94

Pharmacology of the metabolites of toremifene.
Lauri Kangas, Farmos Group Ltd, Turku, Finland

Toremifene is a new antiestrogenic antitumor drug excreted mainly as its metabolites into the feces. There are three main metabolic pathways: a) N-demethylation and subsequent oxidation to alcohols and further to carboxylic acids, b) 4-hydroxylation, and c) 4'-hydroxylation. N-demethylation and hydroxylation are the main metabolic pathways in humans and rats, respectively.

The elimination half lives of unchanged toremifene and N-demethyltoremifene in humans are in average 6 and 14 days, respectively and the steady-state serum concentrations 700 and 1500 ng/ml, respectively, with the daily dose of 60 mg.

N-demethyltoremifene resembles unchanged drug in its hormonal effects. It is bound to estrogen receptors (ER) with similar affinity (relative binding affinity (RBA) being 5% of estradiol with both compounds), inhibits MCF-7 cell growth in vitro (IC-50 1 uM), has slight intrinsic estrogenic and potent antiestrogenic effect in mouse and rat uteri (similar to toremifene). However, the antitumor activity of N-demethyltoremifene is weak in DMBA-induced rat mammary cancer in vivo. 4-Hydroxylation and partly 4'-hydroxylation yield compounds with high binding affinity to ER (RBA 70-150% of estradiol) and potent MCF-7 growth inhibiting properties in vitro. These compounds are also effective antiestrogens in mouse and rat uteri, but have only weak antitumor activity in DMBA induced tumors. Toremifene alcohol and carboxylic acid have only weak, if any, hormonal effects. The antitumor effect of toremifene is therefore due mainly to the parent compound. Some metabolites may contribute to toremifene's hormonal activity.

95

ENHANCED RESPONSE TO TAMOXIFEN (TMX) OF ADVANCED BREAST CANCER (BC) BY BETA INTERFERON (B-IFN) AND RETINOIDS. A PHASE II STUDY.

F.Recchia, C.Ercole, A.Morgante, E.Capaldi, F.Marchionni, G.Rabitti. Division of Internal Medicine. Civil Hospital. 67051 Avezzano, Italy.

B-IFN and retinoids, exerting a differentiating action on BC cells, may increase the expression of estrogen receptors (ER) and may enhance the response to TMX. From 3/88 to 1/90 we treated 22 stage IV BC patients (PTS) with B-IFN 1 MU/M2 3X/W, TMX 10 mg TID, Retinol Palmitate 15000 IU BID. PTS characteristics: median age 64 years. 21 PTS postmenopausal, 1 PT premenopausal. Median P.S. was 70%. Median disease free interval 30 months (MOS) (7-360). Histology: 18 infiltrating ductal carcinomas, 2 lobular infiltrating and 2 inflammatory. ER+ 4 PTS, ER- 3 PTS, ER unknown 15 PTS. Dominant site of disease: bone 8 PTS, soft tissue 9 PTS and viscera 5 PTS. Previous treatments: mastectomy 19 PTS, QUART 1 PT, XRT 17 PTS, chemotherapy 19 PTS (median 7 courses, range 6-24). 12 PTS had been pretreated with TMX and had progressed. Median follow up is 25 MOS (4-94). Toxicity: grade 1 GI toxicity in 20% of PTS, low grade fever in 25% of PTS. Objective responses (WHO); CR 8 PTS (36%), PR 6 PTS (27%), SD 3 PTS (14%), PD 5 PTS (23%). Median response duration is 8+ MOS (range 3-20+ MOS). 12 PTS pretreated with TMX and progressing, are responding to TMX + B-IFN, showing the transition from TMX unresponsive to TMX responsive state.

96

EFFECTS OF RETINOIDS, INTERFERON GAMMA AND TNF ALPHA ON HUMAN BREAST AND OVARIAN CANCER CELLS.

G.Daxenbichler, I.Mayer and Ch.Marth
Department of Obstetrics and Gynecology, Innsbruck University Clinic, Austria

The biological response modifiers retinoic acid (RA), synthetic retinoids, interferon gamma (IFNgamma) and TNFalpha either alone or in combination were tested for their ability to influence growth, expression of various antigens, ornithine decarboxylase (ODC) and 2'5'oligoadenylate synthetase (2'5'OASE) activity in mammary (ZR75.1, 734-B, BT20, MCF7) and ovarian (OVCAR-3, HTB-77, 2780, CRL-1572) cancer cells. Surface antigens were determined by a living cell radioimmunoassay, polyamines were analyzed by HPLC and 2'5'OASE by Northern blot hybridisation. Proliferation was inhibited by IFNgamma in all but one (CRL-1572) cell line, by RA in all exept BT20 and HTB-77 cells, by TNFalpha in all cell lines tested. Synergism with regard to growth reduction was observed for IFNgamma and RA in the breast cancer cells but only in the 2780-ovarian carcinoma cells and was found for TNFalpha and IFNgamma in BT20 and ZR75.1 cells and in all cells of ovarian carcinoma origin.
Expression of HLADR antigens was induced by IFNgamma in all cells tested exept CRL-1572. In BT20 cells neither RA nor TNFalpha induced HLADR but TNFalpha enhanced the effect of IFNgamma synergistically. In this cell line 2'5'OASE was induced by IFNgamma. TNFalpha and RA had no effect per se but enhanced the IFNgamma action. ODC activity was reduced by IFNgamma. RA, which was itself inactive, enhanced the IFNgamma effect. The tumor marker CA125 was augmented in 2/4 ovarian carcinoma cell lines under IFNgamma.
These results and others not described here demonstrate the direct antitumoral effects of biological response modifiers and their interrelationship.

97

INTERFERON ALPHA RECEPTOR EXPRESSION BY HUMAN BREAST CANCER CELLS. J.Martin, B.McKibben* and H.W. van den Berg. Depts.of Therapeutics and Pharmacology and Medicine* ,The Queen's University of Belfast.

Recombinant interferon alpha 2b (IFN) increases oestrogen receptor (ER) expression in ZR-75-1 human breast cancer cells (van den Berg et al Br.J.Cancer 55,255 1987) but we have been unable to demonstrate induction of ER in a tamoxifen resistant, ER negative, variant line (ZR-75-9a1). In this study we have investigated the relationship between IFN receptor expression and steroid hormone receptor content in ZR-75-1 cells, the tamoxifen resistant variant and an oestrogen independent subline (ZR-PR-LT). The latter line lacks binding sites characterisic of the Type 1 ER but expresses elevated levels of progesterone receptor (PGR). Binding of 125-I IFN to whole cells was determined at 4°C. ZR-75-1 cells contained 1498±541 IFN receptors/cell which fell to 802±447 receptors/cell during a 5 day exposure to 10-9M oestradiol (E2). IFN and E2 therefore appear to have opposite effects on expression of each other's receptor in this cell line. This E2 induced reduction in IFN receptor expression is accompanied by a 6-fold increase in PGR concentration in ZR-75-1 cells. However, there was no significant reduction in IFN receptor expression in ZR-PR-LT cells associated with their elevated basal PGR content. An inverse relationship between IFN and PGR receptor expression is apparent in the ZR-75-9a1 line which lacks PGR and expresses the highest concentration of IFN receptors (3443±389 sites/cell). This observation suggests that the apparent inability of IFN to induce ER in this cell line is not a consequence of failure to express IFN receptors.