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Clinical and Endocrine Effects of Cyproterone Acetate in Postmenopausal Patients with Advanced Breast Cancer

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Abstract—*A phase II study with cyproterone acetate (CPA) was done as the primary treatment in female breast cancer patients.*

Twenty-three patients, mean age 64 years, range 52–75 years, were entered and treated with CPA 400 mg daily. Twenty patients were evaluable and responses were sparse. There was one partial and one complete remission, 17 patients were stable and one patient progressed within 3 months. Side-effects were frequent: five patients complained of nausea, three had severe weight loss, one suffered from depression and seven showed disturbed liver function tests. Six patients had to stop treatment for side-effects, while two other patients were taken off treatment because they developed an acute necrotizing hepatitis. The hepatitis recovered after drug withdrawal in both patients.

The serum levels of CPA, cortisol, androstenedione, DHAS, LH, FSH and prolactin were measured during CPA treatment. The levels of cortisol and androstenedione did not change, while LH, FSH and DHAS were suppressed. The DHAS showed an inverse relation to serum CPA concentrations. The prolactin levels rose uniformly.

The therapeutic effect of CPA in postmenopausal patients with advanced breast cancer is disappointing, and inferior to that of other progestins. Side-effects are frequent, possibly as a result of the high dosage used in this study. The hormonal changes are different from those of other progestins, which may explain the different efficacies.

INTRODUCTION

OVER the last decade, renewed interest has been aroused in the use of progestins in patients with advanced breast cancer. The use of higher dosages of these compounds has been advocated, as they are found to be more effective than conventional amounts [1, 2]. Side-effects, however, are frequent and sometimes serious [3, 4]. Cyproterone acetate (CPA) is a progestin which has been used mostly for its anti-androgenic properties, e.g. in patients with hirsutism or acne [5] and in patients with prostatic cancer [6]. Although a partial adrenal suppression was found in children [7], serious side-effects seem to be lacking [8]. Recently, it was found to have substantial activity in male breast cancer [9]. This prompted us to study the anti-tumor effects and side-effects of cyproterone acetate in postmenopausal patients with breast cancer.

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PATIENTS AND METHODS

Twenty-three postmenopausal women with histologically proven, progressive, inoperable or advanced breast cancer were entered in a phase II study. Patients with an age above 75 years or a performance status over WHO grade 2 were excluded. Many patients had no amputation because they had a locally advanced, surgically incurable cancer, or they refused operation or were considered unfit to tolerate the procedure. All patients had measurable tumor and were not treated previously with other hormones. Patients received cyproterone acetate (CPA) orally, the starting dose of 4 × 50 mg daily was increased in all patients after 3 weeks to 4 × 100 mg daily. The response to treatment was evaluated after 3 months, according to standard UICC criteria. Side-effects were scored after 3 months or earlier if the patient went off study for

Table 1. Dominant site of tumor related to response and progression-free period

No. of patients	Dominant site of tumor	CR	PR	NC	Progression	Median duration progression-free period and range (weeks)
15	Primary tumor ± lymph nodes	1	—	13	1	25 (11–62)
3	Skin ± lymph nodes	—	1	2	—	41 (17–59)
—	Bone	—	—	—	—	—
2	Visceral	—	—	2	—	16 and 62
20		1	1	17	1	

this reason. Drug toxicity was evaluated at every 3-monthly visit and graded according to WHO criteria.

Blood samples for determination of hormone levels were obtained before treatment and at 3 and 6 weeks of treatment, as a steady state of CPA levels usually was reached between 5–7 days on a fixed dosage. The serum levels of LH/FSH, prolactin, cortisol, androstenedione and dehydroepiandrosterone sulfate (DHAS) were measured using commercially available RIA kits. The serum concentration of CPA was measured by high pressure liquid chromatography and mass spectrometry (HPLC-MS, using megestrol acetate as an internal standard [9]).

Statistical comparisons were made by the Wilcoxon test for paired values and rank correlations were calculated according to Spearman.

RESULTS

Twenty-three patients entered the study, but three were not evaluable. One patient died early of an unknown cause, another suffered from a myocardial infarction after 2 weeks of treatment, a third patient refused further follow-up. Therefore, 20 patients were evaluable for response. Their age ranged from 53 to 75 years, median 64 years, and the WHO performance score was 0 in 14 and 1 in 6 patients.

The main site of disease was a primary, inoperable tumor in 15, locoregional disease in three and the lung in two patients (Table 1).

One patient progressed within 3 months. One had a complete response of the primary tumor site, and another patient had a partial response of skin metastases, lasting 48 and 59 months respectively. Seventeen patients had stable disease. In eight patients the treatment had to be interrupted because of complications or side-effects. The progression free period could be assessed in 12 patients, with a median of 33 weeks, range 17–117 weeks. The median survival has not been reached yet.

Table 2. Frequency of side-effects during treatment with CPA

	No. of patients	Treatment stopped
Nausea	7	5
Weight loss	4	3
Depression	2	1
Liver function temporary		
WHO grade 2	4	
WHO grade 3	1	
Necrotizing hepatitis		
WHO grade 4	2	2
	20	11
Total no. of patients with side-effects*	13	6

*Some patients had more than one symptom.

Toxicity

Eight of the 20 patients stopped treatment after a median of 17 (range 12–50) weeks. Further treatment was withheld in two patients for, respectively, a cerebrovascular accident and a pulmonary embolism. The overall incidence of side-effects is given in Table 2. There were 13 (65%) patients with side-effects, which resulted in the termination of treatment in six. These were: severe nausea and weight loss exceeding 10% of body weight (3), psychic depression (1) and necrotizing heptatitis (2). The occurrence of a myocardial infarction, CVA and pulmonary embolism could of course not with certainty be related to the use of CPA. Fluid retention, weight gain, hypertension, changes in renal function or vaginal bleeding did not occur during CPA treatment.

Disturbed liver function tests occurred during treatment in seven patients, but recovered spontaneously in five while CPA was continued (Fig. 1). In one patient, the liver function tests were abnormal at presentation but cleared during CPA treatment. In two of the seven patients, however, the liver functions became severely impaired. Transam-

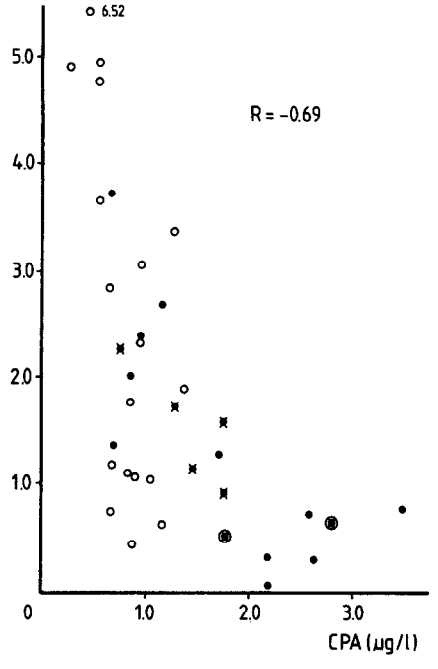

Fig. 1. Correlation between serum CPA and DHAS levels, R −0.69, *P* < 0.01, (○) 200 *mg CPA*, (●) 400 mg *CPA, cross and closed circle, patients with elevated liver function tests, cross and open circle, necrotizing hepatitis.*

inases rose up to 10 times normal (WHO grade 4), with only slightly elevated bilirubin levels (WHO grade 1), after 11 and 21 weeks on 400 mg CPA daily. The liver ultrasound scans and virus serology were negative in both. In these two patients microscopy of the biopsies showed acute and diffuse hepatitis with confluent and bridging necrosis, irregular scarring and evidence of regeneration. There was no granuloma formation, beginning of cirrhosis or cholestasis present. The CPA levels were not exceptionally high in these two patients, 2.8 and 2.0 µg/l respectively (Fig. 1). There was no difference in CPA levels between patients that had disturbed liver function tests or/and the others.

Relation between CPA levels and hormone concentrations

In Table 3 the relation between CPA dose and serum levels of CPA, cortisol, androstenedione, DHAS, LH, FSH and prolactin are given. During the use of 400 mg CPA, the median serum concentration of CPA was about twice as high as during 200 mg orally. During CPA treatment cortisol or androstenedione levels did not change, but a suppression of DHAS was seen, which was inversely correlated with the CPA levels, correlation coefficient *R*–0.69 (Fig. 1). LH and FSH levels were also suppressed during CPA treatment but not in a dose dependent manner. The serum levels of prolactin increased during CPA in all patients.

DISCUSSION

The anti-tumor effect of CPA in this patient group is disappointing, as only two out of 20 patients (95% confidence level 1–31%) responded to this treatment. This is contradictory to the good results found in male breast cancer, where seven out of ten patients responded to CPA [10]. The response in female patients lies significantly below the 40% found for high-dose medroxyprogesterone acetate (MPA) [1–4] and probably also below the reported response rate of 30–40% for megestrol acetate (MA) [11]. Most patients in this study had predominantly soft tissue localization, which usually does respond well to hormone manipulations. Even treatment with androgens, which has shown only limited effect in breast cancer, reaches up to 20% remissions [12]. The dosage of CPA was twice the usual amounts given for other disorders, which must certainly have been sufficient to reach a maximal tumor growth inhibiting effect.

The side-effects found during treatment correspond with those of a pure progestational compound: mood changes, absence of fluid retention or electrolyte changes but substantial nausea and weight loss. In this respect CPA is also considerably different from MPA or MA. These drugs usually will produce euphoria, increase appetite and weight gain together with hypertension [4]. Vaginal spotting or withdrawal bleeding did not occur either in CPA treated patients. The myocardial infarction, CVA and pulmonary embolism may have occurred by chance, in view of the elderly cancer bearing population we studied, or they might be a result of the effect that progestins can have on blood coagulability [13]. In an overview, 2.5% of thromboembolic complications were described [14]. Some investigators, however, also mention an incidence of thromboembolic events of 5–13% in patients with advanced breast cancer treated by chemotherapy or tamoxifen [15]. The occurrence of necrotizing hepatitis in two patients demonstrating a direct hepatotoxic effect by this dose of the drug has been reported in detail previously. The possible mechanisms of this side-effect have been discussed [16]. The liver had the same histological appearance in both patients. A high CPA concentration was found in the serum, although the CPA levels were not significantly higher in the patients with liver disturbance. Factors that may have been of influence are the advanced age of both patients (73 and 75 years) causing changes in drug metabolism [17, 18] and the CPA half-life of 24–36 h causing drug accumulation [19, 20].

The pattern of hormonal changes during CPA treatment differs also considerably from those of MA or MPA. There are changes in cortisol or androstenedione, while DHAS is depressed in a dose-dependent manner. This may indicate an inhibiting effect on DHA-sulfotransferase. *In vitro,* the 3β-hydroxysteroid dehydrogenase system was

Table 3. Serum levels of CPA, DHAS, cortisol, androstenedione, LH, FSH and prolactin (median and range) during 200 or 400 mg CPA daily

	Baseline	200 mg	400 mg
CPA μg/l	—	0.83	1.74**
		0.26–1.38	0.69–3.44
DHAS μM/l	1.79	2.12	1.26*
	0.78–6.95	0.47–6.52	0.08–2.75
Cortisol nM/l	450	—	415
	205–645		130–765
Androstenedione nM/l	3.59	—	3.97
	1.85–8.09		1.70–5.76
LH U/l	44.2	—	16.8*
	9.7–73.2		5.2–51.2
FSH U/l	65.2	—	22.3*
	22.2–137.9		2.9–39.9
Prolactin U/l	204	—	312*
	58–1063		171–1813

*P <0.01 vs. baseline values.
**P < 0.02 vs. 200 mg.

inhibited by CPA, which should have elevated the DHAS levels [21]. There are no signs of a suppression of ACTH or a direct inhibition of adrenal steroidogenesis, as it was found for MA and MPA [4, 10, 22]. The endocrine changes thus indicate that CPA lacks any glucocorticoid effects, which may also explain its therapeutic inferiority to the other two progestins. DHA and its sulfate (DHAS) are non-competitive inhibitors of the enzyme 17β-hydroxysteroid dehydrogenase, which inactivates estradiol to estrone within the tumor tissue [23]. In this way, suppression of DHAS might hamper the therapeutic effect of CPA. CPA also stimulates prolactin levels, while other progestins have no effect on prolactin, but the effects of prolactin on tumor growth still remain controversial.

The suppression of LH and FSH is similar to that found during MA or MPA, although we could find no negative correlation between the CPA levels and the serum concentration of gonadotropins. After menopause these findings do not seem to be of much consequence for cancer treatment, however.

In conclusion, the clinical and hormonal effects of CPA appear to be those of a pure progestin. Its therapeutic effectiveness in breast cancer patients is disappointing compared with other progestins given in high doses, which may be the result of the absence of adreno-corticoid activity of CPA. Thus, its use in female breast cancer cannot be recommended. The frequency of side-effects is considerable and sometimes severe but reversible in most cases. CPA may perhaps induce a hypercoagulable state, as reported for other progestational compounds. The occurrence of a drug-associated hepatitis warrants prudence in its use in male patients with breast or prostatic cancer who have approximately the same age as the population we studied.

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