Cancer Chemother Pharmacol (1990) 26: 75–78

Cancer Chemotherapy and Pharmacology

Treatment of advanced breast cancer in postmenopausal women with 4-hydroxyandrostenedione

Robert C. Stein[1], Mitchell Dowsett[3], Anthea Hedley[1], Joanna Davenport[1], Jean-Claude Gazet[2], Hubert T. Ford[2], R. Charles Coombes[1]

[1] Clinical Oncology Unit, St. George's Hospital Medical School, Cranmer Terrace, London. SW17 ORE, UK
[2] Combined Breast Clinic, St George's Hospital, Blackshaw Road, London SW17 OQT, UK
[3] Department of Biochemical Endocrinology, Royal Marsden, Hospital, Fulham Road, London SW3 6JJ, UK

Received 15 January 1989/Accepted 23 September 1989

Summary. 4-Hydroxyandrostenedione (4-OHA), a new specific aromatase inhibitor, was used to treat 57 postmenopausal women with advanced breast cancer at a dose of 250 mg by i.m. injection every 2 weeks; 55 women were assessable for response. In all, 18 patients (33%) had objective evidence of a response to treatment, with a median duration of 12 months; the disease stabilised in 8 (14%) patients. Serum oestradiol levels, which were measured weekly in nine of the patients, were found to be suppressed to a mean of between 36% and 51% of pretreatment levels during the first 6 weeks of treatment. Three patients were withdrawn from treatment because of toxicity (pain at injection site, sterile abscess and rash). One patient had an isolated episode of anaphylaxis after 6 months of treatment. In comparison with our previous reports of 4-OHA treatment, a dose of 250 mg given i.m. fortnightly appears to be the optimal dose regimen. The efficacy of the drug seems to be similar to that of tamoxifen and aminoglutethimide.

Introduction

The mainstay of endocrine treatment of advanced breast cancer lies in the removal of oestrogen from tumour cells. Oestrogen receptor (ER) is detectable in approximately two-thirds of human breast carcinomas, and one-half of such tumours regress in response to hormonal manipulation [10]. Aminoglutethimide, which prevents the synthesis of oestrogen by inhibiting aromatase, the final enzyme in the synthetic pathway for oestrogen, is an effective treatment for breast cancer in postmenopausal women [7, 9, 14]. Aminoglutethimide treatment is frequently accompanied by troublesome side effects including skin rash, drowsiness and adrenal suppression, which limit its acceptability [13, 14].

Offprint requests to: R. C. Stein, Oncology Clinical Unit, St. George's Hospital Medical School, Cranmer Terrace, London, SW17 ORE, U. K.

The duration of remission induced by individual endocrine treatments is usually limited to between 9 and 18 months. It is frequently possible to treat patients with multiple agents in sequence, achieving a series of remissions [13, 15]. Any effective, well-tolerated endocrine treatment of breast cancer is therefore likely to be value.

4-Hydroxyandrostenedione (4-OHA), a potent aromatase inhibitor with no other known significant pharmacological action, is active in the treatment of advanced breast cancer in postmenopausal women and has few side effects [1, 2]. We have previously shown 4-OHA to be clinically effective at the dose of 500 mg weekly given by i.m. injection [5]. Oral administration results in extensive first-pass metabolism of 4-OHA, but we have nevertheless shown the drug to be clinically and endocrinologically effective at a dose of 500 mg daily [3]. We report on the results of treatment with 4-OHA at the lower and more convenient dose of 250 mg every 2 weeks injected i.m.

Patients and methods

A total of 57 patients with cytologically or histologically proven locally advanced or metastatic breast cancer were entered into the study between January 1985 and September 1987. The age range was 38–86 years (median, 65 years) and all patients were either postmenopausal or had been oophorectomised. In all, 38 patients had received previous endocrine therapy (listed in Table 2), and 12 had previously been treated with chemotherapy. Prior treatment was discontinued at least 4 weeks before entry. ER status was positive in 20 patients (i.e. >15 fmol/mg cytosol protein by the dextran-coated charcoal assay [11], negative in 6 and unknown in 31 patients. No patient with a second primary malignancy or with serious concomitant physical or psychological disease was included. Informed consent was obtained from patients prior to commencement. The study was approved by St. George's Hospital Ethics Committee.

4-OHA was provided in ampoules as a sterile microcrystalline formulation (CGP-32349) by Ciba-Geigy Pharmaceuticals. The drug was stored at 4° C; immediately prior to use it was suspended in physiological saline at a concentration of 125 mg/ml. It was given by deep i.m. injection into the buttock; injection sites were varied to improve local tolerability. All patients were initially treated with 250 mg 4-OHA every 2 weeks.

Table 1. Response to 4-OHA

	Number of patients	Number (percentage) responding:		
		CR/PR	NC	PD
Overall	55	18 (33)	8 (14)	29 (53)
Oestrogen receptor:				
Positive	20	7	3	10
Negative	5	0	0	5
Not known	30	11	5	14

CR, complete response; PR, partial response; NC, no change; PD, progressive disease

Table 2. Response according to previous endocrine treatment

Previous treatment and response	Patients	Response to 4-OHA:		
	(*n*)	CR/PR	NC	PD
No previous treatment	19	6	1	12
Tamoxifen:				
CR/PR	15	7	4	4
NC	4	1	1	2
PD	5	0	0	5
NA	5	0	1	4
Multiple endocrine agents:				
CR/PR	5	2	1	2
NC, PD, NA	0	0	0	0
Oestrogen withdrawal:				
CR/PR	3	1	1[a]	1[a]
NC	2	0	1[a]	1[a]
PD	0	0	0	0
NA	1	1	0	0

[a] Patient was subsequently treated with tamoxifen and therefore is entered twice in the table

Multiple agents = tamoxifen in combination with other endocrine agents. Oestrogen withdrawal = oophorectomy or discontinuation of oestrogen replacement. NA, not assessable

Monitoring and assessment. Full staging, consisting of a clinical examination, full blood count, the measurement of liver function tests and serum calcium, a chest radiograph, an isotope bone scan, a radiographic limited skeletal survey and liver ultrasound, was carried out on entry into the study. Staging was repeated at 3-month intervals and on suspicion of disease progression. Patients were seen 2 weeks after their initial injection and thereafter at monthly intervals. Clinical examination, toxicity assessment, measurement of serum biochemical and haematological parameters and any further relevant investigations were carried out at each visit. Assessments of response were carried out according to standard UICC criteria [8].

Oestradiol analyses. Serum oestradiol levels were measured at weekly intervals for the first 6 weeks of treatment in 13 patients according to a sensitive and specific radioimmunoassay, which has previously been described in detail [4].

Table 3. Response according to disease site

Disease site	Number of patients	Number (percentage) responding
Breast	16	8 (50)
Lymph nodes	24	6 (25)
Skin	16	5 (31)
Bone	21	5 (24)
Lung parenchyma	13	4 (31)
Liver	8	1 (13)

Results

Response to treatment

A total of 55 patients were assessable for response. The response to treatment is shown in Table 1. In all, 18 patients (33%) experienced an objective tumour regression in at least one site as a result of 4-OHA treatment, including 1 with a complete response; disease stabilised for at least 3 months in an additional 8 patients (14%). Of the remaining 29 patients whose disease progressed despite treatment, 7 were withdrawn from the study after receiving only 2 injections; 6, because of life-treatening disease requiring treatment with cytotoxic chemotherapy; and 1, because of side effects due to 4-OHA. No improvement in response status was achieved by increasing the 4-OHA dose to 500 mg fortnightly in eight patients with stable or slowly progressing disease. None of the five assessable patients with ER-negative tumours responded or stabilised in response to 4-OHA treatment. The median duration of response was 12 months.

The response to 4-OHA according to previous endocrine treatment is shown in Table 2. A total of 19 patients had had no previous endocrine treatment, of whom 6 (32%) responded and 1 stabilised on 4-OHA therapy. In all, 34 of the remaining 36 patients had previously been treated with tamoxifen, either on its own or in combination with danazol, aminoglutethimide and hydrocortisone, of whom 20 had responded and 4 had stabilised. Four of the tamoxifen-treated patients had previously undergone oophorectomies; disease regressed in response to both treatments in two of these women and stabilised in the other two. A response to 4-OHA occurred in 9 of the 20 patients who had previously responded to tamoxifen, and disease stabilised in a further 5. One patient whose primary tumour stabilised on tamoxifen treatment subsequently developed distant metastases, which regressed with 4-OHA treatment.

When response to 4-OHA treatment was analysed according to the site of disease, local breast, skin and lung deposits responded best, with response rates of 31%–50%. Bone metastases showed radiographic evidence of healing in 24% of those affected. Liver metastases regressed in only one of eight patients. The data are summarised in Table 3.

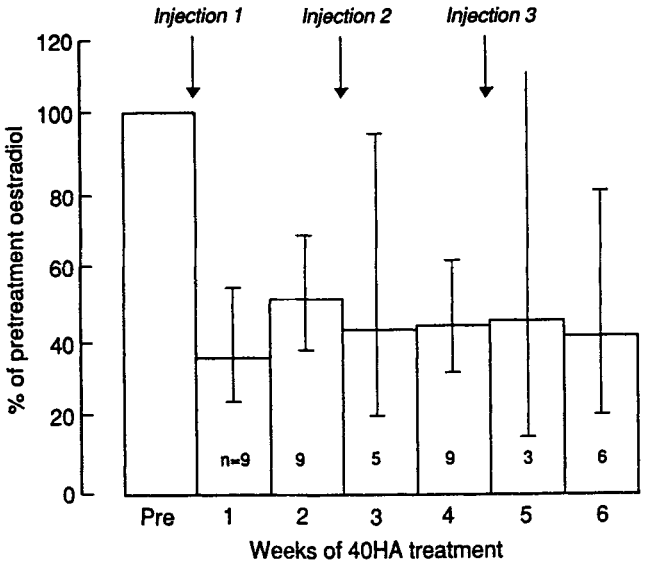

Fig. 1. Serum oestradiol levels, expressed as a percentage of pretreatment levels (geometric mean and 95% confidence intervals of the mean) measured weekly during the first 6 weeks of 4-OHA treatment

Toxicity

No toxic manifestations of 4-OHA occurred in 46 (81%) of the patients in the study. Three patients developed sterile abscesses at injection sites after 3, 13 and 13 months of treatment, respectively, and one patient experienced severe pain related to injections; treatment was discontinued in two of these patients, and a third was changed to the oral formulation [3]. One patient developed a morbiliform skin rash requiring cessation of therapy. Another patient had an anaphylactoid reaction following an injection after she had been on treatment for 6 months, which did not recur after subsequent injections. In addition, one patient experienced mild myalgia affecting the shoulders and thighs; three patients complained of nausea; one, of lethargy; one of dizziness; and one, of facial flushing after starting treatment. All of these reactions were mild and transient.

Oestradiol levels

The effect of the first 6 weeks of treatment on serum oestradiol levels in nine patients is shown in Fig. 1. The mean (± SEM) serum oestradiol value prior to treatment was 36.4 ± 12.0 pmol/l. Levels were significantly suppressed 1 week after the first injection of 4-OHA to 17.9 ± 9.5 pmol/l (i.e. to a geometric mean of 36.2% of pretreatment levels). At 2 weeks after the initial injection, the mean oestradiol level had risen to 22.8 ± 10.3 pmol/l (50.7% of pretreatment levels); this rise was statistically significant ($P = 0.05$, paired t-test). Thereafter, the mean on-treatment levels (measured in 3–9 patients) were between 11.3 and 14.7 pmol/l (i.e. between 41.0% and 45.3% of pretreatment levels).

Discussion

4-OHA given i.m. at a dose of 250 mg every 2 weeks is an effective and well-tolerated treatment for advanced breast cancer in postmenopausal women. Tumour regression was observed in 33% of our patients, which is comparable to a response rate of 27% in 52 similar patients treated at an i.m. dose of 500 mg weekly [5]. The median duration of response, 12 months, is within the range of response durations reported for tamoxifen treatment [12].

The suppression of oestradiol levels 1 week after an i.m. dose of 250 mg appears to be comparable to that achieved with 500 mg given i.m. weekly (to a mean of 37.1% of baseline values in 11 patients) and with an oral dose of 500 mg daily (to 44.5% of baseline in 6 patients) [4]. However, it was noteworthy that a significant increase in oestradiol levels occurred between day 7 and day 14 after the first 250 mg injection, which indicates that this dose might be marginally sub-optimal during the last few days before the second injection. This phenomenon and the completeness of oestradiol suppression with further treatment on this regimen will be fully characterized by a randomized dose-comparison study.

When given by i.m. injection every 2 weeks, 4-OHA is more acceptable to patients than when given by weekly injections. The drug is well tolerated: only four patients were withdrawn from treatment because of side effects; the dose or route of administration was varied in a further three. Local toxicity was experienced by 7% of the patients in the current study, as compared with 16% of patients treated with weekly i.m. 4-OHA, especially at higher doses [5]. The incidence of systemic side effects was similar to that reported in our previous studies. Taken together, in our three main studies we have reported toxicity data for 145 patients, in only 7 of whom was treatment discontinued because of side effects.

When the various considerations discussed above are taken together, the data indicate that future studies of 4-OHA should be based on a dose of 250 mg given i.m. every 2 weeks. The theoretical disadvantage of possibly reduced oestrogen suppression with this dose does not appear to have a significant impact on the clinical efficacy of the drug and is outweighed by the greater convenience and reduced local toxicity of fortnightly administration. The oral administration of 4-OHA, albeit clinically effective, is not entirely satisfactory due to the rapid inactivation of the drug by first-pass glucuronidation in the liver [6]. 4-OHA administration by the parenteral route avoids this problem and is an effective, well-tolerated treatment that also ensures total compliance.

No direct comparison of treatment of breast cancer with 4-OHA with that using other endocrine agents has been made. The majority of our patients had previously received at least one endocrine treatment for metastatic disease, and it is likely that a greater than normal proportion had ER-positive carcinomas. Both of these factors would be expected to modify the probability of response to 4-OHA and complicate the comparison between our results and those ob-

tained in studies of unselected patients. Nevertheless, the overall response rate of our patients is similar to that previously reported for tamoxifen- and aminoglutethimide-treated patients.

In two previous studies in which aminoglutethimide was given to a group of patients similar to ours, Powles et al. [13] reported a response rate of 31%, whereas Smith et al. [15] observed a 23% response rate. It is noteworthy that a greater proportion of patients who had failed to respond to tamoxifen subsequently responded to aminoglutethimide than we observed with 4-OHA-treated patients; the significance of this is uncertain. The median duration of response achieved with 4-OHA, 12 months, is comparable to that reported for both tamoxifen and aminoglutethimide treatment. We believe that 4-OHA is as effective a treatment for postmenopausal breast cancer as is aminoglutethimide, and since it is better tolerated with fewer major side effects, it may be expected to replace aminoglutethimide as the aromatase inhibitor of choice. Furthermore, since the activity of aromatase inhibitors appears to be similar to that of tamoxifen, 4-OHA could become the preferred first-line therapy in cases where parenteral treatment is desirable.

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