Buserelin Treatment of Advanced Prostatic Carcinoma

Long-Term Follow-Up of Antitumor Responses and Improved Quality of Life

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The safety and efficacy of buserelin, a luteinizing hormone-releasing hormone (LH-RH) agonist, was tested in 33 evaluable patients with Stages C or D adenocarcinoma of the prostate. With a minimum follow-up duration of 10 months, there was one complete response and 22 partial responses (69%) by National Prostatic Cancer Project criteria, with a median duration greater than 18 months. Six patients (18%) had stable disease, median duration greater than 25 months, and only 12 patients have progressed. Performance status improved in 67%, patient-scored pain improved in 75%, and quality of life improved in 58%. Symptoms occurring during treatment consisted of hot flashes, loss of libido, and impotence. Buserelin produces a high frequency of durable objective and subjective responses in patients with advanced prostatic carcinoma.

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ADVANCED prostatic carcinoma is the second most common oncologic problem in men. Either orchiectomy or diethylstilbestrol is highly effective palliative treatment. Many patients, however, decline orchiectomy. Diethylstilbestrol produces feminization and fluid retention, and is associated with a risk of cardiovascular complications, including thrombosis, 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). Buserelin produces a marked fall in testosterone levels to castrate concentration.[2,3] Patients with widespread prostatic cancer have subjective and objective responses to buserelin.[4–6] In this Phase II, nonrandomized study, the investigators have been using the widely accepted National Prostatic Cancer Project (NPCP) criteria to define the objective and subjective response rates. In our initial communications, results were preliminary and accrual to the study was continuing.[7,8] Since accrual has been completed for a minimum of 10 months, the response rates, duration of response, and effects on subjective symptoms and quality of life now are better defined in this report.

Patients and 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 (Somerville, NJ). For the first 7 days the dose of buserelin was 500 μg subcutaneously every 8 hours. Thereafter, patients could elect to receive 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 patient history and physical examination, tumor size by rectal examination,

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TABLE 1. Antitumor Responses

Response	No. of patients (%)	Duration of response (mo)
Complete	1 (3%)	9+
Partial	22 (66%)	5-30+*
Stable	6 (18%)	6-30+†
Progression	2 (6%)	—
Off study‡	2 (6%)	—

* 18.0 + median.
† 25.5 + median.
‡ Off study due to intercurrent disease.

computerized axial tomography scans of the prostate and pelvis, uroflowmetry, chest x-rays, nuclear bone scans, bone x-rays of suspected lesions, electrocardiogram, and intravenous pyelogram when indicated, as well as complete blood and platelet counts; chemistry profile; alkaline phosphatase and acid phosphatase levels (total and prostatic fraction); urinalysis; follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, dihydrotestsoterone, estradiol, prolactin, and cortisol levels. These studies were repeated serially. Serum testosterone 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 using a score of 0 to 3 (0, 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.[9]

Patients were evaluated for objective antitumor response according to the National Prostatic Cancer Project criteria.[10] 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 by 3 months.

TABLE 2. Quality of Life Response

Parameter	No. of patients evaluable	Criteria for response	No. of patients responding
Pain	28	Decreased to none or minimal	21 (75%)
Performance	18	Increased to normal	12 (67%)
Quality of life—global scale (range 0–10)	12	Increase by greater than 1.0 U	7 (58%)
Quality of life—global scale (range 0–10)	8	Increase from <8.0 to >8.0 U	7 (88%)
Quality of life—global scale (range 0–10)	4	Maintained >9.0 U	2 (50%)

Results

Thirty-three patients were treated (all are evaluable). Four patients had Stage C2 disease, three had D1, and 26 had D2. Mean age was 71 years. No patient received prior estrogens, orchiectomy, or chemotherapy.

Twenty-three of the 33 patients had objective responses (one complete and 22 partial) for an overall response rate of 69% (Table 1). Six patients (18%) were stable for at least 6 months.

Bidimensionally measurable tumor decreased by over 50% in 23 out of 30 patients. Urinary obstruction disappeared in two of four patients. Elevated prostatic acid phosphatase returned to normal or decreased by more than 50% in 15 of 17 instances. Osteoblastic lesions decreased in size or disappeared in seven patients, and osteolytic metastases recalcified in two cases (by routine radiographs). Two patients died of myocardial infarction, presumably unrelated to buserelin (since this occurrence has not been observed in other trials of buserelin or other LH-RH agonists).

Overall, the median duration of response was over 18 months. Since less than 50% of the patients have relapsed (0/1 complete responses have relapsed, 11/22 partial responses, and 2/6 stable disease), the duration of response will probably be longer. The complete responder had a partial response 3 months after treatment was started and entered a complete response at 9 months, which has lasted another 9+ months (he has not relapsed at 18 months after starting therapy). The median duration of partial

response is 18+ months (disease was in remission, in two patients at 12+ months, four at 18+ months, two at 27+ months, and two at 30+ months). The median duration of stable disease is 25.5 months (disease was in remission, in one patient at 24+ months, one at 27+ months, and two at 30+ months).

Symptomatic responses have been frequent (Table 2). Patients measured their own pain. This decreased to normal or minimal pain in 75% of those with pain. Physicians or nurses evaluated performance status which increased to normal in 12 (67%) of the 18 patients in whom it was impaired before treatment.

All patients in Los Angeles completed the patient-scored quality of life (QL) assessment.[9] Of those 16 patients, four entered with a normal QL greater than 9.0 (on a scale of 0–10). Two continue to maintain a score above 9.0. Twelve had pretreatment QL scores less than 9.0, and seven (58%) have increased by more than 1.0 U. The median time to improvement by more than 1.0 U was less than 3 months, and all responses had occurred by 9 months. The median duration of response in QL was 9.0 months, with four of seven patients continuing to have an improved QL at 6+, 9+, 12+, and 21+ months. Of eight patients with a severely decreased QL less than 8.0, seven improved to above 8.0.

Symptoms occurring during treatment were not severe (Table 3). As expected, hot flashes, loss of libido, and/or impotence were observed. Rarely, patients exhibited local reactions to either subcutaneous or intranasal buserelin (nasal irritation or mild pain at injection site). A few patients had headaches of uncertain relationship to buserelin. Only one patient had a "flare" of symptoms after buserelin and this was temporary.

Six patients received other hormone therapy after failing buserelin. In no instance was an unequivocal partial response produced (Table 4).

TABLE 3. Symptoms Occurring During Treatment

Symptoms	Percentage
Hot flashes	87
Loss of libido	90
Impotence	85
Nasal irritation	38
Headaches	26

TABLE 4. Response to Subsequent Therapy

Therapy	Total	Partial response	Stable	Progression
Orchiectomy	5	0	1	4
Stilphosterol	1	0	1	0

Discussion

These results show a higher response rate than our prior report,[7,8] probably due to continued tumor regression in previously stable patients. This emphasizes the need for evaluating studies of primary hormonal therapy of prostate cancer only after at least 6 to 9 months of treatment have elapsed in each evaluated case.

This study again confirms the excellent antitumor effects of LH-RH agonists.[2–6,11–15] Although all such agents likely produce equivalent antitumor effects based on testosterone suppression, it is possible that one or another of these drugs might be superior based on enhanced binding of analog directly to tumor cell receptors and direct cytotoxic effects.[16] Therefore, the response rates and response duration of each of the LH-RH agonists must be carefully compared.

We have previously published the hormone responses in our patients.[8] All patients had rapid (1 to 3 weeks) and sustained decreases in testosterone to castrate levels. A "flare" or transient elevation in levels occurred in the first week in 36% of patients, but in only one patient was a temporary exacerbation of clinical symptoms observed.

This data compares favorably with previously published results[17] using diethylstilbestrol or orchiectomy (Table 5). This comparison is possible since both this study and the prior one used equivalent evaluation criteria for both objective and subjective responses. The current study, however, also included four patients with stage C2, and three with stage D1. Furthermore, the current study also used pelvic computed tomography (CT) scans to evaluate tumor regression. Although numerically the buserelin results appear superior to diethylstilbestrol or orchiectomy, only a Phase III randomized national study will define if any difference exists between the treatments. Certainly, it appears from this study that buserelin is at least as effective as conventional hormonal therapy, that the buserelin results last at least as long, and that buserelin is less toxic than diethylstilbestrol. Buserelin is effective therapy for advanced prostatic carcinoma.

TABLE 5. Comparison of Buserelin and DES/Orchiectomy

	Response rate (%)	
Response criterion	Buserelin	DES/ Orchiectomy*
Partial objective response†	69	41
Pain control	75	36
Performance status	67	31

* From reference 17.
† NPCP Criteria.

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