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GONADOTROPIN-RELEASING HORMONE ANALOGUE (BUSERELIN) IN TREATMENT OF PREMENOPAUSAL ADVANCED BREAST CANCER
K. Höffken, B. Miller, P. Fischer, R. Becher, E. Kurschel, M.E. Scheulen, A.A. Miller and C.G. Schmidt

In a phase I-II study, 10 premenopausal patients with advanced progressive breast cancer were treated with buserelin. In 6 patients, the drug was administered at a dose of 1 mg q 3 subcutaneously (s.c.) for 7 days followed by 0.4 mg q 6 sprayed intranasally (i.n.) daily thereafter. In 3 patients, 0.3 mg q 2 s.c. was substituted for i.n. application after the 7 day loading course. In 1 patient, 0.4 mg q 6 daily i.n. administration alone was used. Complete remissions were observed in 2 patients with pleuropulmonary and locoregional disease, respectively, lasting 4 and 9+ months. In 3 patients with bone (2 patients) or locoregional metastases, partial remissions with a duration of 4+, 8+ and 15+ months were achieved. 3 of 6 patients with positive estrogen receptors and 2 of 2 patients with unknown estrogen receptors showed objective tumor remissions whereas in both patients with negative estrogen receptors disease progression was observed. Serial quantitation of hormones revealed a significant decrease in serum levels of estradiol after 3 weeks of treatment. Simultaneous decrease in progesterone levels at 3 weeks suggests that estrogen suppression was caused by the treatment and not by a physiological decrease due to the ovulatory cycle phase. There was no statistical correlation between hormone suppression and various doses and routes of application or between hormone levels recorded in responders and non-responders. The only side effects were tolerable menopausal symptoms. In a recent patients a local allergic reaction was recorded at the site of s.c. injection immediately after the first application of buserelin.

Innere Universitätsklinik u. Poliklinik (Tumorforschung), Westdeutsches Tumorzentrum, Hufelandstr. 55, D-4300 Essen

Bre 36

TREATMENT OF ADVANCED MALE BREAST CANCER WITH THE LONG-TERM LHRH AGONIST BUSERELIN
C. Doberauer, N. Niederle, E. Kurschel, M. Stuschke and C.G. Schmidt

The synthetic peptide buserelin is a luteinizing hormone-releasing hormone (LHRH) analogue decreasing testosterone levels by down regulation of pituitary LHRH receptors. Simultaneous administration of the pure antiandrogen flutamide should cause a complete blockade of androgens. Seven male patients (pts) with advanced breast cancer and no prior orchidectomy were treated with buserelin alone (6/7 pts) or in combination with flutamide (1/7 pts). Buserelin was given in dosages of 4x100-400 µg per day intranasally. Flutamide was applied one day before the start of buserelin treatment at a daily dose of 3x250 mg perorally. The pts ranged in age from 46-73 years (median, 57). All pts were pretreated by additive hormone therapy and/or cytostatic chemotherapy. The metastatic sites were skeleton in 6/7 pts, soft tissue in 4/7 pts and lung in 2/7 pts. Hormone receptors were found to be positive in 2/4 pts tested. In all seven pts persisting low plasma testosterone levels were associated with clinical improvement. Stable disease (SD) occurred in 6/7 pts. 1/7 pts died 1 month after start of therapy. The median duration of SD was 8 months (range, 4-15). Buserelin/flutamide combination resulted in SD lasting 4+ months. Main adverse effects consisted of mild hot flushes, decreased libido, impotence and transient increase of bone pain only at the beginning of buserelin treatment.

In conclusion, the reversible medical castration by the LHRH analogue buserelin offers effective nontoxic palliation to male pts with advanced and pretreated breast cancer. The combination of buserelin with flutamide needs further clinical investigations.

Innere Universitäts- und Poliklinik (Tumorforschung), West German Tumor Center, D 4300 Essen

Bre 37

HIGH DOSE MEDROXYPROGESTERONE ACETATE THERAPY IN MAMMARY CARCINOMA PATIENTS: CLINICAL AND BIOCHEMICAL RESULTS.
R. Kreienberg, H.-J. Grill, F. Malchert, K. Pollow

Medroxyprogesterone acetate (MPA), a potent synthetic progestagen, has been widely used in the hormonal treatment of advanced breast cancer, but presently with varying dose schedules. The availability of a sensitive RIA-method for determination of serum MPA has stimulated the research on MPA serum levels in patients after repeated MPA administration. The aim of this study was to assay blood level profiles of MPA as well as of cortisol, ACTH, DHEA-sulfate, androstendione and prolactin during repeated high dose MPA. In this study we are reporting on our experience with a high dose i.m. and peroral MPA-therapy. 121 patients with metastatic breast cancer were treated with MPA, 29 patients 1000 mg/die for 2 weeks, than 1000 mg/week and 92 patients per os 1000mg/die continuously. In 37% of patients under i.m. MPA-therapy (n=29) we observed a distinct clinical response under this treatment (CR,PR,no change). 63% of patients showed progressive tumor growth. Regarding the MPA- and cortisol-plasma-levels of this group of patients it becomes evident that those cases with remissions show significantly higher MPA-serum-levels (>100 ng/ml) than patients in the "no change" or "progression" group (<100 ng/ml). With rising MPA-plasma-levels cortisol is increasingly suppressed. However, the individual variations of the cortisol-plasma-levels are rather great. During orally administered MPA treatment a decrease of cortisol, DHEA-sulfate and androstendione serum levels was observed in nearly all patients. Within the observation time of 10 months 32% responded to the therapy (complete and partial response). No change was observed in 41% and progression in 27% of the patients. Within the remission group (CR and PR) a good correlation between persisting serum levels above 150 ng/ml and remission was observed. But in the no change and in the progression group no such correlation could be observed. Our data demonstrate: 1) only MPA-plasma-levels of >100 ng/ml show a therapeutic effect; 2) the peroral MPA-therapy leads to distinctly higher MPA-plasma-levels with rising MPA-plasma-concentrations. On account of the observed individual variations the cortisol-plasma-level, however seems to be unsuitable for monitoring the efficiency of the MPA-therapy.

Universitäts-Frauenklinik Mainz, Langenbeckstr. 1, D-6500 Mainz

Bre 38

COMBINED CYTOTOXIC AND HIGH DOSE MEDROXYPROGESTERONE ACETATE TREATMENT FOR ADVANCED BREAST CANCER

R. Becher, B. Hoffmann, G. Schimmel, M. Scheulen, U. Gerhold, K. Höffken and C.G. Schmidt

One hundred and one patients with advanced breast cancer and measurable lesions were randomized to receive either chemotherapy with cyclophosphamide, methotrexat and 5-fluorouracil (CMF) alone or in combination with high dose medroxyprogesterone acetate (HD-MPA). Patients prior treated with CMF chemotherapy received an alternative combination with adriamycin, cyclophosphamide and vincristin (ACO). The patients were stratified according to their cytotoxic pretreatment and menopausal status. At time of entry into the study, the age of patients ranged from 30 to 72 years (median age 52 years). At time of diagnosis 52 patients were premenopausal and 42 postmenopausal. HD-MPA was administered as recently reported (MPA, 1.000mg/day i.m. x10 days and 600mg/day p.o. throughout). Ninetyfour patients were evaluable for response. 7 patients (7% of cases) were lost. Treatment results showed a higher response rate in the groups with combined treatment (CMF+MPA and ACO+MPA) as compared with those treated by chemotherapy alone (CMF and ACO). No differences, however, could be found regarding the median duration of remission as well as the survival rates.

Innere Universitätsklinik und Poliklinik (Tumorforschung), Westdeutsches Tumorzentrum, Hufelandstr.55, 4300 Essen 1