Cyproterone Acetate in Advanced Male Breast Cancer

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Three male patients of 55, 63 and 71 years of age, with metastatic breast cancer, were treated with cyproterone acetate. Two patients showed complete remission, one lasting 21 months, another 51+ months and a third achieved partial remission lasting 9 months. These results suggest that cyproterone acetate may be useful in the treatment of advanced male breast cancer.

***Cancer* 49:9–11, 1982.**

CYPROTERONE ACETATE (1,2α-methylene-6-chloro,$\delta^{4,6}$-pregnadiene 17α-01-3,20-dione-17-acetate) is a synthetic 21 carbon steroid with marked antiandrogenic and progestational activity, whose use in the treatment of prostatic carcinoma was first reported by Scott and Schirmer in 1966.[22] It has been shown to inhibit testosterone-induced growth of the prostate, seminal vescicles, sebaceous glands and preputial glands in the rat.[3,19] The mechanism responsible for its antiandrogenic action is not related to an interaction with the 5α-reductase, the enzyme which transforms testosterone in its active intracellular metabolite dehydrotestosterone, but rather to a receptor interaction.[25] Cyproterone acetate has never been used in treating male breast cancer.

This report presents the results of therapy with the use of this drug in three patients with advanced male breast cancer.

Case Reports

Case 1

In March 1973, a 55-year-old man, suffering from angina pectoris since 1970, consulted his physician because of a 1 × 1 cm tumor in his right breast. In October 1973, a right radical mastectomy was performed for medullary carcinoma with three of five axillary lymph nodes involved. Postoperative irradiation was given. On December 13, 1974, multiple pulmonary metastases were found on chest x-ray films, while bone survey, liver scan, urinary 17-ketosteroids and total urinary estrogen values were normal.

The patient refused orchiectomy or estrogens and therefore a combination chemotherapy was begun (VCMF—vincristine, 1.4 mg/m^2 intravenously on day 1; methotrexate, 20 mg/m^2 intravenously on days 1 and 5; cyclophophamide, 300 mg/m^2 intravenously on days 2–5; and fluorouracil, 300 mg/m^2 on days 2–5. Cycle frequency: every three weeks) in association with medroxyprogesterone acetate (250 mg intramuscularly twice a week). Following the fourth cycle of combination chemotherapy, in June 1975, disease progression was manifested by an increase in size and number of pulmonary nodules (Fig. 1). For this reason, the regimen was discontinued and cyproterone acetate, 100 mg twice a day, was administered. By November 1975, pulmonary metastases had disappeared (Fig. 2) and the patient was free of disease until March 1977, when disease progression was observed.

Case 2

In August 1964, a 63-year-old man underwent a right simple mastectomy followed by radiotherapy to the anterior chest wall, for an infiltrating ductal carcinoma. In March 1973, a metastatic axillary lymph node was excised and irradiation to the homolateral axillary areas was given. In September 1973, the patient developed two 1 × 1 cm metastatic nodules on the anterior right chest wall and hormonal therapy (testolactone, 100 mg intramuscularly every two days) was begun. Therapy was discontinued because of an increase in the size of the subcutaneous nodules. In April 1974, a physical examination disclosed three 1.5 × 1.5 cm nodules on the anterior right chest wall, two 1 × 1 cm nodes in the right axilla and severe pain on the lumbar spine. Chest roentgenogram and bone survey displayed pulmonary nodules and osterolytic lesions in the skull, in the posterior portion of three ribs on the left side and in the body of the L-2 vertebra.

The patient refused orchiectomy and therefore diethylstilbestrol, 15 mg/day, was begun. Follow-up showed complete pain relief and the disappearance of the subcutaneous nodules as well as the axillary nodes. In December 1975, the patient suffered diffuse bone pain, fever and abdominal swelling. His clinical state progressively worsened. In March 1976, a physical examination showed three 1 × 1 cm nodules on the anterior right chest wall, two 1 × 1 cm nodules on the right wrist, three 1.5 × 1.5 cm nodes in the right axilla, hepatomegaly and ascites. Liver scan revealed generalized liver enlargement with multiple focal areas of decreased uptake. Chest x-ray and bone

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Accepted for publication November 25, 1980.

0008-543X/82/0101/0009 $0.65

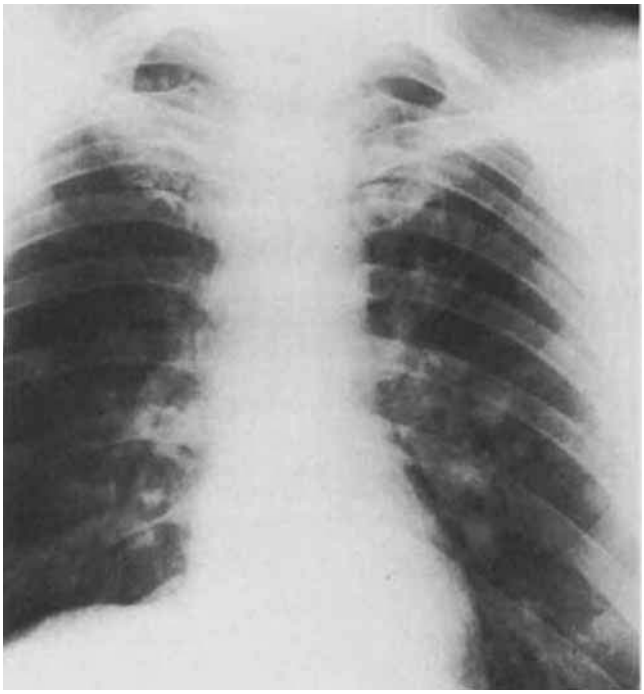

FIG. 1. Case 1. June 1975. Multiple metastatic lesions in both lungs.

survey showed lung metastases and osteolytic areas in the skull, in the upper end of the left femur and in the body of the L-2 vertebra. This latter lesion was also clearly visible by a bone scintigram.

Because of the progression of the disease following the first cycle of VCMF therapy, in April 1976, we began treatment with cyproterone acetate, 100 mg twice daily. One month later, fever, ascites and pain had completely disappeared. Within three months, the patient was well, subcutaneous nodules and axillary nodes had regressed and the liver was not palpable. Follow-up showed progressive improvement of the osteolytic and hepatic lesions. In November 1979, a bone scintigram revealed a slight increased uptake of radioactivity in the upper lumbar spine and the liver scan was normal. In July 1980, x-rays showed a complete regression of the osteolytic metastases in the body of the L-2 vertebra. Today the patient is alive and free of disease.

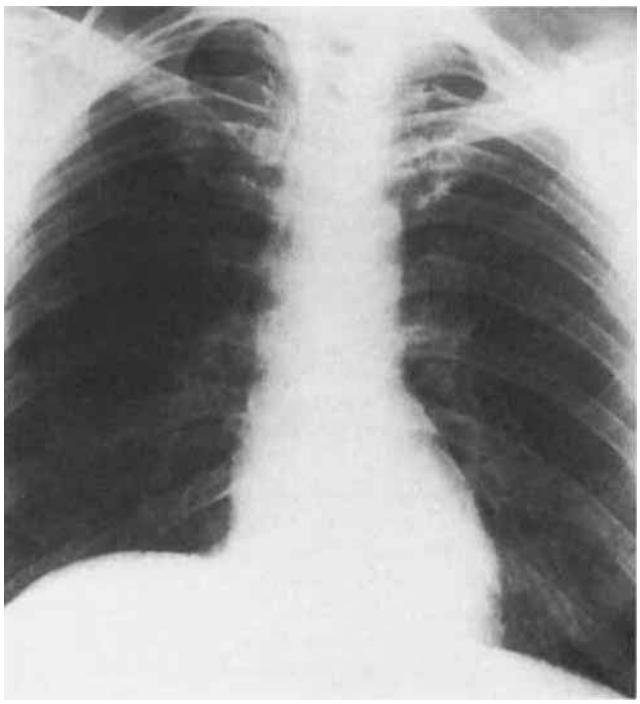

FIG. 2. Case 1. November 1975. Absence of tumor.

Case 3

In July 1962, a 71-year-old man with no previous history of disease underwent a left radical mastectomy for infiltrating ductal carcinoma involving the axillary lymph nodes. The patient was free of symptoms until September 1971 when he developed pulmonary metastases, which disappeared with the administration of diethylstilbestrol diphosphate therapy. In June 1974, concomitant with chest pain, a chest roentgenogram showed the reappearance of lung metastases and osteolytic lesions in four ribs on the left side.

A bilateral orchiectomy was performed and the patient was well until April 1975, when he consulted his physician complaining of bone pain. No therapy was started. In May 1977, a bone survey revealed osteolytic areas in the pelvis, the upper end of the right humerus and ribs on both sides. Hormonal therapy with cyproterone acetate, 100 mg twice daily, was begun. One month later the pain had completely disappeared and within four months we found partial recalcification of the osteolytic lesions. Again by March 1978, the patient suffered severe pain all over. Disease progression was mainifested by an increase in number of bone metastases.

Discussion

Carcinoma of the male breast is an uncommon disease which accounts for only 0.38 to 1.5% of all cancer in males.[21] It is generally agreed that ablative hormonal therapy is helpful in disseminated disease and the first treatment is traditionally castration.[8] Nevertheless, many patients refuse orchiectomy and because so little has been reported on the effects of cytotoxic chemotherapy, it is not possible to give a definite opinion in this regard.[5]

The role of additive hormonal therapy, a mainstay in females, has not yet been well defined in men. There have been both regressions[6,8,9,11,13,20,24] and exacerbations[9,11,15] with the use of estrogens but no well-defined series has been reported. Only one objective response to progestogens has been reported.[7] Corticosteroids have proved useful only in achieving occasional short-term remissions.[24] Recently six objective responses in eight patients treated with tamoxifen[1,2,4,12,18] have been observed, but no meaningful conclusions can be drawn from such a limited number of cases. In addition, tumor

stimulation in female breast cancer has some-times occurred with this agent.[14,16] Except for three cases,[6,10] androgens have generally been said to exacerbate the disease process. This was also observed in one of our patients (Case 2) who had a spontaneous regression following androgen withdrawal, lasting five months. This suggests that antiandrogens may be useful in treating advanced male breast cancer, as well as in prostatic carcinoma.

Cyproterone acetate has the advantage of possessing a two-fold action: it is antiandrogenic and progestational, both of which are potentially useful in treating male breast cancer. Nevertheless, its molecular action mechanism is difficult to explain in one single way. There is, in fact, little known regarding the relationship between hormone receptors, host's hormonal milieu, intratumoral hormonal interconversions and hormonal manipulations, on the one hand, and therapeutic responses on the other.[17] Unfortunately in our patients it has not been possible to determine hormone receptors. Moreover, therapeutic response has been observed both in a progesterone-refractory tumor and in tumors which have stopped responding to estrogen therapy and/or castration.

From this point of view, male breast cancer differs from prostatic carcinoma, where no significant results have been obtained by using cyproterone acetate in estrogen-refractory patients.[23] At the present time, male breast cancer appears to respond to a variety of hormonal manipulations. However, the type of additive hormonal therapy to be used as first-line therapy in advanced disease is difficult to establish because of the few patients available. The tumor responses which we have seen in our patients indicate that cyproterone acetate can be useful in the management of disseminated disease, even in cases which are resistant to other hormonal manipulations.

Clearly, further studies are necessary to determine the degree of activity of this agent and to select the patients on whom it should be used. It is likely that, if clinical correlations prove that steroid hormone receptors are, in the male, an accurate test in predicting the response to endocrine therapy as in the female, it might be possible in the future to carry out endocrine therapy on a more rational basis in advanced stages of male breast cancer.

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