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HORMONE LEVELS DURING TREATMENT WITH BUSERELIN

B.Miller, R. Callies, K. Höffken
Univ. Frauenklinik und Innere Klinik, Westdeutsches Tumorzentrum, Essen FRG

To evaluate the efficacy of the LHRH agonist Buserelin in the treatment of premenopausal metastatic breast cancer it is important to know when and to what extent postmenopausal hormone levels are reached. We determined serum hormone levels in 14 pts q 4h x3 on day 1, daily in the 1'wk and weekly thereafter during treatment with Buserelin 1mg s.c.TID for 1 wk, then 0,4mg by nasal spray x8/d.
LH: maximum rise at 4h, steep decline on day 2, slower decline until low levels around 22 mIU/ml are reached during the 2'wk; complete loss of the pulsatile secretion. FSH: same pattern as LH until minimal levels around 5,24 mIU/ml are reached after 1 wk, then again slow rise to 10 mIU/ml at wk 6.
Estradiol (E2): postmenopausal levels were reached at the beginning of the next menstrual cycle. Progesterone: begin of therapy during the early follicular phase prevented ovulation during the periovulatory period decreased and shortened the progesterone rise, during the luteal phase had no influence. after 4-8 wks pts became amenorrhoic and complained of menopausal symptoms. If later in the course of the disease ovarectomy was performed, LH and FSH rose within 3-4 wks to postmenopausal levels. One pt. was found to continually have high E2 levels after 6 wks of therapy with low LH/FSH levels probably due to a persistant follicle. We found no significant changes in testosterone, DHEAS, TSH and the thyroid hormones.
Conclusion: during treatment with Buserelin postmenopausal hormone levels are reached after 4 wks, at the latest. There are occasionally pts in whom low levels cannot be reached (persistant follicle, inadequate drug delivery). Checking hormone levels after 4 wks seems wise to ensure, that the therapeutic range is reached.

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BUSERELIN IN TREATMENT OF PREMENOPAUSAL ADVANCED BREAST CANCER

K. Höffken, B. Miller[1], P. Fischer[1], R. Becher, E. Kurschel, M.E. Scheulen, A.A. Miller, R. Callies[1] and C.G. Schmidt
Innere Universitätsklinik u. Poliklinik (Tumorforschung) und [1]Zentrum für Frauenheilkunde, Westdeutsches Tumorzentrum, Hufelandstr. 55, D-4300 Essen 1

In a phase I-II study, 15 premenopausal patients with advanced progressive breast cancer were treated with buserelin. The drug was administered at a dose of 1 mg t.i.d. subcutaneously (s.c.) for 7 days followed by 0.8 mg t.i.d. sprayed intranasally (i.n.) or 0.3 mg b.i.d. s.c. daily thereafter. In 1 patient, 0.8 mg t.i.d. daily i.n. administration alone was used. Complete remissions were observed in 3 patients with pleuropulmonal and locoregional disease, lasting 4 to 12 months. In 4 patients with bone (2 patients) or locoregional metastases remissions with a duration of 1+ to 14+ months were achieved.
4 of 9 patients with positive estrogen receptors and 3 of 3 patients with unknown estrogen receptors showed objective tumor remissions whereas in all 3 patients with negative estrogen receptors disease progression was observed. Objective responses were restricted to patients with a relapse-free intervall of more than 2 years. Serial quantitation of hormones revealed a significant decrease in serum levels of estradiol and progesterone after 3 weeks of treatment. 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. A local allergic reaction was recorded at the site of s.c. injection in 2 patients.

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REMISSIONS OF METASTATIC BREAST CANCER IN POST-MENOPAUSAL WOMEN WITH LUTEINISING HORMONE RELEASING HORMONE (ICI 118630) THERAPY

P.N. Plowman, R.I. Nicholson, K.J. Walker
The Breast Unit, St. Bartholomew's Hospital, London EC1, UK

Ten post-menopausal women with previously untreated, asymptomatic metastatic breast cancer were treated with the luteinising hormone releasing hormone analogue $(D\text{-}Ser(Bu^t)^6, Azgly^{10}\text{-}LHRH)$. Two patients obtained objective remissions - one with lung metastases sustained for fourteen months, one with bone metastases sustained for sixteen months. Both these patients had documented suppression of their high gonadotrophin levels. In none of the ten patients were other pituitary hormones, sex steroid hormones or cortisol levels affected by treatment. All seven assessable patients that failed treatment with the LHRH analogue were placed on tamoxifen and two patients (both with ER rich tumours) responded to tamoxifen. The mechanism of action of the LHRH analogue in post-menopausal breast cancer is discussed.

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GROWTH PROMOTING AND ONCOGENIC ACTIVITIES OF PROTEOGLYCANS IN THE EXTRACELLULAR MATRIX.

Anwar A. Hakim and Charles E.Joseph.
Loyola Univ. Med. Ctr. Maywood, Illinois, and School of Dentistry, Univ. Southern Calif. Los Angeles, California, USA.

When grown in cell culture,many tumor cells release polypeptide growth factors in their culture medium(Hakim,AA. Expt. Cell Biol. 47,332,1979; Experientia 34,151,1979).Using serum-free,hormonally-defined media(HMDM), the present studies examined the effects of extracellular matrix on cell proliferation. Amelanotic(HMAmC), melanotic(HMMC) and human skin fibroblasts(HSF) were seeded into plastic dishes and left to proliferate to confluency in HMDM. HSF and HMamC cells formed cell monolayers until confluency, whereas HMMC cells formed cell monolayers to a certain growth period, after which the cells detached forming cellular aggregates. After cell removal, cell from patients with ulcerative collitis(UC),familial polyposis coli(FPC),colon carcinoma(CC),colon normal epithelial cells (NCE), normal mammary epithelial(HNMEC),human mammary carcinoma(HMCC), HMAmC, HMMC and HSF were seeded into plastic plates, and plates coated with collagen, and with foot-prints from HMMC, HMAmC and HSF.The cells were left to proliferate in conditioned culture media,i.e.equal volume of HMDM and spent media from HMMC, HMAmC and HSF) and in HMDM.When cultured on HMMC-foot-prints in HMDM, or in HMMC-preconditioned medium, HMAmC, CC, UC and FPC cells showed an extensive increase (10 folds) in carcinoembryonic antigen CEA production and secretion, and cellular tumorigenicity and metastatic ability, whereas, NCE, HNMEC and HSF cells acquired the ability to produce and secrete CEA, and developed tumors in 18-25% of the athymic Nu/Nu mice. Therefore, similar to compounds in the HMMC-conditioned spent medium, proteoglycans in the extracellular matrix support cell oncogenic transformation and metastatic ability. Only the extracellular matrix from HMMC-foot prints contained 140 KD glycoprotein, which was resistant to collagenase.