ADVANCED PROSTATIC ADENOCARCINOMA: BIOLOGICAL ASPECTS AND EFFECTS OF ANDROGEN DEPRIVATION ACHIEVED BY CASTRATION OR AGONISTIC ANALOGUES OF LHRH

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Twenty-nine patients with advanced prostatic adenocarcinoma were evaluated clinically, biochemically and radiologically and randomly assigned either to orchiectomy or to medical treatment. The latter consisted of the chronic administration of an LHRH agonistic analogue by parenteral and/or intranasal routes. Plasma testosterone levels fell to castrate values and remained so for as long as the follow-up lasted (24 months); estrogen levels fell as well. No change in basal cortisol, thyroxine or prolactin levels was noticed. A decrease in prostate size and improvement in prostatism occurred in all. Bone pain and radiology conventionally or by isotopic scanning, did not parallel the improvement seen in the primary disease locus. Similarly, the changes in alkaline phosphatase were minimal when compared to that of prostatic acid phosphatase. Both enzymes increased prior to or concurrently with relapse of the disease. The longest remission and survival was seen in patients with low enzyme levels, non diffuse bone metastases and high degree of tumor differentiation.

Chronic use of agonistic analogues of LHRH induces effective castration in men with prostatic carcinoma and can replace orchiectomy or estrogen administration. The quantitative analysis of androgen receptors (AR) in subcellular fractions of tumor cells; the use of techniques to enhance the number of AR in the cytosol; and the determination of the type II/I regulatory subunit of protein kinase may be used to identify hormone independent clones and spare patients of unnecessary procedures.

Key words: Prostatic cancer, Castration, LHRH.

CLINICAL ASPECTS

INTRODUCTION
Prostatic cancer rates second after lung cancer as cause of death in the elderly male. Mortality is particularly high in patients diagnosed in the advanced stages C and D. In these stages radiotherapy, chemotherapy (in selected cases), castration and/or estrogens are the usual therapeutic manipulations.

The observations of Huggins and Hodges in the early 1940s that castration inhibited the progression of the disease temporarily, classified prostatic carcinoma as the best known example of hormone dependent tumour in the male.

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Two large scale studies have been done by Nesbitt and Baum in the fifties and by the Veterans Administration Co-Op Urological Research Group in late sixties. These have documented the benefits of hormonal treatment in the course of the disease and the quality of life. It is also now well known that the use of estrogens is probably the single most responsible factor for augmenting morbidity or mortality in patients with prostatic cancer, mainly because of the following side effects: (1) cardiovascular; (2) vasculogenic—hemostatic; (3) gastrointestinal; (4) edema, sodium retention; (5) thrombophlebitis and vascular insults to the myocardium and (6) painful gynecomastia — which is bothersome to 2/3 of all patients receiving high dose estrogens.

It is well documented also, on the other hand, that only 60–70% of patients with prostatic cancer will respond to hormonal manipulation. Therefore 1/3 of such patients will be exposed to the side effects of estrogens or to the physical and psychological impact of castration unnecessarily.
After the discovery of the gonadotropin releasing hormone and its analogues, referred to as LHRH-A and the demonstration of their ability to suppress Leydig cell function in experimental animals or man, we and others explored the possibility of using LHRH-A as an alternative to estrogen or castration in prostatic cancer. In this study we report the long term effects of the chronic use of such an analogue—Buserelin—in patients with advanced prostatic adenocarcinoma.

SUBJECTS AND METHODS

Twenty-nine patients with advanced prostatic carcinoma (stages C: n = 3; D1: n = 7 and D2: n = 19) were evaluated and treated. Six stage D2 and 3 stage D1 patients underwent orchiectomy whereas the other 20 patients were treated chronically with HOE 766 given intranasally (i.n.) and/or parenterally (s.c.).

Of the Buserelin treated group, two patients received 50 μg subcutaneously (s.c.) daily. Two received 50 μg, s.c. daily for 1–2 months and then they were switched to 400 μg, tid., i.n. Five received 500 μg, bid., i.n. for up to 3 months and then were switched to 400 μg, tid., i.n. The remaining 11 patients were given initially 500 μg, tid., s.c. for 7 days and switched thereafter to 400 μg, tid., i.n. All patients signed an informed consent and were assigned to castration or HOE 766 treatment by drawing lots. HOE 766 was obtained by the hospital pharmacy having been provided as a gift by Hoechst Pharmaceuticals. The protocols used had been approved by the local Ethics Committee and the Canadian Health Protection Branch.

Hormone measurements were done by standard radioimmunoassays. The size of the prostate was estimated by transabdominal ultrasonography (ATL Mark 5 and ATL 100 real fine gray scale imager). The response to treatment was evaluated according to the criteria established by the National Prostatic Cancer Project. Student's t and Wilcoxon rank sum tests were used to analyze the data statistically.

All patients were seen every second week for the first 2 months and at monthly intervals thereafter. Prior to any therapy they had (1) standard hematological test (Hemogram, SMA-16); (2) urinalysis; (3) hormone measurements—testosterone (T), estradiol (E2), FSH, LH, PRL, cortisol (F), thyroxine (T4); (4) radiological evaluation—chest, intravenous pyelography, metastatic bone survey; (5) transabdominal ultrasonography; (6) nuclear imaging, bones, liver, spleen, kidneys; (7) electrocardiogram; (8) determination of prostatic acid phosphatase by radioimmunoassay.

All patients had prostatic biopsy and, when indicated, lymph node resection for staging purposes. Following orchiectomy or HOE 766 administration evaluations [(1)–(8)] were performed at frequent intervals of 1–6 months; plasma T was measured at bi-weekly intervals for the first two months and at monthly intervals thereafter.

RESULTS

Hormonal data

Buserelin suppressed plasma testosterone levels to castrate values after 8 weeks of therapy (plasma T ng/dl X ± SE: castrate 22 ± 10; Buserelin 42 ± 11, P = N.S.). In contrast to the similar effect of both above therapies upon plasma sex steroids (T, E1, E2) orchiectomy increased whereas Buserelin decreased serum gonadotropin levels (Fig. 1). No effect was seen on serum concentration of PRL, T4 and cortisol levels measured at different follow-up periods (Fig. 2). Of particular interest was the finding of identical values for T and cortisol in our patients irrespective of whether these were at remission or relapse of the disease as defined by the N.P.C.P. criteria (Fig. 3).

Clinical response

1. Performance. Fourteen out of twenty-three patients had severely decreased performance. After therapy, 13 (5 orchiectomized and 8 Buserelin treated) showed a significant improvement within 1–3 months; 1 patient showed a rapid deterioration despite effective castration with Buserelin.

2. Prostatism. All patients who had prostatism improved within 1–4 months after treatment initiation. In