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TREATMENT OF HORMONE-RESPONSIVE RAT MAMMARY AND PROSTATE TUMOURS WITH ZOLADEX DEPOT

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A biodegradable depot formulation of the LHRH agonist, Zoladex (D-Ser(Bu^t)^6, $Azgly^{10}$-LHRH), has been developed in which the drug is dispersed throughout a matrix of D,L-lactide-glycolide co-polymer. This formulation, which releases biologically effective concentrations of Zoladex over at least 28 days in rats and primates including man, is more effective and convenient than daily aqueous injection of the drug.

A single subcutaneous depot containing 300µg Zoladex causes a reduction of serum oestradiol to castrate values and marked regression of dimethylbenzanthracene-induced (DMBA) rat mammary tumours; repeated administration at 28 day intervals produces a greater effect on tumour growth which is comparable to surgical castration. When given at 28 day intervals starting 30 days after carcinogen, Zoladex depots prevent the appearance of mammary tumours in the majority of animals.

Administration of depots containing 1mg Zoladex at 28 day intervals to rats bearing Dunning R3327H transplantable prostate tumours, causes serum testosterone to fall to castrate values and accessory sex organs to regress to sizes found after surgical castration. A marked reduction in prostate tumour growth also occurs similar to that achieved by castration. Co-administration of an antiandrogen produces no greater response. In this model maximal inhibition of tumour growth and increased survival is achieved if treatment is commenced early after tumour transplantation.

These results show that Zoladex depot is effective in limiting the growth of hormone-response rat mammary and prostate tumours and when given in an adjuvant setting will delay the appearance of carcinogen-induced mammary tumours. Co-administration of antiandrogens produces no greater effects on prostate tumour growth than Zoladex alone. Early treatment produces optimal responses; this argues that consideration should now be given to treatment of patients with early stages of prostate cancer.

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LONG-TERM TREATMENT WITH THE LHRH-AGONIST BUSERELIN IN METASTATIC PROSTATIC CANCER. F.H. Schröder (1), F.J.M. Debruyne (2), H.J. de Voogt (3), J.G. Klijn (4) and F.H. de Jong (5). Departments of Urology (1) and Internal Medicine III (5), Erasmus University, Rotterdam; Departments of Urology, University of Nijmegen (2) and Free University of Amsterdam (3) and Department of Internal Medicine, Dr Daniel den Hoed Cancer Center Rotterdam (3), The Netherlands.

During the years of 1983-1984, two simultaneous studies of previously untreated M1 prostatic carcinoma patients were carried out. A total of 71 patients was treated, 58 with an LHRH-agonist (Buserelin) alone, 13 with Buserelin and the antiandrogen Cyproterone Acetate (CPA). These latter patients, in addition to having M1 status, were required to have an elevated acid phosphatase. Buserelin was given in a dosis of 3 times 400 µgram/24 hours subcutaneously during the first week and later on intranasally. The dosis of CPA was 50 mg p.o./t.i.d. Duration of response and time to progression were evaluated according to slightly modified response criteria of the National Prostatic Cancer Project of the U.S.A. The endocrine effects of the drugs on plasma testosterone and other parameters were followed by an independent, central laboratory. All patients were studied in a prospective, non-randomized fashion according to the same protocol.

The following results were obtained: in the Buserelin part of the study, 6 (10.3%) CR and 23 (39.6%) PR were achieved, 22 patients (38%) showed progression after 2-12 months. In the group of patients treated with Buserelin and CPA, progression occurred in 5 of 13 patients after 3-11 months (mean 7.0). The addition of CPA resulted in a faster decrease of the initially elevated acid phosphatase values during the first 3 weeks of treatment. The results are comparable to those obtained by standard treatment. The equal progression rates in both parts of the study suggest that there is no advantage of the long-term use of CPA in addition to Buserelin.

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LONG-TERM GERMAN EXPERIENCE WITH PERNASAL AND INTRAMUSCULAR LHRH AGONIST TREATMENT OF PROSTATE CANCER

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Experience with the LHRH agonist BUSERELIN (Hoe 766) derive since 5 years in Germany from R. Nagel (Berlin) and our institution. We herein report the results from Mainz of 85 completely evaluable patients, and 22 cases treated with i.m. LHRH analogue D-Trp-6.

Characteristics: Tumor stage, 61 Category M_0, 24 Category $\geq T_3N_0$; average age 69 yrs. (range 49-86); grade I = 6; II = 17; III = 56; GX = 6. Average follow-up was either 2 years or time to progression.

Endocrine Results: Stimulation phase of serum testosterone (T) between day 3 and 7; down-regulation of T between 2. and 4. week with castrate levels after 4 weeks; interrupted castration effect in 7 patients due to non-compliance; no demonstration of LHRH antibodies; application of 3x300 µg/d pernasally showed same endocrine pattern as initial s.c. treatment (2x200 µg/d) and continuation pernasally.

Clinical Results: Subjective response in 25 of 31 patients with painful bone metastases (81 %); using E.O.R.T.C. criteria objective response (regression) was 54 % (25 % no change, 21 % progression); average duration of response was 23 months.

Depot-Application: 22 patients of comparable tumor characteristics were treated with the i.m. applicable LHRH Agonist D-Trp-6 (single i.m. injections every 5 weeks). Follow-up ranges from 12-18 months. Complete down-regulation of serum -T is reached after 3 weeks and castrate levels are maintained thereafter. Subjective and objective response is comparable to that seen after pernasal Hoe 766 treatment, compliance and castration effect are 100 %.