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Testosterone and LH supression in disseminated prostatic cancer, during long term treatment with a LH-RH analogue.

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Introduction

Long term treatment with LH-RH analogues shows two opposite effects: first, they stimulate pituitary function and second, they inhibit pituitary function. Kerle et al. (1) reported the failure of the inhibitory effect in some patients suffering from disseminated prostatic cancer treated from 6 to 12 months with ICI 118630. The failure was shown by testosterone (T) "scape", some hours after LH-RH analogue administration. Subsequently, Lock et al. (2) reported that when administering the analogue buserelin (BUS), the "scape" response was not seen, since in 8 patients with disseminated prostatic cancer treated with BUS from 6 to 22 months, T plasma levels stayed at castration values before and after BUS administration. We present our experience on this matter.

Methodology

6 patients were selected at random, from a group of 18 patients with disseminated prostatic cancer, treated with BUS, 200 mcg/day, from 12 to 18 months. In these 6 cases, plasma levels of LH, before BUS administration, and 1, 2, 6 and 24 hours afterwards, were determinated. T plasma levels before BUS administration and 6, 12 and 24 hours afterwards were also determinated. Determinations were perfcrmed by RIA kits from Pharmacia (LH) and Sorin (T) Laboratories, both with certified quality control. Post castration T plasma level in our laboratory is 1.5 nmol/l.

Results

Pictures 1 and 2 show T and LH plasma levels determination finding at scheduled time. In 5 patients no scape response was seen, while in patient Nr. 6 (patient c), T baseline plasma level was already above 1.5 nmol/l. LH plasma level was found to be below or within the normal range, in all of the patients.

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EFFECTS OF THE COMBINED ADMINISTRATION OF ANTIANDROGENS WITH AN LHRH-AGONIST ON THE PROSTATE GLAND OF INTACT MALE RATS

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LHRH-agonists are now being intensively discussed as an alternative therapy of prostate cancer. To eliminate all androgenic influences, a simultaneous treatment with an antiandrogen has been suggested. It was the aim of this study to investigate two different types of antiandrogens, flutamide (FL) and cyproterone acetate (CPA) alone and in combination with the LHRH-agonist Lutrelin (Wyeth) in adult male rats. After 1, 7, 14 and 21 days of treatment the testes, prostate, seminal vesicles, adrenals and pituitary were weighed and histologically investigated. Radioimmunoassay of serum LH and testosterone concentrations was performed. Synergistic antiandrogenic effect of the combined treatment is evident. Efficient neutralization of the androgenic action at the prostatic level in intact animals requires inhibition of LH secretion by an antiandrogen like CPA due to its additional antigonadotropic effect or by the combined administration of an antiandrogen (FL or CPA) with an LHRH-agonist. The long-term simultaneous treatment with an LHRH-agonist seems to prevent the induction of the counterregulatory mechanism normally induced by the treatment with a pure antiandrogen. However, the combination of Lutrelin with CPA especially in the initial phase of treatment is obviously more effective in depressing LH secretion and/or synthesis than the combination with FL or Lutrelin alone. This may support the recommendation of the use of an antiandrogen of the CPA-type rather than a pure antiandrogen in combination with LHRH-agonists for the treatment of prostatic cancer.

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LHRH AGONIST ICI 118.630 (ZOLADEX DEPOT) (Z) versus Z plus CYPROTERONE ACETATE (CPA) IN ADVANCED PROSTATIC CANCER. PRELIMINARY REPORT.

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From Dec 84 to Jan 85, 25 patients (pts) with advanced, previously untreated, prostatic cancer, were randomized to receive either Z 3.6 mg s.c. every 28 days (arm A), or Z + CPA 200 mg/day p.o. (arm B). 18 pts have been treated for at least 3 months (9 in arm A and 9 in arm B) with a median follow up of 217 days (range 98-415). Tumors were graded G1 in 2 pts, G2 in 11 and G3 in 5. Pts median age wase 73 years (range 49-88); Performance Status (ECOG) was 0 in 11 pts, 1 in 4 and 2 in 3. 14 pts had bone metastases while 4 pts only loco-regional disease.

Toxicity has been negligible in both arms: 7 pts had flushes (4 in A, 3 in B), 1 patient had hyperpigmentation in the site of Z injection, 3 pts (arm B) had transient hepatotoxicity. All pts who were sexually active (10) had loss of libido and erection after therapy. All pts but one had weight gain (mean: +5,4 Kg; range: -4 +20). Partial Response had been observed in 13 pts, No Change in 2; 3 pts (with G3 tumour) progressed.

In all pts serum testosterone dropped to castrate levels within 1 month of treatment, while changes of LH levels were not significant.

LH-RH agonist ICI 118.630 is a non toxic medication which seem to be active against prostatic cancer. Further evaluation is warranted on large number of patients.