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Trilostane in the Treatment of Advanced Breast Cancer

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Summary. *The combination of trilostane 960 mg daily and either dexamethasone 0.5 mg b.d. or hydrocortisone 10 mg b.d. has been used to treat advanced metastatic breast cancer in post-menopausal women. Twenty-three patients had assessable discase and received treatment for a minimum of 8 weeks. Six (26%) showed an objective response and three (13%), stabilisation of previously progressive disease, sustained for at least 3 months. Side-effects were mainly gastrointestinal. Biochemical studies suggest that the mechanism of action may be inhibition of conversion of androstenedione to oestrone.*

Introduction

Trilostane (4 α, 5 epoxy-17 β-hydroxy-3-oxo 5 α androstane-2-carbonitrile) is an effective inhibitor of the 3β-hydroxysteroid dehydrogenase, Δ5-4 isomerase system in the rat adrenal, inhibiting the conversion of the biologically inactive Δ5 steroids to their Δ4 derivatives [8, 9]. It is also capable of decreasing cortisol secretion in some patients with Cushing's sydrome [11], apparently by the same mechanism [6]. These observations suggested that it might be used to inhibit adrenal androgen synthesis in patients with metastatic breast cancer and thus inhibit progression of disease in those with hormone-sensitive tumours. We therefore elected to study the effects of a combination of trilostane and a replacement dose of glucocorticoid in post-menopausal patients with advanced breast cancer.

Patients and Methods

All patients had histologically proven breast primaries, and were either naturally post-menopausal or had received an X-ray-induced artificial menopause. They were consecutive patients with evidence of disease progression referred to one unit. The majority had progressed while receiving either combination chemotherapy or previous hormone therapy, and were considered unsuitable for further chemotherapy due to age or general condition. Patients who had received treatment with aminoglutethimide or had undergone hypophysectomy or adrenalectomy were excluded. Before entry to the study all hormone or chemotherapy had been discontinued for at least 1 month.

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Initially a pilot study was undertaken to establish the effects on steroid biosynthesis and the toxicity of treatment. Data from these patients are included in the analyses of biochemical results and side-effects. However, patients were only considered evaluable for response if they had measurable disease and completed more than 8 weeks of therapy. Twenty-three patients fulfilled these criteria. Of these, 11 had received no previous systemic therapy and were included late in the study when it became clear that trilostane was active.

In all instances informed consent was obtained from the patients. The study was approved by the Ethical Committee of the University Hospital of South Manchester.

Drug Administration. The first 23 patients were admitted to hospital for the first 2 weeks of therapy; subsequent patients followed the same regimen as out-patients. Trilostane 60 mg q.d.s. was given orally. After 3 days the dose was increased to 120 mg q.d.s., and at 7 days, to 240 mg q.d.s. At 10 days from the start of treatment either dexamethasone 0.5 mg b.d. or hydrocortisone 10 mg b.d. was added, to prevent possible glucocorticoid deficiency and to limit the rise in ACTH concentration that might be anticipated. In patients in whom there was any evidence of salt depletion, as shown by the development of postural hypotension, fludrocortisone 0.05 mg to 0.1 mg was given as necessary. Treatment was only discontinued if a patient was unable to tolerate the medication or if disease progressed.

Assessment of Response. Clincal response was assessed using UICC criteria [3]. Stable disease was defined as no progression of disease from the start of treatment for at least 3 months, and objective response had to be maintained for at least 3 months. Measurements of assessable disease were made independently by two of the clinical authors (ACH and GGR). Radiographs were assessed independently by a consultant radiologist.

Biochemical and Haematological Assessment. Full blood count, serum calcium, phosphorus, alkaline phosphatase, albumin, globulin, aspartate aminotransferase, urea, and electrolytes were determined by standard methods immediately before the start of treatment and at 3, 7, and 14 days thereafter. Subsequent estimations were obtained at each out-patient clinic attendance, usually 4-weekly.

Serum for steroid estimations was taken at similar intervals and stored at $-20°$ C prior to assay. Serum cortisol was measured by radioimmunoassay on unextracted serum [5], as

was dehydroepiandrosterone sulphate (DHEA-S), using the Guildhey antiserum HDS 481A. Plasma androstenedione, testosterone, oestrone, and oestradiol were measured by radioimmunoassay following celite chromatography [7].

Radiology. A chest radiograph, partial skeletal survey, and technetium^{99m} methylene diphosphonate bone scan were carried out at the start of therapy. Further radiographs were obtained during therapy if clinically indicated, and at 3-monthly intervals in those patients still receiving therapy.

Results

Forty-one patients were studied between June 1981 and August 1982. Eighteen of these had advanced, refractory disease and were studied in the context of a phase 1 study to assess potential toxicity and endocrine effect. Details of age, menopausal status, and previous systemic therapy of the 23 assessable patients are given in Table 1.

Response

There were 23 patients assessable for response, of whom six (26%) had an objective response, three (13%) had stable disease, ten showed progressive disease, and four stopped therapy because of side-effects. In five of the 23 patients there was symptomatic relief of bone pain, two of these achieving an objective response while one had stable disease.

Of 11 patients with soft tissue or lymph node involvement three (27%) responded, and four of 16 (25%) patients with bone metastases attained an objective response, as did two of four patients with pulmonary metastases. Neither of the two patients with liver metastases gained any benefit.

Side-Effects

Of 41 patients, 18 experienced mild side-effects while receiving trilostane alone, the commonest being nausea (10 patients), followed by lethargy (7 patients) and vomiting (6 patients). In all but four of the 10 patients with nausea and two of the six with vomiting, the side-effects had settled by day 14. In two patients vomiting settled on the addition of dexamethasone. Asymptomatic postural hypotension developed in 17 of the 41 patients after completion of 14 days' treatment and was corrected in all cases by the addition of fludrocortisone. In eight patients treatment was subsequently discontinued because of vomiting (3), diarrhoea (2), hot flushes alone (2), and hot flushes and epigastric discomfort (1).

Table 1. Details of assessable patients receiving > 8 weeks' therapy

Mean age	54.1 years
Time post-menopause 1–5 years	10
Time post-menopause > 5 years	13
XRAM[a]/oophorectomy	14
Natural menopause	9
(a) Previous endocrine treatment	12
Response to (a)	9
(b) Precious combination chemotherapy	4
Response to (b)	3
No previous treatment	11
Total number of patients	23

[a] XRAM, radiation-induced menopause

Biochemical Data

Results from biochemical studies, to be reported in detail elsewhere, suggest that the mechanism of action of trilostane may not be as previously suggested [8, 9]. In addition to increased concentrations of dehydroepiandrosterone sulphate (DHEA-S, a Δ5 steroid), we have also noted increased concentrations of androstenedione (Δ 4A, a Δ4 steroid) and decreased concentrations of oestrone in patients receiving trilostane alone. After the addition of dexamethasone further falls in oestrone and oestradiol concentrations were seen, and DHEA-S and Δ4A concentrations returned to basal levels or below.

Discussion

These results suggest that the combination of trilostane with either dexamethasone or hydrocortisone is active in achieving remission in breast cancer. The response rate of 26% in post-menopausal patients not selected on the basis of oestrogen receptor status, is encouraging. It is not dissimilar to that expected for other hormonal therapy [1, 4], and similar to that observed with aminoglutethimide [11]. Hydrocortisone was substituted for dexamethasone in ten patients, since some patients receiving dexamethasone showed marked weight gain, suggesting the possibility of an excessive glucocorticoid effect. We wished to see whether a similar biochemical effect could be obtained with a smaller dose of glucocorticoid. These patients are included in the analyses as no difference was apparent in biochemical effect or tumour response when they were compared with patients receiving dexamethasone.

It is of interest that our biochemical studies suggest some resemblance in the enzyme-blocking effects of trilostane and those of aminoglutethimide [11, 13]. Both seem to lead to an increase in plasma androstenedione concentrations, while a concurrent fall in oestrone levels suggests inhibition of the aromatase enzyme system.

Aminoglutethimide is now used with increasing frequency, particularly in the post-menopausal patient with bone metastases. Side-effects with this drug are common [12] and this may be a reflection of the dose used as there is controversy at present concerning the precise mode of action and optimum dose [2]. It is clear, though, that enzyme inhibitors are going to play an increasingly important role in the treatment of the post-menopausal patient with metastatic disease [10], and any drug with a similar mechanism of action but with less toxicity would be beneficial.

Side-effects were frequent in this series, although many patients could tolerate the drug without particular difficulty. However, it is possible that the dose selected initially (960 mg/day) was too high and was responsible for the necessity to discontinue treatment, as side-effects in subsequent patients treated with 480 mg/day were negligible. The elevations in serum androstenedione and falls in serum oestrone observed were similar whether doses of 480 mg or 960 mg trilostane daily were given.

Further studies are in progress to confirm the above results, to elucidate more fully the mode of action of trilostane, and to define the sub-groups of patients most likely to benefit from its uses.

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