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IN VIVO MANIPULATION OF HUMAN BREAST CANCER GROWTH BY ESTROGENS AND GROWTH HORMONE: KINETIC AND CLINICAL RESULTS

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Experimental studies.

[1] In vivo tumor cell recruitment after low doses of diethylstilbestrol (DES) has been demonstrated by our group. Tumor proliferative activity was evaluated in 78 patients (pts) with locally advanced breast cancer (LABC) and metastatic breast cancer (MBC) at the following times: at diagnosis; after DES 1 mg per os on day 1 to 3; 24 hours after the first chemotherapy; and, whenever feasible, at mastectomy after 3 DES-chemotherapy.

[2] Previous studies showed that growth hormone (GH) can induce in vitro cell proliferation by the increase of Insulin-like Growth Factor I (IGF-I). Therefore we measured in vivo tumor proliferative activity, serum and tumor IGF-I levels before and after administration of human recombinant GH (4 U/die im. day 1-2) in 12 pts. with advanced breast cancer.

Clinical studies.

In order to verify if the recruiting activity of DES may improve the efficacy of chemotherapy in human breast cancer, we have carried out the following 3 randomized clinical trials in advanced breast cancer:

[1] In LABC, 93 pts were randomized to receive 3 FAC (±DES for 3 days before chemotherapy), followed by local treatment and 3 FAC alternating with 3 CMF (±DES).

[2] In the first trial on MBC, 117 pts were treated with 11 CEF on d.1 vs. 11 DES-CEF (CTX d.1, DES d 5-7, FU + ADM d 8).

[3] In the ongoing trial on MBC, 258 pts received 11 CEF on d.1 (±DES for 3 days before chemotherapy).

Supported in part by a grant of CNR n. 88.00601.44 and A.I.R.C.

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ASSESSMENT OF ESTROGENIC RECRUITMENT BEFORE CHEMOTHERAPY IN ADVANCED BREAST CANCER: PRELIMINARY RESULTS OF A DOUBLE-BLIND RANDOMIZED EORTC STUDY.

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We investigated whether estrogenic recruitment could enhance antitumor effect of chemotherapy in advanced breast cancer. 165 pts with ER+ and/or PgR+ lesions were treated by: (a) aminoglutethimide 1g/d + hydrocortisone 40mg/d; surgical castration in premenopausal pts only; (b) FAC (5FU 500mg/m2; ADM 50mg/m2; CPA 500 mg/m2) q. 3 wks; (c) following randomization, 24h prior to chemo, 1 tablet of either placebo (PL) or 50 mcg ethinylestradiol (EE2). Tolerance, responses, time to progression and median survival were identical in both groups. Only performance status (PS) and menopausal status seemed to influence response (CR+PR): 22%+45% if PS=0 vs 5%+54% if PS=1-2; 24%+52% if pre- vs 10%+48% if postmenopause. Thus, EE2 before chemo did not change results.

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ANDROGEN-PRIMED CHEMOTHERAPY - EXPERIMENTAL CONFIRMATION OF EFFICACY

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A current hypothesis suggests that androgen administration prior to chemotherapy (androgen priming) may potentiate tumor cytotoxicity in prostate cancer. The Dunning R3327G rat prostatic tumor model was used to test this concept experimentally. Control groups without priming included 1) intact untreated, 2) castrate alone, 3) castrate + chemotherapy (cyclophosphamide, 30 mg/kg/day for 2 days with repeat cycle in 25 days - CTX). Two experimental groups received androgens, 1 before and 1 after chemotherapy. Treatment effect was monitored by quantitating tumor volume and animal survival.

Control groups receiving castration and chemotherapy had a retardation of tumor growth and a prolongation of survival when compared to untreated animals. Androgen priming before but not after chemotherapy enhanced the degree of tumor suppression. With the androgen priming protocol, all androgen-primed tumors had regressed, 3/6 tumors had disappeared and 3 were only palpable. At the same time point, tumors in all the other groups were actively growing and had volumes greater than the initial values ($p<.01$). Median survival was significantly prolonged in primed animals to 191 days vs. 40 days for untreated animals and 150 days for the nonprimed castration + chemotherapy animals ($p<.02$). These observations confirm the efficacy of androgen priming in an experimental system.

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RELATIONSHIP BETWEEN EPIDEMIOLOGICAL AND TUMORAL FACTORS IN 149 BITCHES WITH MAMMARY TUMORS.

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The dog has a higher natural incidence of mammary lesions than the other mammalians, included man. In order to better understand the behaviour of this special tumor which is prevented by early ovariectomy, we studied the relationship between epidemiological factors (race, age, neutering, pregnancy, progestagen treatment, pseudopregnancy) and tumoral parameters (histological types, number of lesions and amout of oestrogen and progesterone receptors) in 149 bitches bearing mammary lesions. Purebred bitches seem to develop more benign lesions (dysplasias and tumors) than crossbred (72% versus 58%). The malignant lesions arise later than benign (median 11 versus 9,5 years). Only nine bitches were ovariectomised before the emergence of the tumors. They were all sterilised after 6 years and they were mostly suffering from malignant tumors (55% versus 33%). In accord with Rutteman et al. (1988) we found that benign lesions and malignant tumors that conserve a papillary or tubulary structure contain more steroid receptors than solid or anaplastic carcinoma. There is no significant relationship between the frequence of pregnancies, progestagen treatments or pseudopregnancies and the type or the number of developped lesions, nor the emergence time or the amount of receptors.