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Long-Term Follow-Up of Patients With Advanced Prostatic Carcinoma Treated With Either Buserelin (HOE 766) or Orchiectomy: Classification of Variables Associated With Disease Outcome

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We compared the clinical efficacy and safety of Buserelin treatment versus orchiectomy in 29 patients with newly diagnosed advanced prostatic cancer. There was no significant difference between the two treatment modalities in 1) reduction of plasma testosterone to below 100 ng/dl after 8 weeks, 2) objective clinical response rates in patients with stage D_2 carcinoma, 3) induction of complete remission in patients with stages C and D_1 carcinoma, or 4) relapse rates and death rates in patients with stage D_2 carcinoma. After scoring stage D_2 disease according to our aggressiveness analysis system, we found that patients with less aggressive neoplasms displayed a qualitatively better response and more prolonged remission. These data and the absence of estrogenic effects confirm Buserelin as a favorable alternative to orchiectomy in the treatment of prostatic cancer. Additionally, the study demonstrates the importance of considering the heterogeneity of the aggressiveness of stage D_2 disease in assessing the benefits of clinical trials in prostatic carcinoma.

Key words: Buserelin, HOE766, LHRH-A, orchiectomy, prostatic cancer

INTRODUCTION

Prostatic cancer is the best-known hormone-dependent neoplasm in the male. Therapeutic means of palliation of patients with disseminated disease includes surgical castration or estrogen administration. Both of these procedures are associated with psychological and/or somatic side effects, even though clinical response is not documented in all patients. The latter is thought to be due to the existence of hormone-insensitive carcinoma. The availability of luteinizing hormone-releasing hormone agonistic analogues (LHRH-A) and the demonstration of their efficacy in suppressing gonadal function without resulting in estrogenic side effects have prompted us and others to assess their safety and efficacy as an alternative to orchiectomy and estrogen in the treatment of disseminated prostatic carcinoma [1–8]. In the course of our studies, it became apparent that there is a certain heterogeneity concerning the outcome of patients with advanced prostatic carcinoma that we treated with LHRH or orchiectomy. The identification of variables associated with the clinical responsive-

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ness and disease outcome, as well as our long-term clinical, biochemical, hormonal, and radiological data, forms the present report.

SUBJECTS AND METHODS

Twenty-nine patients with stage C (N = 3), stage D_1 (N = 6), and stage D_2 (N = 20) prostatic cancer (biopsy proven) were studied. Nine of them, three stage D_1 and six stage D_2, underwent surgical castration and were followed up to 24 months. The other 20 patients were treated with a gonadotropin-releasing hormone agonistic analogue (GnRH-A or LHRH-A), Buserelin (HOE 766), for up to 36 months. Two of them received a dose of 50/μg subcutaneously (SC) daily and the rest received 3 × 500 μg SC daily (N = 11) or 2 × 500 μg intranasally (IN) daily for either 7 or 60 days, respectively, followed by a maintenance dose of 3 × 400 μg IN daily thereafter. All patients signed an informed consent for random selection of medical or surgical castration. The protocol of this study had been approved by the Institutional Review Committee of McGill University.

Hormone estimations were based on standard radioimmunoassays [1]. Prostatic size was estimated by both digital examination and by transabdominal ultrasonography; the results were expressed in cm^2 (length × width) [9]. Treatment response was evaluated according to the criteria established by the National Prostatic Cancer Project (NPCP). The data were analyzed statistically with Student's t-test, the Wilcoxon signed-rank test, and analysis of variance.

Patients were followed every week for the first 2 months, then every month during the first year and every 1–3 months thereafter. Evaluation prior to the initiation of either castration or HOE 766 consisted of a complete physical examination and biochemical investigation, including SMA_{16}, prostatic acid phosphatase (PAP) [1], hemogram and hormonal assessment (plasma testosterone (T), estrone (E_1), estradiol (E_2), FSH, LH, prolactin (PRL), thyroxine (T_4), and cortisol (F). Radiological evaluation included chest X rays, metastatic bone survey, nuclear scans (bone, renal, liver, and spleen), and CT scan when indicated. Clinical and hormonal assessments were scheduled for every visit; radiological evaluation was done at 3- to 6-month intervals or more frequently if the need arose. According to histological grading, extent of bone involvement, and the PAP and alkaline phosphatase levels, a disease aggressiveness score was arbitrarily derived (Table I) and was correlated with the type of response, duration of response, and length of survival.

RESULTS

Hormonal Data

After the 8–10 weeks of treatment with HOE 766, mean ± SE levels of T (ng/dl) were found to be similar to those achieved in patients subjected to surgical

TABLE I. Arbitrary Score of Disease Aggressiveness: Stage D_2

	Pretreatment values		
Histological differentiation	Prostatic acid phosphatase (ng/ml)	Alkaline phosphatase (U/L)	Bone scan No. of foci
Good = 1	⩽ 2.8 = 0	< 105 = 0	1–3 = 1
Moderate = 3	2.8–10 = 1	105–200 = 1	4–10 = 5
Poor = 5	> 10 = 5	> 200 = 5	> 10 = 10

castration (HOE 766-treated: $T = 42 \pm 11$; orchiectomized: $T = 22 \pm 10$) ($P > 0.02$) (Fig. 1). The mean levels of E_2 and E_1 (ng/dl) were also decreased, and the two treatment groups did not differ (HOE 766-treated: $E_2 = 0.68 \pm 0.8$; orchiectomized: $E_2 = 0.60 \pm 0.1$; and HOE 766-treated: $E_1 = 2.35 \pm 0.17$; orchiectomized: $E_1 = 2.2 \pm 0.42$) (Fig. 1). Mean basal FSH and LH levels were decreased by 30–45% from their pretreatment values in HOE 766-treated patients. FSH levels showed a trend to return to pretreatment levels, unlike basal LH levels which remained suppressed throughout the HOE 766 therapy. In the orchiectomized group, FSH and LH basal levels showed a prompt elevation after surgical castration (Fig. 1). Serum T_4, PRL, and plasma F basal levels were unchanged during either therapy.

Clinical Data

From 14 patients (5 orchiectomized, 9 HOE 766-treated) with reduced general well-being, 13 (5 orchiectomized, 8 HOE 766-treated) experienced marked improvement within 3 months of therapy. One patient treated with HOE 766 deteriorated rapidly despite effective medical castration with HOE 766.

Both treatments improved symptoms of prostatism, when present, within 1–4 months. Symptoms of prostatism recurred in one stage C and in four stage D_2 patients. In four of five stage D_2 patients (1 orchiectomized and 3 HOE 766-treated), this was in association with an escape of disease from the initial objective clinical response to therapy.

Twelve of 20 (6 orchiectomized and 6 HOE 766-treated) patients with stage D_2 disease initially had severe bone pain. In every orchiectomized patient, bone pain decreased significantly, and in 2 out of 4 pain disappeared after 2–4 months. Seven of eight cases treated with HOE 766 showed the same pain control, and 5 out of 7 were free of pain after 4–5 months of treatment.

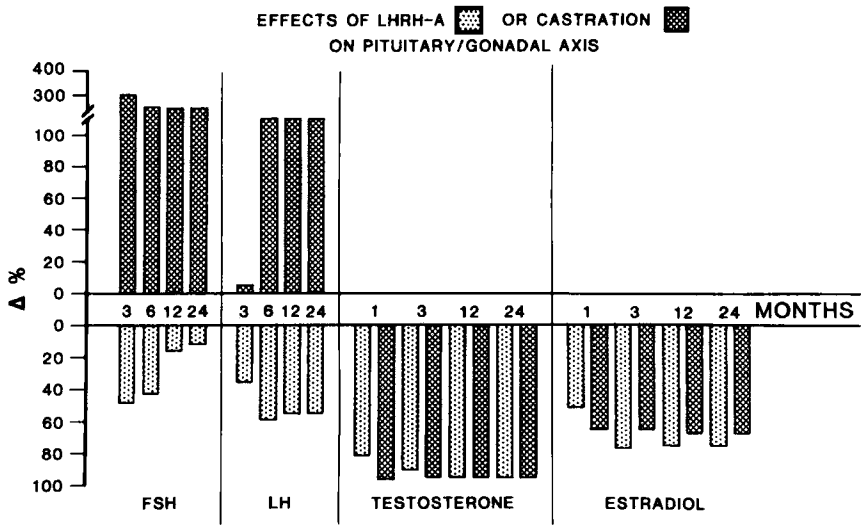

Fig. 1. Mean basal FSH, LH, testosterone, and estradiol levels expressed as percent above or below pretreatment values in 20 HOE 766-treated and nine orchiectomized patients at different times throughout follow-up.

In none of the HOE 766-treated patients was the so-called disease flare-up observed.

Radiological Data

Nineteen of 20 patients with bone disease had blastic metastases. One had both blastic and lytic lesions. None of the patients demonstrated or developed lung or liver parenchymal metastases during the study.

Transabdominal Ultrasonography

Transabdominal ultrasonography documented a significant shrinkage of the prostate gland in all patients (N = 29). Patients treated with orchiectomy showed a more rapid decline in prostatic size than those treated with HOE 766. By the third month of either treatment, the reduction of prostatic mass did not differ significantly among the two groups (Fig. 2). Ultrasonographic estimations were usually in good correlation with the digital estimations. Local regrowth was readily documented ultrasonographically by an increase in prostate size.

Bone Scan

In all patients with stage C and D_1 disease, bone scans showed an absence of metastases initially and throughout follow-up in both treatment groups. All patients with stage D_2 disease had a positive bone scan; one of the 14 patients treated with HOE 766 showed rapidly advancing disease, seven showed disease stabilized (slight improvement or no progression), and six showed a sustained marked improvement. Of the six who improved markedly, five relapsed isotopically within 12–32 months of therapy. All seven stable disease patients relapsed isotopically within 6–15 months.

Among the six stage D_2 patients treated with orchiectomy, three showed a significant improvement and three remained stable; two of the three patients who showed improvement and all of the stable patients relapsed isotopically at 12 and 15 months and at 9, 13, and 13 months, respectively. Regardless of the initial response and excluding the one patient who failed to respond, the mean time to relapse isotopically in the orchiectomized patients (5 of 6 relapsed) was 12.4 months and 13.4 months for HOE 766-treated patients (12 of 13 relapsed).

Enzyme Markers

Prostatic acid phosphatase. Prostatic acid phosphatase levels (PAP) were found to be elevated in 27 of 29 patients. All stage D_2 patients had abnormal

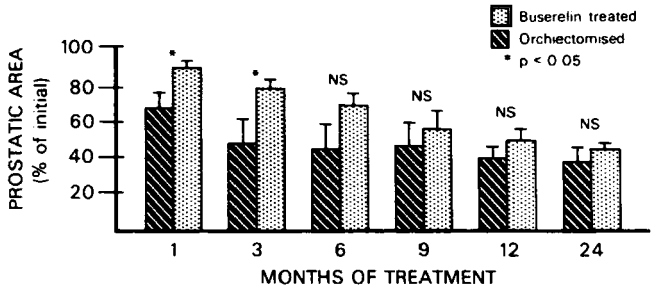

Fig. 2. Comparison of the prostatic size (cm^2) expressed as percent of initial between the orchiectomized and HOE 766-treated patients at 1, 3, 6, 9, 12, and 26 months of follow-up. Note the statistically different values during the first 3 months of follow-up ($P < 0.05$).

pretreatment values ranging from 3 to 1,200 ng/ml (normal range $\leqslant$ 2.8 ng/ml). Five of six D_1 and two of three stage C patients also had abnormal PAP levels ranging from 3 to 10 ng/ml. For stage C and D_1 patients, PAP levels became normal within 1–2 months of initiation of either treatment (3 D_1, orchiectomized; 3 D_1 and 3 C, HOE 766-treated).

Among the 14 D_2 HOE 766-treated patients, PAP levels normalized in six, decreased in seven, and remained unaffected in one. Among the six D_2 orchiectomized patients, levels of PAP normalized in three and in three others the values decreased but were not normalized. Clinical relapses were always associated with rising levels of PAP (Fig. 3).

Alkaline phosphatase. Alkaline phosphatase levels were elevated in 16 of 20 stage D_2 patients (orchiectomized, 5 of 6; HOE 766-treated, 11 of 14). Although alkaline phosphatase concentration declined in seven of 16 patients, this was not in correlation with initial levels or clinical response. As with the PAP in all patients, clinical relapse (N = 17; 5 orchiectomized and 12 HOE 766-treated) was accompanied by an increase in alkaline phosphatase levels.

Initial Clinical Response in Stage D_2 Patients According to NPCP Criteria (Table II)

Analysis of response to therapy after 6 months showed among orchiectomized stage D_2 patients that half (3 of 6) had partial response; disease in the remaining patients was stabilized. Of the 14 stage D_2 HOE 766-treated patients, one showed progression, half (7 of 14) had disease stabilized, and six of 14 were partial responders. Total rate of response (objective partial plus objective stable) was 93%.

Relapses in Stage D_2 Patients

Orchiectomized group. Among the orchiectomized patients who had objectively stable disease, one relapsed during the first year of follow-up and two during the second. Of the three patients who showed objective partial response, two relapsed

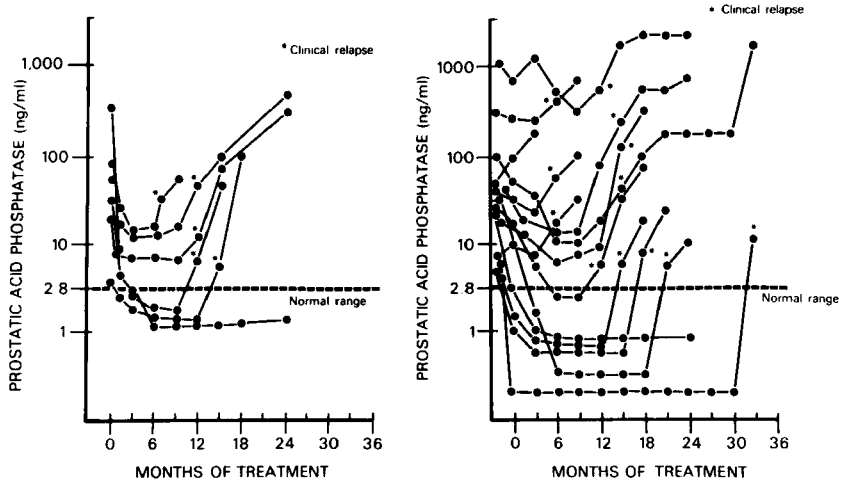

Fig. 3. Prostatic acid phosphatase (PAP) level in stage D_2 patients treated with orchiectomy (left) or HOE 766 (right). Note that disease escape was readily accompanied by rising titers of PAP.

TABLE II. Stage D_2 = Prostatic Adenocarcinoma

NPCP Criteria of response		
Objective partial response	Objective stable disease	Progression
Orchiectomy = 3/6 (50%) LHRH-A = 6/14 (42.8%)	Orchiectomy = 3/6 (50%) LHRH-A = 7/14 (50%)	Orchiectomy = 0/6 (0%) LHRH-A = 1/14 (7.2%)
Total rate of response according to NPCP criteria		
LHRH-A = 93% Orchietomy = 100%	In newly diagnosed stage D_2 prostatic cancer patients	

TABLE III. Relapse in Bones vs Local Prostatic Regrowth

Orchiectomy		LHRH-A	
Bones	Prostate gland	Bones	Prostate gland
5/5 (100%)	1/5 (20%)	12/12 (100%)	3/12 (25%)

TABLE IV. Stage D_2 Prostatic Cancer

Death rates within 1 year of follow-up Orchiectomy: 1/6 (16%)	LHRH-A: 2/13 (15.4%)
Death rates within 2 years of follow-up Orchiectomy: 3/6 (50%)	LHRH-A: 7/13 (53.9%)
Death rates within 3 years of follow up —	LHRH-A: 10/13 (77%)

during the second year of follow-up, whereas the third continued to be in remission 2 years after orchiectomy.

HOE 766-treated group. Among the HOE 766-treated patients who had an objectively stable response, relapse was documented in three during the first 12 months and in four during the second year. Among the six patients with objective partial responses, four of five relapsed during the second year and one during the third year of follow-up.

Relapse in stage D_2 patients was evident in bone metastases (Table III). Of the 17 patients who relapsed, all had disease reactivation in skeletal metastases. In contrast, only four of 17 showed local regrowth of prostatic tissue, as documented by transabdominal ultrasonography, accompanied by increasing symptoms of prostatism.

Deaths (Table IV)

Three of six (50%) orchiectomized patients died within 2 years after initiation of therapy and within 2 months after relapse had occurred; each of these cases had shown an initial response (2 of 3 stable, 1 partial).

Among the HOE766-treated patients who showed an initial response, two died during the first year and an additional five and three died at the second and third years, respectively (54% within 2; 77% within 3 years); among these patients, eight of ten had shown an objectively stable and two an objectively partial response.

Disease Aggressiveness Score

Arbitrary score of disease aggressiveness versus type of clinical response. When the patients who responded to therapy were grouped according to

clinical response (ie, objective partial; objective stable), there was a highly significant ($P < 0.001$) difference between the two groups in aggressiveness score (objective partial: 10.7, range 6–18; objective stable: 20, range 16–25).

Arbitrary score of disease aggressiveness versus time of clinical relapse. A highly statistically significant ($P < 0.001$) negative relationship was documented between the aggressiveness score and the time at which clinical relapse occurred (Fig. 4).

Side Effects

Hot flashes and loss of libido were noticed in every patient treated. There was no subjective or objective evidence of other untoward effects following either castration or long-term HOE766 therapy.

DISCUSSION

Our data indicate that chronic use of LHRH-A effectively reduces plasma testosterone to castrate levels, and responses of stage D_2 prostate cancer patients are comparable to those produced by orchiectomy. A long-term remission was also achieved in stage C and D_1 patients; since such patients are known to stay in remission for more than 3 years, our data do not permit any conclusion concerning the LHRH-A treatment. Both orchiectomy and LHRH-A effectively reduce prostatic tumor size. In all but one of our 20 stage D_2 cases, disease stabilized or there was a partial response initially (100% in orchiectomized and 93% in HOE766-treated). With the passage of time, however, it became evident that the disease escaped from testicular hormonal dependence despite continued suppression of gonadal function. This suggests that the tumor cells responsible for relapse had become hormonally independent. It appears that there is a considerable heterogeneity in the type and duration of response among stage D_2 patients. Retrospective analysis led us to formulate an assessment scale based on the degree of tumor differentiation, titers of acid and alkaline phosphatases, and extent of bone involvement. On the basis of this aggressiveness scoring system, a significant difference emerged among patients who initially had a partial vs stable response; the latter group had a higher score than the former, relapsed earlier and

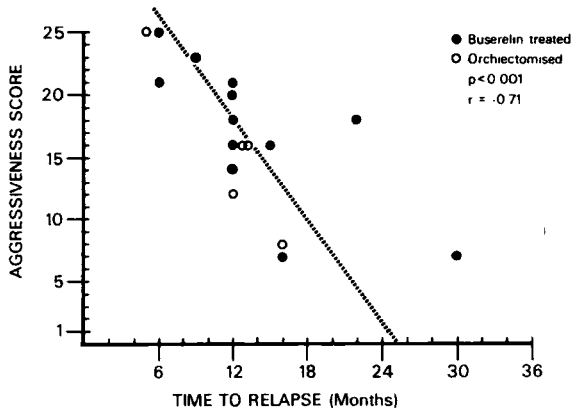

Fig. 4. Linear regression analysis between the disease agggressiveness score and the time of clinical relapse in months.

accounted for more deaths than the group with low aggressiveness scores. These findings point to the need for homogeneous grouping of patients, whenever possible, in order to further validate the interpretation of data [10,11].

In addition, since relapsing patients did so in a different time-related manner while exhibiting a great similarity in both the level of plasma testosterone and type of initial response, nonhormonal variables may account for the differences in tumor progression dynamics. It is possible that from the very beginning the tumor comprises both hormonally and nonhormonally dependent clones and that the latter continue to grow and lead to tumor progression. If that proves to be the case for human prostate cancer, as it has for the Dunning rat tumor model [12], then it may be beneficial for the patient to begin treatment with a combination of chemotherapy and hormonal manipulation. If we now consider that spread of disease can be documented even in stages B_2, C, or D_1, it may be necessary to revise treatment strategies and not wait to interfere only at the very late stage D_2. Finally, since disease-free interval can be documented in patients given LHRH-A who had testosterone values within the normal female range, albeit sometimes differing twofold, the question arises as to whether this is a level of plasma testosterone below which tumor kinetics cannot be further suppressed. If, as recently suggested for a rat model [13], this is also the case for humans, then the need for additional therapy aimed at complete neutralization of androgen action becomes questionable [14]. Certainly a randomized trial comparing orchiectomy versus LHRH-A therapies plus antiandrogens may shed light on this important issue.

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