Buserelin as Primary Therapy in Advanced Prostatic Carcinoma

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The effectiveness of buserelin, a luteinizing hormone-releasing hormone agonist, was tested in 28 patients with Stages C or D adenocarcinoma of the prostate. Of 24 evaluable patients, there were 13 partial responses (54%) by National Prostatic Cancer Project criteria, median duration greater than 6 months. Nine patients had stable disease (38%), median duration greater than 5 months, and only two patients progressed. Performance status improved in 38%, patient-scored pain improved in 46%, and quality of life improved in 57%. Symptoms occurring during treatment consisted of hot flashes, loss of libido, and impotence. A flare of symptoms was observed in only one patient, despite a transient 25% increase in testosterone in 36% of patients. Buserelin is an effective treatment for inducing frequent and meaningful remissions in advanced prostatic cancer.

Cancer 56:2416–2419, 1985.

ADVANCED PROSTATIC CARCINOMA is a common oncologic problem. Although standard therapy for metastatic prostatic cancer with the use of either orchiectomy or diethylstilbestrol is highly effective palliative treatment, side effects are common. Many patients decline orchiectomy because of the irreversible "demasculinizing" effects; diethylstilbestrol produces feminization and fluid retention and is associated with a risk of cardiovascular complications, including stroke and cardiac death.[1]

An alternative method for decreasing testosterone levels is the use of analogues of natural luteinizing hormone-releasing hormone (LH-RH). One such peptide analogue is buserelin acetate (HOE 766). This nonapeptide differs from the naturally occurring LH-RH in the substitution of glycine in position 6 by D-serine O-t-butylether and the substitution of glycinamide in position 10 by ethylamide. Buserelin by acute bolus administration has an enhanced LH-RH effect 20 to 170 times greater than that of natural LH-RH, and the duration of action is longer. After chronic administration of buserelin, the LH-RH responsiveness of anterior pituitary receptors is down-regulated and LH and follicle-stimulating hormone (FSH) levels fall. As a consequence, testosterone levels fall to castrate concentration.[2,3] It has also been suggested that patients with widespread prostatic cancer have subjective and objective responses to buserelin.[4–6]

In an effort to substantiate the clinical activity of buserelin in patients with advanced prostate cancer with widely accepted response criteria, a nonrandomized study was initiated to determine how buserelin affected testosterone levels and how response rates compared with those previously reported with orchiectomy or diethylstilbestrol.

Methods

Patients were eligible for this study if they had Stage C or D prostatic carcinoma without previous antitumor therapy (including hormonal therapy, chemotherapy, immunotherapy, or recent radiation therapy). Patients were between the ages of 40 and 90 years and had a minimum life expectancy of at least 1 year. Patients were required to give voluntary informed consent before participation. Patients with other neoplasms or a history of alcohol or drug abuse were excluded from this study.

Subcutaneous and intranasal buserelin were provided by Hoechst-Roussel Pharmaceuticals, Inc. For the first 7 days, the dose of buserelin was 500 μg subcutaneously every 8 hours. Thereafter, patients could elect to receive

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Supported by a grant from Hoechst-Roussel Pharmaceuticals, Inc.

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Accepted for publication February 9, 1985.

either 200 μg of buserelin subcutaneously daily (administered by themselves or relatives) or 400 μg intranasally three times a day. Therapy was continued until tumor progression.

Information collected included history and physical examination, tumor size by rectal examination, computerized axial tomography scans of the prostate and pelvis, uroflowmetry, chest x-rays, nuclear bone scans, bone x-rays of suspected lesions, electrocardiogram, and intra venous pyelogram when indicated, as well as complete blood count, platelet count, chemistry profile, alkaline phosphatase, acid phosphatase (total and prostatic fraction), urinalysis, FSH, LH, testosterone, dihydrotestosterone, estradiol, prolactin, and cortisol levels. These studies were repeated serially. Hormone levels were obtained weekly for the first month, then every month. In addition, physicians evaluated the performance status of the patient on a 0 to 4 scale (0, normal; 1, symptomatic but ambulatory; 2, in bed less than 50% of the time; 3, in bed more than 50% of the time, 4, totally bedridden), and patients were required to complete a patient diary, which included the subjective evaluation of pain (score of 0 to 3; 0 representing none; 1, mild; 2, moderate; 3, severe). In addition, patients treated in Los Angeles were evaluated with a patient-scored quality of life questionnaire, which evaluated 14 estimates of various aspects of quality of life in a linear analogue method, with a derived score of 0 to 10 (0 representing worst, 10 representing best); this analysis was repeated every 3 months.[7]

Patients were evaluated for objective antitumor response according to the National Prostatic Cancer Project criteria.[8] Objective partial regression included at least one tumor mass reduced by greater than 50% in cross-sectional area, elevated acid phosphatase (if present) returned to normal, osteolytic lesions (if present) having undergone partial recalcification in one or more areas, osteoblastic lesions not progressing, no increase in size in other lesions and no new areas of malignant disease, and no significant cancer-related deterioration in weight (greater than 10%), symptoms, or performance status. For a partial regression, all improvements must have persisted until at least the 3-month evaluation. Progression was defined as a significant cancer-related deterioration in weight (greater than 10%), symptoms, or performance status, appearance of new areas of malignant disease, increase in previously measureable lesions by greater than 25% in cross-sectional area, development of recurring anemia secondary to cancer of the prostate, or development of ureteral obstruction. Patients with stable disease had neither partial response nor progression.

Results

Twenty-eight patients were treated in this program. One patient was removed from the study because of intercurrent illness, two patients died of acute myocardial infarctions after less than 2 months of therapy (these were presumed unrelated to buserelin therapy), and one patient's disease was too early for antitumor analysis. Excluding these patients, 24 patients' disease remains evaluable currently. Mean age was 71 years, and most patients had Stage D2 carcinoma. Prior surgery was most frequently transurethral resection of the prostate (17 patients), but 8 patients had no prior therapy. No patient received prior estrogens, orchiectomy, or chemotherapy. Of the 24 patients, 86% had a performance status of 0, 1, or 2, and 79% had bone pain. Patients treated in Memphis had more advanced disease and were more symptomatic than patients treated in Los Angeles.

TABLE 1. Response

Parameter	Objective tumor measurement	Performance level	Pain level	Quality of life
Evaluator	Physician	Physician	Patient	Patient
No. of patients evaluable	24	24	24	7*
Partial response	13 (54%)	9 (38%)	11 (46%)	4 (57%)
Stable	9 (38%)	13 (54%)	7 (29%)	2 (29%)
Progression	2 (8%)	2 (8%)	6 (25%)	1 (14%)

* Evaluated on Los Angeles patients only.

Buserelin reduced serum testosterone to castrate levels (less than 100 ng/dl) in all patients. However, 10 of 28 patients (36%) had a transient increase of testosterone greater than 25% of the pretreatment value (all 28 patients had disease evaluable for determination of serum testosterone response to buserelin). Only one of these patients exhibited a transient "flare" of symptoms, which was of 2 weeks' duration, associated with a transient 40% increase in testosterone concentration (he subsequently had a partial response to buserelin therapy, which was continued).

The mean time to reach castrate testosterone level was 2.7 weeks. The mean time was similar in patients receiving intranasal buserelin, compared with patients receiving subcutaneous buserelin. The median testosterone level at 4 weeks was only 25 mg/dl.

Twenty-four patients were evaluable for antitumor responses, and to date 54% have had a partial response (Table 1). Only 8% had progression. Duration of response to date was more than 1 to more than 11 months, with a median of more than 6 months. Only two patients (both with stable disease) have progressed. Physicians scored performance status themselves. Compared with pretreatment performance status, physicians defined performance status as having improved at least one level in 38% of patients. Of patients with ambulatory status before treatment, 90% remained at that level after treatment; six of

eight patients who were partially bedridden became ambulatory. All four patients who were bedridden more than 50% of the time showed marked improvement in performance status. Patients scored their pain on a scale of 0 (no pain) to 3 (Table 1).

Forty-six percent of patients evaluated their pain as improved at least one level. Patients in Los Angeles used a patient-scored quality of life assessment. Previous studies[7] have indicated that a significant change in score is greater than 1 unit on a scale of 0 to 10. Of seven patients with serially evaluable determinations (others did not have adequate testing), 57% showed an increase of greater than 1 unit (including a patient whose two initial evaluations before 3 months of treatment were 8.5 and 7.9). Two patients reported no change in quality of life, and in both cases the quality of life was above 9 before treatment. One patient with a pretreatment quality of life score of 9.1 decreased to 8.1, and that patient had increasing shortness of breath related to procainamide-associated autoimmune hemolytic anemia (which improved after withdrawal of procainamide).

Symptoms occurring during treatment were not severe. As expected, hot flashes (54%) and loss of libido and/or impotence (25%) were observed. Rarely, patients exhibited local reactions to either subcutaneous or intranasal buserelin (nasal irritation, 43%; mild pain at injection site, 49%).

Discussion

Buserelin is an effective agent for decreasing testosterone levels to castrate concentrations. A transient increase in testosterone was observed during the first week in 36% of patients, but only one flare in symptoms was reported in our patients. The frequency of increased testosterone after buserelin may have been higher than 36%, but the first postbuserelin testosterone concentration was determined only at 1 week after therapy was begun. The fact that all patients had a reduction in testosterone to castrate levels implies that there was high patient compliance with buserelin administration, despite its parenteral route of administration. We were surprised to find that despite the discomfort of subcutaneous shots, most patients preferred that route of administration to intranasal buserelin. None of the 75% of patients electing subcutaneous buserelin switched to intranasal.

The objective partial response rate to buserelin (54%) compared favorably with the response rate cited for diethylstilbestrol or orchiectomy (41%) when evaluated by the National Prostatic Cancer Project criteria.[9] In addition, pain symptoms as evaluated by the patient improved at least as much in response to buserelin (46%) as in response to diethylstilbestrol (36%). Similarly, improvement in performance status after buserelin (38%) was good, compared with diethylstilbestrol (31%).

Because the high frequency of response in our patients was associated with significant subjective improvement in performance status as evaluated by physicians, subjective improvements in pain symptoms as evaluated by patients, and subjective improvement in quality of life as evaluated by patients, we conclude that buserelin is an effective treatment for advanced prostatic carcinoma. Buserelin produces frequent and meaningful responses rapidly in patients with Stages C and D prostatic carcinoma.

These results are consistent with the prior data published on the use of other methods of buserelin administration.[2-6] Those studies approached description of therapeutic effects in a manner that did not allow for a comparison of their results with those of the National Prostatic Cancer Project,[9] which represented a multicenter study performed in the United States.

These results seem numerically inferior to those of Labrie *et al.*,[10,11] who used not only buserelin but also an antiandrogen to give "complete . . . . withdrawal of androgens." They reported a 97% objective response rate. However, although our data reported here are consistent with multiple other studies,[2-6] the results of Labrie *et al.* require confirmation by other groups before general acceptance. It confirmed, a randomized trial of LH-RH agonists (buserelin or leuprolide), *versus* the same agonist plus an antiandrogen, would be warranted.

The relative efficacy of buserelin, compared with standard treatment with diethylstilbestrol or orchiectomy, remains to be studied by a definitive randomized prospective trial. We feel that this nonrandomized study provides a persuasive rationale for conducting such a randomized prospective study. Although a study of buserelin *versus* orchiectomy is scientifically desirable, such a study with prerandomization informed consent involving permanent "demasculinizing" orchiectomy on one arm, *versus* only temporary drug administration on the other arm, may be difficult if not impossible to perform. Such a study may present the patient and physician with unethical options. Further, it would be difficult for a pure randomized study of diethylstilbestrol *versus* buserelin to safely include patients with preexisting cardiovascular disease because the treatment arm containing estrogen is known to predispose patients to further cardiovascular complications (if more than 1 mg diethylstilbestrol is administered daily).

If the antitumor activity of buserelin that we have demonstrated is confirmed by others and if the drug is marketed, one possible use of the drug may indeed be to select patients for subsequent therapy. Patients could initially receive buserelin for 2 to 3 months, and those who respond to such treatments could consider other alternative ther-

apies, such as diethylstilbestrol or orchiectomy, with higher expectations of response than is currently possible.

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