[CANCER RESEARCH (SUPPL.) 42, 3442s–3444s, August 1982]
0008-5472/82/0042-0000$02.00

Phase II Study of Aminoglutethimide and Medroxyprogesterone Acetate in the Treatment of Patients with Advanced Breast Cancer[1]

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Abstract

Forty-five women with far-advanced metastatic breast cancer were treated with a combination of aminoglutethimide (AG), 1000 mg p.o. daily, and medroxyprogesterone acetate (MPA), 1500 mg p.o. daily. Of 41 patients evaluable for treatment response, there were two complete responses, five partial remissions, 26 patients with minor tumor responses or no change, and eight nonresponders. Major side effects included those known for AG and MPA, *i.e.*, impairment of mental functions, depressive syndromes, fatigue, ataxia, skin rash, changes in body weight, and transient increase of γ-glutamyltransferase. Most side effects disappeared spontaneously after 4 to 6 weeks of treatment. Plasma hormone measurements in 28 patients revealed no impairment of adrenocorticotropic hormone and cortisol levels. In conclusion, in the AG combination, it is feasible and safe to replace cortisol by MPA. Treatment results warrant further investigation of AG-MPA in patients with breast cancer of a more favorable prognosis.

Introduction

AG[3] has been shown to cause regression of disease in patients with metastatic breast cancer. Overall objective response rates are 32% for all patients and 52% for patients with estrogen receptor-positive tumors (5).

In the regimen used for the treatment of metastatic breast cancer, cortisone is given together with AG in order to compensate for the impaired cortisol synthesis and to prevent the reflex ACTH increments observed when AG is given without cortisone substitution (5).

MPA at a dosage of over 1000 mg daily has been reported to induce remissions in over 40% of patients with metastatic breast cancer and to suppress ACTH secretion (3).

We report preliminary data of a Phase II trial in women with metastatic breast cancer treated with a combination of AG and MPA without the addition of hydrocortisone. Goals of the study were to gain information on the efficacy and toxicity of AG-MPA and to evaluate whether MPA could be used as hydrocortisone substitute when combined with AG.

Patients and Methods

Forty-five patients with advanced metastatic breast cancer were studied and evaluated for drug side effects. Forty-one patients were evaluable for response after a minimum of 6 weeks of treatment. Two patients were inevaluable because hypercalcemia and skin rash required cessation of therapy after 2 weeks. Early death occurred in 2 additional patients.

Patient characteristics are given in Table 1. Most of the patients were heavily pretreated, having end-stage disease. All of them had progessive and measurable tumor lesions at the start of AG-MPA. The protocol called for a first treatment response evaluation after 6 weeks followed by monthly clinical assessments. Lesion measurements were done at 3-month intervals or earlier if there was clinical or laboratory evidence of relapse. Toxicity evaluation was done weekly.

Therapy consisted of AG, 1000 mg/day p.o., with a starting dose of 125 mg twice a day for 3 days and continuous dose escalation up to 1000 mg within 12 days. MPA was given at a dose of 500 mg 3 times daily (total, 1500 mg daily) p.o. from Days 1 to 42, when the MPA dose was reduced to a single dose of 500 mg/day p.o. Criteria used for response evaluation were those described by Hayward *et al.* (2).

Plasma ACTH and cortisol were measured in 28 patients before treatment and/or on Days 14 and 42 of the treatment. ACTH was measured by radioimmunoassay using ^{125}I-ACTH (Isotopendienst, West Germany). Plasma cortisol was determined with a protein-binding method (4). Variation coefficients were about 5% intraassay and 10% interassay. A control group of 11 patients received MPA, 1500 mg/day p.o., in order to evaluate hormone levels without the addition of AG. Blood samples for aldosterone, prolactin, luteinizing hormone, follicle-stimulating hormone, triiodothyronine, thyroxine, thyroid-stimulating hormone, and MPA determinations are stored and will be evaluated altogether at the end of the trial.

Results

A synopsis of the treatment results with numbers broken down according to pretreatments is presented in Table 2. Complete and partial remissions were achieved in 7 of 41 patients. The overall response rate including patients with no change status is 80%. Three of 24 patients with extensive prior hormone and chemotherapy treatments (average, 4 treatments/patient), *i.e.*, after the exhaustion of every conventional regimen, experienced a measurable tumor reduction. In contrast to the rather low number of patients with objective tumor regressions, there was a high percentage showing minor responses or disease stabilization, indicating a considerable activity of AG-MPA. As remembered from Table 1, a large proportion of the patients presented with bone metastases as either single organ involvement or in combination with other sites. Even if there was objective tumor regression of visceral lesions in the presence of bone involvement, patients were classified as no change due to the known difficulty of objectively assessing regression of bone metastases. Virtually all patients with bone pain secondary to bone metastases after 2 to 3 weeks of treatment experienced partial or complete pain relief regardless of whether there was tumor stabilization.

Side effects of the treatment are shown in Table 3 and

[1] Presented at the Conference "Aromatase: New Perspectives for Breast Cancer," December 6 to 9, 1981, Key Biscayne, Fla.

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[3] The abbreviations used are: AG, aminoglutethimide; MPA, medroxyprogesterone acetate; ACTH, adrenocorticotropic hormone.

appear extraordinarily frequent. It must be stated, however, that most side effects including those affecting mental functions, personality changes, general malaise, fatigue, and weakness as well as skin rashes are seen predominantly in the first few weeks of the treatment, tend to diminish thereafter, and disappear in the majority of cases after 6 weeks of treatment. In patients presenting bedridden with low Karnofsky index, weight loss, and neuropsychiatric symptoms, mainly depressive syndromes, before the initiation of AG-MPA treatment, side effects were much more pronounced than in ambulatory women with a better performance status. The AG-MPA combination did not lead to side effects other than those described for AG or MPA monotherapy. Mental and personality changes, however, appeared to be more severe and frequent for the combination than for either drug alone. There was no change in routine laboratory determinations, *i.e.*, Sequential Multichannel Autoanalyzer 24 and complete blood count, other than a frequently observed γ-glutamyltransferase elevation. Side effects were the reason to discontinue AG-MPA after two weeks to months of treatment in 7 cases. Reasons were general deterioration in 3 patients, psychotic episodes after 12 treatment months in one patient, hypercalcemia in one patient, and skin rash after Days 14 or 42 in 2 patients. There was no toxic death.

Data of ACTH and cortisol measurements are presented in Chart 1 for the patients and the MPA monotherapy control group. Whereas MPA in every single case suppresses ACTH and, in consequence, cortisol to subnormal levels, these hormones remain fairly within the normal range when the AG-MPA combination is given.

Table 1

AG-MPA Phase II trial: patient characteristics

	No. of patients
Menopausal status	
Premenopausal	9
Postmenopausal <5 yr	15
Postmenopausal >5 yr	21
Disease-free interval (yr)	
0	3
<2	21
>2	21
Karnofsky index	
<40	0
40–70	18
>70	27
Metastatic type	
Skin	1
Bone	13
Lung	1
Mixed type, 2 organs	16
Mixed type, >2 organs	14
Previous systemic therapy	
None	3
Hormones	6
Chemotherapy	9
Hormone + chemotherapy	27

Table 2

AG-MPA Phase II trial: treatment results

Previous treatment	No. of patients	Complete remission	Partial remission	No change	Progression
None	3	1		1	1
Hormones	5		2	3	
Chemotherapy	9		1	6	2
Hormone + chemotherapy	24	1	2	16	5
Total	41	2	5	26	8
Median remission duration (wk)		30.5	39	21	

Table 3

AG-MPA Phase II trial: side effects of treatment

	No. of patients
γ-Glutamyltransferase elevation (maximum 5-fold normal value)	26
Sleepiness, fatigue, restlessness	22
Wt loss	22
Wt increase	11
Ataxia	15
Constipation	11
Deterioration of general condition	8
Vaginal bleeding	6
Cushingoid	6
Tremor	4
Hypercalcemia	3
Skin rash	
Days 10 to 14	7
Day 42	1

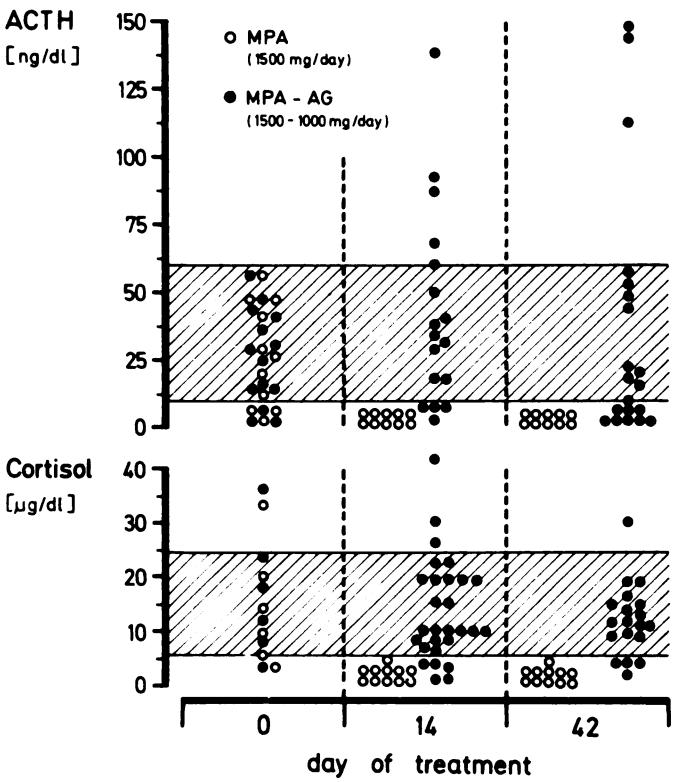

Chart 1. AG-MPA Phase II trial. ACTH and cortisol plasma levels for patients treated with either AG-MPA or with MPA alone.

Discussion

In 41 patients with metastatic breast cancer of distinctly unfavorable prognosis, the combination of AG-MPA was able to reach an overall tumor remission rate, including patients with no change status, of 80%. Clear-cut progressive disease was registered in 8 of 41 patients only. Improvement of symptoms and well-being was seen in the majority of patients once subjective side effects, rendering the treatment difficult for the first 2 to 3 weeks, subsided. The obvious therapeutic activity

of the combination and excellent improvement of symptoms experienced even by patients lacking objective signs of tumor regression make the AG-MPA combination an attractive new hormonal combination therapy for patients with metastatic breast cancer. The combination is recommended to be tested in patient subsets of a more favorable prognosis. Whether treatment results with AG-MPA will differ from those of the conventional combination with AG-cortisol awaits further investigation.

A disadvantage of the AG-MPA combination is that it causes a variety of neuropsychiatric side effects within the first weeks of treatment, predominantly so in patients with pretreatment impairment of mental, psychological, and physical condition. In such patients, the AG-MPA side effects might accentuate symptoms to intolerable proportions. In this situation, it is well possible that some patients of low compliance would spontaneously reduce drug intake. This could lead to insufficient compensation by either cortisol or MPA of the AG-induced cortisol deficiency. Consequently, it is mandatory to monitor the patients closely within the first six weeks of treatment and take appropriate steps once side effects tend to compromise an effective treatment. Such a step is the temporary dose reduction of AG down to 500 or 750 mg every day, maintaining the full dose of MPA. In the majority of cases, this procedure will help to control symptoms within days.

From the ACTH and cortisol measurements, it is evident that MPA is an effective hormonal substitute for cortisone in the AG combination. It is currently being investigated whether some high ACTH blood levels are correlated to low MPA blood levels and whether there is a means to monitor drug intake and/or resorption of both AG and MPA. After abrupt discontinuation of the treatment, there is no evidence of impaired adrenal function. No case of adrenal insufficiency is registered in an ongoing study of the German Association of Interdisciplinary Oncology in which 112 breast cancer patients are currently treated with AG-MPA. Thus, the AG-MPA combination appears to be not only a useful but also a safe drug combination. Finally, it must be stressed that in the study MPA was given p.o. There is no experience with AG plus i.m. MPA application. It is known that MPA blood levels after i.m. application build up much more slowly than when MPA is given p.o. (1). It is well possible that i.m. MPA might not suffice initially to compensate for the AG-induced adrenal insufficiency.

Acknowledgments

AG, Elipten tablets of 250 mg, was kindly provided by CIBA-GEIGY, Basel, Switzerland. MPA, Farlutal, tablets of 200 mg, was kindly provided by Farmitalia Carlo Erba, Freiburg, Federal Republic of Germany.

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Discussion

Dr. Santen: I believe we are the only individuals who have studied the effect on AG[1] on MPA metabolism. Since your data would be best interpreted by an acceleration of MPA metabolism by AG, it raises the question of how we did our metabolic clearance rate studies and perhaps whether the clearance studies should be repeated. We had patients on 40 mg of MPA p.o. per day for over a month and then studied their MPA metabolic clearance rate by the single-injection technique. The doses of MPA that you are using are much higher than the doses we used. I think it would be worthwhile to go back and study the metabolic clearance rate of MPA under these particular experimental conditions.

Dr. Nagel: The only thing I can say to this point is that we have measured MPA blood levels in these patients. With the continuing 1500 mg and 500 mg/day, there is no sign that blood levels drop after awhile.

Dr. Siiteri: There is an alternate explanation for this MPA phenomenon. In studies which Dr. Fukishima and Dr. Zumoff carried out, there seemed to be good evidence that the actual product lowering the ACTH was not MPA itself but a metabolite of it, and AG may well be inhibiting the further metabolism of MPA to the specific compound affecting the ACTH. That may be why you see the difference between MPA alone and the combined treatment. You could still have the same clearance rate, just going to different products.

[1] The abbreviations used are: AG, aminoglutethimide; MPA, medroxyprogesterone acetate; ACTH, adrenocorticotropic hormone.

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Cancer Res 1982;42:3442s-3444s.