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The treatment of postmenopausal women with advanced breast cancer with buserelin

J. H. Waxman[1], S. J. Harland[2], R. C. Coombes[3], P. F. M. Wrigley[1], J. S. Malpas[1], T. Powles[2] and T. A. Lister[1]

[1] St. Bartholomew's Hospital, West Smithfield, London EC1A 7BE, England
[2] Royal Marsen Hospital, Sutton, England
[3] Ludwig Institute for Cancer Research, Royal Marsden Hospital, Sutton, England

Summary. *Repeated administration of long-acting analogues of gonadotrophin-releasing hormone down-regulates the pituitary gonadotrophins and gonadal hormones. The activity of these compounds in premenopausal women with breast cancer has been previously noted. In an attempt to cause a highly selective medical hypophysectomy 18 consecutive postmenopausal women with symptomatic advanced breast cancer were treated with intranasal buserelin in divided dosages of either 600 or 1000 μg daily. The pituitary gonadotrophins were suppressed in all patients, without objective evidence of response. This is in contrast with an earlier finding that the long-acting analogues of gonadotrophin-releasing hormone were effective in postmenopausal patients with breast cancer.*

Introduction

Schinzinger first suggested that oophorectomy might cause regression of breast cancer [11], and this was demonstrated by Beatson in 1896 [2, 3]. Since that time a plethora of hormonal manipulations modifying the course of breast cancer have been described. Each palliates or postpones the development of symptoms, and none is curative. The rationale for the response to all of these hormonal manipulations remains obscure. The hormonal basis for response to hypophysectomy is of particular interest and does not correlate with the ablation of growth hormone [8], prolactin [9], or thyroid-stimulating hormone [7]. In only a small number of patients has the importance of the pituitary gonadotrophins been assessed; in these women the relationship between the gonadotrophins and a response to hypophysectomy is controversial [1, 12].

Long-acting analogues of gonadotrophin-releasing hormone were initially reported as causing supraphysiological gonadotrophin release. However, with repeated administration their effect is paradoxical, the synthesis and secretion of the gonadotrophins is decreased, and gonadal hormone concentrations fall [10]. Effectively the pituitary gonadal axis is down-regulated. The activity of buserelin (D Ser[Bu^t]^6 LHRH ethylamide) in premenopausal women with breast cancer has been demonstrated [6]. It has been investigated in postmenopausal patients, because it provides a unique noninvasive method for specifically ablating the pituitary gonadotrophins and thereby might possibly yield an insight into the mechanisms of hormonal responsiveness in breast cancer. Eighteen postmenopausal women with symptomatic advanced breast cancer were treated with buserelin for periods of up to 8 months.

Offprint requests to: T. A. Lister

Patients and methods

Eighteen women with histologically proven symptomatic advanced adenocarcinoma of the breast gave informed consent to be treated in this study (Table 1).

Thirteen patients (cases 2–6, 9, 10, 12, 14–18) had previous hormonal therapy and five (patients 6, 9, 14, 17, 18) had responded to treatment. Oestrogen receptor status was only available in two patients (cases 12 and 17) and was borderline positive (10 and 14 fmol/l, respectively). Three patients (cases 2, 8, 14) had previously responded to cytotoxic chemotherapy. The following were performed in each patient prior to treatment: full blood count, erythrocyte sedimentation rate, liver function tests, measurement of calcium, phosphate, urea, creatinine and electrolytes, X-ray films of chest and pelvis, liver ultrasound and a radioisotope bone scan. Patients were staged according to UICC criteria. After basal blood samples had been taken for measurement of concentrations of prolactin (mean of 3 readings), sex-hormon-binding-globulin, testosterone, progesterone, 17B oestradiol, growth hormone, and thyroid-stimulating hormone, a standard gonadotrophin-releasing hormone test (100 μg LHRH) was performed. Concentrations of luteinizing hormone, follicle-stimulating hormone, growth hormone, prolactin, and thyroid-stimulating hormone were measured by specific double-antibody radioimmunoassays using Medical Research Council standards 68/40, 78/549, 66/217, 75/104, and 68/38, respectively. After ether extraction, concentrations of testosterone and 17B oestradiol were measured by tritiated radioimmunoassay. Concentrations of sex hormone-binding globulins were measured by saturation radioimmunoassay [4].

After preliminary assessment treatment was started with buserelin. The first 11 patients received 600 μg daily in three divided intranasal dosages. Thereafter, patients were treated with 1000 μg daily in five divided intranasal dosages in an attempt to suppress the pituitary gonadotrophins further. Treatment was given for between 2 weeks and 8 months.

After 1 month of therapy clinical response was assessed, and all the investigations were repeated. Relevant abnormal findings were repeated at monthly intervals with the measurement of serum concentrations of circulating luteinizing hormone, follicle-stimulating hormone, 17B oestradiol and progesterone.

Table 1. Details of the patients at time of buserelin

Pt	Age	DFI (years)	Disease sites	Previous hormone therapy/(response)	Duration of therapy	Response
1	56	4	Lung, bone lymph nodes	None marrow	3 months	Progression
2	48	1	Bone, liver, bone marrow, lung	Oophorectomy (no response)	2 weeks	Progression
3	37	2	Bone, liver	Oophorectomy (no response)	6 weeks	Progression
4	54	4	Lymph nodes, liver	Oophorectomy (no response)	4 months	Progression
5	57	3	Bone, lung, liver	Tamoxifen (no response)	1 month	Progression
6	78	2	Lung	Tamoxifen (response)	8 months	Stable disease
7	64	0	Lung, liver	None	3 months	Progression
8	52	3	Bone	None	2 weeks	Unassessable
9	72	6	Lung, bone	Tamoxifen (response)	2 months	Stable disease
10	61	16	Lung, liver	Oophorectomy (no response)	6 weeks	Progression
11	52	1	Bone, liver, brain, lung	None	6 weeks	Progression
12	32	2	Lung, bone	Oophorectomy (no response)	1 month	Progression
13	57	9	Lymph nodes, infiltrating bowel	None	4 months	Minimal response
14	54	1	Liver, abdominal lymph nodes,	Fluoxymestrone and tamoxifen (response to both);	3 weeks	Progression
15	54	2	Bone	Oophorectomy (no response)	3 months	Stable disease
16	54	4	Liver, abdominal wall	Oophorectomy (no response)	4 month	Stable disease
17	55	1	Bone, bone marrow liver/lung	Aminoglutethamide/ danazol/tamoxifen (response)	16 days	Progression
18	67	12	Bone, liver, ascites	Aminoglutethamide/ tamoxifen; medroxyprogesterone (responses)	1 month	Progression

Results

Clinical

No patient responded according to UICC criteria. However, one patient (case 13) had regression of symptomatic lymphatic metastases infiltrating the bowel demonstrated by computed tomography, and two (cases 6 and 9) with pleural effusions had resolution of breathlessness, which in case 6 had required daily pleural aspiration. All three received buserelin for at least 2 months. Five patients (cases 5, 8, 14, 17, 18) died within 1 month of the initiation of therapy, four with disease progression and one (case 8) from pulmonary embolism. No patient responded to subsequent hormonal treatment.

Hormonal changes

The hormonal changes with treatment are summarized in Table 2. The two regimens produced similar suppression of serum concentrations of luteinizing hormone and follicle-stimulating hormone, both basal and after 100 μg luteinizing hormone-releasing hormone ($P < 0.01$: Student's *t*-test). Serum concentrations of progesterone, 17B oestradiol, sex-hormone-binding-globulin, testosterone, thyroid-stimulating hormone, growth hormone and prolactin did not change significantly with treatment.

Discussion

This study was undertaken to determine the potential role of buserelin and investigate the significance of the pituitary gonadotrophins in postmenopausal women with breast cancer. It has been demonstrated that the dosage and schedule of the drug suppressed the pituitary gonadotrophins, thereby achieving a highly selective medical hypophysectomy, without objective response.

Only one other study describes the use of a gonadotrophin-releasing hormone analogue in postmenopausal women with breast cancer, reporting, without hormonal data, early responses in 12 of 31 patients [5]. Our results suggest that in the dosage and schedule investigated bus-

Table 2. Hormonal changes with treatment

	Minutes	Pretreatment		After 1 month		Normal range
		Mean	Range	Mean	Range	
Luteinizing	0	30 (18)	1.6–77	9.6	4–19 (14)	> 25 U/l
hormone	20	95 (16)	25–344	14.4	7–24 (12)	> 25 U/l
	60	108 (16)	33–394	13.5	4–22 (12)	> 25 U/l
Follicle-	0	46 (18)	0.7–119	13.2	1.7–23 (14)	> 50 U/l
stimulating	20	77 (16)	5.4–166	18.1	7–47 (12)	> 50 U/l
hormone	60	93 (16)	19–200	18.3	7–37 (12)	> 50 U/l
after 100 g luteinizing hormone-releasing hormone						
Sex-hormone-binding-globulin		81 (15)	27–> 120	88	9–>120 (13)	38–103 nmol/l
Testosterone		1.05 (15)	< 0.5–2.1	1.2	0.6–2.1 (13)	0.5–3.0 nmol/l
Progesterone		11.6 (16)	1.5–62	7.4	1.5–19 (14)	< 3–12 nmol/l
17 B Oestradiol		50 (16)	<50–140	94	<50–550 (14)	< 140 pmol/l
Prolactin		465 (14)	122–1693	590	101–1977 (13)	< 360 mU/l
Thyroid-stimulating hormone		3.07 (10)	<1–8.4	2.63	1.0–8.2 (12)	< 6 mU/l
Growth hormone		5.04 (12)	0.5–22.8	3.74	0.5–16.7 (13)	–

(Number of observations)

erelin is ineffective in postmenopausal women with breast cancer. Whethter administration of the drug over a longer period or the use of higher dosages given as depot preparations would be more effective remains to be seen.

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