this trial, 14 patients took AG over a period of 12 months (13 to 54 months), equivalent to a mean AG intake of 790 g (390 to 1620 g AG), without any evidence of late side effects. Only a late type skin toxicity was seen in two patients.

The therapeutic activity of AG/MPA in patients with bone metastases and the improvement of bone pain, experienced even by patients lacking objective signs of tumor regression, justify a prospective randomized trial to compare AG/cortisone *versus* AG/MPA in this particular subgroup.

REFERENCES

1. Santen RJ, Worgul TJ, Samojlik E *et al.* A randomised trial comparing surgical andrenalectomy with aminoglutethimide plus hydrocortisone in women with advanced breast cancer. *N Engl J Med* 1981; 305: 545–551.
2. Lipton A, Harvey HA, Santen RJ *et al.* A randomised trial of aminoglutethimide *versus* tamoxifen in metastatic breast cancer. *Cancer Res* 1982; (Suppl) 42:3434–3436.
3. Smith IE, Harris AL, Morgan M *et al.* Tamoxifen *versus* aminoglutethimide in the treatment of advanced breast carcinoma: A controlled randomised cross-over trial. *Br Med J* 1981; 293:1432–1434.
4. Cash R, Brough AJ, Cohen MNP, Satoh PS. Aminoglutethimide (Elipten-CIBA) as an inhibitor of adrenal steroidogenesis: Mechanism of action and therapeutic trial. *J Clin Endocrinol Metab* 1967; 27:1239–1248.
5. Santen RJ, Santner S, Davis B, Veldhuis J, Samojlik E, Ruby E. Aminoglutethimide inhibits extraglandular oestrogen production in postmenopausal women with breast carcinoma. *J Clin Endocrinol Metab* 1978; 47:1257–1265.
6. Santen RJ, Henderson IC, eds. Pharmanual: A Comprehensive Guide to the Therapeutic Use of Aminoglutethimide. Basel: S Karger, 1981; 101–125.
7. Pannuti F, DiMarco AR, Martoni A *et al.* Medroxyprogesterone acetate in treatment of metastatic breast cancer: Seven years of experience. In: Iacobelli S, DiMarco AR, eds. Role of Medroxyprogesterone in Endocrine-Related Tumors, vol. 1. New York: Raven Press, 1980; 73–92.
8. Campio L, Robustelli Della Cuna G, Taylor RW, eds. Role of Medroxyprogesterone in Endocrine-Related Tumors, vol. 2. New York: Raven Press, 1983; 69–104.
9. Robustelli Della Cuna G, Preti P, Pavesi L. Overview of clinical results with high dose medroxyprogesterone acetate (HD-MPA) in advanced breast cancer. In: Robustelli Della Cuna G, Nagel GA, eds. High Dose Medroxyprogesterone Acetate (MPA) in Advanced Breast Cancer, Aktuelle Onkologie 14. Munich: Zuckschwerdt Verlag, 1984; 27–36.
10. Tamassia V, Battaglia A, Ganzina F *et al.* Pharmacokinetic approach to selection of dose schedules for medroxyprogesterone acetate in clinical oncology. *Cancer Chemother Pharmacol* 1982; 8:151–156.
11. Blossey CH, Nagel GA, Wander HE, Köbberling J. Pharmacokinetic and pharmacodynamic basis for high-dose medroxyprogesterone acetate in metastatic breast cancer. *Cancer* 1984; (Suppl) 54:1208–1215.
12. Nagel GA, Wander HE, Blossey HC. Phase II study of aminoglutethimide and medroxyprogesterone acetate in the treatment of patients with advanced breast cancer. *Cancer Res* 1982; (Suppl) 42:3442–3444.
13. Nagel GA, Wander HE, Blossey HC, Kleeberg UR. Aminoglutethimide and medroxyprogesterone acetate in advanced breast cancer: A phase II trial of the Association of Medical Oncology of the German Cancer Society. In: Nagel GA, Santen RJ, eds. Aminoglutethimide as an Aromatase Inhibitor in the Treatment of Cancer. Bérn: Hans Huber Publishers, 1984; 95–100.
14. Hayward JC, Carbone PP, Heuson JC, Kumaoka S, Segaloff A, Reubens RD. Assessment of response to therapy in advanced breast cancer. *Cancer* 1977; 39:1289–1294.
15. Van Deijk WA, Blijham GH, Mellink WAM. Phase I–II study of aminogluethimide (AG) plus medroxyprogesterone acetate (MPA) in metastatic breast cancer (Abstr). *Proc Am Soc Clin Oncol* 1984; 3:130.
16. Samonis G, Bafaloukos D, Pektasides D, Tsatsaronis A, Lissaios B, Razis DV. A prospective randomized trial of aminogluethimide (AG) *versus* medroxyprogesterone acetate (MAP) *versus* AG + MAP in cancer of the breast (Abstr). *Proc Am Soc Clin Oncol* 1985; 4:75.
17. Ingle JN, Ahmann DL, Green SJ, Edmonson JH, Creagan ET, Hahn RG, Rubin J. Randomized clinical trial of megestrol acetate *versus* tamoxifen in paramenopausal or castrated women with advanced breast cancer. *Am J Clin Oncol* 1982; 5:155–160.
18. Legha SS, Blumenschein H. Systemic therapy of metastatic breast cancer: A review of the current trends. *Oncology* 1982; 39:140–145.
19. Henderson C, Canellos GP. Cancer of the breast. *New Engl J Med* 1980; 302:(two parts)17–30, 78–90.
20. Harris AL, Powles TJ, Smith IE. Aminoglutethimide in the treatment of advanced postmenopausal breast cancer. *Cancer Res* 1982; (Suppl) 42:3405–3408.
21. Rossof AH, Gelman R, Creech RH. Randomized evaluation of combination chemotherapy *vs.* observation alone following response or stabilization after oophorectomy for metastatic breast cancer in premenopausal women. *Am J Clin Oncol* 1982; 5:253–259.
22. Lawrence BV, Lipton A, Harvey HA *et al.* Influence of estrogen receptor status on response of metastatic breast cancer to aminoglutethimide therapy. *Cancer* 1980; 45:786–791.
23. Taylor RE, Powles TJ, Humphreys J *et al.* Effects of endocrine therapy on steroid-receptor content of breast cancer. *Br J Cancer* 1982; 45:80–85.
24. Schuchter L, Bitran J, Rochman H, Desser RK, Michel A, Recant W. Progesterone receptor (PR) status does prognosticate for relapse free survival (RFS) in patients (PTS) with Stage II, adenocarcinoma of breast (B-CA) (Abstr). *Proc Am Soc Clin Oncol* 1984; 3:111.