Cyproterone Acetate in the Treatment of Metastatic Cancer of the Male Breast

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Ten male patients with advanced cancer of the breast were treated with cyproterone acetate, an antiandrogenic compound with additional progestational properties. Seven patients achieved a response, for a median duration of 8 months. Plasma testosterone and estradiol levels fell significantly during therapy, but quantitatively this drop was not related to the therapeutic response. Cyproterone acetate is an effective and well-tolerated treatment for metastatic male breast cancer.

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HORMONAL THERAPY plays an important role in the management of male breast cancer (MBC). For many years, the evaluation of hormonal therapies in inoperable or disseminated disease has been restricted primarily to orchiectomy,[1,2] which has been considered the best primary treatment. This has recently been questioned. High response rates and excellent tolerance observed with tamoxifen,[3] and high-dose medroxyprogesterone acetate,[4,5] led some investigators to consider these agents a valuable alternative to castration in patients with disseminated MBC. In 1982, we first reported on three male patients with metastatic breast cancer treated with another useful agent, cyproterone acetate (CPA).[6] This study presents our updated experience with the use of this drug in the treatment of metastatic cancer of the male breast.

Materials and Methods

Ten male patients with recurrent or progressive carcinoma of the breast were treated with CPA, 100 mg twice a day, between the years 1975 and 1983. The major clinical characteristics of these patients are summarized in Table 1. All patients had a histologically confirmed diagnosis of breast carcinoma, a life expectancy of at least 2 months, and a clearly measurable disease to serve as an indicator of response to therapy. None had undergone anti-cancer therapy for at least 1 month. Pretreatment studies included history and physical examination, assessment of Karnofsky performance status, complete blood cell and platelet counts, tests for serum chemistry values, chest x-ray, skeletal survey, and liver isotopic or ultrasonic scan. Additional studies were only done if clinically indicated. Hormone receptors were not measured. In seven patients, serum levels of ten hormones (testosterone, progesterone, cortisol, estradiol, triiodo-thyronine, thyroxine, thyroid-stimulating hormone, luteinizing hormone, follicle-stimulating hormone, prolactin) were determined by specific and sensitive radioimmunoassay methods to evaluate what are the expected changes in all patients receiving CPA, and the eventual difference in hormone levels between responders and nonresponders. For this analysis, a mean of two pretreatment determinations provided the baseline values and the mean of all measurements during the therapy yielded data for calculation of percent change of each hormone for each patient.

Objective response was evaluated according to criteria outlined by the International Union Against Cancer.[7] A diminution in lesion size had to be present for at least 4 weeks to be considered a response. Duration of response was calculated from the first day of treatment to date of progression. Survival was calculated from the date of initiation of therapy until death.

Results

As reported in Table 1, seven of the ten patients achieved an objective remission, for a median duration of 8 months (range, 3+–52 months). Noteworthy is Patient No. 2 who, although with a life-threatening disease resistant to cytotoxic drugs, had a complete remission (CR) of his liver, lung, bone, and soft tissue metastases lasting 52 months. On relapse, he was given tamoxifen with CR lasting 40 months. All partial responses were observed in patients with bone metastases. Three patients had stable disease, with a median duration of 4 months. No pretreatment characteristic provided a

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TABLE 1. Cyproterone Acetate in Advanced Male Breast Cancer

Patient no.	Age (yr)	Time from mastectomy (mo)	Disease-free interval (mo)	Previous treatment of metastases and response	Metastatic site(s)	Performance status	Dose (mg/day)	Response	Duration of response (mo)	Survival (mo)
1	55	20	14	CMFV + MPA(NC)	Lung	70	200	CR	21	24
2	63	140	103	Testolactone(P), DES(PR), CMFV(P)	Liver, lung, bone, soft tissue	30	200	CR	52	94+
3	71	179	111	Fosfestrol(CR), orchiectomy(PR)	Bone, lung	40	200	PR	9	13
4	58	141	137	None	Bone	70	200	NC	4	12
5	42	12	8	Radiotherapy(PR), (adjuvant CMF)	Bone	50	200	PR	5	18
6	68	16	13	FAC(PR)	Bone	80	200	PR	7	8
7	60	35	34	(Adjuvant CMF)	Bone	40	200	NC	6	16
8	62	28	21	Radiotherapy (PR)	Bone	80	200	PR	8	28+
9	77	84	18	Radiotherapy (P), CMF(NC)	Bone, soft tissue	50	200	NC	4	6
10	67	88	40	CMF + MPA(PR), Radiotherapy(PR)	Bone	60	200	PR	3+	3+

CMF: cyclophosphamide, methotrexate, and 5-fluorouracil; CMFV: CMF and vincristine; FAC: 5-fluorouracil, Adriamycin (doxorubicin), and cyclophosphamide; MPA: medroxyprogesterone acetate; DES: diethylstilbestrol; CR: complete response; PR: partial response; NC: no change; P: progressive disease.

uniquely different information for identifying patients most likely to respond to CPA.

Hormonal changes during therapy were those expected from the pharmacologic properties of CPA.[8] Plasma testosterone and estradiol levels fell to 37.6% ± 28.9% (mean values ± standard deviation) and 57% ± 34.6% of basal, respectively. The values of these hormones, both decreased significantly ($P < 0.05$), despite a high standard deviation. Progesterone achieved levels of 33.9% ± 29.6% of basal during therapy. The pituitary tropins, luteinizing hormone (LH), and follicle stimulating hormone (FSH) were suppressed to a minor extent, reaching 62.9% ± 64.4% of initial values for LH, and 64.5% ± 41.9% for FSH. Triiodo-thyronine, thyroxine, thyroid-stimulating hormone, and cortisol did not change as a result of treatment. In contrast, prolactin increased by 277.6% ± 77.6% due to the progestational properties of CPA.[8,9] No difference was observed in plasma hormone levels between the responder and the stable disease groups of patients.

Treatment with CPA was well tolerated. Apart from the sexual impotence, which is clearly related to the mechanism of action of CPA, only a few side effects were recorded, with weight gain in one patient, and gynecomastia and tiredness in another.

Discussion

Hormonal manipulations are frequently effective in the management of advanced MBC. Objective responses to orchiectomy can be expected in 38% to 67% of the patients,[10-12] with an additional proportion responding to subsequent major ablations.[10] For many years, additive hormonal therapy has been poorly defined. Regressions[1] as well as exacerbations[13] were observed in patients treated with estrogenic compounds. Subjective improvement was noted in a few instances with corticosteroids,[14] and occasional remissions were recorded with the use of progestins.[15] Recently the role of hormonal supplementation has been somewhat better outlined. Tamoxifen has been reported to be effective in 48% of 37 males with metastatic breast cancer,[3,16,17] and high-dose medroxyprogesterone acetate seems to be of value in this disease, with 8 responses observed in 10 patients.[4,5]

It is generally predicated that androgens stimulate the growth of MBC, although on occasion they have been beneficial.[18] This suggests that elimination of androgens from the hormonal milieu of patients harboring this disease would be of benefit. These considerations led us to treat disseminated MBC with cyproterone acetate, an anti-androgenic compound with additional pronounced progestational properties, and thus with a twofold potentially useful action. Therapeutic responses were seen in seven of ten patients, but we were unable to find any useful discriminant for predicting response. Remissions were obtained irrespective of patient age, performance status, disease-free interval, metastatic sites, and prior hormonal therapy or chemotherapy. No plasma hormone change could be considered as a valid indicator of treatment response. The prompt and prolonged fall of plasma testosterone after CPA can be accepted as one of the modes of action of this type of treatment. However, quantitatively this drop was not related to the therapeutic response. Patient No. 6, whose plasma tes-

tosterone fell to 66.5% of basal, had a partial response, whereas Patient No. 4 failed to respond, even though his testosterone level decreased to 10% of initial values. The same was true for plasma estradiol and gonadotropins. On the other hand, a fall in serum testosterone, estradiol, and gonadotropin levels is not absolutely necessary for achieving a response in advanced MBC. Remissions in this disease are observed with tamoxifen, although this drug is reported to cause a rise in serum testosterone, estradiol, and gonadotropin levels both in normal men and in men with breast cancer.[19,20]

A few comments about serum prolactin levels seem appropriate. An increase in prolactin levels is frequently observed after CPA treatment,[8] as it was in our patients. Antiprolactin agents affect the growth of experimental mammary tumors, but they were found of little value when used in advanced breast cancer of female patients.[21] Since the influence of prolactin increases on the growth of MBC is still unknown, the addition of prolactin inhibitors to CPA treatment in this disease warrants further investigation.

At the current time, the exact place of CPA in the treatment of metastatic MBC and its relation to other hormonal manipulations is not yet defined. Clearly, more patients are needed. Nevertheless, it has proved useful in achieving responses either in a patient refractory to medroxyprogesterone acetate, and in a patient who had stopped responding to orchiectomy. Furthermore, prior exposure to CPA does not preclude a subsequent response to other endocrine maneuvers.

In view of the physiologic and psychologic impact of orchiectomy, alternatives to this ablative procedure are of great value. Tamoxifen and high-dose medroxyprogesterone acetate should be considered in the primary treatment of disseminated MBC. To these agents cyproterone acetate should be added.

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