Advanced Male Breast Cancer Treatment With the LH-RH Analogue Buserelin Alone or in Combination With the Antiandrogen Flutamide

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Ten men with advanced breast cancer were evaluated for response to treatment with the luteinizing hormone-releasing hormone (LH-RH) analogue, buserelin, alone or in combination with the antiandrogen, flutamide. One of five patients receiving buserelin as a single agent had a partial remission lasting 12 months, and with the addition of flutamide, this lasted over 24 additional months. Three patients had stable disease with a median duration of 6 months (range, two to 14). One patient had progressive disease. Of five patients receiving the combination of buserelin and flutamide from the beginning of therapy, four patients had a partial remission with a median duration of over 15 months (range, over five to 16). One patient's disease remained stable for 12 months. Major side effects were hot flushes, loss of libido, and impotence. Buserelin initiates a castration-like endocrine response and has potential in the treatment of men with disseminated breast cancer when used either alone or in combination with flutamide.

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E NDOCRINE THERAPY plays an important role in the management of advanced male breast cancer. In 1942, Farrow and Adair[1] first reported a remarkable response after bilateral orchidectomy. For many years, this ablative hormonal therapy was considered the initial palliative procedure.[2] However, this operation might result not only in surgical morbidity but more importantly in major psychologic adverse reactions. Therefore, additive hormonal therapy has been employed in many studies because of ease of administration, its reversibility, low morbidity, and nontoxic effects. Mechanisms of action of endocrine therapy in male patients with breast cancer include reduction of hormone concentrations and blockage of both androgen and estrogen hormone receptors.[3] Serum concentrations of estradiol-17β are often elevated in men with breast cancer.[4] The exact reason for this increase is not known.

Recently, new approaches to the therapy of endocrine-dependent tumors using analogues of luteinizing hormone-releasing hormone (LH-RH) have been developed on the basis of experimental studies in animal models.[5] Long-term administration of synthetic LH-RH agonists results in a paradoxically decreased release of LH and follicle-stimulating hormone (FSH) after initial stimulation.[6] This process of down-regulation of pituitary gonadotropins and the subsequent chemical castration can inhibit the growth of prostate cancer[7] and female breast cancer.[8] Studies with the LH-RH agonists in advanced prostate cancer have shown that an initial rise in serum androgens has often been accompanied by disease flare.[9] In contrast, patients treated with combination LH-RH agonist and antiandrogen therapy do not have exacerbations.[10] Moreover, the simultaneous administration of these drugs seems to result in prolonged remission and survival due to a blockage of the remaining adrenal androgens.[11] We report our preliminary results after treatment with the LH-RH analogue, buserelin, alone or in combination with the nonsteroidal antiandrogen, flutamide, in men with advanced breast cancer.

Patients and Methods

Since September 1983, ten men with recurrent or progressive cancer of the breast have given voluntary informed consent to participate in this study. All patients had a histologically confirmed diagnosis of breast cancer and clearly measurable lesions, which served as indicators of response to therapy. They were pretreated with additive hormonal therapy, cytostatic chemotherapy, and/or radiotherapy. Patients who had undergone or-

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Table 1.   Characteristics of Ten Male Patients with Advanced Breast Cancer

Patient no.	Age (yr)	Primary tumor status	Disease-free interval (mo)	Sites of metastases	Receptor status	Previous therapy of metastases and response	Performance status (WHO)	Dose (mg/day)	Response	Duration of response (mo)	Survival (mo)
1	72	pT4pN1M0	10	Soft tissue	E– P–	TAM (SD)	2	B 0.6–1.2	PD		34
2	57	pT1N1M0	11	Bone	E+ P+	CMF (adjuvant) TAM (SD) Radiotherapy (PR)	3	B 0.4–0.8	SD	2	5
3	54	pT2pN0M0	41	Soft tissue, bone	E– P–	CMF (SD) MPA (PD) CPA (PD) Radiotherapy (PR)	2	B 0.4–1.2	SD	6	18
4	49	pT1pN1M0	37	Soft tissue, lung, bone	NI	CMF (adjuvant) CMF (PD) AV (PD) TAM (SD) Radiotherapy (PR)	2	B 0.4–1.2	SD	14	20
5	46	pTXN0M0	13	Bone	NI	FAC (SD)	1	B 1.2 F 750 (24+ mo)	PR	12 24+	36+
6	66	pT2pN0M0	4	Bone	NI	TAM(PD)	2	B 1.2 F 750	SD	12	28+
7	53	pTXN0M0	36	Lung, bone	NI		2	B 1.2 F 750	PR	16	19+
8	73	pT2pN0M0	26	Soft tissue, lung, bone	NI	TAM (SD)	2	B 1.2 F 750	PR	15+	15+
9	60	pT1N0M0	19	Lung, bone	NI	Radiotherapy (PR)	2	B 1.2 F 750	PR	15+	15+
10	46	pT2pN2M0	5	Lung	E+ P+		1	B 1.2 F 750	PR	5+	5+

E = estradiol; P = progesterone; NI = not investigated; CMF = cyclophosphamide, methotrexate, 5-fluorouracil; AV = adriamycin, vincristine; FAC = 5-fluorouracil, adriamycin, cyclophosphamide; TAM = tamoxifen; MPA = medroxyprogesterone acetate; CPA = cyproterone acetate; B = buserelin; F = flutamide.

chidectomy were excluded from the study. The major clinical characteristics of the patients are summarized in Table 1.

The LH-RH analogue, buserelin, (D-Ser(Bu^t)^6-LH-RH(1-9)-nonapeptide-ethylamide) was provided by Behringwerke AG, Marburg, FRG. All patients received the drug as a nasal spray. The initial dose was 0.6 mg daily in patient 1, 0.8 mg in patient 2, and 1.2 mg in the other eight patients. Patients 2 to 4 received 0.4 mg buserelin temporarily as a maintenance dose.

Flutamide was obtained from Essex Pharma, München, FRG. This nonsteroidal antiandrogen was given at a dose of 250 mg orally every 8 hours. Flutamide treatment was started 24 hours before the first dose of buserelin in patients 6 to 10. In patient 5, flutamide was added after 12 months of buserelin treatment.

Therapy was continued until tumor progression with the exception of patient 1, who after receiving 0.6 mg buserelin for 4 weeks, underwent further treatment with 1.2 mg buserelin daily.

The following investigations were carried out before starting therapy and at regular follow-ups: history, physical examinations, assessment of World Health Organization (WHO) performance status,[12] complete blood counts, biochemical profile, carcinoembryonic antigen,

electrocardiogram, chest radiograph, nuclear bone scan, bone radiograph of suspected lesions, and ultrasound scan. Serum concentrations of LH, FSH, and testosterone were determined weekly during the first month, at monthly intervals for the next 2 months, and quarterly thereafter. In addition, serum concentrations of estradiol-17β were measured in patient 10.

Patients were evaluated for tumor response according to the following criteria: (1) complete remission (CR), defined as complete disappearance of all known disease for a minimum period of 1 month; (2) partial remission (PR), defined as ≥50% decrease in the sum of the bidimensional products of the two largest perpendicular diameters of all tumor masses for at least 1 month; (3) stable disease (SD), defined as <50% decrease or <25% increase in the size of measurable lesions; and (4) progressive disease (PD), defined as ≥25% increase of any tumor manifestation or the appearance of new lesions. Duration of response was dated from the start of therapy until tumor progression. Survival was dated from the beginning of buserelin treatment until death.

Results

Table 1 outlines the therapeutic results. Ten patients were evaluated for response. One of five patients receiv-
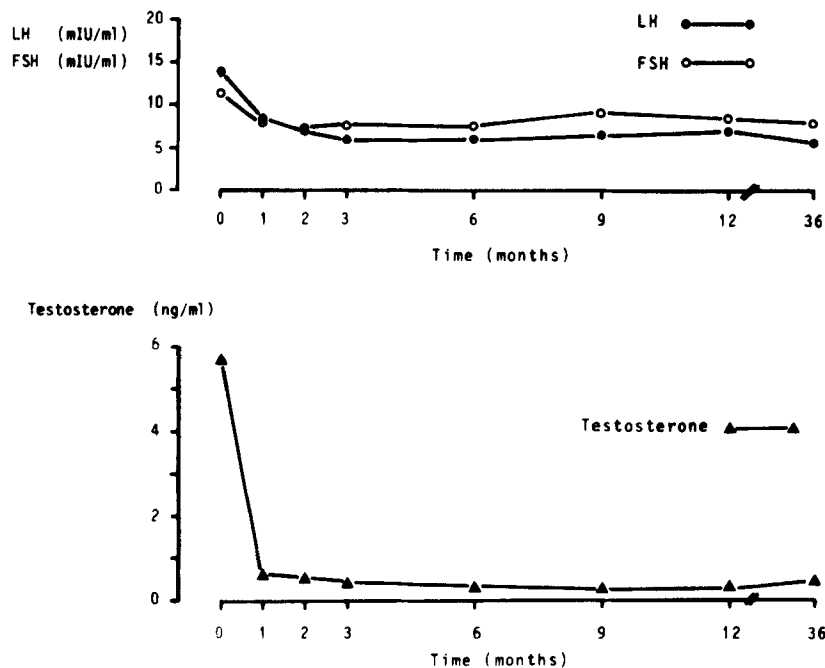
FIG. 1. Hormonal changes in eight patients during treatment with 1.2 mg buserelin alone or in combination with 750 mg flutamide. n = number of patients; x̄ = mean.

Patients	n	8	8	8	8	7	6	6	1
LH	x̄	14	8.5	7	5.9	5.9	6.4	6.7	5.5
	+SEM	1.7	1.5	1.3	0.9	0.7	2.4	3.1	
FSH	x̄	11.6	8.3	7.2	7.9	7.7	9.1	8.7	7.9
	+SEM	2.2	1.8	1.6	1.7	1.4	2.7	3.5	
Testosterone	x̄	5.6	0.6	0.5	0.4	0.4	0.3	0.3	0.4
	+SEM	0.9	0.1	0.2	0.1	0.2	0.1	0.1	

ing buserelin as a single agent had a PR lasting 12 months. At this time he reported a recurrence of bone pain without a measurable increase of suppressed serum concentrations of testosterone. The addition of fluta-mide caused disappearance of pain, and the PR contin-ued for more than 24 additional months. Three patients showed SD with a median duration of 6 months (range, two to 14). One patient had PD. Combined administra-tion of buserelin and flutamide from the start of therapy in five patients resulted in four PR with a median dura-tion of over 15 months (range, over five to 16). One patient had SD lasting 12 months. All patients with SD had improvement in performance status of at least one level according to the WHO scale. Patients with a pre-ceding disease-free interval of more than 12 months had a better response to the additive hormonal treatment schedules compared with those who had a shorter dis-ease-free interval.

In eight patients receiving 1.2 mg buserelin daily, serum testosterone concentrations (normal range, 4 to 11 ng/ml) were suppressed to castration levels (<1

ng/ml) after a median of 3 weeks (Fig. 1). Patient 2, with an initial dose of 0.8 mg buserelin, also showed castra-tion levels of testosterone after 3 weeks. Patient 1, with an initially elevated testosterone value (19.9 ng/ml) and treated with a relatively low daily dose (0.6 mg) of bu-serelin, had a high testosterone level (2.1 ng/ml) after 4 weeks. By increasing the dosage to 1.2 mg/day, a thera-peutic testosterone level was achieved after a total of 3 months. However tumor progression could not be halted. It is possible that buserelin was not properly in-haled. In all patients, testosterone concentrations re-mained low throughout treatment. A dose reduction of buserelin to 0.4 mg daily for a period of 4 to 18 weeks in three patients did not alter the serum testosterone levels. The initially elevated serum concentrations of LH (mean ± SEM, 14 ± 1.7 mIU/ml) and FSH (mean ± SEM, 11.6 ± 2.2 mIU/ml) were decreased to within the normal ranges (LH, 3.3 to 11.3 mIU/ml) and FSH, 2.2 to 8.7 mIU/ml) after a median of 3 weeks. The pure antiandrogen, flutamide, did not interfere with the changes in secretion of gonadotropins induced by the
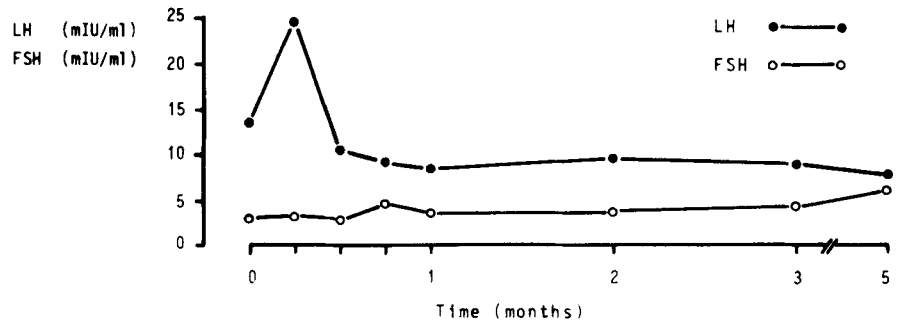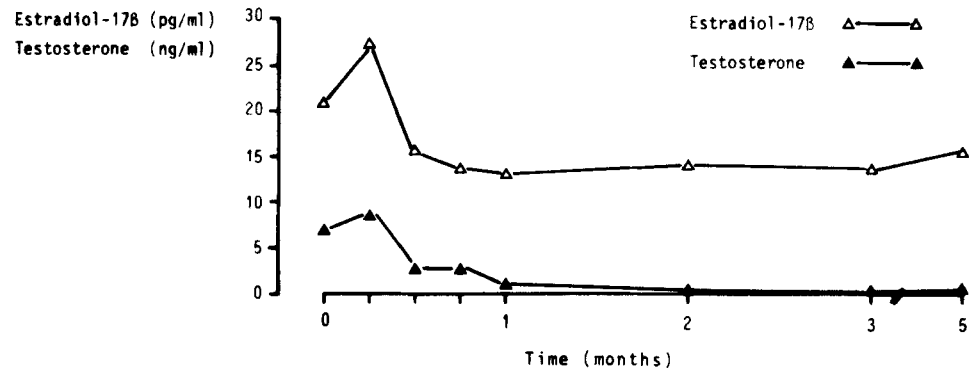
FIG. 2. Hormonal changes in patient 10 during treatment with 1.2 mg buserelin in combination with 750 mg flutamide.

LH-RH analogue. In patient 10 serum concentrations of estradiol-17β (normal range, 30 to 40 pg/ml) decreased too (Fig. 2).

All patients complained of mild hot flushes, decrease or loss of libido, and impotence. A transient increase of bone pain during the first week of therapy occurred in four of five patients treated with buserelin alone, independent of tumor response. This disease flare did not appear in patients treated with concomitant flutamide. No patient experienced a local reaction to intranasally administered buserelin. Renal or hepatic dysfunctions in relation to therapy were not observed.

Discussion

Endocrine therapy has proved effective in the management of advanced male breast cancer. Orchidectomy as an initial ablative procedure yields objective response rates ranging from 31% to 68%.[13,14] The median duration of the remissions varies between 17 and 30 months.[14,15] A small series with bilateral adrenalectomy or hypophysectomy showed 76% and 59% tumor responses, respectively.[16] Patients who did not respond to orchidectomy often demonstrated response to subsequent adrenalectomy, but only rarely to hypophysectomy.[16]

Additive hormonal therapy for men with locally advanced or disseminated breast cancer follows the same schedule used in female patients. Tamoxifen was found to be effective either before or after ablative hormonal therapy.[17] Summarizing the results of 31 patients, 48% had CR and PR lasting for a median of 9 months.[17] Treatment with high-dose medroxyprogesterone acetate induced PR in five of six patients with a median duration of 7 months.[18] Moreover, seven of ten patients receiving cyproterone acetate had an objective response for a median of 8 months.[19] Recently, effective therapy with aminoglutethimide after orchidectomy was reported in two patients.[20,21] However, none of four patients with intact testes responded to aminoglutethimide.[21]

In our study, we observed one PR in five patients treated with buserelin alone and four PR in five patients receiving the combination of buserelin and flutamide from the beginning of therapy. These patients had favorable clinical characteristics (Table 1), which could account in part for the encouraging results. Four of ten patients had SD with an improvement in performance status. The failure of response and the short median duration of SD in these patients might be partly due to widespread and bulky disease, intensive pretreatment, and rather low doses of buserelin. A prognostic factor which might indicate a positive response to both hormonal treatment schedules seems to be a disease-free interval of more than 12 months.

The LH-RH analogue, buserelin, is an effective agent

for decreasing serum testosterone concentrations to castration levels. By intranasal administration, a daily dose of 1.2 mg buserelin seems to be sufficient. However, a higher dose would probably reduce testosterone levels more rapidly since there is a dose-response effect. This is supported by the progressive decline of testosterone levels over a period of 9 months in patients receiving 1.2 mg buserelin (Fig. 1). The decrease of estradiol-17β probably reflects the reduction of testosterone and subsequent decrease in peripheral aromatization during treatment with buserelin. Therefore, the efficacy of buserelin in male breast cancer might be partly due to the deprivation of estrogens. This cannot be achieved by the pure antiandrogen, flutamide, alone. The temporary increase of testosterone during the first week of therapy was associated with an intensification of bone pain in our patients treated with buserelin alone. This could be avoided by addition of flutamide at the beginning of treatment. Other side effects, such as mild hot flushes, decrease or loss of libido, and impotence were well tolerated by all patients.

The significance of reversible medical castration with buserelin in the hormonal therapy of advanced male breast cancer remains to be established. The antitumor effect of buserelin alone, at the dosage used, is inferior to the results obtained by surgical castration. This might be a result of the less sudden decrease and the remaining production of androgens in patients who retain their testes compared with those who undergo surgery. One possible use of the LH-RH agonist would be to select patients with hormone-dependent breast cancer for subsequent orchidectomy. Whether flutamide alone is responsible for the improvement in results, or whether it is the combined effect of buserelin and flutamide, will require further investigation.

REFERENCES

1. Farrow JH, Adair FE. Effect of orchiectomy on skeletal metastases from cancer of the male breast. *Science* 1942; 95:654.

2. Neifeld JP, Meyskens FL, Tormey DC, Javadpour N. The role of orchiectomy in the management of advanced male breast cancer. *Cancer* 1976; 37:992–995.

3. Nirmul D, Pegoraro RJ, Jialal I, Naidoo C, Joubert SM. The sex hormone profile of male patients with breast cancer. *Br J Cancer* 1982; 48:423–427.

4. Calabresi E, De Giuli G, Becciolini A, Giannotti P, Lombardi G, Serio M. Plasma estrogens and androgens in male breast cancer. *J Steroid Biochem* 1976; 7:605–609.

5. Redding TW, Schally AV. Inhibition of prostate tumor growth in two rat models by chronic administration of D-Trp6 analogue of luteinizing hormone-releasing hormone. *Proc Natl Acad Sci USA* 1981; 78:6509–6512.

6. Vilchez-Martinez JA, Pedroza E, Arimura A, Schally AV. Paradoxical effects of D-Trp6-luteinizing hormone-releasing hormone on the hypothalamic-pituitary-gonadal axis in immature female rats. *Fertil Steril* 1979; 31:677–682.

7. Tolis G, Ackman D, Stellos A *et al.* Tumor growth inhibition in patients with prostatic carcinoma treated with luteinizing hormone-releasing hormone agonists. *Proc Natl Acad Sci USA* 1982; 79:1658–1662.

8. Klijn JGM, de Jong FH. Treatment with a luteinizing hormone-releasing hormone analogue (buserelin) in premenopausal patients with metastatic breast cancer. *Lancet* 1982; i:1213–1216.

9. Kahan A, Delrieu F, Amor B, Chiche R, Steg A. Disease flare induced by D-Trp6-LHRH analogue in patients with metastatic prostatic cancer. *Lancet* 1984; i:971–972.

10. Labrie F, Dupont A, Belanger A, Edmont J, Monfette G. Simultaneous administration of pure antiandrogens, a combination necessary for the use of luteinizing hormone-releasing hormone agonists in the treatment of prostate cancer. *Proc Natl Acad Sci USA* 1984; 81:3861–3863.

11. Labrie F, Dupont A, Belanger A *et al.* Combined treatment with flutamide and surgical or medical (LHRH agonist) castration in metastatic prostatic cancer. *Lancet* 1986; i:49.

12. Zubrod CG, Schneiderman M, Frei E III *et al.* Appraisal of methods for the study of chemotherapy of cancer in man: Comparative therapeutic trial of nitrogen mustard and triethylene thiophosphoramide. *J Chronic Dis* 1960; 11:7–31.

13. Everson RB, Lippman ME, Thompson EB *et al.* Clinical correlations of steroid receptors and male breast cancer. *Cancer Res* 1980; 40:991–997.

14. Treves N. The treatment of cancer, especially inoperable cancer, of the male breast by ablative surgery (orchiectomy, adrenalectomy, and hypophysectomy) and hormone therapy (estrogens and corticosteroids). An analysis of 42 patients. *Cancer* 1959; 12:830–832.

15. Kantarjian H, Yab HY, Hortobagyi G, Buzdar A, Blumenschein G. Hormonal therapy for metastatic male breast cancer. *Arch Intern Med* 1983; 143:237–240.

16. Meyskens FL, Tormey DC, Neifeld JP. Male breast cancer: A review. *Cancer Treat Rev* 1976; 3:83–93.

17. Patterson JS, Battersby LA, Bach BK. Use of tamoxifen in advanced male breast cancer. *Cancer Treat Rep* 1980; 64:801–804.

18. Pannuti F, Martoni A, Busutti L, Gramellini M, Piana E. High-dose medroxyprogesterone acetate in advanced male breast cancer. *Cancer Treat Rep* 1982; 66:1763–1765.

19. Lopez M. Cyproterone acetate in the treatment of metastatic cancer of the male breast. *Cancer* 1985; 55:2334–2336.

20. Patel JK, Nemoto T, Dao TL. Metastatic breast cancer in males. Assessment of endocrine therapy. *Cancer* 1984; 53:1344–1346.

21. Harris AL, Dowsett M, Stuart-Harris R, Smith IE. Role of aminoglutethimide in male breast cancer. *Br J Cancer* 1986; 54:657–660.