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Use of Cyproterone Acetate in Prostate Cancer

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Cyproterone acetate, a synthetic 21-carbon hydroxyprogesterone derivative, yields a potent androgen withdrawal effect due to both central and peripheral modes of action. Its progestational activity causes partial suppression of pituitary gonadotropins. In the target 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. This combination of activities results in decreased intranuclear concentrations of free and bound dihydrotestosterone.[9, 38] Cyproterone acetate was first introduced in clinical trials in 1966 by Scott and Schirmer,[43] who observed a 70% objective response rate in a small number of previously untreated patients with advanced carcinoma of the prostate. Although it has been used most often as a single agent in the treatment of metastatic disease, cyproterone acetate can be combined with orchiectomy, estrogens, and luteinizing hormone-releasing hormone (LHRH) agonists and yields tumor response rates similar to those of other forms of medical or surgical castration. In this article, the mechanism of action, clinical experience, toxicity, and new applications of cyproterone acetate in the treatment of prostate cancer are reviewed.

MECHANISM OF ACTION

The normal pathway of the neuroendocrine control of gonadal function is summarized in Figure 1*A*. The synthesis of testosterone by the Leydig cells of the testis is stimulated by pituitary luteinizing hormone (LH) and accounts for 90% or more of the dihydrotestosterone formed in the prostate. The remaining sources of testosterone are weak adrenal androgens and dietary sources. Serum testosterone, by acting as a negative feedback signal to the hypothalamus, regulates the secretion of LHRH and thus also of LH. Cyproterone acetate, owing to its progestational activity, overrides this negative feedback inhibition. The result is suppression of LHRH, LH, and, consequently, androgen production by the testes (Fig. 1*B*).

The predominant activity of cyproterone acetate, however, is competitive inhibition of androgens at the target cell level[31] (Fig. 1*B*). After drug administration, the concentrations of dihydrotestosterone and nuclear androgen receptor are markedly reduced. Cyproterone acetate has no effect on the conversion of testosterone to dihydrotestosterone by 5α-reductase. However, the blocking of dihydrotestosterone uptake into the nucleus inhibits androgen-dependent DNA and RNA synthesis. Consequently, protein synthesis is reduced, cellular autophagic mechanisms are triggered, and cell death occurs. In rodent and canine experiments, cyproterone acetate causes total loss of secretory activity in the prostate and significant tissue regression.[31] Histologic studies of treated canine prostates show almost complete disappearance of epithelium with an apparent increase in the stromal components.[31] Clinically, treatment of

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transsexuals also results in stromal hyperplasia,[11] possibly reflecting a stromal reaction in response to dihydrotestosterone depletion.[7]

PHYSIOLOGICAL EFFECTS AND REVERSIBILITY

Serum Testosterone

The clinical effects of cyproterone acetate on serum testosterone levels have been well documented. Mulder and associates[29] demonstrated a therapeutic decrease during 3 months of oral therapy. Knuth et al[26] treated 20 healthy young men with 100 mg per day for 14 days and observed that serum testosterone declined from a mean value of 14.6 to 3.3 nmol/L. Becker and Klosterhalfen[2] 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 cyproterone acetate therapy. In Jacobi's experience,[23] weekly intramuscular administration resulted in a rapid and sustained 70% decrease in testosterone levels. Only high doses of estrogen or castration plus cyproterone acetate exceeded this effect.

Spermatogenesis

The marked anti-androgenic effect of cyproterone acetate also is observed in the testes. Distinct tubular atrophy and variable inhibition of spermatogenesis are observed in both animals and humans given therapeutic doses of cyproterone acetate. The extent of the inhibition of spermatogenesis is dose dependent and differs from species to species. It is believed that cyproterone acetate acts primarily to limit the secretory activity of the androgen-dependent Sertoli cells. The decrease in the production of androgen-binding protein and FSH binding capacity of the Sertoli cells leads to a proportional decrease in spermatogenesis. Both animal and human studies have shown that testicular changes are reversible, at least within the first 12 months of therapy.[31]

Serum Prolactin

Cyproterone acetate increases the concentration of serum prolactin. In a study by Goldenberg et al,[18] a steady increase in the concentration of serum prolactin was observed; from an initial mean value of 8 ng/ml, a new threshold of about 16 ng/ml was established after 3 to 4 months, which then was maintained throughout the duration of therapy. In 15 of 51 patients, the level peaked at, or only slightly above, the upper limit of normal (20 ng/ml). Graf et al[19] found a 2- to 3-fold increase in the serum prolactin concentration in 14 young men treated with 10 or 20 mg of cyproterone acetate daily over a period of 24 weeks and in another 8 men treated with 50 or 100 mg for as long as 2 months; again, the prolactin values remained within the normal range. In a well-conducted randomized double-blind protocol, Knuth et al[26] found no significant prolactin increase in normal men receiving 100 mg of cyproterone acetate daily. Bartsch et al[1] found significant increases in prolactin after 3 months of therapy in orchiectomized patients being treated by intramuscular injection of 300 mg of cyproterone acetate. Sander et al[41] found similar elevations in orchiectomized patients treated with cyproterone acetate. They inferred that prolactin might have played a role in promoting tumor growth in this group of patients; however, their numbers were small (13 patients). Spona and Lunglmayr[46] managed 16 patients with 300 mg weekly by intramuscular injection and found insignificant elevations of prolactin compared with those in patients treated with estradiol undecylate, who had significant rises within 1 month of initiating therapy. Tunn et al[52] treated patients for 3 months, and although they observed rises of prolactin to 20 ng/ml, no patient had true hyperprolactinemia.

The mild effect that cyproterone acetate has on serum prolactin levels may explain why gynecomastia occurs less frequently than with estrogen therapy. When Goldenberg et al[18] grouped patients according to the concentration of prolactin at 4 months, no correlation with prognosis was found, in agreement with the observation of Stege et al.[47]

Salt and Water Metabolism

The effect of cyproterone acetate on salt and water metabolism has been studied during treatment of metastatic carcinoma of the prostate.[56] The mean plasma volume remains the same, and there is no significant change in serum albumin. This result differs significantly from the effects of estrogens, which increase plasma volume and consequently the risk of congestive cardiac failure.

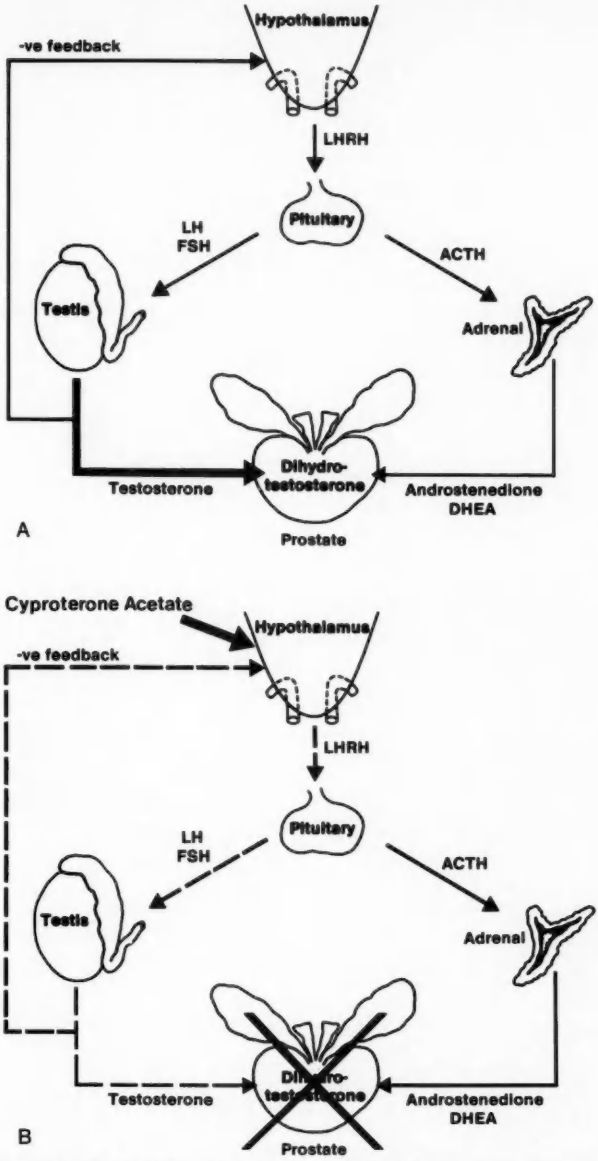

Figure 1. Neuroendocrine regulation of the testis. *A*, Normal axis. *B*, Effects of cyproterone acetate. −ve = negative. (Copyright Nicholas Bruchovsky, MD, PhD. Used with permission.)

Anticlotting Factors and Lipoprotein Concentrations

Unlike the changes observed with estrogen therapy, cyproterone acetate increases antithrombin III and fibrinolytic activity within the blood.[54] This fact, when taken in association with the unchanged plasma volume, implies that treatment with cyproterone acetate carries a lower risk of thromboembolism and congestive heart failure than does estrogen therapy.

Studies have shown that the concentration of high-density lipoproteins is lower at the same time that low-density lipoprotein levels are in-

creased.[32, 55, 58] This finding would favor an increased risk of cardiovascular complications; however, clinical experience in randomized studies has shown a lower incidence of cardiovascular side effects with cyproterone acetate than with estrogen therapy.[12]

Reversibility

Interruption of treatment with cyproterone acetate alone or in combination with other agents results in a return of serum testosterone levels to normal,[6, 18] usually within 8 to 14 weeks. The potential applications of such reversible action include intermittent therapy of advanced prostatic disease in sexually active men, adjuvant and neoadjuvant hormone withdrawal, and treatment of urologic emergencies related to prostate cancer.

BIOLOGIC EFFECTS

In most clinical studies, cyproterone acetate has been effective in bringing about the regression of the soft-tissue components of prostate cancer, including resolution of hydronephrosis and shrinkage of the primary tumor and involved lymph nodes. Response has been assessed objectively by a variety of means, including digital palpation, computed tomography (CT) scan, and transrectal ultrasound. In the earliest work, by Scott and Schirmer,[43] there was a marked reduction in local disease in 7 to 10 cases. Review of subsequent studies has shown positive objective effects on the primary lesions in 247 of 370 evaluable tumors (67%), with a response range of 40% to 100%. Goldenberg et al[18] noted a decrease in evaluable soft-tissue disease (local and metastatic) in 41 of 49 patients (84%). In contrast, improvement occurred in only 13 of the 48 initially abnormal bone scans (27%). This difference, and the fact that 22 of the 26 patients with progressive disease relapsed in the bone, whereas only 6 relapsed in nonskeletal sites, demonstrated the relative resistance of skeletal metastases to potent androgen withdrawal therapy and the dissociation between the two components of prostatic carcinoma. Tunn[51] examined radical prostatectomy specimens in patients pretreated with 300 mg of cyproterone acetate weekly by the intramuscular route for 2 months. Marked regressive changes in the morphology of the excised tumors and reduced immunohistochemical staining of acid phosphatase were observed.

It has been suggested[36] that in addition to its anti-androgenic and antigonadotropic effects, cyproterone acetate has an androgenic activity on the prostate gland and a glucocorticoid-like effect on the adrenal glands of adult male rats. In some of these experiments, differences in relative rates of regression of the prostate were questionably ascribed to androgenicity. Glucocorticoids in high doses will retard the involution of prostate tissue,[37] and the slowing effect is probably mimicked to some extent by the glucocorticoid-like activity of cyproterone acetate if administered to castrated animals in sufficiently large doses. It is highly unlikely that the minute changes observed in the degree of involution in rodent experiments employing huge amounts of anti-androgen are of clinical relevance. In fact, El Etreby and associates[15] showed that cyproterone acetate has a strong inhibitory effect on the prostate and seminal vesicle of intact adult rats and is unable to stimulate the regrowth of involuted prostate. To our knowledge, no instance of androgenization or its exacerbation has been reported among large numbers of women treated with cyproterone acetate for acne, hirsutism, alopecia, virilism, or precocious puberty.

CLINICAL APPLICATIONS

First-line Therapy of Advanced Prostate Cancer

Cyproterone Acetate as a Single Agent. When administered as daily oral tablets or as weekly intramuscular injections, cyproterone acetate is capable of producing response rates equivalent to those of diethylstilbestrol with a relatively lower incidence of cardiovascular side effects.[12, 34, 60] Scott and Schirmer[43] reported the first clinical experience with cyproterone acetate, noting a therapeutic response in patients treated with 100 to 250 mg/day. Three of ten patients who did not respond failed to improve after subsequent castration and estrogen therapy. In 1968, Geller et al[17] treated 11 patients (9 with stage D2 disease, 2 with stage C disease) with 250 mg/day orally. Objective remissions lasting 5 to 14 months were observed in nine patients and no response in two. Regression of the primary tumor was noted in most patients, and 2 of 11 developed gynecomastia. Other small phase II trials show similar objective response rates (80%) with a mean duration of remission of 17 months and minimal morbidity arising from treatment.[22, 39, 53, 59]

In a large multicenter randomized trial, Wenderoth and Jacobi[60] demonstrated that cyproterone acetate as monotherapy (300 mg weekly by intramuscular injection) was comparable to standard estrogen therapy (estradiol undecylate 100 mg weekly by intramuscular injection). Of the 91 patients completing the cyproterone acetate arm of the study, 91% had improvement in performance status, with 37% experiencing side effects. Almost identical therapeutic effects were observed in the 87 patients in the estrogen arm, 95% of whom had improvement in performance status but with a 94% incidence of untoward effects. Local tumor regression occurred in 67%, and the local mass was stabilized in a further 14% of the patients treated with cyproterone acetate.

Similar results were obtained by the European Organization of Research on Treatment of Cancer (EORTC) Urological Group, as reported by Pavone-Macaluso et al[34] in 1986. In a randomized phase III trial, those investigators compared cyproterone acetate (250 mg/day orally), medroxyprogesterone acetate (500 mg by intramuscular injection three times per week for 8 weeks followed by a maintenance dose of 200 mg/day orally) and diethylstilbestrol (3 mg/day orally). In a total of 210 patients with advanced prostatic cancer (T3–T4, Nx or N0, M0 or M1), complete and partial remissions occurred in 33% of the cyproterone acetate–treated patients and in 44% of the patients receiving estrogen (not statistically significant). Local tumor mass reduction of at least 50% was observed in 24 of 60 (40%) of the patients treated with cyproterone acetate. Overall, the incidence of side effects and complications was less in the group receiving cyproterone acetate. Initially, it was suggested that the patients given cyproterone acetate had less overall cardiovascular toxicity but a higher number of cardiovascular deaths. However, subsequent analysis by the authors revealed no significant differences in the cardiovascular death rates of the three treatment groups.

Cyproterone Acetate Combined with Low-dose Diethylstilbestrol. It has been observed that cyproterone acetate therapy alone is unable to suppress gonadotropin release and androgen production completely, with its effect apparently weakening after 6 to 9 months.[52] In animal studies, Voigt and Bartsch[57] found that cyproterone acetate did not lower nuclear dihydrotestosterone concentrations to zero. The possible advantage of reinforcing the neuroendocrine action of cyproterone acetate with a low dose of diethylstilbestrol was explored by Rennie et al[38] in a study that compared the relative ability of 12 different androgen withdrawal procedures to mimic the acute results of surgical castration on the rat prostate. The most potent androgen withdrawal was obtained with the combination of cyproterone acetate and low-dose diethylstilbestrol, which reduced the concentration of whole tissue dihydrotestosterone, nuclear dihydrostestosterone, and androgen receptor by 90% to 96%, approximating, but not surpassing, the effects of surgical castration.

Taking advantage of the synergism between progestational and estrogenic compounds,[40] Goldenberg et al[18] studied the effects of a low dose of diethylstilbestrol (0.1 mg/day orally) combined with cyproterone acetate (200 mg/day orally) in 51 patients with stage D2 prostate cancer. Serum testosterone decreased from an initial mean concentration of 360 ng/dl to 56 ng/dl after 1 week and reached a plateau of approximately 30 ng/dl after 2 months, a decrease of 92%. If the administration of diethylstilbestrol was interrupted, the concentration of serum testosterone increased from the baseline of 30 ng/dl to between 135 and 200 ng/dl, representing the concentration range attained with the use of cyproterone acetate alone.[52] Moreover, the weakening of the antigonadotropic effect of cyproterone acetate expected after 6 to 9 months of treatment was not evident with the co-administration of diethylstilbestrol. The rapid decrease of serum testosterone into the castrate range (often within 1 week, and in all patients by 2 months; mean 25 days) could not be ascribed to diethylstilbestrol alone, because at a dose of 0.1 mg daily, this drug has no effect on serum testosterone.[24]

A complete response was observed in 7 patients (13%), a partial response in 35 (69%), and stable disease in 8 (16%), yielding an overall objective response rate of 98%. The actuarial median time to progression was 17 months and the median survival time, 24 months. True surviving fractions at 12, 24, 36, and 60 months were 84%, 51%, 34%, and 15%, respectively. It was concluded that cyproterone acetate and low-dose diethylstilbestrol could be used as a potent form of androgen withdrawal therapy to bring about regression of the primary tumor and soft-tissue metastases with a high degree of reliability.

Low-dose Cyproterone Acetate Combined with Low-dose Diethylstilbestrol. The synergistic combination of a low dose of cyproterone acetate (100 mg/day orally) and a low dose of diethylstilbestrol (0.1 mg/day orally) has been studied by the authors as a means of achieving

and maintaining castrate levels of serum testosterone with a minimum-dose protocol. At the lower dose, the potential adverse effects of either drug, as well as the monthly costs of therapy, are reduced. In 50 patients treated with this drug combination, a rapid fall in the mean concentration of serum testosterone was noted; this paralleled the rate of decline observed with a higher dose of cyproterone acetate (200 mg/day) plus low-dose diethylstilbestrol (0.1 mg/day). The medical castration effect was maintained for as long as 16 months, the longest follow-up period. Minimal toxicity was encountered; therapy was stopped in one patient because of severe lassitude and depression, and a second patient refused to continue after developing diarrhea. In two patients, breast tenderness and swelling necessitated modification of the drug dosage for relief of symptoms. In six patients whose therapy was purposely discontinued, serum testosterone returned to normal level within a mean time of 2.6 months, accompanied by recovery of libido and potency.

Cyproterone Acetate Combined with an LHRH Agonist. The LHRH agonists are synthetic analogues of the natural gonadotropin-releasing factor and, owing to minor changes in amino acid composition, possess greater potency than the parent hormone. After administration, a paradoxic effect is observed consisting of an initial stimulation of pituitary release of LH and FSH followed, after 1 to 2 weeks, by a gradual inhibition.[30] In synchrony with the LH and FSH levels, the concentration of serum testosterone first rises and then falls to castrate levels. This transient elevation of serum testosterone may initially stimulate tumor growth (flare reaction), and about 10% of patients experience exacerbation of pain symptoms.[30, 42] To avoid such complications, anti-androgens are sometimes administered concurrently with an LHRH agonist either temporarily or on a continuous basis.

During the initial phase of LHRH agonist therapy, the central inhibitory effect of cyproterone acetate effectively blocks the flare phenomenon. Jacobi[23] treated 23 patients with buserelin acetate together with cyproterone acetate (150 mg/day orally) and found no significant stimulation of serum testosterone compared with LHRH agonist alone. Prior administration of cyproterone acetate for 5 days caused a significant drop in serum testosterone, although not into the castrate range;[23] subsequent LHRH injection led to a rise of serum testosterone into the normal range but not higher. This observation was confirmed by Klijn et al.[25] Svensson et al[49] pretreated prostate cancer patients with cyproterone acetate for 15 days and found that goserelin acetate (Zoladex) only brought the level of serum testosterone back into the range measured before therapy. Castrate levels of serum testosterone were reached promptly and maintained despite discontinuation of cyproterone acetate. Similar results were obtained by Boccon-Gibod et al.[4]

In a study by Bruchovsky et al,[6] cyproterone acetate (100 mg/day orally) was administered with diethylstilbestrol (0.1 mg/day orally) for 30 days prior to initiating goserelin acetate therapy to suppress the pituitary completely. Serum testosterone levels were suppressed to the castrate range, generally within 1 week, and there was no significant increase with administration of goserelin acetate. In this protocol, diethylstilbestrol was discontinued after 60 days, and patients were maintained on goserelin acetate and cyproterone acetate.

After the pituitary has been downregulated by an LHRH agonist and the period of flare has passed, the continued use of an anti-androgen may or may not be advantageous. Schroeder et al[42] have published a randomized study of 71 patients with metastatic prostate cancer in which they observed a nonsignificant difference in progression rates of 38% and 41% between the LHRH agonist and LHRH agonist plus cyproterone acetate arms, respectively; the median time to progression in both groups was 13 months.

Cyproterone Acetate Combined with Orchiectomy. Medical-surgical combination therapy (total androgen blockade) began in 1966 with the work of Bracci,[5] who treated patients with orchiectomy followed either immediately or later (at the time of disease progression) by cyproterone acetate. As part of a larger study of the effects of cyproterone acetate on stage D2 prostate cancer, Di Silverio and Sciarra[13] compared the survival in a subgroup of 27 patients treated with cyproterone acetate immediately after orchiectomy with that of 26 patients treated at the time of tumor progression.[13] The proportion of patients alive at 36 months in the immediately treated group was 62%, significantly better ($P < 0.05$) than the 54% in the delayed-treatment group.

Becker and Klosterhalfen[2] randomized 78 orchiectomized patients with metastatic cancer to receive either cyproterone acetate (n = 26), diethylstilbestrol diphosphate (n = 24), prednisone (n = 12), or placebo (16). The survival times after 2 years were 62%, 42%, 58%, and 69%, respectively. After 5 years, the survival

rate was 25% (3 of 12) in the prednisone group and 23% (6 of 26) in the cyproterone acetate group. Only 1 of the 16 patients initially randomized to receive placebo remained alive at 5 years.

Pescatore et al[35] managed 38 previously untreated patients with stage D2 disease using castration plus cyproterone acetate, 150 to 300 mg/day orally. Clinical follow-up ranged from 10 to 60 months. A complete or partial response was observed in 12 patients (32%) and stable disease in another 50%, for a total initial objective response rate of 82%. The 3- and 5-year survival rates were 27% and 18%, respectively, with 78% of the deaths attributable to cancer.

In a randomized study of 34 patients with advanced disease, Sander et al[41] found that 13 patients treated by orchiectomy and cyproterone acetate (200 mg/day orally for 6 weeks) fared significantly worse (remission rate of 62%) than a comparable group of 14 managed with 10 mg of prednisone/day orally for 6 weeks (remission rate of 93%) after surgery. In the control group of patients managed by orchiectomy alone, six of seven responded initially. Two of the three patients who were not aided by cyproterone acetate were brought into remission on secondary prednisone therapy.

Second-line Therapy of Advanced Prostate Cancer: Cyproterone Acetate as Secondary Endocrine Therapy

Cyproterone acetate has been used to treat patients who relapse after primary therapy, on the basis that it may block residual androgens at the target cell level. Smith et al[44] treated 35 patients, all of whom had either not responded to estrogen therapy or had relapsed afterwards, with 300 mg of oral cyproterone acetate daily. Bone pain was reduced in 12 of 19 (61%), energy was increased in 5 of 13 (39%), and the size of the prostate was decreased in 12 of 28 (43%) of those who could be assesed. Overall, those investigators noted subjective and objective improvement in 68% of the patients, with minimal toxicity and a decrease in estrogen-induced gynecomastia, nausea, and fluid retention. Wein and Murphy[59] managed 15 previously treated patients with cyproterone acetate (200 or 250 mg/day orally). Pain decreased in 4 of 10, and voiding improved in 1 of 4. As was reported by Smith et al,[44] these authors found that the prostate shrank in 6 of 13 patients (46%), and the investigators concluded that cyproterone acetate may offer a chance for improvement in patients relapsing after another form of hormonal therapy.

Continuation of Therapy in Hormone-resistant Disease

Advanced prostate cancer that has become refractory to initial hormone withdrawal therapy carries a poor prognosis, and the question arises whether the patient would benefit from continuation of anti-androgen therapy. If the primary treatment was based on cyproterone acetate as a single agent, measurement of serum testosterone may reveal a level slightly above the baseline of 1.5 nmol/L. If this is the case, low-dose diethylstilbestrol (0.1 mg/day) may be administered to reinforce the suppressive action of cyproterone acetate on the pituitary and testes; this measure also allows the dose of cyproterone acetate to be reduced. If there is no effect on disease progression, orchiectomy should be considered. In the face of progressive disease, it is not advisable to stop therapy with anti-androgens. We have observed that the recovery of testicular function results in accelerated tumor growth, as evidenced by an increase in the rate of change of the level of prostate-specific antigen. These observations are consistent with the findings of Manni et al,[27] who concluded that androgen priming had an adverse impact on the natural history of the disease.

Intermittent Therapy of Prostate Cancer

The reversibility of the antigonadotropic and anti-androgenic effects of cyproterone acetate makes it possible to alternate a patient between periods of treatment and no treatment. This approach affords the possibility of recovering sexual function and has been helpful in managing the younger patients with prostate cancer. In our experience, optimum results have been obtained in men with inoperable locally advanced disease and no evidence of skeletal metastases. Treatment is stopped when the prostate-specific antigen level has been normal for at least 4 months and restarted when the level of this marker reaches the pretreatment value. Generally speaking, the cycles with and without cyproterone acetate (or alternative androgen withdrawal therapy) last about 6 months each, and treatment has been successfully repeated as many as four times with no loss of tumor androgen dependency. In a somewhat

unorthodox application of cyclic therapy, two male vocalists have recovered normal singing pitch before important musical performances.

Neoadjuvant Therapy of Prostate Cancer

A better understanding of the biology of prostate cancer has highlighted the fact that the risk of systemic spread is already appreciable at the time of initial diagnosis. Under such conditions, the results of radical prostatectomy will be less than optimal, although the operation may still be indicated for control of locoregional disease. Preoperative treatment for 3 to 4 months with a reversible androgen withdrawal agent such as cyproterone acetate affords the possibility of downstaging the primary tumor and eradicating micrometastases. Theoretically, this approach should improve the survival rate, and it is the subject of several preliminary trials.

The same principle has been used in the downstaging of prostate cancer prior to external-beam irradiation. Porter has conducted a pilot study in which 15 patients with stage B2 or C prostate cancer were treated with cyproterone acetate (300 mg/day orally) for 3 months prior to radiotherapy. In 12 of 15 patients (80%), digital rectal examination suggested complete resolution of the tumor with this combination (AT Porter: personal communication).

Adjuvant Therapy of Prostate Cancer

The role of hormone withdrawal therapy in patients with pathologic stage C disease after radical prostatectomy has not been studied before. The advantage of this form of therapy is that both local and subclinical metastatic disease may be responsive. In animal studies, Henry and Isaacs[20] demonstrated that the probability of cure decreased as the size of the primary tumor increased and as there was a delay in starting adjuvant chemotherapy. Similarly, Isaacs[21] demonstrated that androgen ablation therapy is optimally effective when used early. In clinical trials, Zincke et al[61] combined surgery and immediate androgen ablation in 43 patients with pathologic stage C prostate cancer. These patients did as well as a historical control group who had pathologic stage B prostate cancer. These observations are consistent with the results of Benson et al,[3] who projected a 76% 10-year survival rate in 40 patients treated by radical prostatectomy and immediate orchiectomy.

Bruchovsky et al[8] have demonstrated that androgen withdrawal produces a 2-logarithm cell kill in the androgen-dependent Shionogi mouse mammary carcinoma model. This finding implies that a tumor should be treated when fewer than 100 stem cells are present in each metastatic lesion. If we assume that failure rates after local therapy are attributable to metastatic disease present at the time of initial treatment, then immediate hormone withdrawal may lead to killing of sufficient stem cells in small metastatic foci to cure early disseminated disease. The optimal duration of adjuvant hormonal therapy has not been established. Regression of soft-tissue tumor commonly occurs within 3 to 6 months of starting therapy, suggesting that 6 to 12 months of treatment may be sufficient. This would be consistent with the observations of Spirnak and Resnick,[45] who noted that patients treated with orchiectomy for metastatic disease experienced regression of prostatic tumor within 6 months.

Treatment of Emergency Conditions

Urinary retention is a common presentation of patients with prostate cancer. Rapid relief of urethral obstruction can be obtained with catheterization and subsequent transurethral resection. Procedures that result in a rapid decline of serum testosterone may also be used to bring about regression of the obstructing lesion, particularly in the high-risk surgical patient or the individual with extensive local disease.[16] Orchiectomy and the use of cyproterone acetate or ketoconazole are recommended for this purpose.

When a patient presents with signs of impending spinal cord compression or hydronephrosis, it seems reasonable to add an agent such as cyproterone acetate to conventional management. The use of an LHRH agonist is not advised, because an acute elevation in the concentration of serum testosterone may stimulate tumor growth and exacerbate the condition.

Treatment of Hot Flushes

The normal neuroendocrine mechanism for control of thermoregulation is centered in the hypothalamus.[30] When orchiectomy or LHRH agonist therapy leads to a peripheral androgen deficit, inhibitory factors, presumably opioid peptides, which normally are stimulated in the

presence of sex steroids, are no longer released from the hypothalamus. This results in increased central adrenergic activity, with release of norephinephrine and inappropriate stimulation of thermoregulatory centers; body heat is lost through peripheral vasodilation and manifests as hot flushes.

This effect can be blocked by the administration of central anti-adrenergic medication (clonidine)[33] or of steroids with central inhibitory action such as exogenous testosterone (clearly contraindicated in prostate cancer), estrogens[48] (relatively contraindicated because of side effects), or progestogens.[10] Cyproterone acetate in a dose of 100 mg/day orally has significantly suppressed hot flushes with a minimum of side effects.[6, 14, 28] This effect cannot be achieved with a pure nonsteroidal anti-androgen (such as flutamide) that lacks a central antigonadotropic effect.

SIDE EFFECTS

Hormone-related Effects

The most frequently recorded adverse effects of cyproterone acetate are those related to the hormone deprivation. Virtually all patients become impotent, and spermatogenesis is inhibited. Central nervous system effects such as fatigue, weakness, and headache are attributable to the lowering of serum testosterone. Nipple tenderness and breast swelling and enlargement, although having different emotional and physical effects on patients, are usually considered together as gynecomastia. In the randomized study conducted by Wenderoth and Jacobi,[60] the incidence of gynecomastia was 13%; in the EORTC study,[34] it was 6%. In contrast, in the two estrogen-treated groups, the occurrence rates were 40% and 77%, respectively.

Cardiovascular Effects

Cerebrovascular accidents, fluid retention including peripheral edema, venous thrombosis, pulmonary embolus, cardiac ischemia, congestive heart failure, and sudden death have all been reported in patients taking cyproterone acetate. A careful study of cardiovascular toxicity was published by the EORTC Urological Group.[12] The risk of severe cardiovascular effects was lowest with cyproterone acetate (10% compared with diethylstilbestrol 34%, estramustine phosphate 15%, and medroxyprogesterone acetate 18%) and occurred most commonly during the first 6 months of therapy. Careful monitoring of patients during the early treatment period was advised.

Goldenberg et al[18] noted a cardiovascular complication in 6 of 51 patients (11%), while Wenderoth and Jacobi[60] documented a 9% rate of edema or thrombosis. The relatively low risk of cardiovascular toxicity may be attributable to the unchanged plasma volume, the increased level of antithrombin III, and increased fibrinolytic activity, as described by Varenhorst.[54] In a study by Tveter et al,[53] a higher incidence of serious complications (8 of 16) was reported; however, the pretreatment cardiovascular status of the patients was not given.

Other Side Effects

A variety of mild reactions have been reported with the use of cyproterone acetate. They include depression, diarrhea, nausea, indigestion, abnormal liver function tests (increased transaminase concentrations), decreased response to ACTH with lowered cortisol, hypochromic anemia, changes in plasma lipid profiles, and impaired carbohydrate metabolism. These effects rarely necessitate discontinuation of therapy. Cyproterone acetate is contraindicated in patients with renal insufficiency, hepatic dysfunction, or known hypersensitivity to the drug.

CONCLUDING REMARKS

Cyproterone acetate has been available for the treatment of prostatic carcinoma since 1980. It is a proven effective agent and, in combination with low-dose diethylstilbestrol, affords a very potent form of androgen withdrawal therapy. Because the resultant fall in serum testosterone is rapid, it is possible to institute treatment almost immediately. This is generally reassuring to both the patient and the urologist and allows surgical orchiectomy to be considered under more propitious circumstances. For example, operation might be deferred until it is clear that the disease is hormone responsive or carried out if the patient finds that the side effects of the drug are unacceptable.

Cyproterone acetate can be used to block LHRH agonist-induced flare reactions and to reduce the frequency of therapy-related hot flushes. With the increasing popularity of LHRH agonists, cyproterone acetate must be

considered as having a useful role in this context, although it is equally effective on its own.

Cyproterone acetate provides a reversible form of androgen withdrawal; with its low side effect profile, it enables the clinician to consider intermittent therapy of advanced disease in patients who wish to recover sexual function during treatment. It also allows therapy of earlier stages of cancer while not seriously affecting the quality of life. Early experience with this approach has been positive, and prospective studies are being planned.

SUMMARY

Cyproterone acetate is a progestational antiandrogen with potent antigonadotropic activity that results in rapid suppression of serum testosterone. Used as a single agent, cyproterone acetate yields a total androgen blockade. It may be combined with low-dose diethylstilbestrol, orchiectomy, or LHRH agonists to improve, in theory, the results of such therapy. In clinical testing, cyproterone acetate has proved equivalent to diethylstilbestrol with markedly less toxicity. It is useful in conjunction with LHRH agonists, either transiently to block the flare phenomenon, or continuously to block peripheral androgen receptors; the necessity for this latter action has not yet been proved. Cyproterone acetate may afford transient objective improvement in patients not responding to other forms of hormone deprivation. Experience in this role is limited. The drug may be used to suppress the hot flushes associated with orchiectomy or LHRH agonist therapy. Cyproterone acetate induces local tumor regression; owing to its reversible effects, it is useful as neoadjuvant or adjuvant androgen withdrawal therapy in patients with lower-stage disease undergoing radical surgery or radiotherapy.

Adverse effects are mostly those related to hormone withdrawal, namely, impotence, infertility, and lassitude. Gynecomastia and breast tenderness occur in less than 18% and cardiovascular complications in approximately 10% of treated men.

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