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CLINICAL RESEARCH WITH THE DEPOT PREPARATION ZOLADEX (ICI 118,630) IN PROSTATE CANCER. F.M.J. Debruyne and the South-East Cooperative Urological Group. Dept. of Urology, Radboud University Hospital, Nijmegen, The Netherlands.
75 patients with histologically proven previously untreated metastatic carcinoma of the prostate were treated with a four weekly depot formulation of the luteinizing hormone releasing hormone superanalogue ICI 118,630, 3.6 mgr.
The age of the patients ranged from 51-76 years (mean 70,08 years). Pretreatment score (ECOG/WHO), 0: 49%; 1: 41%; 2: 7%; 3: 4%. Tumor grade (Mostofi): GrI 15%; GrII 45%; GrIII 40%.
The end point of the study was time to progression.
5 patients were unevaluable due to protocol violations.
Follow-up was at least 9 months in all remaining patients.
Endocrinological response was noticed in all patients, with castrate level of testosteron obtained after 3 weeks and maintained during the follow-up period (up to 24 months).
Subjective response consisted of improvement in WHO scale in 62.8%.
Objective response after 9 months of treatment: CR: 3.3%; PR: 73.8%; SD: 1.6%; PD: 21.3%. Acceptance and compliance of the depot formulation was 100%.
Side effects were minimal. Flare up in the first weeks of therapy was seen in 27% of the patients although no serious deterioration of the symptoms were noticed.
Conclusions: From this study can be concluded that ZOLADEX 4 weekly depot therapy is effective in reducing testosteron in patients with metastatic prostate cancer and therefore is a clinically valuable and non-toxic alternative in the management of these patients.

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USE OF LH-RH ANALOGS FOR THE TREATMENT OF HORMONE SENSITIVE TUMORS, COMBINATION THERAPY, AND DIRECT EFFECTS
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Recently, we showed that D-Trp-6-LH-RH directly inhibits the growth of several human prostate cancer cell lines in vitro. The therapy for prostate cancer and other sex-steroid-dependent tumors has been made more practical and efficacious by the development of long-acting microcapsules of the agonist D-Trp-6-LH-RH (Decapeptyl). The antiandrogen flutamide, (25 mg/kg daily), and microcapsules of D-Trp-6-LH-RH releasing 25 µg/day, injected i.m. once a month, were studied in the Dunning R-3327H rat prostate adenocarcinoma model. The microcapsules inhibited tumor growth more than flutamide. Moreover, the combinéd treatment of flutamide and microcapsules did not exert a synergistic effect on tumor growth. Thus, the addition of an antiandrogen may not offer an advantage over the use of microcapsules of D-Trp-6-LH-RH alone. Combination of microcapsules of D-Trp-6-LH-RH with cyclophosphamide was also investigated. Microcapsules of D-Trp-6-LH-RH reduced tumor weights and volumes more than Cytoxan, and the combination of the two drugs appeared to completely arrest tumor growth. Novantrone (Mitoxantrone) in combination with microcapsules of D-Trp-6-LH-RH produced similar results. Again, the combination with Novantrone led to a better inhibition of prostate cancer than D-Trp-6-LH-RH alone. These results suggest that the combination of microcapsules of D-Trp-6-LH-RH with chemotherapy might further improve the therapeutic response, and increase the survival rate.

III - h

STUDIES WITH NAFARELIN AND A LONG ACTING LHRH ANTAGONIST: ENDOCRINE AND ANTITUMOR EFFECTS IN PATIENTS WITH PROSTATIC CANCER
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Nafarelin is the most potent LHRH agonist under clinical evaluation. The high potency in vivo is due to an extended plasma $t_{\frac{1}{2}}$ of 2.5-3.5 hours, in part a reflection of a high plasma protein binding. In controlled Phase III clinical trials in stage D_2 prostatic cancer patients 300 µg nafarelin administered intranasally twice daily rapidly suppresses testosterone to castrate levels and is equivalent in efficacy to 3 mg daily of DES but better tolerated. Also under evaluation is an injectable microsphere controlled release formulation of superior kinetics and efficacy. The LHRH antagonist, [D-Nal(2)^1, D-pCl-Phe^2,D-Trp^3,D-hArg(Et$_2$)^6,D-Ala^{10}]LHRH, is also the most potent of its class in clinical trial. It has a circulatory $t_{\frac{1}{2}}$ of 22 hours in man. A single injection of 5 mg suppresses plasma gonadotropins and testicular steroids from 2 to at least 24 hours after injection. However steady state plasma levels are not reached until 4-5 consecutive days of dosing so that 1 mg per day is expected to be sufficient to give chronic testicular suppression. The high potency and tolerability of the LHRH agonists make agents such as nafarelin the first choice for medical orchiectomy in prostatic cancer. However, it appears that LHRH antagonists could be an important alternative in a subpopulation of patients who cannot tolerate even a transitory testosterone increase ("flare") and/or in whom rapidity of suppression is essential. Such patients could include those having extensive metastases to the lungs and those with spinal/neurological involvement.

III - i

COMBINATION THERAPY WITH FLUTAMIDE AND CASTRATION (SURGICAL OR MEDICAL) IN PREVIOUSLY UNTREATED AND TREATED PATIENTS WITH ADVANCED PROSTATE CANCER.
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In order to achieve a more complete blockade of androgens of both testicular and adrenal origin at the start of treatment, we have administered the pure antiandrogen Flutamide in association with orchiectomy (13 patients) or the LHRH agonist [D-Trp^6] LHRH ethylamide (128 patients) to previously untreated patients having clinical stage D_2 prostate cancer. The main duration of treatment is 619 days (88 to 1367 days). Complete, partial and stable responses assessed according to the criteria of the U.S. NPCP have been observed in 26, 38 and 32% of patients, respectively, while progression has occurred in 4% of patients. The probability of continuing response (Kaplan and Meier) after 2½ years is 47.3% while the probability of survival at the same time is 71.8%. Two hundred and three patients showing relapse after orchiectomy, estrogens or LHRH agonists alone received the same combination therapy. Complete, partial and stable objective responses were observed in 5.4, 8.4 and 18.7% of patients, respectively for a total objective response rate of 32.5%. The present data show that combined therapy at the start of treatment increases the rate of objective response, the length of the remission period and prolongs survival as compared to previous therapies. In relapsing patients, one third of them can benefit from the combination therapy while, otherwise, progression would have continued. It is concluded that the combination therapy should be administered to all patients having advanced prostate cancer and continued for life in all cases. The beneficial effects of the combination therapy are obtained with an excellent quality of life, the side effects being limited to hot flashes and decrease or loss of libido.