

Answer 1:

Bibliographic Information

Effects of a phytoestrogen-containing soy extract on the growth-inhibitory activity of ICI 182 780 in an experimental model of estrogen-dependent breast cancer. Gallo, Daniela; Mantuano, Elisabetta; Fabrizi, Manuela; Ferlini, Cristiano; Mozzetti, Simona; De Stefano, Ilaria; Scambia, Giovanni. Department of Obstetrics and Gynecology, Catholic University of the Sacred Heart, Rome, Italy. *Endocrine-Related Cancer* (2007), 14(2), 317-324. Publisher: Society for Endocrinology, CODEN: ERCAE9 ISSN: 1351-0088. Journal written in English. CAN 147:514581 AN 2007:1096028 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The study reported here was designed to det. whether a phytoestrogen-contg. soy ext. (SSE) could negate/overwhelm the inhibitory effects of ICI 182 780 on the growth of estrogen-sustained human breast cancer xenografts (MCF-7), in ovariectomized athymic mice. As expected, estradiol-supplemented tumors did not grow over the study period in ICI 182 780-treated females; concomitant administration of 50 mg/kg per day SSE slightly potentiated the inhibitory activity of the drug, while at 100 mg/kg per day, SSE partially negated ICI 182 780 activity. In keeping with these in vivo outcomes, we obsd. that the level of cyclin D1 (and progesterone receptor) in MCF-7 xenografts was considerably reduced by ICI 182 780, an effect enhanced by concomitant treatment with 50 SSE, but reduced by the higher dosage (i.e. 100 mg/kg per day). Thrombospondin-1 (TSP-1) and kallikrein 6 (KLK6) levels were also reduced following ICI 182 780, although to a lesser degree; again, combined anti-estrogen and SSE produced a dose-dependent regulation in TSP-1 and KLK6 tumor level, with a further redn. in the mRNA gene expression at 50 SSE (compared with ICI 182 780) and a partial reversion of the drug-induced down-regulation at 100 mg/kg per day. No modulation was detected in the serum concn. of IGF-1 (a potent mitogen for estrogen receptor-pos. breast cancer cell lines) either upon treatment with ICI 182 780 or concomitant administration of the anti-estrogen with SSE. In conclusion, results from this study raise concerns about the consumption of isoflavone supplements in conjunction with ICI 182 780 therapy, in postmenopausal women with estrogen-dependent breast cancer.

Answer 2:

Bibliographic Information

Role for HER2/neu and HER3 in fulvestrant-resistant breast cancer. Osipo, Clodia; Meeke, Kathleen; Cheng, Dong; Weichel, Alyssa; Bertucci, Anne; Liu, Hong; Jordan, V. Craig. Department of Pathology, Oncology Institute, Cardinal Bernadin Cancer Center, Loyola University Medical Center, Maywood, IL, USA. *International Journal of Oncology* (2007), 30(2), 509-520. Publisher: International Journal of Oncology, CODEN: IJONES ISSN: 1019-6439. Journal written in English. CAN 146:308719 AN 2007:198897 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Tamoxifen resistance is common for estrogen receptor α (ER α) pos. breast cancer. Second-line therapies include aromatase inhibitors or fulvestrant. We have shown previously that fulvestrant reversed 17 β -estradiol-induced tumor regression of tamoxifen-stimulated MCF-7 xenografts (MCF-7TAMLt) treated for >5 years with tamoxifen in athymic mice and paradoxically stimulated growth. We investigated mechanisms responsible for growth by fulvestrant in the presence of physiol. estradiol and therapeutic strategies in vivo. The results demonstrated that only estradiol increased expression of the estrogen-responsive genes, c-myc, igf-1, cathepsin D, and pS2 mRNAs, in MCF-7E2 and MCF-7TAMLt tumors. Tamoxifen or fulvestrant decreased the estradiol-induced increase of these mRNAs in both tumor models. However, tyrosine-phosphorylated HER2/neu, HER3, phospho-extracellular-regulated kinase-1/2 (ERK-1/2), and phospho-glycogen synthetase kinase 3 α (GSK3 α) and β proteins were increased in MCF-7TAMLt tumors treated with fulvestrant compared to estradiol, control, or tamoxifen. Phospho-HER2/neu interacted with HER3 protein in MCF-7TAMLt tumors. In order to det. whether the functional interaction of HER2/neu with HER3 is crit. for growth of fulvestrant-stimulated MCF-7TAMLt tumors, pertuzumab (an antibody that blocks HER2/neu-HER3 interaction) was used in an in vivo xenograft growth assay. Only growth of fulvestrant-treated MCF-7TAMLt xenografts was decreased significantly by 37.2% in response to pertuzumab (P = 0.004). Pertuzumab specifically decreased the interaction of HER2/neu protein with HER3 in fulvestrant-stimulated MCF-7TAMLt tumors. These results suggested growth of MCF-7TAMLt tumors by tamoxifen or fulvestrant is potentially independent of ER α transcriptional activity as evidenced by lack of induction of four estrogen-responsive genes. The results suggested that growth of MCF-7TAMLt

tumors treated with fulvestrant in the presence of physiol. estradiol is in part mediated through enhanced signaling from the HER2/neu-HER3 pathway as pertuzumab partially inhibited growth and the interaction of HER2/neu with HER3 in vivo.

Answer 3:

Bibliographic Information

Therapeutic Observations in MCF-7 Aromatase Xenografts. Brodie, Angela; Jelovac, Danijela; Macedo, Luciana; Sabnis, Gauri; Tilghman, Syreeta; Goloubeva, Olga. Department of Pharmacology and Experimental Therapeutics, University of Maryland School of Medicine, Baltimore, MD, USA. *Clinical Cancer Research* (2005), 11(2, Pt. 2), 884s-888s. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal; General Review written in English. CAN 142:384841 AN 2005:271400 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A review. In previous studies using a xenograft model with tumors of human estrogen receptor (ER)-pos. breast cancer cells transfected with aromatase (MCF-7Ca), we explored the antitumor efficacy of treatment combining the nonsteroidal aromatase inhibitor letrozole with tamoxifen. However, treatment with this combination resulted in tumor suppression similar to tamoxifen alone but was less effective than letrozole alone. Clin. findings with the nonsteroidal inhibitor anastrozole in combination with tamoxifen (ATAC trial) were consistent with our results. Although letrozole was the most effective single agent in the model, tumors ultimately began to grow during continued treatment. To investigate the mechanisms by which tumors adapted to growth during letrozole treatment, we detd. the expression of proteins in tumors during letrozole treatment compared with the tumors of control mice. We found that tumors initially up-regulated the ER, but subsequently receptor levels decreased in tumors unresponsive to letrozole. Adapter proteins (p-Shc and Grb-2) as well as all of the signaling proteins in the mitogen-activated protein kinase cascade (p-Raf, p-MEK1/2, and p-MAPK) but not Akt were increased in tumors no longer responsive to letrozole. The results suggest that tumor cells adapt to estrogen deprivation during letrozole treatment by activation of alternate signaling pathways. When letrozole was combined with the pure antiestrogen fulvestrant, which down-regulates ER, the combination was extremely effective. Tumors regressed by 45% and were maintained without growth for the duration of the expt. (29 wk). Thus, achieving more complete estrogen blockade may delay development of hormone-independent signaling pathways regulating proliferation.

Answer 4:

Bibliographic Information

Combined targeting of the estrogen receptor and the epidermal growth factor receptor in non-small cell lung cancer shows enhanced antiproliferative effects. Stabile, Laura P.; Lyker, Jennifer S.; Gubish, Christopher T.; Zhang, Weiping; Grandis, Jennifer R.; Siegfried, Jill M. Department of Pharmacology, University of Pittsburgh, Pittsburgh, PA, USA. *Cancer Research* (2005), 65(4), 1459-1470. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 142:290872 AN 2005:156962 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Identifying new effective therapeutic treatments for lung cancer is crit. to improving overall patient survival. The authors have targeted both the estrogen receptor (ER) and the epidermal growth factor receptor (EGFR) pathways using an ER antagonist, fulvestrant ("Faslodex"), and the selective EGFR tyrosine kinase inhibitor, gefitinib ("Iressa"), in nonsmall cell lung cancer (NSCLC) cells. Rapid activation of phospho-EGFR and phospho-p44/p42 mitogen-activated protein kinase by estrogen was obsd., indicating nonnuclear ER transactivation of EGFR. Addnl., EGFR protein expression was down-regulated in response to estrogen and up-regulated in response to fulvestrant in vitro, suggesting that the EGFR pathway is activated when estrogen is depleted in NSCLC cells. Cell growth and apoptosis were examd. in several NSCLC lines that express varying amts. of ER β , EGFR, and Neu but no full-length ER α . One cell line contained an EGFR mutation. Cells were exposed to 10 nmol/L estrogen and 10 ng/mL EGF and either 1 μ mol/L fulvestrant or 1 μ mol/L gefitinib alone or in combination. In all cell lines, the drug combination decreased cell proliferation up to

90% and increased apoptosis 2-fold. The relative responses to gefitinib and fulvestrant were similar regardless of ER and EGFR expression and mutation status. In an in vivo lung tumor xenograft model, the drug combination decreased tumor vol. in severe combined immunodeficient mice by .apprx.60% compared with 49% and 32% for gefitinib and fulvestrant treatment alone, resp. Antitumor effects of the combination therapy were accompanied by biochem. and histol. evidence of increased apoptosis, decreased phospho-p44/p42 mitogen-activated protein kinase expression, and increased Ki-67 expression compared with individual treatment. These studies provide evidence of a functional interaction between the ER and the EGFR pathways in NSCLC.

Answer 5:

Bibliographic Information

Characterization of New Estrogen Receptor Destabilizing Compounds: Effects on Estrogen-Sensitive and Tamoxifen-Resistant Breast Cancer. Hoffmann, Jens; Bohlmann, Rolf; Heinrich, Nikolaus; Hofmeister, Helmut; Kroll, Joerg; Kuenzer, Hermann; Lichtner, Rosemarie B.; Nishino, Yuki; Parczyk, Karsten; Sauer, Gerhard; Gieschen, Hille; Ulbrich, Hannes-F.; Schneider, Martin R. Research Laboratories of Schering AG, Berlin, Germany. Journal of the National Cancer Institute (2004), 96(3), 210-218. Publisher: Oxford University Press, CODEN: JNCIEQ ISSN: 0027-8874. Journal written in English. CAN 141:219128 AN 2004:106785 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Antiestrogens of the selective estrogen receptor modulator (SERM) type, such as tamoxifen, have two major limitations: their mixed agonist and antagonist profile and the development of tumor resistance. We characterized two new pure antiestrogens-ZK-703 and ZK-253-that belong to the class of specific estrogen receptor destabilizers (SERDs), which includes fulvestrant, and compared their activity with that of fulvestrant and tamoxifen. Effects of antiestrogens on the growth of estrogen-dependent breast tumors in vivo were detd. using several mouse xenograft models (including the tamoxifen-sensitive tumors MCF7, T47D, and MV3366 and the tamoxifen-resistant tumors ZR75-1 and MCF7/TAM) and chem. induced (nitrosomethyl urea [NMU] and dimethylbenzanthracene [DMBA]) rat breast cancer models (groups of 10 animals). We detd. the initial response and effects on hormone receptor levels and the time to relapse after treatment (i.e., time to reach a predetd. tumor size threshold). Estrogen receptor (ER) levels were detd. by immunoassay. ZK-703 (administered s.c.) and ZK-253 (administered orally) were more effective than tamoxifen or fulvestrant at inhibiting the growth of ER-pos. breast cancer in all xenograft models. For example, MCF7 tumors relapsed (i.e., reached the size threshold) in 10 wk in mice treated with tamoxifen but in 30 wk in mice treated with ZK-703. ZK-703 and ZK-253 also prevented further tumor progression in tamoxifen-resistant breast cancer models to a similar extent (more than 30 wk in mice with ZR75-1 and MCF7/TAM tumors). In the chem. induced rat breast cancer models, orally administered ZK-703 and ZK-253 caused a nearly complete (>80%) inhibition of tumor growth. ER levels were dramatically reduced in MCF7 tumors after 5 wk of ZK-703 treatment compared with ER levels in vehicle-treated tumors; by contrast, ER levels in tamoxifen-treated tumors were higher than those in control tumors.

ZK-703 and ZK-253 are potent, long-term inhibitors of growth in both tamoxifen-sensitive and tamoxifen-resistant breast cancer models.

Answer 6:

Bibliographic Information

Paradoxical Action of Fulvestrant in Estradiol-Induced Regression of Tamoxifen-Stimulated Breast Cancer. Osipo, Clodia; Gajdos, Csaba; Liu, Hong; Chen, Bin; Jordan, V. Craig. Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA. Journal of the National Cancer Institute (2003), 95(21), 1597-1608. Publisher: Oxford University Press, CODEN: JNCIEQ ISSN: 0027-8874. Journal written in English. CAN 140:280903 AN 2003:903987 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: Long-term tamoxifen treatment of breast cancer can result in tamoxifen-stimulated breast cancer, in which estrogen inhibits tumor growth after tamoxifen withdrawal. The authors investigated the mol. mechanism(s) of estradiol-induced tumor

regression by using an in vivo model of tamoxifen-stimulated human breast cancer. Methods: Growth of parental estradiol-stimulated MCF-7E2 and long-term tamoxifen-stimulated MCF-7TAMLT xenografts in athymic mice was measured during treatment with vehicle, estradiol, estradiol plus tamoxifen, tamoxifen alone, estradiol plus fulvestrant, or fulvestrant alone. Apoptosis was detected by the terminal deoxynucleotidyltransferase-mediated deoxyuridine triphosphate nick-end labeling (TUNEL) assay. Protein expression was assessed by western blot anal. mRNA expression was assessed by real-time reverse transcription-polymerase chain reaction. All statistical tests were two-sided. Results: MCF-7E2 tumor growth was stimulated by estradiol (cross-sectional area at week 13=1.06 Cm², 95% confidence interval [CI] = 0.82 to 1.30 Cm²; P<.001) compared with control (0.06 Cm², 95%CI = -0.02 to 0.14 Cm²), but tumor growth was inhibited by tamoxifen or fulvestrant. MCF-7TAMLT tumor growth was stimulated by tamoxifen (cross-sectional area at week 10=0.60 Cm², 95% CI = 0.50 to 0.70 Cm²; P<.001) compared with control (0.02 Cm², 95% CI = 0.00 to 0.04 Cm²). For MCF-7TAMLT tumors that were initially 0.35 Cm², estradiol-induced regression to 0.18 Cm² (95% CI = 0.15 to 0.21 Cm²; P<.001), and tamoxifen or estradiol plus fulvestrant enhanced tumor growth to 1.00 Cm² (95% CI = 0.88 to 1.22 Cm²). Estradiol increased the no. of apoptotic cells in tumors by 23% (95% CI = 20% to 26%; P<.001) compared with all other treatments, decreased estrogen receptor α (ER α) protein expression, increased the expression of Fas mRNA and protein, decreased the expression of HER2/neu mRNA and protein and nuclear factor κ B (NF- κ B) protein but did not affect Fas ligand protein expression compared with control.

Paradoxically, fulvestrant reversed this effect and stimulated MCF-7TAMLT tumor growth apparently through ER α -mediated regulation of Fas, HER2/neu, and NF- κ B. Conclusion: Physiol. levels of estradiol induced regression of tamoxifen-stimulated breast cancer tumors, apparently by inducing the death receptor Fas and suppressing the antiapoptotic/prosurvival factors NF- κ B and HER2/neu.