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Clinical Trial Summary

Norethisterone Acetate as Secondary Endocrine Treatment in Advanced Breast Cancer

RICARDO J. M. DA LUZ* and ROBERT D. RUBENS
ICRF Clinical Oncology Unit, Guy's Hospital, London SE1 9RT, U.K.

INTRODUCTION

NORETHISTERONE (17-α-ethinyl-19-nortestosterone) acetate, a progestogen, has been used in the treatment of advanced breast cancer for many years [1]. The exact mode of action for its growth-inhibiting effects is still uncertain. It is known to have oestrogenic, anti-oestrogenic, androgenic and anti-gonadotrophic effects. The latter has been considered to be responsible for its anti-tumour properties in breast cancer, but the observation that patients who had previously responded to hypophysectomy could still show a response to this drug [2] suggests otherwise. It seems likely that norethisterone's therapeutic effect is an aggregate result of a number of effects of the drug, including a direct action on the tumour cells.

Our two previous studies have demonstrated the activity of norethisterone acetate in advanced breast cancer [2, 3]. The response rate of 16% was achieved in extensively pretreated patients [3] and has led us to evaluate norethisterone earlier in the course of metastatic disease. We report here on the use of norethisterone acetate in patients with metastatic breast cancer who have relapsed after receiving only primary endocrine therapy.

PATIENTS AND METHODS

Forty-seven patients with evaluable recurrent or metastatic breast cancer progressing either on adjuvant endocrine therapy with tamoxifen or after failure of primary endocrine treatment (ovarian ablation ± prednisolone in premenopausal patients or tamoxifen 20 mg daily ± prednisolone in postmenopausal) were studied. Norethisterone acetate 20 mg was given orally three times daily. Prior prednisolone was usually stopped, but resumed if any symptoms suggestive of adrenocortical insufficiency developed.

UICC guidelines for assessment of response [4] were followed. Duration of response was from the date treatment started to the date of first progression. Time to disease progression in patients with no change was dated from the start of treatment until progression was first observed.

RESULTS

The characteristics of the patients are shown in Table 1.

Three patients were not assessable for response to norethisterone and were excluded from the final analysis. The reasons were: (1) stopping treatment within the first month owing to gastrointestinal intolerance; (2) baseline studies incompletely performed; and (3) no evaluable disease at start of treatment.

Ten patients (23%) achieved objective regressions (Table 2). Of two complete responders one is alive and free of disease 18 months after starting treatment, while the other remained free of disease for 14 months. The median duration of response was 7 months (range: 3–18). No change was noted in 13 patients (29%) with disease progressing after a median time of 4 months (range: 2–15). In 21 patients (48%) the disease continued to progress on treatment; these include four women who died within the first month of treatment.

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Correspondence and reprint requests: R.J.M. da Luz, ICRF Clinical Oncology Unit, Guy's Hospital, London SE1 9RT, U.K.

Table 1. Characteristics of patients

	n	%
Age:		
Median 59 years		
Range 39–84 years		
Menstrual status at diagnosis:		
Premenopausal	6	13
Postmenopausal	41	87
Stage at diagnosis:		
Operable (I and II)	28	60
Inoperable (III and IV)	19	40
Hormone receptor levels (n = 33):		
ER+ PgR+	14	30
ER+ PgR−	12	25
ER− PgR+	5	11
ER− PgR−	2	4
Unknown	14	30
Post-operative disease-free interval (years):		
0	2	
<2	21	
≥2	24	
Previous endocrine treatment:		
Adjuvant tamoxifen	5	
Tamoxifen ± prednisolone	38	
Ovarian ablation ± prednisolone	4	
Response to previous treatment (42 patients):		
CR	4	9.5
PR	16	38
NC	16	38
PD	4	9.5
Non-assessable	2	5

Table 2. Results

Response	Patients *n*	Patients %	Duration of Response (months)	Time to Progression (months)
CR + PR	10	23	7 (3–18)	—
CR	2	5	16 (14–18)	—
PR	8	18	5 (3–15)	—
NC	13	29	—	4 (2–15)
PD	21	48	—	—

Side-effects occurred in 15 patients (34%). Oedema (6), gastrointestinal intolerance (4), dyspnoea (4) and uterine bleeding (3) were the most common effects of norethisterone acetate, but tended to lessen as treatment continued. Two patients who developed cholestatic jaundice and two others with severe gastrointestinal intolerance had to stop treatment. Cholestatic jaundice resolved in both patients one of whom remains in complete remission after 18 months on no treatment.

DISCUSSION

The response rate of 23% to norethisterone acetate observed in patients who had had only one prior endocrine treatment and no other systemic treatment for breast cancer is better than the response rate of 16% previously observed in more extensively treated patients [3]. An attempt to identify possible subgroups with differing probabilities of response to treatment with norethisterone did not yield any significant factor.

The addition of prednisolone has been shown to increase the response frequency and duration of response [5] to primary endocrine treatment, but seems to reduce the response rate to subsequent treatment with aminoglutethimide and hydrocortisone [6]. In this study, prednisolone did not appear to compromise the response to norethisterone acetate.

Standard primary endocrine treatment for metastatic breast cancer is still ovarian ablation in premenopausal patients and tamoxifen in postmenopausal. The response rate to these treatments is enhanced by the addition of prednisolone [5] and, when this has been given, the response to norethisterone is equivalent to that achieved with aminoglutethimide. Side-effects of these treatments are well described and the necessity to avoid any of them, particularly fluid retention by progestogens, should be the major factor in selecting which drug to use for secondary endocrine treatment in an individual patient rather than the decision being based on any difference in likelihood of response achievement.

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