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Treatment of Advanced Prostatic Cancer, Resistant to Conventional Therapy, with Aminoglutethimide

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Abstract—*Fifty-eight patients with advanced, progressing prostatic cancer resistant to conventional therapy have been assessed for their response to treatment with aminoglutethimide (A/G). Eleven men (19%) had objective regression of their disease while in a further eight (14%) progression of the disease was arrested. Median survival in the objective remitters (15 months) and in the group in whom stabilization of disease occurred (9.3 months) was significantly longer than in the non-remitting patients (4.7 months). The drug was well tolerated and no serious side-effects occurred. A/G appears to be a useful treatment in patients with advanced prostatic cancer resistant to conventional therapy.*

INTRODUCTION

CARCINOMA of the prostate is estimated to have an incidence of 16 per 100,000 in Western Society and to cause 7-8% of all tumour deaths in men over 50 yr of age [1]. If metastases are evident at presentation 69% of untreated patients die within 18 months [2], while even with treatment the median survival of patients with stage D is less than 3 yr [3].

Although surgical castration or treatment with oestrogens has been shown to lead to subjective and objective improvement in 60-80% of patients with advanced prostatic cancer [4-6], relapse of the disease usually occurs after a variable time [7] and median survival following this is only 6 months [8]. The variety of treatments tried in patients who have relapsed from, or failed to respond to, orchidectomy and/or oestrogen therapy have had only limited success [9]. It is frequently difficult to evaluate results of these treatments due to variation in response criteria used and to the fact that often only small numbers of patients have been treated.

In this paper we present results of evaluation of treatment in 58 patients who had progressive disease following orchidectomy and/or oestrogen treatment and who were treated by adrenal inhibition with aminoglutethimide and corticosteroid replacement.

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MATERIALS AND METHODS

All patients had actively progressing advanced prostatic cancer which was resistant to conventional therapy. Prior to commencing treatment each patient had a thorough history and examination and the following tests were carried out: full blood examination, measurement of urea and electrolytes, liver function tests (alkaline phosphatase, gamma GT, AST bilirubin, albumin and total proteins), serum calcium and prostatic phosphatase, dehydroepiandrosterone and testosterone. All patients had a skeletal survey, bone scan and liver scan, while CT scanning was carried out if clinically indicated.

Treatment was started with cortisone acetate 25 mg a.m. 12.5 mg p.m., fludrocortisone 0.1 mg a.m. (unless the patient had hypertension or oedema) and aminoglutethimide 250 mg twice a day. After 3-5 days the dosage of A/G was increased to 250 mg three times a day unless the patient complained of drowsiness or lethargy, in which case the dose was left at the lower level until those symptoms disappeared. If the patient had no side-effects the dose of A/G was increased to 250 mg four times a day after a further 3-5 days.

Repeat measurements of the biochemical, haematological and hormonal parameters were carried out at least monthly while the skeletal survey, bone scan and liver scan were repeated at 3-monthly intervals. Classification of response was by two observers according to the National Prostatic Cancer Project criteria [10]. In patients

who had not had an orchidectomy but had been treated with oestrogens, the latter drug was continued in the same dose.

RESULTS

Fifty-eight men with an age range of 53–84 yr were assessed for their response to A/G. All but nine had had a previous orchidectomy and 43 had received treatment with oestrogens. In those patients who had not had an orchidectomy pretreatment testosterone levels were all in the orchidectomized range. Many patients had also received treatment with progestogens and all but eight had received at least one course of radiotherapy for metastatic disease. In the majority of instances the response to the previous therapy could not be accurately determined because of poor documentation, inadequate investigation, concurrent other treatment or no assessable lesion present.

Eleven (19%) of the 58 patients had an objective response to the treatment and a further 8 (14%) had stabilization of disease. One of those 11 remitters and two of the patients who had stabilization of previously progressing disease had not had a previous orchidectomy but had been continued on their previous oestrogen therapy. Table 1 lists the major sites of disease, the duration of remission and the basis on which the objective and subjective decisions were made for the 11 patients with objective remission and the eight who had stabilization of disease. No patient had a mixed response with regression of some lesions and progression of others. The mean duration of remission is in excess of 10 months for the patients who had objective regression and 7 months for those that had stabilization of disease. The clinical characterization of the patients divided according to their response to treatment are shown in Table 2. There was no significant difference in mean age, the average number of previous treatments, the free interval, the percentage of patients with bony metastases or more than one site of involvement between the three groups. Furthermore, the average duration between the time of diagnosis of metastatic disease and starting aminoglutethimide is the same for both remitting and non-remitting patients. This is of particular importance when survival is analysed, as it can be seen that the median survival for the remitters of 15 months is significantly longer ($P < 0.0001$) than that of the non-remitters' survival of 4.7 months. (Fig. 1). Similarly, the median survival of the static group (9.3 months) is significantly longer ($P < 0.01$) than that of the non-remitters.

All patients who experienced a remission and all but two who had stabilization of disease also had a subjective response with weight gain, a decrease in analgesic requirement and/or an improvement in performance status. The latter signicantly improved in the remitting and static groups ($P < 0.0001$ and < 0.05 respectively) and worsened in the non-remitters ($P < 0.0001$). No patient with progressive disease had a subjective response at the 1 month or later assessments.

Aminoglutethimide was well tolerated and in no instance was the drug stopped because of toxicity. Fourteen percent of patients developed the transient erythromatous rash which is a recognized side-effect of A/G, while lethargy and giddiness (four and one instance respectively) responded to a reduction in dose in the remitting and static groups. Thirty percent of patients with progressive disease complained of lethargy; however, this was felt to be disease related as it failed to respond to a reduction in dose and was associated with a general deterioration in health.

DISCUSSION

The treatment of choice in patients who have relapsed following a remission to, or failed to benefit from, orchidectomy or oestrogen treatment is uncertain. Many patients are elderly, medically unfit and poor candidates for surgical procedures (such as surgical adrenalectomy or hypophysectomy) or chemotherapy. Newer hormones and antihormones such as progesterone derivatives, cyproterone acetate and flutimide have been reported to be of some benefit, but their exact role has not yet been determined [11].

Smith and co-workers reported results of treatment with cyproterone acetate in 28 patients who had all relapsed on or failed to respond to stilboestrol; most patients had also had an orchidectomy. Twelve patients experienced relief of bone pain but only five patients noticed improvement in other symptoms. Twelve patients were stated to have a decrease in prostatic size and there was definite improvement in bone surveys in four patients and questionable improvement in another four. Side-effects were minimal [12]. Wein and Murphy noted decreased tumour size in 19/20 and relief of bone pain in 6/13 patients given cyproterone who had received previous treatment [13].

Flutimide (a non-steroidal antiandrogen) has been reported as causing a decrease in pain relief of obstructive symptoms and a decrease in the size of the prostate in 7/10 previously treated patients [14]. More recently, Sogani and Whitmore have reported a clinical response in 6/26 patients with metastatic prostatic cancer which was refractory to conventional treatment [15].

Spironolactone, a steroidal aldosterone antagonist, has been shown to lower plasma

Table 1. Sites of disease, durations of remission or stabilization and major basis for response

Patient and response	Site of disease	Duration of remission or stabilization (months)	Basis of response			
			Objective	Weight	Subjective analgesic requirements	Performance status
1 R	bone and marrow	26	improved bone scan. Correction of anaemia	increased	decreased	3 → 1
2 R	bone/lungs	12	improved scan. Decrease in lung lesions	constant	decreased	3 → 2
15 R	bone/lymph nodes	6	no change on X-ray. Decrease in lymph nodes	constant	decreased	2 → 1
18 R	bone	11	improved bone scan and X-ray	increased	decreased	2 → 1
20 R	bone/soft tissue	7	improved CT scan. Decrease in mass clinically	increased	decreased	3 → 2
21 R	bone	26+	improved scan and X-ray	constant	decreased	3 → 1
25 R	bone	4+	improved scan and X-ray	increased	decreased	3 → 2
30 R	bone	10	improved scan and X-ray. Improved anaemia	increased	no change (0)	no change (0)
39 R	bone/lymph nodes	7	improved X-ray. Decrease in nodes on CT scan	increased	decreased	no change (3)
52 R	bone/local	8	improved X-ray. Disappearance of urinary obstruction	increased	decreased	no change (2)
63 R	lymph nodes	12+	disappearance of enlarged nodes	increased	no change (0)	no change (0)
4 S	bone and marrow	6	improved anaemia. No change on scan or X-ray	constant	decreased	no change (3)
5 S	bone and marrow	6	no change on X-ray or scan	constant	decreased	4 → 3
35 S	bone	10	no change on X-ray or scan	constant	no change (0)	no change (1)
38 S	bone	8	no change on X-ray or scan	constant	decreased	2 → 1
56 S	bone/local/lymph nodes	6	no change on X-ray or scan	constant	no change	no change (3)
58 S	bone and marrow	7	no change on X-ray or scan. Improved anaemia	increased	decreased	no change (3)
67 S	bone/marrow/lungs	6	no change on X-ray or scan. Improved anaemia	increased	decreased	2 → 1
79 S	bone/local	10+	no change clinically or on X-ray and scan	increased	no change (0)	no change (1)

R = remission; S = stabilization.

Table 2. Clinical characteristics of the patients divided according to their response to treatment

	Objective response (11)	Objectively stable (8)	Objective progression (39)
Age of patients (yr)*	68.3 ± 9.3	74.5 ± 5.5	67.9 ± 7.2
Average No. of previous systemic treatments	2.2	2.1	1.9
Free interval (months)*	10.8 ± 11.5	6.0 ± 16.8	7.6 ± 11.6
Duration between diagnosis of metastatic disease and starting A/G (months)*	29.9 ± 20.8	25.0 ± 9.5	27.3 ± 17.6
% with bony metastases	91	100	100
% with more than one site	36	37	46
Pre-treatment performance status (ECOG)*	2.3 ± 0.8	2.4 ± 1.1	2.5 ± 0.8
On treatment performances status*	1.4 ± 0.9	2.0 ± 1.1	2.9 ± 0.9

†Mean ± S.D.

testosterone levels in castrated men and is reported to have been associated with relief of pain in 3/7 castrated patients who had metastatic carcinoma of the prostate [16]. Hypophysectomy has been used in the treatment of refactory carcinoma of the prostate but, owing to different criteria used, it is difficult to determine objective remission rates, although pain relief appears to be quite common. In a recent report 11/15 patients with progressive metastatic cancer who had failed primary endocrine therapy had a subjective improvement with reduced pain following transphenoidal hypophysectomy but no patient showed any evidence of objective response [17].

Aminoglutethimide, which when used in combination with replacement glucocorticoid inhibits adrenal steroid synthesis, is now an accepted treatment for patients with advanced breast cancer [18,19]. Although its main action in this disease may be due to a decrease in circulating oestrogen, it has also been shown in some studies to reduce plasma testosterone levels [20]. Similarly, when used in orchidectomized patients with prostatic cancer testosterone levels fell in 8/11 patients in one study [21] and 8/9 in another [22]. This fall in plasma testosterone may be responsible for regression of hormone-dependent prostatic cancer and suggests that the rational role for aminoglutethimide in patients with prostatic cancer should be following relapse or failure of orchidectomy.

This study shows clearly that aminoglutethimide is an effective and safe treatment for patients with advanced prostatic cancer who have failed orchidectomy and/or oestrogen. While it cannot be entirely excluded, it is unlikely that the objective remission and the stabilization of disease seen in our patients is due only to the concurrent administration of cortisone acetate and fludrocortisone. Firstly, not all of these patients received fludrocortisone (which has never been reported as a treatment for prostatic cancer), and secondly, the dose of cortisone acetate given represents only physiological steroid replacement. Patients on this dose have been shown to have normal 24-hr urine free cortisol

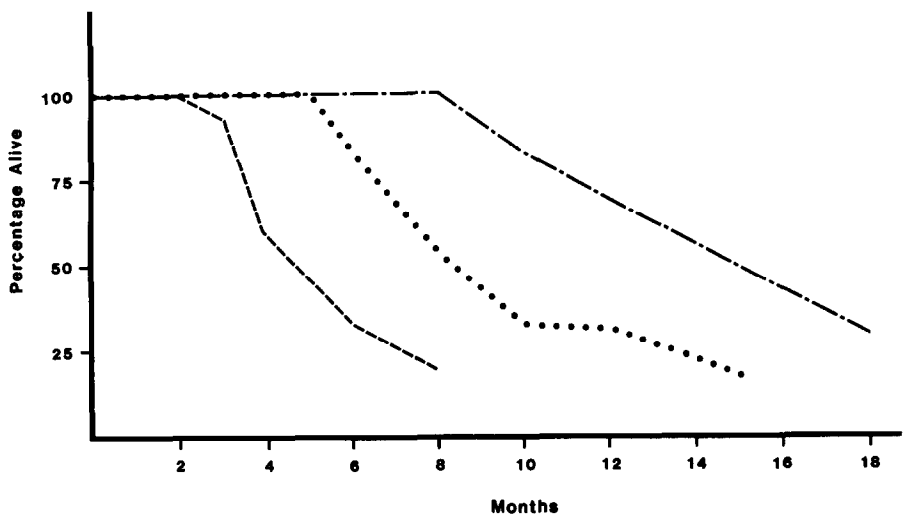

Fig. 1. Survival of patients with advanced prostatic cancer treated with aminoglutethimide (non remitters————; static disease.....; remitters ._._.).

levels. It is likely that the effectiveness of the combination of A/G+ steroid replacement is due to a lowering of plasma androgens [20-22]. While only 33% of the patients appeared to benefit from the treatment, it should be pointed out that these were 'end-stage' patients who had received more than two previous systemic treatments on average, as well as large amounts of radiotherapy. Not only did the remitting and stabilized groups have a subjective response and improvement in their quality of life, but their survival was also significantly prolonged. A similar result was also noted by Worgul and associates, who reported a 47.8% response rate in 23 patients treated with aminoglutethimide [22]. Their higher response rate may be related to the smaller number of patients treated, or possibly to patient selection. Rostom and associates reported a 75% subjective improvement in 12 patients treated with aminoglutethimide but failed to detect an objective remission [21].

Although the non-remitting patients had a slightly shorter free interval (the time between diagnosis and development of metastases) and a higher percentage had more than one site of involvement than the remitting patients, these differences are not statistically significant. It appears that it is not possible to select likely remitters on clinical grounds as the mean age, number of previous treatments and duration between the diagnosis of metastases and the time of starting A/G were also similar in these remitting and non-remitting groups. In view of the good tolerance of A/G and its clinical effectiveness, it is rational to offer more patients this treatment. Further studies are necessary to determine if the response rate and survival can be further increased by immediate use of the drug as second-line treatment rather than at the 'end stage' of the disease, and to compare it with other second-line treatments such as antiandrogens and progestational agents.

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