

IN VITRO EFFECT OF DIHYDROTESTOSTERONE (dHT), ESTRADIOL (E_2), PROGESTERONE (Pg) AND PROLACTIN (PRL) ON CELL PROLIFERATION OF HUMAN PROSTATIC CANCERS.

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Small tumor samples of ten freshly excised human prostatic adenomas cultured in minimal essential medium (MEM, without serum) either alone (control) or supplemented with dHT (10^{-9} M), or E_2 (10^{-9} M), or PRL (1 ug/ml), or Pg (10^{-7} M), for 12, 24, 36, 48 or 72 hrs. Two hrs before the end of incubation, 2 uCi of tritiated thymidine/ml MEM were added, after which the samples were fixed and processed for autoradiography. The mean TLI (% labeled cells/1000 counted cells $\pm$ SEM) were assessed and among these 10 tumors, 60%, 70%, 60%, 0% of the glandular parts showed a significant increase of TLI to dHT, E_2 , PRL, Pg respectively. The stroma was never sensitive to hormonal stimulation. In conclusion, human prostatic adenomas display in vitro a mitogenic response to dHT, E_2 and PRL, but not to Pg; the present methodology might represent a dynamic test of hormone-dependence.

ENDOGENOUS ANDROGENS, ADRENAL ANDROGEN PRECURSORS, AND THEIR METABOLISM IN PRIMARY TUMORS AND LYMPH NODE METASTASES OF HUMAN PROSTATIC CANCER.

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New data on steroid metabolism of human BPH tissue as well as controversial discussions about an optimal antihormonal therapy for human prostatic cancer have focused interest on the steroid metabolism of prostatic cancerous tissues and their ability to accumulate and to use DHT for proliferative stimulation. The activities of steroid metabolizing enzymes (steroid sulfate-sulfatase, 17 β -hydroxysteroid dehydrogenase, 5 α -reductase, and 3 α /17 β -hydroxysteroid dehydrogenase) as well as total tissue content and subcellular distribution (nuclear-extranuclear) of several androgen precursors, active androgens, and androgen deactivation products (DHEA sulfate, DHEA, androst-5-ene-3 β , 17 β -diol, androst-4-ene-3,17-dione, testosterone, DHT, and androstane-3 α , 17 β -diol) were quantified in primary tumors and lymph node metastases of human prostatic cancer obtained from pts without previous endocrine manipulation. Primary tumors were compared to benign parts of the same prostates, and metastases were compared to primary tumors. Nearly all of the specimens were pure or nearly pure (10% contamination by benign epithelium) cancer tissues. The enzymes and steroids found in benign prostatic tissue could qualitatively also be detected in the cancerous tissues. The cancers showed quantitative variations of their steroid and enzyme pattern, and a general tendency towards decreased enzyme activities, particularly when expressed per DNA. The most striking characteristic of the malignant tissues was a substantial diminution of their 5 α -reductase activity, which was often accompanied by an increased ratio testosterone/DHT. Some interesting parallels between aspects of histology, localization, and endocrinology were recorded, but there was no obvious general correlation between histological pictures and endocrinological characteristics of the tumors.

A RANDOMIZED, COMPARATIVE STUDY OF BUSERELIN WITH DES/ORCHIECTOMY IN THE TREATMENT STAGE D₂ PROSTATIC CANCER PATIENTS.

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This multicenter, randomized study compared the LHRH agonist buserelin with DES/orchiectomy in the treatment of patients with Stage D₂ prostatic carcinoma. Subjects were randomized to treatment with buserelin or DES/orchiectomy in a 2:1 ratio. Data from 160 subjects were available for analysis: 105 buserelin treated subjects (89 SC and 16 IN), 41 DES treated subjects, and 14 subjects who underwent orchiectomy. Either subcutaneous (200 mcg qd) or intranasal (400 mcg tid) maintenance doses of buserelin in suppressed serum testosterone values to below castrate levels (<100 ng/dl) by week 3 and maintained suppression for over 24 months. Times to treatment failure for specific reasons were analyzed and compared between treatment groups. There was a significant difference between treatment groups in favor of buserelin in the time to treatment failure due to an adverse event (p<0.05).

There were no statistically significant differences between the treatment groups in the progression-free survival, best response, and life survival analyses. In addition, buserelin treatment improved quality of life parameters such as pain, performance status, and GU symptoms. With the exception of symptoms of androgen deficiency, few side effects were reported in the buserelin subjects and most were of a minor nature. The incidence of severe side effects was significantly higher among the DES/orch subjects. The results clearly indicate that buserelin is an effective alternative to DES/orchiectomy for metastatic prostate cancer with important safety advantages over DES.

LH-RH AGONIST, ZOLADEX (GOSERELIN) DEPOT FORMULATION IN THE TREATMENT OF PROSTATIC CANCER. RANDOMIZED DOSE-FINDING TRIAL IN JAPAN

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Ninety patients with advanced prostatic cancer (15 with stage B, 23 with stage C, 52 with stage D) were randomized to receive 0.9 mg, 1.8 mg or 3.6 mg of Zoladex depot subcutaneous injection every 28 days for 12 weeks. The serum levels of LH, FSH and testosterone elevated after the first injection, and it was followed by significant decrease. The suppression of testosterone levels in the blood to castrate levels was observed in all patients except two treated with 0.9 mg.

Objective response (CR and PR) was seen in 63.6% (0.9 mg), 47.8% (1.8 mg), 68% (3.6 mg), under Japanese Prostatic Group Criteria. Subjective improvement (performance status, analgesic consumption) was also observed in 75% - 88% without statistical significant difference between each dose group. Only minor adverse effects were found during the treatments. The drug was detected dose-dependently in the blood by RI-assay.

These results suggest that Zoladex depot in doses of 3.6 mg subcutaneously every 4 weeks is useful as endocrine therapy alternative to surgical castration in patients with prostatic cancer.