II - e

THE PROGNOSTIC SIGNIFICANCE OF HYPERPROLACTINAEMIA IN BREAST CANCER.

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The importance of prolactin (prl) in human breast cancer is unclear despite the clear prl-dependence of some chemically induced rodent mammary cancers and prl suppression is included in the rationale of very few therapeutic regimes. We have performed 3 studies to determine the relationship between serum prl and prognosis in postmenopausal breast cancer patients. Prl was measured in 75 patients with advanced disease during treatment with aminoglutethimide (AG, Study I), 135 with advanced disease before treatment with AG or AG + tamoxifen ± danazol (Study II) and 152 patients with primary breast cancer 2-14 days before operation (Study III). Results: Study I: more non-responders (14/40) than responders (2/35) had prl >500mIU/L ($p<0.01$). Study II: mean prl was higher in non-responders, and in that group survival was shorter in patients with prl >500mIU/L ($p=0.006$). There was no evidence that this finding was stress-related. Study III: prl was lower than in patients with advanced disease. Patients with prl >350 mIU/L (n=14) had a shorter survival than those with lower values (follow-up: 5-9 years, $0.10>p>0.05$). Recent work by others (Wang et al 1986, Eur J Cancer Clin Oncol, in press) supports a relationship between prognosis and prolactin in operable breast cancer. It appears that high prl levels are associated with poor response to oestrogen deprivation and a poor prognosis in both early and advanced breast cancer. Although dopamine agonists have been ineffective as single agents in breast cancer their use in combination with conventional endocrine agents should be investigated.

II - f

MEDROXYPROGESTERONE ACETATE HIGH-DOSE (HD-MPA) vs HD-MPA plus BROMOCRIPTINE (Br) IN ADVANCED BREAST CANCER: PRELIMINARY RESULTS OF A MULTICENTRIC RANDOMIZED TRIAL.

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A previous pilot study (Dogliotti et al.,1983)showed that combining HD-MPA plus Br results in better responses when historically compared to HD-MPA alone. On this basis,a controlled randomized trial was started in March 1984 to evaluate the efficacy and safety of HD-MPA plus Br vs HD-MPA alone. As to March 1986, 160 postmenopausal women with measurable metastatic breast cancer were randomized to receive one of the following treatment until progression: A (MPA: 1 g/i.m./daily x 4 weeks,then 500 mg/i.m./twice weekly); B (MPA as in regimen A plus Br 10 mg orally/4 times daily).Response and toxicity were assessed according to UICC and WHO criteria,respectively. 103 patients are at present evaluable: 49 in group A, 54 in group B. 29 are not evaluable,whereas for the remaining 28 entry was too early for evaluation.Both groups are well balanced as previous treatment,receptor status,dominant site. Response rates (CR+PR) were 35% (17/49) for regimen A and 44% for regimen B (24/54).Both regimens were well-tolerated:the overall incidence of side-effects was 41% in group A and 35% in group B.

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III - a

ENDOCRINE CHANGES DURING TREATMENT OF PROSTATE CARCINOMA (PCA) PATIENTS WITH THE LHRH-AGONIST BUSERELIN (HOE 766)

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LHRH-agonists can suppress gonadotropin secretion, resulting in decreased plasma testosterone (T). We studied endocrine effects of treatment with the LHRH-agonist HOE 766 in 58 PCA patients who were followed for periods up to 3 year.

Before therapy,patients had normal plasma T (16.7±0.9nmol/l). They were treated s.c. with 3x500 µg/d for 7 days, followed by 3x400 µg/d intranasally (i.n.). 34 patients showed no progression of disease within 1 year (Group I),while progression occurred within 1 year in 24 patients (Group II). Plasma T,LH and FSH before and after i.v. LHRH,E_2,DHT and SHBG were not different in Groups I and II at any time during treatment, basal cortisol levels were lower in Group I.

After 3 days of treatment, plasma T was 25.8±2.3 nmol/l,after 3 weeks T was <3.0 nmol/l in 32/49 patients. After 1 and 2 years of treatment,plasma T was 1.9±0.2 and 1.6±0.2 nmol/l (n=34 and 18). Basal and LHRH-stimulated LH and FSH were progressively suppressed.E_2 and DHT were suppressed to 30 and 16 % of control after 3 months,SHBG increased significantly and adrenocortical function was not affected. Short-term effects of HOE 766 were studied by measuring T,LH and cortisol in blood collected before and 0.5,1,2 and 4 h after i.n. HOE 766 application. T and LH levels showed no significant changes; T levels were correlated with those of cortisol, not with LH.

It is concluded that plasma T remains effectively suppressed during long-term i.n. therapy with HOE 766.Diurnal variations of T are due to the adrenal diurnal rhythm rather than to changes of LH secretion.

III - b

PHARMACOKINETICS OF LHRH AGONISTS IN DIFFERENT DELIVERY SYSTEMS AND THE RELATION WITH ENDOCRINE FUNCTIONS

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The dose and regimen for suppression of pituitary-gonadal function depends on the therapeutic indication. Female contraception is achieved by single dose daily nasal spray, endometriosis and other oestrogen-dependent disorders require multiple daily nasal spray doses. In hormone-dependent tumours, therapy is facilitated by sustained release systems. Pharmacokinetics were monitored to adjust effective suppression according to peptide concentrations found in serum and/or urine. At low doses, cumulative urinary excretion provides a reliable parameter of absorption, serum concentrations remain low. At high doses, serum concentrations are dose-related, the availability to pituitary receptors can be deduced from their time course. Reference values for serum concentrations and urinary excretion were established by s.c. infusion in male contraception, and oestrogen-dependent disorders. Evaluation of implant formulations was based on these studies. Monitoring of therapy by urinary excretion of buserelin provides a simple and practical control of absorption and compliance. During injections or infusions, 20-30 % of the dose are found in the urine. About 50 % are intact buserelin (biologically active when tested in rats), C-terminal metabolites identified by HPLC/RIA are the (5-9)pentapeptide, (6-9)tetrapeptide, and (7-9)tripeptide. The pattern of metabolites is consistent in treatment of endometriosis and prostate carcinoma (by infusion, injections or by biodegradable implants). Serum concentrations indicate 95 % intact buserelin and a small fraction of the (5-9)pentapeptide. Pharmacokinetic monitoring has provided useful information for adjustment of doses for the spectrum of indications from female contraception to hormone-dependent tumours.