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Cyproterone Acetate Monotherapy in Advanced Prostatic Carcinoma

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Cyproterone acetate was given as monotherapy to 18 patients with advanced prostatic carcinoma at a weekly dose of 300 mg. Progression was observed in all of the patients; median time to progression was 35 months and median survival time was 48 months. Partial response, stabilization, progression and exitus rates by years also showed favourable results, as compared with other forms of therapy in advanced prostatic carcinoma.

Introduction

The major source of androgens in men are the testes. However, the adrenal glands secrete some weak androgens; androstenedione, dehydroepiandrosterone that can be converted to testosterone and dihydrotestosterone. By blocking the androgen effect, different treatment modalities for advanced prostatic cancer have been reviewed extensively [1].

Cyproterone acetate (CPA) is a synthetic 21-carbon hydroxyprogesterone derivative that produces a potent androgen withdrawal effect. It acts both centrally and peripherally. In the target prostatic cell, it acts as a competitive inhibitor of the binding of dihydrotestosterone to cytosol receptor sites and inhibits the translocation of the androgen receptor complex into the nucleus. In its central action, it lowers LH and plasma testosterone because of its progestin-like activity [1].

Cyproterone acetate usually has been used in combination therapies [2, 3, 4, 5, 6, 7] and during the last several years no new studies evaluating CPA as a single agent have been initiated. In our study CPA was used as a single agent in advanced prostatic carcinoma.

Patients and methods

The eligibility of consecutively referred patients was determined by histologically confirmed prostatic carcinoma of Grades 1 and 2; metastatic disease involving bone, lymph nodes above the bifurcation of the aorta or other soft tissues outside of the pelvis; adequate renal function with a serum creatinine level of less than 2.0 mg/dl; normal liver function studies; normal haemoglobin,

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white blood cell and platelet counts; Eastern Cooperative Oncology Group performance status of 2 or less, and life expectancy of more than 3 months. No patient had previously received hormones, cytotoxic drugs or irradiation for metastatic disease, and orchiectomy had not been performed in these patients.

We investigated 18 patients meeting these criteria, who were treated with CPA at a weekly dose of 300 mg i.m. Their mean age was 72 (64–85) years and the patient who discontinued CPA treatment was excluded from the study.

Pretreatment evaluation included a full history and tests for serum testosterone, serum prostatic acid phosphatase (PAP), prostate specific antigen (PSA), serum electrolytes, blood urea nitrogen, creatinine and complete blood count. Radiological studies included chest X-rays and computerized tomography (CT) scan of the abdomen and pelvis to determine the extent of disease and lymphadenopathy. To complete the evaluation of metastatic disease a bone scan also was performed.

Follow-up assessments were conducted for 1 week, 1, 2 and 4 months, and every 4 months thereafter. During the course of treatment, digital rectal examination was done and serum testosterone, PSA and PAP levels were assessed at each visit. The other biochemical tests, X-rays and bone scan were repeated every 4 months. A CT scan was done every 6 months if initially abnormal or earlier signs of progression were observed. Patients were questioned about side effects of treatment at each visit.

In the assessment of response and progression the 1980 criteria of the national prostatic cancer project were used. A complete response was defined as resolution of the primary tumour, return of PAP and PSA levels to normal, radiological evidence of healing of skeletal metastases and disappearance of abnormal areas of uptake on the bone scan. For a partial response the criteria included absence of new sites of disease, a decrease of 50% in the cross sectional area of any measurable soft tissue lesion, return of serum PAP and PSA levels to normal, no cancer-related deterioration in weight, symptoms or performance status, and no increase in the number of uptake areas on the bone scan. Stable disease included absence of new sites of disease, a decrease of elevated concentrations of serum PAP and PSA, stabilization of osteolytic and osteoblastic metastases if present, and growth of measurable disease limited to 25% of the original cross sectional area. The disease was considered to have progressed when there was an increase in the size of the primary tumour, soft tissue as skeletal metastases, or when PSA and PAP levels were increased.

Results

A total of 18 patients with stage D_2 disease had been monitored for 2 to 60 months (median 48 months). Complete response (CR), partial response (PR), stable disease (SD) and progression (P) rates were evaluated for each year (Table 1).

Table 1
Complete response (CR), partial response (PR), stable disease (SD), progression (P) and exitus (Ex) percentages for each year of follow-up

Follow-up (year)	CR		PR		SD		P		Ex	
	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)
1	1	5.55	7	38.88	7	38.88	2	11.10	1	5.55
2	1	5.88	5	29.41	7	41.16	3	17.64	1	5.88
3	–	–	3	18.75	4	25	4	25	5	31.25
4	–	–	–	–	1	9.09	6	54.54	4	36.36
5	–	–	–	–	–	–	2	28.57	5	71.43

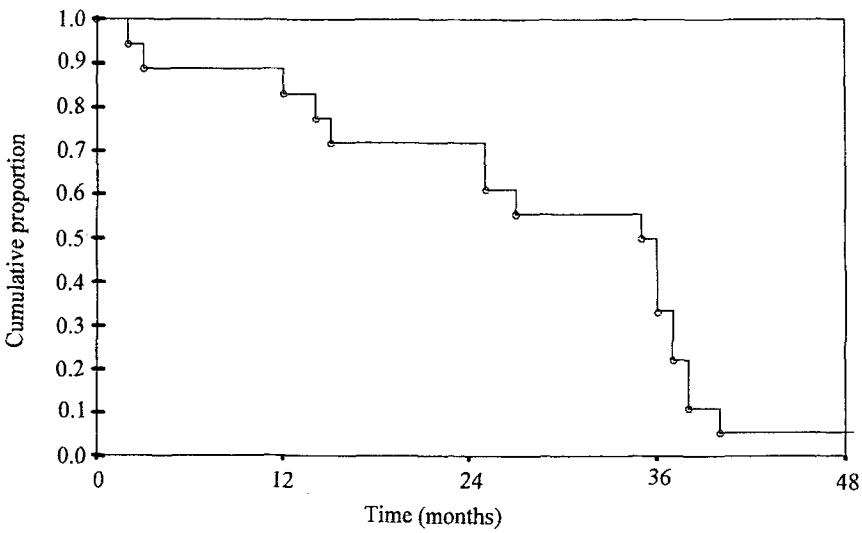

Fig. 1. Kaplan–Meier analysis of the time to progression for patients with stage D_2 prostatic cancer treated with CPA

Three patients with SD died of cardiovascular disease. Median time to progression was 35 months and median survival time was 48 months (Figs 1 and 2). Survival rates were evaluated for each year (Table 2). Patients who met the progression criteria were accepted as having hormone refractory prostatic carcinoma and were switched to the chemotherapy programme epirubicin+ medroxyprogesterone acetate after cessation of CPA monotherapy.

At the time of entry into the trial the serum PSA was abnormal in 100% of patients with a mean level of 68 ng/ml (range 40–150 ng/ml), and PAP was

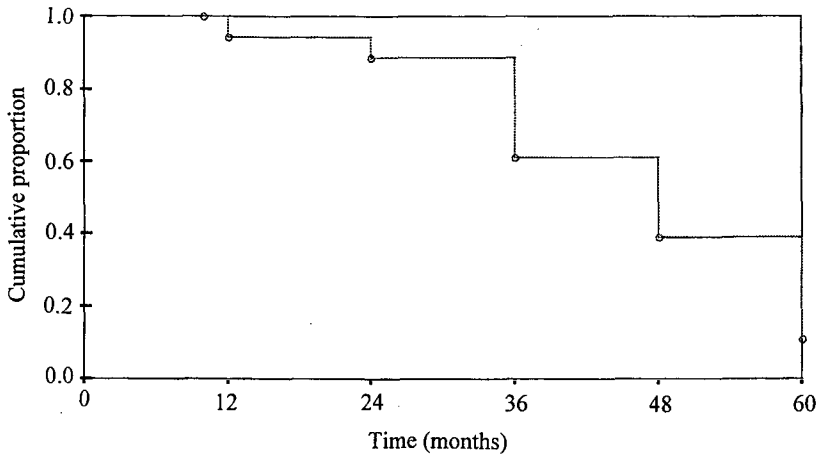

Fig. 2. Kaplan–Meier analysis of the time to death for patients with stage D_2 prostatic cancer treated with CPA

Table 2
Survival rates in advanced prostatic carcinoma

Duration (year)	Survival rate without progression (percentage)	Survival rate (percentage)
1	83.33	94.44
2	61.11	88.89
3	39.33	61.11
4	0.566	38.89
5	0.00	11.11

abnormal in 72%. The percentage of patients with abnormal PSA values declined in about 36 weeks. The rate of normalization was faster in the first 10 weeks. PSA remained abnormal in about 25% of patients.

Abnormal levels of serum PAP were observed in 72% of patients. The initial rate of normalization parallel to serum PSA decline and abnormal values remained in about 20% of patients.

A marked change occurred in the mean concentration of serum testosterone. The initial value of 320±18 ng/dl (mean± SD) decreased to 210±16 ng/ml after 1 day and to 78±7 ng/ml after 1 week. The mean level then reached a plateau of approximately 48 ng/ml after 2 months of treatment. The baseline concentration remained relatively constant throughout the follow-up.

The most frequent side effect was nipple tenderness observed in 3 patients (16.66%). The mean time to onset was 3.5 months and the mean spontaneous resolution time was 7 months, observed in 2 patients.

Discussion

Our study shows the effectiveness of hormonal therapy using CPA monotherapy in the treatment of advanced prostatic carcinoma. CPA has a dual mechanism of action: it is a strong antiandrogen and also exerts gestagenic and glucocorticoid effects. This substance has been shown in humans to be equally effective as standard treatment and is associated with significantly fewer side effects than the other agents. It can be regarded as the only antihormone that produces total androgen blockade as monotherapy [8].

CPA has been used in combination therapies for many years and during the last several years no new studies evaluating CPA as a single agent have been initiated [1]. Although it is not certain whether a beneficial effect of total androgen blockade using pure antiandrogens will ever be proven [9] and whatever the positive attitude to the concept of total androgen blockade is, no studies can at the present time confirm the superior improvement in the uncontrolled study [10].

Relevant studies were designed with prospective placebo-controlled, randomized protocols for non-pretreated patients with newly diagnosed metastatic prostatic cancer, and aimed at testing the hypothesis that combined therapy was superior to monotherapy. These studies can now be reviewed and the results of two international metaanalysis meetings (Atlanta 1989 and Paris 1992) are now available. From this indepth statistical evaluation of more than 5400 patients it was concluded that there is no overall survival advantage for patients with combined maximal androgen blockade treatment [11] that is suitable for patients with good prognostic characteristics, such as a good performance status, asymptomatic disease with minimal metastatic involvement, low alkaline phosphatase at the time of diagnosis, and a rapid decrease of PSA to normal levels after initiating the therapy [12].

CPA is capable of producing response rates equivalent to those of diethylstilboestrol with a relatively lower incidence of cardiovascular side effects when administered as daily oral tablets or as weekly intramuscular injections [13, 14, 15]. Bosch et al. compared the effect of LHRH analogue buserelin to that of 200 mg of CPA per day. Prostatic volume reductions achieved with the two regimens were very similar [16]. Small phase II trials were reviewed and a 70–80% objective response rate was found with a mean duration of remission of 18 months [3].

In one study CPA and low-dose diethylstilboestrol were combined; complete (13%), partial (69%) and stable (16%) response rates were found [17]. Schroder et al. have published a randomized study of 71 patients in which they found a non-significant difference in progression rates of 38% and 41%

between the LHRH agonist and LHRH agonist plus CPA arms, respectively; the median time to progression in both groups was 13 months [18]. CPA was also used with LHRH analogues to block the flare phenomenon [19].

In a randomized phase III trial, investigators compared CPA, medroxyprogesterone acetate and diethylstilboestrol in a total of 210 patients with advanced prostatic carcinoma. Complete and partial remissions occurred in 33% of the CPA group and in 44% of the patients receiving oestrogen [14].

Although the strikingly good results of the non-randomized studies of Labrie et al. [10] were never confirmed by consecutive randomized studies, some of these studies showed a minor, but significant advantage of combined treatment modalities over single treatment (medical or surgical castration) with respect to response rate, subjective response or progression free overall survival as parameters [20, 21, 22, 23].

In one study the actuarial median time to progression was 17 months and actuarial median survival time was 23.5 months with CPA and low-dose diethylstilboestrol treatment [13]. In another study, after about 20 months half of the patients with stage D_1 prostatic carcinoma in each group (castration + placebo, castration + CPA) had progressed and after 36 months 75% of the patients had progressed in both arms [24].

In our study the actuarial median time to progression was 35 months and median survival time was 48 months. High percentages that were observed could be due to the fact that our patients had only histologically Grades I and II patterns.

The clinical effects of CPA on serum testosterone have been well documented. Mulder and associates demonstrated a therapeutic decrease during 3 months of oral therapy [25]. Becker and Klosterhalfen demonstrated statistically significant reductions in the concentrations of plasma testosterone (from 10.9 to 3.8 nmol/l) and prostatic tissue dihydrotestosterone (from 7.1 to 2.5 pmol/mg of DNA) after 6 weeks of CPA therapy [26]. In one study weekly intramuscular administration resulted in a rapid and sustained 70% decrease in testosterone levels [27].

We observed 85% decrease in testosterone levels after 2 months of treatment (from 320 ng/dl to 48 ng/dl).

In a longitudinal study of serum PSA in 48 patients with stage D_2 prostatic cancer who were treated by orchiectomy, monthly LHRH agonist injection or diethylstilboestrol, Miller et al. observed that the mean time to PSA normalization was 36 ± 4 weeks [28]. In another study the percentage of patients with abnormal PSA values declined over a period of about 32 weeks and the PSA result remained abnormal in about 30% of patients [20]. In the same study abnormal levels of serum PAP were observed in 72% of patients and the initial rate of normalization paralleled that of serum PSA, with abnormal values found in about 25% of patients.

In our study the percentage of patients with abnormal PSA values declined in about 36 weeks and the PSA level remained abnormal in 20% of patients. PAP values changed parallel with the serum PSA levels.

The most frequently recorded adverse effects of CPA are those related to hormone deprivation. Nipple tenderness, breast swelling and enlargement, although having different emotional and physical effects on patients, are usually considered together as gynaecomastia. In the randomized study conducted by Wenderoth and Jacobi the incidence of gynaecomastia was 13% [15]; in the EORTC study it was 6% [14]. Cerebrovascular accidents, fluid retention including peripheral oedema, venous thrombosis, pulmonary embolism, cardiac ischaemia, congestive heart failure, and sudden death have all been reported in patients taking cyproterone acetate [3]. In our series nipple tenderness occurred in 16.66% and resolved spontaneously within 7 months in two patients.

In conclusion it can be stated that despite small series results CPA is an effective monotherapeutic agent in the treatment of D_2 prostatic cancer just like the other agents and combination therapies. It is also cost effective and can be used easily, but the use of CPA monotherapy in advanced prostatic carcinoma should be subject to further investigation.

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