Effect of combination therapy with aminoglutethimide and hydrocortisone on prostate-specific antigen response in metastatic prostate cancer refractory to standard endocrine therapy

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A prospective study was performed to investigate the combination of the aromatase inhibitor aminoglutethimide and hydrocortisone in androgen-independent prostate cancer with changes in prostate-specific antigen (PSA) level as main determinant for response. Thirty-five patients were treated with aminoglutethimide 1000 mg daily and hydrocortisone acetate 40 mg daily. PSA measurements were performed every month. If evaluable lesions were present, objective tumor assessment was done by computed tomography scan and X-ray investigations. In 12 patients (37%) the PSA value showed a confirmed response with a decline in serum level of at least 50%. Median time to progression in responding and all patients was 10.5 and 4.5 months, respectively. Median duration of response in responding patients was 9 months. Median survival for these two groups was 23 and 14.5 months, respectively. Of seven patients with measurable disease, two showed a partial response and five a stable disease. Improvement in general condition, pain and feeling of well-being was noted in two-thirds of patients. Therapy was well tolerated with mainly grade I and II adverse events in 20% of patients. We conclude that aminoglutethimide is a valuable second-line therapy for patients with androgen-independent prostate cancer. *Anti-Cancer Drugs* 15:843–847 © 2004 Lippincott Williams & Wilkins.

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Introduction

Standard first-line therapy of proven efficacy for metastatic prostate carcinoma consists of hormonal manipulation by androgen ablation, achieved either by surgical castration or by the use of a luteinizing hormone-releasing hormone agonist (LHRH) in combination with antiandrogen therapy [1]. However, all patients will eventually relapse and once the disease becomes progressive after complete androgen blockade, further therapeutic options are limited [2]. As second-line therapy, various modalities have been explored such as other hormonal manipulations, cytotoxic chemotherapy and also the naphthylurea derivative suramin, but none of these treatments has demonstrated substantial efficacy, while they are accompanied by sometimes significant side-effects [2]. Only recently, a new class of cytostatics, the taxanes, has shown notable antitumor activity in hormone-refractory prostate carcinoma. However, the final significance of taxanes has to be demonstrated in phase III trials [3].

A major problem in determining the exact antitumor activity of agents in metastatic prostate cancer is the objectivity of response assessment. In most patients disease is restricted to bone localizations which are notoriously difficult to evaluate. Prostate-specific antigen (PSA) is a glycoprotein almost exclusively present in normal and malignant prostate cells. Approximately 10 years ago a correlation was demonstrated between changes in PSA levels and tumor response [4]. Since then, PSA measurements have become an early indicator of progression and response [5–8]. After a consensus conference held in the USA, PSA had been accepted as a surrogate parameter for response evaluation in prostate cancer [9–11]. Standards were defined and guidelines were formulated.

In patients with progressive disease after first-line endocrine therapy, a small proportion can respond to a secondary hormonal manipulation, suggesting that the prostate cancer cells have retained a certain degree of hormone sensitivity. After surgical or medical castration the adrenal gland is the main extratesticular source of androgens and can produce sufficient testosterone to maintain a continued stimulation of tumor cells. Initially, adrenal ablation was achieved by major surgical procedures such as adrenalectomy and hypophysectomy, which yielded some antitumor activity [12–15]. Later on, surgical adrenalectomy was replaced by medical

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adrenalectomy with adrenal-suppressive agents. Aminoglutethimide is a potent inhibitor of adrenal steroid biosynthesis by blocking the enzyme aromatase. The effectivity of aminoglutethimide as second-line therapy in patients with metastatic prostate carcinoma was suggested in a number of studies [16–27]. However, most of these reports were published in the 1980s. At that time, PSA determinations were not yet available and response evaluation was mainly done by difficult to interpret X-rays and bone scintigraphy. We have carried out a prospective phase II study with aminoglutethimide and hydrocortisone in patients with prostate cancer refractory to standard hormone therapy with the predominant use of PSA measurements to determine antitumor activity.

Patients and methods

Patients with biopsy-proven stage D2 prostate carcinoma and disease progression following orchidectomy or refractory to standard endocrine therapy with LHRH agonists with or without the concomitant use of an antiandrogen were prospectively included in the study. Prior treatment with chemotherapy was allowed. A rising PSA level and/or radiological investigations demonstrated progressive disease. Prior to start of treatment an initial evaluation was carried out including medical history, physical examination, hematology, serum biochemistry with PSA measurement, urinalysis, bone scintigraphy, skeletal X-rays and, if indicated, computed tomography (CT) or magnetic resonance imaging. All patients gave their informed consent.

Aminoglutethimide 250 mg 2 times a day was given orally for the first 2 weeks. All patients received hydrocortisone acetate 40 mg daily (20 mg in the morning, 10 mg in the afternoon, 10 mg in the evening) as glucocorticoid replacement. If no side-effects such as skin rash, lethargy, nausea and dizziness occurred, aminoglutethimide administration was further escalated to 500 mg 2 times a day. In case of grade 2 toxicity the hydrocortisone dose was increased to 80 mg/day until the adverse event subsided. In patients who developed grade 3 other than skin toxicity, aminoglutethimide was discontinued permanently. Toxicity was determined according to NCI-CTC criteria. In patients under therapy with a LHRH agonist this medication was continued. Other antitumor medication was not allowed.

Repeat clinical evaluation and measurement of hematology and biochemical indices including PSA were carried out monthly for the first 3 months and at 2-monthly intervals thereafter. At each visit patients were routinely asked to indicate whether there was any improvement in pain or other symptoms during treatment with study medication.

PSA response criteria were those proposed by the National Prostate Cancer Project Group for phase II trials in hormone refractory prostate cancer [9]. A PSA response was defined as a decline in PSA value by at least 50%, which had to be confirmed by a second PSA measurement four or more weeks later. Moreover, no increase in the size of pre-existing metastases, no appearance of new lesions and no clinical signs of tumor progression were allowed. The term 'complete PSA response' was not used. In patients whose PSA had not decreased, progressive disease was a 25% increase over the baseline level and confirmed by a second value. In patients whose PSA had decreased but had not reached response criteria, progressive disease was considered to have occurred when PSA had increased 25% over the nadir and was confirmed by a second measurement. Time to PSA progression was defined from the first treatment day until the date PSA values had increased by 50% from the nadir levels for responders or by 25% for patients not reaching a 50% decline in PSA levels. Duration of PSA response was measured from time at which PSA had declined to 50% or less to the time when PSA had risen by 50% above nadir. If clinical progression occurred before PSA progression, the date of clinical progression was used.

In patients with measurable soft tissue lesions response evaluation by PSA measurements was complemented by repeated radiological examinations. A complete response was defined as the disappearance of any pre-treatment tumor lesions for a duration of at least 4 weeks. Partial response was a 50% or greater reduction in the sum of the products of the largest perpendicular diameters of all measurable lesions for at least 4 weeks. Other criteria for progressive disease were an increase of more than 25% of any of the measurable lesions and/or the appearance of a new lesion, decline in performance status (WHO) or the need for radiation therapy.

The survival and progression-free survival durations were calculated from the on-study date until date of progression, death or last follow-up as appropriate.

Results

Patient characteristics

Thirty-five patients were included in the study. An overview of the demographics is given in Table 1. The median age was 67 years (range 39–92). The median WHO performance status was 1 (range 0–2). Thirty-three patients (94%) had bone, six (17%) lymph node and one (3%) lung metastases. Metastatic disease was confined to one, two or three organ sites in 26 (74%), eight (23%) and one patients (3%), respectively. Fifteen patients (43%) had undergone an orchidectomy with or without the concomitant use of an antiandrogen, and 20 (57%) had received prior treatment with the combination of a

Table 1 Patient characteristics

No. patients	35
Age (median, range)	67 (39–92)
Performance status (WHO)	1 (0–2)
Initial PSA level (ng/ml) (median, range)	216 (15–6719)
Localization of metastases	
bone	33
lymph node	6
lung	1
liver	0
miscellaneous	3
No. metastatic sites	
1	26
2	8
3	1
Prior therapies	
orchidectomy	9
orchidectomy + antiandrogen	6
LHRH agonist + antiandrogen	20
chemotherapy (including estramustine)	12
estrogens	1
radiotherapy (for metastasis)	15
No. prior therapies	
1	12
2	15
3	8

LHRH agonist and an antiandrogen. Twelve patients (37%) were progressive after chemotherapy including estramustine. The patient group was heavily pre-treated with 23 patients (66%), who had received at least two prior treatment regimes.

Treatment results

All 35 patients were evaluable for response. An overview of the treatment results is given in Table 2. According to the defined criteria for PSA response, 13 patients (37%) developed a confirmed response [95% confidence interval (CI) 22–53%]. Furthermore, minor reductions in PSA levels (37, 38, 40 and 43%) were seen in another four patients. Only five patients (14%) demonstrated a straightforward progressive increase in PSA levels within 8 weeks after treatment start. For the total patient cohort the median PSA value fell from 216 ng/ml at baseline to 43 ng/ml, a decrease of at least 80%.

The median time to progression for responding patients was 10.5 months (range 3.5–23.5). The median response duration was 9 months (range 3–21.5). Median survival for responding patients was 23 months (range 7–38). For all patients median time to progressive disease as measured by PSA levels was 4.5 months (range 0.5–23.5). The median survival was 14.5 months (range 0.5–38). The progression-free survival after 1 year with aminoglutethimide based on PSA determinations was 14%.

In seven patients, measurable soft tissue metastases were present at the start of therapy with aminoglutethimide. One patient developed a complete response of retroperitoneal lymph node metastases with a concomitant decline in PSA level of more than 50%. A second patient with lymph node metastases showed a partial response of these tumor localizations accompanied by a PSA response. In the other five patients, tumor evaluation by CT revealed stable disease. In three of them, PSA levels remained unchanged, and in two, PSA increased progressively. All other patients had non-evaluable or non-measurable lesions, mostly bone.

Table 2 Treatment results

PSA response	12 (37%)
Time to progression—responders (median)	10.5 months (3.5–23.5)
Response duration (median)	9 months (3–21.5)
Time to progression—all patients (median)	4.5 months (0.5–23.5)
Survival (median)	14.5 months (0.5–38)
Survival—responders (median)	23 months (7–38)
Survival—non-responders (median)	13 months (0.5–32)
Progression-free survival at 1 year	14%

Although no validated quality of life questionnaire or standardized symptom improvement scoring system was used in this study, therapy with aminoglutethimide showed subjective benefits as improvement of performance status, increase in appetite, weight gain and decrease of pain complains in a considerable number of patients. All responding patients except one showed a clear improvement in their sense of well-being. These positive effects of treatment were not limited to responding patients only, because overall 24 patients (69%) indicated an improved general condition and quality of life while on therapy with aminoglutethimide. In addition, 22 patients (62%) indicated a significant decrease in pain complaints.

Toxicity

The median treatment duration was 4.5 months. In all patients the dose of aminoglutethimide could be escalated to 1000 mg/day. The frequency of adverse events induced by aminoglutethimide in this patient group was low. Only eight episodes of toxicity, mostly grade I and II, were observed in seven patients. Fever (grade II) occurred in two patients. One patient developed grade I anorexia. Increase in liver transaminase levels was observed twice (one grade I, one grade II). There were three episodes of skin toxicity consisting of an erythematous itching skin rash, one grade I and two grade III. In both patients with grade III skin toxicity treatment with aminoglutethimide was interrupted and the hydrocortisone dose doubled. In one patient aminoglutethimide could be resumed without reappearance of any adverse event, in the other patient treatment had to be discontinued permanently. No dose modifications of aminoglutethimide in the other patients turned out to be necessary.

Discussion

In this study of the combination of aminoglutethimide and hydrocortisone in patients with androgen-independent prostate cancer a PSA response rate of 37% was

achieved with a median response duration of 9 months. Overall for the whole group the median survival was 14.5 months and for the responders 23 months. The response analysis was based on PSA measurements, which have been shown to accurately reflect the treatment benefit for the patients, both in terms of palliation and survival [8–10]. In previously published trials using aminoglutethimide, response percentages of 0–50% have been reported (Table 3) [16–28]. However, all these studies were performed more than a decade ago with response evaluation based on non-reproducible imaging with X-rays and bone scans. Of note, in most of these trials patients with clinically stable disease have been considered as responding patients and were included in the response percentage. The observed median survival of more than 14 months is noteworthy in comparison with survival data reported in androgen-independent prostate cancer patients, varying between 6 and 12 months [18,21,23–26]. It is clear that the treatment results of the study presented here, based on the course of PSA values, are at least comparable with those observed in other trials. Additionally, the improvement in subjective feelings of well-being and symptom control in two-thirds of patients is striking.

The assumption that PSA changes could be of value in predicting the outcome of therapy in patients with androgen-independent prostate cancer was first introduced by Ferro *et al.* [4]. Since then several investigators have reported a correlation between a decrease in PSA levels and clinical benefit and survival [5–8]. A decline of at least 50% in PSA during therapy was associated with improved survival. Meanwhile an increasing number of phase II trials has incorporated PSA as a marker. In 1999 the Prostate-Specific Antigen Working Group formulated eligibility criteria and response guidelines for the use of PSA as a parameter for treatment outcome [9]. It was concluded that PSA determinations could be used as an accurate method to evaluate new agents for the treatment of metastatic prostate cancer. The experience in the here presented study is in agreement with this observation. To our knowledge, one other study has been published demonstrating a therapeutic effect of aminoglutethimide on PSA in hormone-refractory prostate cancer [27]. A PSA decrease of at least 80% was observed in 48% of patients with a concomitant improvement in soft tissue lesions, bone scans, anemia and thrombocytopenia if present. The authors reported a median decrease in PSA levels of 73%, remarkably comparable with the nadir of 80% of the baseline value found in our study. In another study the combination of aminoglutethimide and suramin was investigated in patients with androgen-independent prostate cancer. The response rate (greater than 50% decline in PSA) was 23.5%, time to progression 4.4 months and survival time 15.3 months [28].

Treatment with aminoglutethimide resulted in a significant improvement of general condition in more than two-thirds of our patients. This was not only the case in patients with a clear PSA response, but also patients without a decrease in PSA level of 50% or more fared significantly better with regard to subjective parameters such as feeling of well-being, pain, appetite and performance status. Other investigators have also documented these positive effects of aminoglutethimide on

Table 3 Summary of prior performed trials with aminoglutethimide

Author/year/reference	Patient no.	Response objective	Response subjective	Response marker	TTP	Survival
(A) Monotherapy aminoglutethimide						
Robinson 1974 [16]	26	0	70%	31%	NE	NE
Rostom 1982 [18]	15	0	75%	NE	NE	6.5 months
Ponder 1984 [19]	40	15% 1 PR, 5 SD	48%	20% 2 CR, 6 PR	resp: 8 months non-resp: NE	NE
Drago 1984 [20]	43	40% 1 CR, 6 PR, 10 SD	NE	NE	34 weeks	NE
Murray 1985 [21]	58	33% 1 CR, 10 PR, 8 SD	29%	NE	10 months	resp: 12 months non-resp: 5 months
Harnett 1987 [22]	34	21% 1 PR, 6 SD	21%	NE	4–18 months	NE
Elomaa 1988 [23]	20	22% 4 PR	75%	40% 8 PR	4 months (subjective)	8 months
Samojlik 1988 [24]	50	50% 8 PR, 17 SD	NE	NE	NE	resp: 88 weeks stable: 38 weeks non-resp: 18 weeks
Labrie 1989 [25]	119	14% 1 CR, 2 PR, 14 SD	NE	NE	NE	resp: 21 months non-resp: 9 months
Chang 1989 [26]	28	32% 9 SD	32%	11% 1 CR, 2 PR	NE	6 months
Sartor 1994 [27]	29	21% 6 PR	56%	48% 7 CR, 7 PR	16 weeks	NE
(B) Combination therapy/aminoglutethimide and suramin						
Dawson 1998 [28]	81	20%	NE	24% 19 PR	4.5 months	15 months

subjective indicators of therapeutic efficacy [16,18,19, 21–23,26,27]. The precise mechanism of action of aminoglutethimide is unknown. It is unlikely that suppression of estrogen production by aromatase inhibition is responsible for the observed tumor regression or clinical improvement. In several small studies the new selective aromatase inhibitors such as 4-hydroxyandrostenedione and anastrozole have been investigated in androgen-independent prostate carcinoma [29,30]. No objective antitumor activity or PSA response was observed.

In conclusion, combination therapy with aminoglutethimide and hydrocortisone is an effective treatment modality for androgen-independent prostate cancer.

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