86

SIGNIFICANCE OF ER AND PR QUANTITATIVE VALUES IN RESPONSE TO ADJUVANT THERAPY OF OPERABLE BREAST CANCER

L.Vuletić, D.Nikolić, Z.Konstantinović-Nešković, Dj.Vukotić and I.Spužić
Institute of Oncology and Radiology, Belgrade, Yugoslavia

In subgroup of 70 operable breast cancer patients (pts) selected according to lymph node involvement and tumor grade (Tp1-3, Npo, GrIII; Tp1-3, Np1-3, GrII; Tp1-3, Np≥4, GrI), adjuvant therapy was directed according to progesteron receptor (PR) positivity (cut off PR≥ 20fmol/mg/p) on hormonotherapy for PR+ and chemotherapy for PR- pts.
The early relapse was statistically more frequent in chemotherapy than in hormonotherapy group ($p < 0,01$).
In premenopausal pts there was no significant difference in early relapse rate between chemo and hormonotherapy group. In postmenopausal pts early relapse was statistically more frequent in chemotherapy group.
Results will be discussed through significance of quantitative values for ER and PR in hormonotherapy group and for ER in chemotherapy group.

87

COMPARISON OF THE ACTION OF TAMOXIFEN AND ITS 4-IODO DERIVATIVE AGAINST A RESISTANT VARIANT OF THE MCF-7 HUMAN BREAST CANCER CELL LINE.

I.B. Parr, C. Hills and R. McCague.
Cancer Research Campaign Laboratory, Drug Development Section, Institute of Cancer Research, Sutton, Surrey, SM2 5NG, England.

In an attempt to obtain a tissue culture cell line as an in vitro model of tumours in breast cancer patients that have relapsed following a response to tamoxifen (TAM) therapy, we have generated a resistant line by treatment of wild type MCF-7 cells with the mutagen methylnitrosourea and passage over one year in the presence of 1 to 8 μM tamoxifen. Growth of both the wild type MCF-7 and the resistant variant was stimulated to some extent (15 and 12% respectively) after culture with 10^{-8}M oestradiol over 3 days.

The 4-iodo-derivative of tamoxifen (4-IT) has been identified (R. McCague, Brit. Pat. Appl. 8621908/1986) as having greater oestrogen receptor affinity than TAM but without the propensity for conjugate formation suffered by the potent TAM metabolite 4-hydroxytamoxifen.

After 5 days in culture, TAM at 1 μM was without effect on the resistant line despite the presence of the oestrogenic phenol red which TAM might have been expected to antagonise. On the other hand 1 μM 4-IT inhibited cell growth by 23%, viable cell numbers determined by a methyltetrasolium dye assay. Against wild type MCF-7 1 μM TAM and 4-IT inhibited growth by 28% and 54% respectively.

The cytotoxic action of 4-IT was demonstrated in a colony assay. Cells of the resistant variant were plated, exposed to 1 μM TAM or 4-IT for 24 h, then incubated for 10 days. Colonies of ≥ 50 cells were counted. Cloning efficiencies determined as the percentage of cells forming colonies were: Control - 8.2%, TAM - 8.2%, 4-IT - 5.9%. Thus TAM was without effect but 4-IT inhibits colony formation.

As the drug concentrations (1 μM) used in these experiments is of the order of TAM plasma levels reached in patients (P. Daniel et. al., Eur. J. Cancer Clin. Oncol., 1981, 17, 1183-9), our results indicate that evaluation of the effectiveness of 4-IT against tamoxifen resistant tumours in vivo would be worthwhile.

88

INFLUENCE OF SERUM, GROWTH FACTORS, ESTRADIOL AND TAMOXIFEN ON CELL PROLIFERATION AND SYNTHESIS OF SECRETED PROTEINS IN THE HUMAN BREAST CANCER CELL LINE MCF-7.

Anne E. Lykkesfeldt, I. Laursen and P. Briand.
The Fibiger Institute, The Danish Cancer Society, Ndr. Frihavnsgade 70, DK-2100 Copenhagen N, Denmark.

Two sublines of the estrogen responsive human breast cancer cell line MCF-7 have been used to elucidate the role of addition of serum, growth factors, estradiol and tamoxifen on cell proliferation and synthesis of secreted proteins. Both tamoxifen (5×10^{-7}M) and newborn calf serum (10%) inhibit cell proliferation whereas addition of growth factors and estradiol stimulates cell proliferation. Estradiol stimulation is associated with an increased synthesis of 3 secreted proteins with mw. 66kDa, 61kDa and 52kDa and a decreased synthesis of one protein with mw. 42kDa. A partially purified preparation of the 66 kDa protein from conditioned medium from MCF-7 cells exerts a growth stimulation in 1 nM concentration. The 61kDa protein is immunoreactive with antibodies to antitrypsin and estradiol stimulation of cell proliferation of MCF-7 cells is reduced if antibodies to antitrypsin is added to the growth medium. Our results show that cell proliferation of breast cancer cells can be regulated by several factors, and our aim is to examine whether a limited number of regulatory factors plays a dominating role in controlling cell proliferation of human breast cancer.

89

EFFECT OF EMBRYONIC MOUSE CELLS (BALB-3T3) ON THE PROLIFERATION OF THE MAMMARY CANCER CELL LINE T47D.

G. Chetrite, C. Parrondo and J.R. Pasqualini,
C.N.R.S. Steroid Hormone Research Unit,
Foundation for Hormone Research,
26 Boulevard Brune, 75014 Paris, France.

It is very well established that different growth factors (EGF, TGF-α, IGF) can be involved in cell growth of different mammary cancer cell lines. These factors can act by an autocrine or paracrine process and could be controlled by estrogens or anti-estrogens in hormone-dependent mammary cancer cell lines. In the present study we explore the effect of the cellular extracts (CE) and of the culture medium (CM) of the embryonic mouse cell line BALB-3T3 (clone A31) on the proliferation and DNA content of the T47D breast cancer cell line. These effects were also studied in the presence of the potent anti-estrogen ICI164,384. All experiments were prepared in MEM medium containing 5% of fetal calf serum (FCS) treated with dextran charcoal (DC), as well as the homogenization of the BALB-3T3 cells to obtain the cellular extract. Aliquots of CE (2%) corresponding to 2×10^6 cells, or CM (20%), are incubated with the T47D cells. After 9 days of culture CE and CM provoke an intense proliferative effect corresponding respectively to 5 and 11 times the control value of T47D cells. These effects on cell proliferation are correlated with DNA content. Although the anti-estrogen ICI164,384 alone decreases to half the proliferation of T47D cells, the presence of CM abolishes this effect and, on the contrary, increases 7-fold the cell proliferation.
It is concluded that the embryonic cells of mouse (BALB 3T3) contain factor(s) which stimulate very intensively the proliferation of the T47D mammary cancer cells. These factor(s) are present in both the cell and the culture medium and also antagonize the anti-proliferative effect of the anti-estrogen ICI164,384.