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PAIN AND PERFORMANCE STATUS DURING INITIAL TREATMENT OF PROSTATIC CANCER (PC) WITH A GNRH AGONIST: COMPARISON WITH DES. P.G. Hoffman and the Nafarelin Study Group. Syntex Research, Palo Alto, California, U.S.A.

During the initial two weeks of therapy in a randomized trial of the GnRH agonist nafarelin (Naf) 300 µg BID intranasally and DES 1 mg TID orally, 166 patients with stage D2 PC completed the ECOG Performance Status Scale (Perf. Scale: 0 = normal activity, 1 = symptomatic but ambulatory, 3 = in bed less than 50% of the time, 4 = 100% bedridden), and an analgesic use assessment (Pain Scale: 0 = no analgesics, 1 = occasional use of analgesics, 3 = chronic use of analgesics, 4 = uncontrollable pain). Serum Testosterone (T) was measured before the first dose of test drug and at day 5 to 9 of treatment. The peak increase in T (ΔT) on Naf occurred on day 5 with a mean ΔT of 3.54 (95% CI 2.56 - 4.52) ng/ml. After day 6, ΔT was not significantly greater than 0. On DES, ΔT was significantly less than 0 by day 7 and a significant improvement in Perf. Status and Pain Status occurred by day 5 and was maintained thereafter. On Naf, Perf. Status was significantly worse than baseline only on day 4. Pain Score did not differ significantly from baseline on any day. An adverse change of 2 or more units in Perf. Status occurred in 2/82 on DES (1 due to a pulmonary embolus, 1 transient requiring no specific therapy) and 4/84 on Naf (1 due to ureteral obstruction, 1 to pneumonia, 2 transient requiring no specific therapy). Neither initial T, peak T, nor ΔT correlated with increased pain or decreased performance. We conclude that nasally administered Naf is associated with a brief increase of symptoms of PC during the first week of therapy and a slower relief of symptoms than can be accomplished with DES. In only a small fraction of patients, however, is the increase of symptoms of consequence. Measurement of T before Naf or during the first week of Naf is not useful in predicting those patients who will experience an increase in symptoms or an adverse event.

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ZOLADEX TREATMENT OF SYMPTOMATIC PROSTATIC CARCINOMA.

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The depot LRH analogue Zoladex has been used to treat 24 patients with symptomatic metastatic prostatic carcinoma. 21 patients had bone metastases and 3 had advanced soft tissue disease. Patients have been followed for 6-18 months on treatment (mean 12 months). Using the NPCP criteria to assess response, 4% of patients were in complete remission (CR) after 3 months treatment, 44% were in partial remission (PR), 36% were stable (S) and 16% showed no response. After 12 months of therapy the ficures were 7% (CR) 33% (PR) 20% (S), and 40% were dead or had progressive disease. Subjective improvement was seen in 21 patients although initial tumour flare occured in 4 subjects (17%). Peak urine flow rates improved by 52% at 6 months of treatment, and mean ± SD prostatic volume decreased from 37±20ml to 14±7ml. Serum acid phosphatase concentrations fell from 11.4±14 to 0.9±0.9u/l (N=0-0.6) and serum osteocalcin levels increased from 13.3±10ng/ml to 24±15ng/ml at 6 months of treatment. Serum LH and FSH levels decreased from 14.8±7.8iu/l to 5.8±3.5iu/l and from 11.1±9.3 to 6.6±3.3iu/l respectively, and total serum testosterone and derived free testosterone levels fell from 9.1±6.1 to 0.2±0.2nmol/l and from 250± 168 to 6±5pmol/l respectively. Serum androstenedione levels were unaltered whereas serum DHEAS levels decreased from 2±0.8 to 1.5±0.7umol/l ($p<0.05$). This study confirms that Zoladex reliably reduces serum testosterone levels in patients with prostatic carcinoma to the castrate range, and induces remission or stabilises disease in 84% of patients. By one year 50% of patients remain in remission, suggesting Zoladex is equivalent to other hormonal therapies in prostate cancer.

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CLINICAL EVALUATION OF FLUTAMIDE AND ESTRAMUSTINE AS INITIAL TREATMENT OF METASTATIC CARCINOMA OF PROSTATE.

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Thirty patients with metastatic cancers but with no serious cardiovascular (CV) conditions were randomly assigned to receive treatment either with flutamide (250 mg x 3) (F) or with estramustine (280 mg x 2) (E). Clinical examination, bone scan, laboratory measurements were performed prior to randomization and at regular intervals thereafter. During an observation period of between one and two and one-half years, F was discontinued in 1 case (7%) because of icterus, and E in 3 cases (20%) because of CV complications. Of the remaining 14 F-treated patients, 13 responded initially. Eleven of them relapsed, and 5 died of cancer. In the corresponding group of 12 E-treated patients, there were 11 primary responders. Of these, only 2 relapsed and died as did the only nonresponder. The difference between the two groups with regard to relapse is significant ($P < 0.01$), but not with regard to mortality. In the present material there was an initial favorable response to F without signs of CV complications and with maintained libido in most cases. However due to significantly increase risk for relapse compared with E, F cannot be recommended as single therapy except in cases where estrogens are contraindicated or when interferens with libido and potency is unacceptable.

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EORTC PHASE II CHEMOTHERAPY STUDIES IN PROSTATE CANCER

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The EORTC Genito-Urinary Group began Phase II chemotherapy studies in prostate cancer in 1979. Very strict entry criteria are used and only bi-dimensionally measurable soft tissue or visceral lesions are employed to assess response. The first study tested Vindesine (3 mg/m2 i.v. q weekly). A 19% objective response (CR+PR) rate was seen, but there was a high incidence of neurotoxicity. The next study with Mitomycin-C showed an encouraging response rate of 29% with little toxicity in a dose schedule of 15 mg/m2 i.v. q 6 weeks to cumulative dose of 2 mg/kg (set for fear of increased marrow/kidney toxicity). The third study with weekly low dose (12 mg/m2 i.v.) Epirubicin gave a disappointing result (CR+ PR=12%) but toxicity was low. This agent may be tested again at more conventional doses. The present study is with Methotrexate 40 mg/m2 i.v. q 2 weeks.