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ANTISTEROIDAL AND ANTI-GROWTH FACTOR ACTIVITIES OF ANTESTROGENS AND ANTIPROGESTINS.

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Both steroid hormones, such as estrogens and progestins acting via nuclear receptors, and growth factors, such as EGF, IGFI and IGFII acting via transmembrane receptors, are able to modulate the growth of human breast cancer cells. In addition to its antiestrogenic action requiring estrogen receptor (ER) and leading to growth arrest, we have previously shown that the antihormone Tamoxifen (Tam) is able to block EGF, Insulin and IGFI mitogenic activities in total absence of estrogens (BBRC,146,1502,1987). This anti-growth factor activity is observed exclusively in ER+ cells and is rescued by estradiol addition, thus suggesting that it is mediated by accessible ER sites. In the same culture conditions, progestins and antiprogestins do not display such an inhibition, whereas retinoic acid does, thus indicating that this anti-growth factor effect is not restricted to ER ligands. To progress in the understanding of this inhibition, we first analysed how Tam could affect EGF and IGFI binding in responsive cells. We have shown that Tam neither affects EGF and IGFI binding to their respective receptors by direct competition nor modulates their affinities. However, Tam pretreatment (6 days) decreases IGFI binding sites by 60% which could explain its anti-IGFI effect. On the contrary, it increases EGF binding by 40% thus implying that it could affect the functionality of EGF receptors.

In conclusion, we propose that some steroid antagonists can inhibit not only the action of agonist ligands of the receptors they are binding to, but can also modulate the action of growth factors by decreasing their receptor concentrations or altering their functionalities.

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ANTITUMOR ACTIVITY AND MECHANISM OF ACTION OF *DIFFERENT ANTIPROGESTINS IN EXPERIMENTAL* BREAST CANCER MODELS

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Onapristone and other antiprogestins proved to possess a potent antitumor activity in several hormone-dependent experimental breast cancer models. This activity is as strong or even better than that of tamoxifen or ovariectomy in the MXT-mammary tumor of the mouse and DMBA- and MNU-induced mammary tumor of the rat. The antitumor activity is evident in these models in spite of elevated serum levels of ovarian and pituitary hormones. The detail analysis of all our data including the morphological (ultra-structure) studies of the mammary tumors of treated animals and the effects on growth and cell cycle kinetics using DNA Flow Cytometry indicates that the antitumor action of antiprogestins is mediated via the progesterone receptor and related to the induction of terminal cell differentiation leading to increased cell death. The strong antitumor activity of antiprogestins in our experimental breast cancer models does not primarily depend on a classical antihormonal mechanism.

The antiprogestin-related reduction of the number of mammary tumor cells in the S-phase in our experimental tumor models (G_0,G_1arrest) emphasizes the unique innovative mechanism of action of these new agents in the treatment of human breast cancer.

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TREATMENT OF BREAST CANCER WITH DIFFERENT ANTIPROGESTINS; PRECLINICAL AND CLINICAL STUDIES

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Treatment with antiprogestins is a new treatment modality for breast cancer. Previously, in rats with DMBA-induced mammary tumors we observed significant growth inhibitory effects of chronic treatment with the antiprogestin mifepristone (RU486). In addition, in 11 postmenopausal breast cancer patients, we observed one objective response, 6 instances of short-term stable disease, and 4 instances of progressive disease. Side-effects appeared mainly due to antiglucocorticoid properties of the drug. Increased plasma estradiol levels were observed which probably resulted from ovarian (rat) and adrenal (patients) steroidogenesis. Combined treatment with an antiestrogen in the rat model caused additive growth inhibitory effects. Tumor inhibition after single treatment with mifepristone or tamoxifen was 90% and 75%, resp. In contrast, when combined, tumor remission similar to that caused by LHRH-agonist treatment (50%) was observed. Even higher tumor remission was found after combined treatment with mifepristone plus LHRH-agonist (75%). In preliminary studies in the rat model we observed significant tumor growth inhibitory effects with several new antiprogestins of greater potency which cause less unfavorable side-effects.

In conclusion: Combined treatment (antiprogestin plus antiestrogen or LHRH-agonist) may be of value in endocrine therapy of breast cancer.

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ANTIPROGESTAGENS IN THE TREATMENT OF MENINGIOMAS

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The majority of meningiomas contain high affinity progesterone receptors. RU 486 binds to these receptors. Experiments with cultured meningioma cells showed that progesterone enhanced thymidine incorporation in response to epidermal growth factor. This effect can be blocked by RU 486. The fact that progesterone increases the sensitivity of meningioma cells to mitogenic stimuli, whereas RU 486 counteracts this was further investigated in a clinical study. We treated 10 patients with inoperable meningiomas for 12 months with 200 mg RU 486 daily. Two patients died during the treatment period. Most patients had complaints of nausea, vomiting and tiredness. In 4 patients prednisone (7.5 mg/day) was given simultaneously, in order to overcome these side-effects. CT-scan analysis of tumor size showed stable disease in three, regression of the tumor in three, and progression in four patients. A decrease in complaints of headaches and an improved general well-being was observed in 6 patients. Therapy with RU 486 resulted in activation of the HPA-axis with a resetting at a higher level, with a normal diurnal rhythm and stimulability to CRH, with a diminished sensitivity to dexamethasone. Secondarily the production of androstenedione and estradiol increased considerably. These changes were caused by a partial cortisol receptor resistance during therapy with RU 486.