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ENHANCEMENT OF CYCLOPHOSPHAMIDE'S ANTITUMOR ACTIVITY BY ESTROGENIC RECRUITMENT IN THE MXT MOUSE MAMMARY TUMOR.

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Previous studies have shown that one single intraperitoneal (i.p) injection of estradiol (E2) produced a transient mitogenic effect in MXT mammary tumors borne by castrated mice. The present experiments aimed at testing the hypothesis that such manipulation (estrogenic recruitment) might amplify the antineoplastic effect of a cycle-active cytotoxic agent. Therefore, 90 mice underwent s.c. transplantation with 2 small pieces of MXT on day 1 and were randomly allocated into 9 groups of 10 animals (groups A to I). Group A was left intact while all other groups underwent ovariectomy on day 10. On day 15, 8 cycles of treatment with either placebo, and/or cyclophosphamide (CPA 30 mg/kg) and/or E2 (0.25 mcg or 2.5 mcg) given in various schedules were administered at 72 h intervals and tumors were measured weekly. Treatments were as follows : (A) placebo; (B) placebo; (C) E2 .25 mcg; (D) E2 2.5 mcg; (E) CPA; (F) E2 .25 mcg followed by CPA 24 h later; (G) E2 2.5 mcg followed by CPA 24 h later; (H) CPA followed by E2 .25 mcg 24 h later; (I) CPA followed by E2 2.5 mcg 24 h later. The results indicate that : (1) castration does not produce a significant modification of tumor growth nor does E2 injection in castrated animals; (2) CPA is effective in castrated mice; (3) CPA followed by E2 is not different from CPA; (4) E2 2.5 mcg followed by CPA is significantly better than any other treatment. It is concluded that a synergism between oestrogenic recruitment and chemotherapy is demonstrated.

Supported by grants from CGER - Belgium.

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CHEMOTHERAPY WITH ESTROGENIC RECRUITMENT IN BREAST CANCER : EXPERIMENTAL BACKGROUND AND CLINICAL STUDIES CONDUCTED BY THE EORTC BREAST CANCER COOPERATIVE GROUP.

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Experimental studies with a murine mammary tumor model (MXT) have shown that one single pulse of low dose estrogens given to castrated animals induced a transient and synchronous mitogenic response in hormonedependent neoplastic cells. This manipulation performed 24 hours before cyclophosphamide administration, and not the reverse sequence, resulted in a synergistic antitumor effect. The EORTC Breast Cancer Cooperative Group has devised a clinical protocol for patients with advanced breast cancer, in which estrogen suppression is first obtained by aminoglutethimide (Orimeten) plus hydrocortisone; after two weeks ethinylestradiol (50 mcg) is given to induce cell division and followed 24 hours later by a combination of 3 cytotoxic agents (FAC) given intravenously. The chemotherapy is repeated every three weeks. A phase II study involving 57 patients, for which the response to therapy (UICC criteria) was evaluable, has been completed, showing that the regimen was tolerable and that high remission rates (partial remissions 40 %; complete remissions 35 %) could be obtained. A randomized double-blind phase III study is now underway (100 patients already accrued), intending to test the validity of the hormonal recruitment concept : patients receive either ethinylestradiol or placebo 24 hours before chemotherapy.

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CYTOKINETIC STUDIES AND TREATMENT RESULTS OF ESTROGENS FOLLOWED BY CHEMOTHERAPY IN LOCALLY ADVANCED (LABC) AND METASTATIC (MBC) HUMAN BREAST CANCER.

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We have carried out studies on possibility of overcoming kinetic resistance of breast cancer cells by means of estrogenic recruitment.1)Diethilstilbestrol(DES)was able to significantly increase the rate of cycling cells as evaluated in a series of 29 patients(pts)with LABC who underwent evaluation of cell kinetics by TLI and Primer Dependent DNA Polymerase on tumor biopsies before and after DES 1mg p.o. per 3 days.2)A pilot study in 39 consecutive LABC pts has been carried out with 3 courses of FAC preceded by DES(DES-FAC),followed by surgery + radiotherapy followed by other 3 DES-FAC alternated with 3 DES-CMF.Presurgical chemotherapy produced 12.8%CR,58.9%PR, 25.6%NC and 2.5%PD.Actuarial 24 months survival(OS)and progression free survival(PFS)were 65% and 47% respectively.3)117 MBC pts were randomized to receive CEF(CTX 600mg/sm,EPI-DX 60 mg/sm,5FU 600mg/sm d 1,every 21 days)or DES-CEF(CTX 600mg/sm d 1,EPI-DX 60mg/sm and 5FU 600mg d 8,DES 1mg d 5-7,every 21 days).Results obtained are:CEF:10.2%CR,40.8%PR,42.8%SD,6.2%PD DES-CEF:23.9%CR,28.3%PR,39.1%SD,8.7%PD. No difference in OS and PFS were observed.

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A PHASE II TRIAL OF TAMOXIFEN, PREMARIN, METHOTREXATE AND 5-FLUOROURACIL IN METASTATIC BREAST CANCER

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Complete remissions in patients with advanced breast cancer using either endocrine therapy or chemotherapy are infrequent. Breast tumors are known to be heterogeneous with respect to estrogen receptor (ER) status, and the low complete remission rate may be secondary to this biochemical heterogeneity. Laboratory experiments using breast cancer cells in long-term tissue culture revealed that tamoxifen is cytotoxic, estrogen stimulates the growth of ER-positive cells and can rescue cells from tamoxifen's effect, and sequential MTX/5-FU is synergistic in rapidly growing breast cancer cells. Based on this, a phase II protocol was designed using tamoxifen, 10 mg PO bid, for days 1 to 10. This was followed by premarin, 0.625 mg PO bid, on days 11 to 14. On day 14 the patients were given MTX, 200 mg/m^2 IV, followed in 1 hour by 5-FU 600 mg/m^2 IV. The patients were rescued with leucovorin, 10 mg/m^2 24 hours later. The cycle is repeated every 18 days. Thus far, 57 patients have been entered and all are currently evaluable for response. The overall response rate was 62%; 37% attained a complete remission and 25% had a partial remission. Toxicity was minimal. Over 752 cycles of therapy have been administered with Grade I leukopenia occurring in only 16% of patients. No patient had a WBC count less than 1000, or platelet count less than 50,000. With respect to non-hematologic toxicity, 42% of all cycles had no toxicity whatsoever. Twelve percent had mild nausea and 30% had easily controlled vomiting. In summary, this combination hormonal-chemotherapy regimen is highly effective with a high complete remission rate and minimal toxicity.