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Anti-hormone Treatment for Prostate Cancer Relapsing after Treatment with Flutamide and Castration

Addition of Aminoglutethimide and Low Dose Hydrocortisone to Combination Therapy

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Summary—The effect of further adrenal androgen blockade with aminoglutethimide (AG) plus low dose hydrocortisone (HC) was studied in 119 patients with clinical stage D2 prostate cancer who previously progressed after standard hormone therapy and were under progression while receiving the combination therapy with Flutamide and castration. Using the objective criteria of the US NPCP, 1 complete, 2 partial and 14 stable responses were obtained for a total response rate of 14.3%, while 102 patients continued to progress. The 50% probability of survival was 21.0 months for the responders and 9.2 months for the non-responders. The present data indicate that further androgen blockade with AG + low dose HC is well tolerated and can be of benefit to a significant proportion of patients in progression at a very late stage of the disease.

A major problem facing the treatment of advanced prostate cancer is the lack of response as well as interruption of response to first-line endocrine therapy. Since the observation of Huggins and Hodges (1941), first-line endocrine therapy has been the neutralisation of testicular androgens by orchiectomy or oestrogens (Mettlin *et al.*, 1982) and, more recently, by LHRH agonists (Labrie *et al.*, 1980, 1986). Following such neutralisation of testicular androgens, 20 to 40% of patients are left in progression with no response at the start of treatment, while relapse of the disease is generally seen within 6 to 24 months in all of those who initially respond (Resnick and Grayhack, 1975). At the time of relapse, the median life expectancy is only 6 months (Johnson *et al.*, 1977). Our approach for these patients showing disease progression following treatment by orchiectomy, oestrogens or LHRH agonists alone has been the addition of the antiandrogen Flutamide with an objective positive response rate of 34% (Labrie *et al.*, 1988).

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An important advance in the first-line endocrine therapy of advanced prostate cancer has been combination therapy or the association of a pure antiandrogen to castration at the start of treatment. As shown by open (Labrie *et al.*, 1986, 1987a) and randomised (Labrie *et al.*, 1985; Ojasoo, 1987; Benson *et al.*, 1988) trials, the rate and duration of response as well as survival are improved by the additional blockade of androgens achieved by a pure antiandrogen. However, 5 to 10% of patients do not respond to combination therapy and relapse of the disease, although markedly delayed compared with standard monotherapy, occurs in 60% of patients within 2 years (Labrie *et al.*, 1987).

The next and most difficult question is which treatment should be used in those patients showing lack of response or relapse of the disease under combination therapy. The present study investigated the effect of adding the inhibitor of adrenal steroid biosynthesis, aminoglutethimide, plus a low replacement dose of hydrocortisone to combination therapy in stage D2 patients in relapse or not responding to the association of Flutamide and

castration. All of these patients had previously failed to respond to standard endocrine therapy.

Patients and Methods

All patients with biopsy-proven stage D2 prostatic carcinoma had disease progression following orchiectomy or treatment with diethylstilboestrol (DES) or an LHRH agonist alone. They were entered into the study after written informed consent. Flutamide 250 mg (orally every 8 h) was then given alone in castrated patients or in combination with the LHRH agonist [D-Trp^6, des-Gly-$NH_2{}^{10}$]LHRH ethylamide (LHRH-A) 500 μg s.c. daily for the first month, followed by 250 μg s.c. daily, to those previously treated with DES or another LHRH agonist. The oestrogen or other LHRH agonist was replaced by LHRH-A in all cases.

Patients who did not respond or who relapsed while receiving the combination therapy with Flutamide received aminoglutethimide and hydrocortisone. Aminoglutethimide 250 mg 3 times a day was given orally for the first 3 weeks followed by 250 mg 4 times a day, unless the patient complained of lethargy associated with the soporific side effects of the drug. If side effects such as lethargy, nausea, ataxia or dizziness became clinically significant, the dose of AG was temporarily reduced until the signs and/or symptoms disappeared or became acceptable. The dose was then re-established to 1000 mg/day in 4 divided doses. A low dose of hydrocortisone acetate was given as glucocorticoid replacement, namely 20 mg daily (10 mg at 0700 h, 5 mg at 1500 h and 5 mg at 2300 h). As shown in Figure 1, this schedule and dose of HC was used in an attempt to reproduce the physiological nycthemeral cycle of cortisol secretion.

Complete clinical, urological, biochemical and radiological evaluation of the patients was performed before the start of treatment and during the study as described (Labrie *et al.*, 1985). The initial evaluation included medical history, physical examination, haematology, serum biochemistry, urine analysis, flowmetry, chest X-ray, bone scan, skeletal survey, ultrasonography of the prostate and abdomen and, when indicated, computed axial tomography (CAT), nuclear magnetic resonance imaging (NMI) and intravenous urography (IVU). The same tests were performed after 3 and 6 months of treatment and then every third or sixth month or more frequently, depending upon the evolution of the disease.

Classification of response was performed according to the objective criteria of the National Prostatic

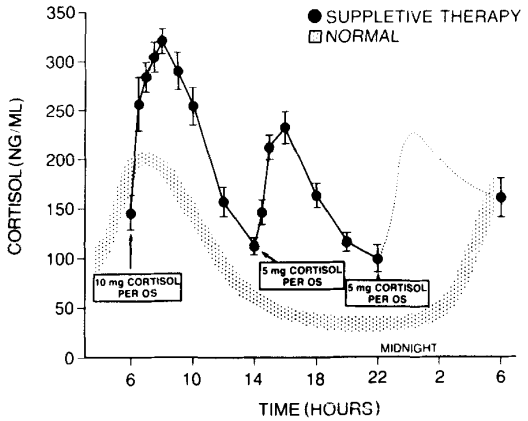

Fig. 1 Profile of serum cortisol concentration in 15 prostate cancer patients receiving the indicated doses of hydrocortisone acetate compared with control circadian rhythm in 20 untreated patients of similar age.

Cancer Project (NPCP) (Slack *et al.*, 1984). Bone scans were evaluated by an independent group of radiologists unaware of the treatment of the patients. All measurements of serum prostatic acid phosphatase (PAP) and prostatic specific antigen (PSA) as well as serum levels of testicular steroids, adrenal steroids and pituitary hormones were performed at the Laboratory of Molecular Endocrinology, Laval University Medical Center, Quebec City.

The first reported evaluation of positive objective response was after 3 months' treatment. Patients were considered as non-responders if there was no objective stabilisation or regression of their disease at that time, even though there had been subjective benefits. Performance status and pain were evaluated on a scale of 0 to 4 according to the ECOG criteria.

In 72 patients (57%), orchiectomy was the first treatment. In those previously treated with an LHRH agonist alone or DES, serum testosterone levels were all in the orchiectomised range; 34 patients (27%) had received at least 1 course of radiotherapy for metastatic disease but none had received chemotherapy. Among the 126 patients entered into the study, 7 were not evaluated: 5 stopped therapy on their own and 2 were lost to follow-up. Thus 119 patients with an age range of 48 to 83 years (mean 66) were evaluated for their objective response to the addition of aminoglutethimide and low dose hydrocortisone to combination therapy.

Among the patients included in the study, 94 (74.6%) complained of pain (58 had pain permitting normal activity, 29 had pain interfering with daily activity and/or sleep, 5 were constantly suffering from pain and 2 had intolerable pain requiring 100% of time in bed); 35 patients (27.7%) were ambulant but symptomatic, 17 (13.5%) were bedridden less than 50% of the time, 5 (3.9%) were bedridden more than 50% of the time and 2 (1.6%) were 100% bedridden. Loss of body weight and appetite was present in 50 patients (40%). Location of metastases prior to the addition of aminoglutethimide and hydrocortisone included bone metastases in all patients, lung involvement in 10 (7.9%), pelvic and distant lymph nodes in 10 (7.9%), liver in 4 (3.2%), central nervous system in 1 (0.8%) and bone marrow in 1 (0.8%); 79 patients (62.7%) had elevated levels of serum prostatic acid phosphatase (PAP).

Calculations

Radioimmunoassay data were analysed using a program based on model II of Rodbard and Lewald (1970). Statistical significance was measured according to the multiple-range test of Kramer (1956). The probability of continuing response and survival was calculated according to Kaplan and Meier (1958).

Results

As shown in Table 1 and Figure 2, the addition of AG+HC to combination therapy led to a 14% objective response rate in patients progressing under combination therapy with Flutamide; 1 patient (0.8%) had a complete response, 2 (1.7%) had a partial response, 14 (11.8%) had a stable response and 102 (85.8%) continued to progress. In the latter group, 2 patients showed simultaneous disappearance of old lesions and appearance of new ones, thus suggesting heterogeneity of the androgen sensitivity of the tumours. As illustrated in Figure 2, the 50% probability of survival was 21.0 months for responders (curve A) and 9.2 months for non-responders, the difference between the 2 curves being highly significant ($P=0.0056$, log rank test) (Knudsen and Strom, 1986).

The most frequent side effect was lethargy (12 patients) (Table 2). Nausea was seen in 5 patients and skin rash and fever occurred in 4 cases; 1 patient needed replacement therapy with Florinef for symptomatic low blood pressure.

Discussion

The present data show that an objective response can be obtained in a small but significant (14%) proportion of patients in progression under combination therapy (Flutamide and castration) by additional blockade of adrenal androgen secretion achieved by AG+HC and that the therapy is well tolerated. We found that the addition of Flutamide to patients in relapse after standard endocrine therapy produced an objective response in 34.5% of 209 patients (Labrie *et al.*, 1988). The present data indicate that an additional 14% can benefit from further adrenal androgen blockade achieved by AG and low dose HC, making a total response rate of 48% in this difficult group of patients with disease progression after standard hormonal therapy.

Since most of the objective responses were in the stable category, it was important to establish that every patient was in real progression at the start of treatment with AG+HC and not already stable. In this regard it should be recalled that all of the patients were first seen in progression under standard endocrine therapy, namely blockade of testicular androgens by orchiectomy, DES or an LHRH agonist alone. Combination therapy with Flutamide was then given to all patients and a decision about further androgen blockade with AG+HC was not taken until 3 to 6 months later. In patients already castrated, Flutamide was given alone, and for those treated with DES, Flutamide was given in combination with the LHRH agonist

Table 1 Effect of Addition of Aminoglutethimide and Low Dose Hydrocortisone on the Objective Response Rate

Total evaluated	*Days of treatment mean (limits)*	*Objective response*			
		Complete	*Partial*	*Stable*	*Progression*
119	323 (85–943)	1 0.8%	2 1.7%	14 11.8%	102 85.7%
			14.3%*		

* 10.8% to 17.2% (95% confidence limits).

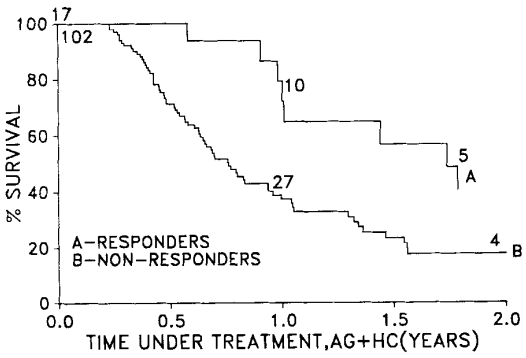

Fig. 2 Comparison of the probability of survival in stage D2 prostate cancer patients progressing under combination therapy and responsive to the addition of aminoglutethimide and hydrocortisone (AG + HC) (curve A) and the non-responders to the same treatment (curve B). The numbers on the curves indicate the number of patients assessed at each time interval. The two curves are statistically different ($P=0.0056$, log route test (Knudsen and Strom, 1986).

[D-Trp^6, des-Gly-NH$_2{}^{10}$]LHRH ethylamide. In a study of 209 evaluable patients relapsing after standard monotherapy, 6.2, 9.6 and 18.7% achieved complete, partial and stable responses respectively, *i.e.* a total objective response rate of 34.5% to combination therapy (Labrie *et al.*, 1988). Coupled with the patients' excellent tolerance of this treatment, this response rate appears to make it the treatment of choice for prostate cancer patients in relapse after standard endocrine therapy.

Unfortunately, 65.5% of patients relapsing after monotherapy do not respond to the addition of the antiandrogen (Labrie *et al.*, 1988). Moreover, for the 34.5% of patients who initially respond, the mean duration of response is 24 months before a second progression occurs. The patients included in the present study are those who did not respond to the combination therapy as well as those who progressed after a variable period of response to such therapy. All 119 evaluated patients who received AG + HC were thus in clear progression under our observations for a minimal period of 3 months before the addition of AG + HC. It is thus unlikely that any of the stable responses observed correspond to patients already having stable disease before further blockade of adrenal androgens was achieved by AG + HC.

Table 2 Side Effects of Treatment with AG and HC

	No. of patients	%
Adrenal insufficiency	0	0
Nausea	5	4.2
Rash	4	3.4
Lethargy	12	10.1
Fever	4	3.4
Dizziness	0	0
Thrombocytopenia	0	0
Leucopenia	0	0
Mineralocorticoid deficiency	1	0.8

The present approach, namely blockade of adrenal androgen secretion in patients relapsing under combination therapy, is based on the premise that tumours remain sensitive to the low concentration of androgens remaining free to activate the androgen receptor in castrated patients receiving Flutamide, and that aminoglutethimide associated with a low and near-physiological dose of hydrocortisone efficiently blocks adrenal androgen production.

Clinical data demonstrate that androgen-sensitive tumours are also present in patients who relapse after castration. These pertain to the findings that 34% of patients already castrated or treated with oestrogens or LHRH agonists alone show a positive objective response to the addition of Flutamide (Labrie *et al.*, 1988). That more than 95% of patients at the time of relapse have androgen-sensitive tumours is shown by the observation of a rapid exacerbation (within 3 days) of symptoms in 97% of relapsing patients treated with exogenous testosterone (Fowler and Whitmore, 1981).

Although AG has never been used in patients relapsing under combination therapy, the benefits of this drug have been observed in 30 to 60% of patients in progression after orchiectomy or treatment with DES (Robinson *et al.*, 1974; Drago *et al.*, 1984). Using the objective criteria of response of the NPCP, Drago *et al.* (1984) reported positive objective responses in 17 of 43 patients (40%) and Murray and Pitt (1985) observed 33% positive objective responses in 58 patients. In a study of 129 patients relapsing after castration, treatment with AG (1000 mg/day) and HC (40 mg/day) caused objective partial and stable remission in 9 and 33% of patients respectively, making a total objective response rate of 42% while 58% had disease progression (Crawford *et al.*, 1988).

A potentially important characteristic of the regimen AG-HC used in this study is the low dose of hydrocortisone used (20 mg/day), while all other reported studies used 40 or more mg HC/day as glucocorticoid replacement therapy. Crawford *et al.* (1988) used 100 mg HC during the first 2 weeks followed by 40 mg daily, Ponder *et al.* (1984) used cortisone acetate 50 mg/day and Drago *et al.* (1984)

and Murray and Pitt (1985) used 40 mg HC and 37.5 mg cortisone acetate daily respectively.

Although greater inhibition of adrenocortical activity could be achieved with higher doses of glucocorticoids, it is likely that such an approach has potential harmful effects on the immune system and on the evolution of cancer itself. It is of interest to recall the immunosuppressive properties of glucocorticoids. The secretion of interleukin-1 (IL-1) originating from monocytes as well as interleukin-2 and lymphotoxin from T-lymphocytes is suppressed by glucocorticoids (Mishell *et al.*, 1981). These steroids also block natural killer cell activity, possibly by inhibiting the production or release of specific cytotoxic factors. It has been shown that corticosteroids inhibit IL-1 production through an inhibition of the transcription of IL-1 encoding mRNA and thereby blocking cell-mediated immunity (Knudsen and Strom, 1986). With this knowledge of the role of the immune system in cancer, it seems logical to avoid the use of high doses of glucocorticoids, an approach which might have apparent short-term benefits but may well be responsible for an accelerated growth of the cancer.

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