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ANTIPROLIFERATIVE EFFECT OF PROGESTINS AND ANTIPROGESTINS IN HUMAN BREAST CANCER CELLS

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Progestins, such as medroxyprogesterone acetate are commonly used in the treatment of breast cancer. However, the mechanism by which they prevent tumor growth is unknown. We have addressed this question in vitro in human breast cancer cells (HBC) in culture (MCF7 and T47D cell lines). Synthetic progestin R5020 was shown to inhibit totally the estradiol (E2) induced growth of HBC while it was inefficient in estrogen deprived cells. This suggests that R5020 has essentially an antiestrogenic activity in HBC. The antiprogestin (and antiglucocorticoid) RU38486 was strongly antiproliferative in HBC whether or not E2 was present (S. Bardon et al., J. Clin. Endocrin. Metab., 60, 692, 1985). Both progestin and antiprogestin acted via the progesterone receptor. They both decreased the general secretion of proteins released by HBC and the production of the estrogen-regulated autocrine mitogen 52 K glycoprotein. Moreover, the progestin R5020 stimulates the production of several specific proteins which are inhibited by the antagonist RU38486. We have shown that both a progestin and an antiprogestin could exert similar antiproliferative effect in HBC. We will now attempt to define the molecular mechanism of this effect : Stimulation of inhibitory factors or inhibition of growth factors ?

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THE ANTIPROGESTIN RU486 IN ADVANCED BREAST CANCER : PRELIMINARY CLINICAL TRIAL

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The antiprogestin and antiglucocorticoid RU486 inhibits in vitro the growth of human breast cancer cell lines via the progesterone receptor. This trial was initiated to apreciate long-term tolerance and the effect in vivo of RU486 over evolution of breast cancer. Twenty-three oophorectomized or post-menopausal women with metastatic breast cancer resistant to several medical therapies (tamoxifen or other endocrine therapy, and chemotherapy) were treated in a preliminary trial with 200 mg per day of RU486 for 1 to 3 months. The long-term tolerance was good but there was a moderate decrease in plasma potassium. We had not observed clinical hypocorticism and plasma cortisol was increased 2-fold during the treatment. Thirteen patients had a partial objective response or a stabilization of metastatic lesions as shown by evaluating the CEA level and cutaneous and pleural metastasis. Estrogen and progesterone receptor when available in these patients (n=4) were positive. This preliminary trial shows for the first time partial remissions of advanced breast cancer treated by the antiprogestin RU486. Further studies are necessary for determining the best conditions to use RU486 as endocrine therapy of breast cancer.

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**STEROID RECEPTORS IN CEREBRAL TUMOURS: POSSIBLE CONSEQUENCE FOR ENDOCRINE TREATMENT.** M.A. Blankenstein, G. Blaauw, J.W. van 't Verlaat and J.H.H. Thijssen. Academic Hospital Utrecht and De Wever Hospital Heerlen (G.B.) The Netherlands.

Human meningioma tissue is rich in progestin receptors (PR). Oestrogen receptors (ER), by contrast, can not be detected in the majority of emningiomas by radioligand and immunological techniques. Twenty-four other intracranial tumours were assayed for the presence of ER and PR. Low levels of PR (12 and 14 fmol/mg protein respectively) were found in two neurinomas. Two other neurinomas, 2 pituitary tumours, 7 astrocytomas, 1 glioma, 1 Schwannoma, 1 neurofibroma, 3 fibrosarcomas, 1 ependymoma and 4 intracranial metastases were negative for ER and PR. Meningiomas are thus quite unique in their capacity to express PR. The biochemical properties of this receptor were further investigated. It was found that, with respect to the binding affinity and capacity the steroid specificity and the sedimentation pattern on sucrose gradient analysis, the PR extracted from human meningioma is not distinguishable from the PR in human uterine tissue.

Recent reports have shown that tamoxifen is ineffective as a treatment for meningiomas. This might have been anticipated from the virtual absence of ER from these tissues. In view of the presence of progestin receptors, clinical trials with (anti-)progestins may be much more pertinent.

Current experiments on the effects of (anti-)progestins on meningioma cells in culture will answer the question whether meningioma is a true progestin target tissue. If this is true, then administration of (anti-)progestins may be evaluated as a means of decreasing the tumour volume prior to neurosurgery or as a treatment for recurrent or inoperable meningiomas.

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INHIBITION OF AROMATASE AS TREATMENT OF BREAST CARCINOMA IN POSTMENOPAUSAL WOMEN. R. Santen, Division of Endocrinology, The Milton S. Hershey Medical Center. P.O. Box 850, HERSHEY, PA, USA, 17033.

Recent treatment strategies have been directed toward blockade of estrogen biosynthesis as a means of inducing regression of hormone-dependent breast cancer. The major source of estrogen in postmenopausal women is the peripheral conversion of androstenedione to estrone through the enzyme aromatase. Aminoglutethimide, a first generation inhibitor of aromatase, has been extensively studied in patients with breast cancer. In randomized clinical trials, aromatase inhibition with aminoglutethimide produced tumor regression with similar frequency as did surgical hypophysectomy, surgical adrenalectomy or tamoxifen administration. Consistently greater but not statistically significant increases in the rate of bone healing were observed with aminoglutethimide when compared to tamoxifen in three large collaborative trials. The side effects of aminoglutethimide, including lethargy, skin rash and ataxia complicate its use even though these problems are generally transient and dose dependent. Regimens of low dose aminoglutethimide are being developed to reduce these side effects. Low dose aminoglutethimide (i.e. 125mg bid) blocks aromatase effectively and limits side effects. Second generation aromatase inhibitors with greater specificity and fewer side effects are now also undergoing clinical trial.

These second generation aromatase inhibitors may be most useful when "hormone clamp" techniques are used to allow effective sequencing of chemo- and hormonal therapy.