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Oral 4-hydroxyandrostenedione, a new endocrine treatment for disseminated breast cancer

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Summary. Thirty-one post-menopausal female patients, with locally advanced or disseminated breast cancer were treated with the aromatase inhibitor 4-hydroxyandrostenedione given orally at a dose of 500 mg daily. Twenty-nine patients had assessable disease. Eight patients (28%) had objective evidence of partial response and six remain in remission 7–10 months later. A further four patients (14%) had stabilisation of disease and 11 patients (37%) had progressive disease in spite of treatment. Plasma oestradiol levels were measured throughout therapy in 16 patients and were lowered to 53%±8% of baseline levels within 7 days of commencing 4-hydroxyandrostenedione.

With regard to toxicity, one patient developed a transient skin rash and another patient some facial swelling. A further patient developed a transient leucopaenia and treatment was therefore discontinued. Twenty-seven of the 30 evaluable patients (90%) experienced no side effects. These results indicate that oral administration of 4-hydroxyandrostenedione is an acceptable new treatment for post-menopausal women with disseminated breast cancer.

Introduction

The majority of post-menopausal patients with advanced breast cancer respond to the anti-oestrogen tamoxifen providing there is a significant amount of oestrogen receptor (ER) in the tumour tissue. However, the response often lasts only 12–18 months and second-line therapy is then indicated. Currently this consists of either aminoglutethimide [5] or medroxyprogesterone acetate [3], but these agents possess the major side effects of severe drowsiness and fluid retention respectively. To overcome these problems we designed a specific potent aromatase inhibitor, 4-hydroxyandrostenedione (4-OHA) [1], and found that, given parenterally, it had significant anti-tumour activity in post-menopausal women with breast cancer [2]. The sole significant side effect of 4-OHA was local abscess formation following parenteral administration [4] and we have therefore developed an oral dosage regime.

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Patients and methods

Patients. We treated 31 female patients, mean age 65.7 years (range 40–82 years), with histologically confirmed locally advanced or metastatic breast cancer. All were post-menopausal; 24 were naturally post-menopausal and seven were ovariectomised. Twenty-nine had assessable disease as defined by the International Union Against Cancer (UICC) [6]. Sixteen (52%) had already received a single trial of endocrine therapy, 6 (19%) had received two previous endocrine agents and 3 (10%) had received three previous endocrine agents with an overall response rate of 62%. Details of previous endocrine treatment are given in Table 1. Seven patients (23%) had been given previous chemotherapy. None had received therapy for 4 weeks prior to the start of treatment with 4-OHA. The mean tumour-free interval was 43 months (range 0–160 months). Patients were fully staged before the start of therapy and 3-monthly during treatment by means of clinical examination, chest radiograph, limited skeletal survey, liver ultrasound, isotope bone scan, full blood count, liver function tests, gamma GT, calcium, phosphate, urea and electrolytes. Clinical examination, biochemistry and toxicity assessment were repeated every 4 weeks. Tumour ER content was measured where possible by a modification of the method of McGuire et al. [8]. Response to treatment was assessed according to standard UICC criteria [6]. All patients gave full informed consent and the protocol was approved by the participating hospitals' ethical committees.

Treatment. 4-OHA was provided by Ciba-Geigy Pharmaceuticals as a sterile micro-crystalline formulation (CGP-

Table 1. Details of previous endocrine therapy

	No. of patients	No. responding
Tamoxifen	23	15
Medroxyprogesterone acetate	3	1
Aminoglutethimide	3	1
Decadurabolin	2	2
Danazol	2	1
Norethisterone acetate	1	1
Radiation menopause	2	2
Surgical menopause	1	0

32349) in ampoules and was stored at 4° C. The powder was suspended in physiological saline (125 mg/ml) immediately prior to oral ingestion. The first 10 patients were given 250 mg 4-OHA daily for 4 weeks and thereafter the dose was increased to 500 mg daily. All other patients were given 500 mg daily from the outset. This was reduced if patients complained of significant side effects.

Oestradiol estimations. Plasma oestradiol was measured daily for 2 days before and serially after the start of therapy in 16 patients. Six of these patients (group 1) were given 500 mg 4-OHA daily for a period of 7 days and then 4-OHA was discontinued for 7 days. The remaining 10 patients (group 2) were given 250 mg 4-OHA daily for 4 weeks and the dose was then increased to 500 mg daily. Blood sampling was performed weekly.

4-OHA estimations. We measured 4-OHA in five patients following 250 mg of oral 4-OHA. Plasma 4-OHA was measured using a radioimmunoassay technique outlined previously [4]. Blood samples were taken where possible, at 0, 1, 3, 4, 5, 6 and 24 h.

Results

Response to 4-OHA

Eight of the 29 patients (28%) showed a partial response to treatment. The median time to response was 3 months and the median duration of response is currently greater than 10 months; six patients remain in remission. In a further four patients (14%), the disease stabilised for a median of 7.5 months. Seven of the eight responding patients had received previous endocrine therapy and all had responded to first-line therapy [tamoxifen (n = 5), norethisterone acetate (n = 1) and ovariectomy (n = 1)]. Of the four patients whose disease stabilised, three had been given tamoxifen as first-line endocrine therapy and responded. Two of the three had also been given second-line endocrine therapy consisting of Danazol and Decadurabolin respectively and had responded. One of the three had received third-line endocrine therapy with aminoglutethimide but had not responded. Only one of the eight responders was known to have a negative ER status. Response was more common in soft tissue (38%) than in visceral or bony sites (20% and 16% respectively).

Nine of the 11 patients who failed to respond had been given endocrine therapy (tamoxifen) in the past. Four had not responded and five had responded. Eight patients were not evaluable: six had treatment for less than 4 weeks and two did not have assessable disease according to UICC criteria.

Toxicity of 4-OHA

Thirty patients were evaluable for toxicity. One patient was excluded because only a single dose of 4-OHA was given. Twenty-seven patients had no side effects. One patient developed an erythematous skin rash which was self-limiting and one patient complained of facial swelling. In only a single case was treatment discontinued because of toxicity. This patient developed leucopaenia (white cell count = 2.5×10^9/l) 11 days after starting 4-OHA. The white cell count returned to normal on withdrawal of 4-OHA.

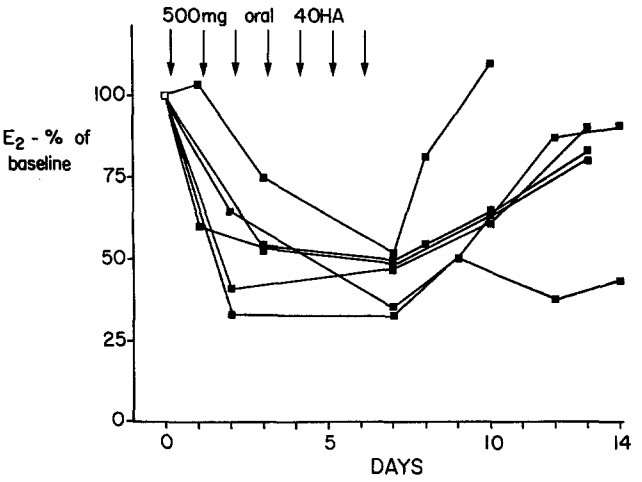

Fig. 1. Oestradiol levels in six patients measured serially during the first 7 days of treatment with 4-hydroxyandrostenedione (*4-OHA*)

Oestradiol estimations

In group 1 progressive suppression of oestradiol levels was found in the six patients during the 7-day treatment period (Fig. 1). At 7 days the mean suppression was 44.5% ± 7.9% of the baseline levels, from 22.6 ± 2.5 pmol/l before treatment to 9.8 ± 0.9 pmol/l after 7 days. In group 2, in which oestradiol was measured for 1 month, there was no evidence that oestradiol levels fell below those achieved after 7 days treatment at either the 250 mg daily dose or the 500 mg daily dose. For that reason the mean on-treatment level was calculated for each patient at each dose level to allow comparison between the effects of the two doses. No significant difference in degree of suppression was found between the two doses: pretreatment 19.2 ± 2.4 pmol/l, 250 mg 10.5 ± 1.1 pmol/l (58.3% ± 6.1% of pretreatment); 500 mg 10.1 ± 1.8 pmol/l (50.8% ± 7.9% of pretreatment).

4-OHA estimations

Peak levels (44 ± 7.3 ng/ml) were found 1–3 h after oral ingestion. At 24 h (four subjects only) levels were undetectable (< 0.3 ng/ml) in three patients and 0.8 ng/ml in a fourth.

Discussion

This is the first report of oral 4-OHA, and the results indicate that this is an effective treatment of breast cancer in post-menopausal women, associated with little toxicity. The response rate is similar to that of parenteral 4-OHA [4].

Optimisation of the dose and scheduling of 4-OHA for oral administration is clearly the next priority before proceeding to assess 4-OHA as an adjuvant in primary breast cancer. Our preliminary endocrine data suggest that 250 mg daily is nearly as potent as 500 mg daily in lowering plasma oestradiol. We are not certain that measurement of plasma oestradiol levels is totally appropriate, since some breast carcinomas themselves possess significant amounts of aromatase and it is possible that the con-

tinued growth of these tumours is more dependent on local oestrogen production than on circulating oestrogens [7]. However, it seems likely that the inhibition of tumour aromatase will be accomplished at similar dosage to peripheral aromatase in other tissues and that circulating oestrogen levels will be an indirect reflection of this inhibition. We are currently comparing the effect of 4-OHA on peripheral and tumour aromatisation to examine the relationship between the two.

The only serious toxicity related to oral 4-OHA treatment was the transient leucopaenia which occurred in one patient. Over 170 patients [2, 4] (unpublished data) have now received 4-OHA by the oral and parenteral routes and this remains the only case of treatment-related leucopaenia. The other side effects related to 4-OHA were mild, and indeed the vast majority of patients experienced no toxic reactions whatsoever. This contrasts sharply with aminoglutethimide, with which side effects are frequent. A review of 213 patients treated by this group with aminoglutethimide and hydrocortisone showed that 33% developed drowsiness and lethargy, 23% had a skin rash and 15% experienced nausea. Also, with 4-OHA there is no need for corticosteroid replacement therapy.

4-OHA represents a new treatment of breast cancer. The mode of action and the lack of toxicity indicate that 4-OHA should be considered as the treatment of choice for patients who have responded and then relapsed after tamoxifen therapy. Its use as an adjuvant to surgery is shortly to be examined by our group.

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