

Answer 1:

Bibliographic Information

Activation of Mitogen-Activated Protein Kinase in Xenografts and Cells during Prolonged Treatment with Aromatase Inhibitor Letrozole. Jelovac, Danijela; Sabnis, Gauri; Long, Brian J.; Macedo, Luciana; Goloubeva, Olga G.; Brodie, Angela M. H. Department of Pharmacology and Experimental Therapeutics, University of Maryland Greenebaum Cancer Center, University of Maryland School of Medicine, Baltimore, MD, USA. *Cancer Research* (2005), 65(12), 5380-5389. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 143:109199 AN 2005:513610 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Ovariectomized mice bearing tumor xenografts grown from aromatase-transfected estrogen receptor (ER)-pos. human breast cancer cells (MCF-7Ca) were injected s.c. with 10 $\mu\text{g/d}$ letrozole for up to 56 wk. Western blot anal. of the tumors revealed that ERs ($\text{ER}\alpha$) were increased at 4 wk but decreased at weeks 28 and 56. Expression of erbB-2 and p-Shc increased throughout treatment, whereas growth factor receptor binding protein 2 (Grb2) increased only in tumors proliferating on letrozole (weeks 28 and 56). In cells isolated from tumors after 56 wk and maintained as a cell line (LTLT-Ca) in 1 $\mu\text{mol/L}$ letrozole, $\text{ER}\alpha$ was also decreased whereas erbB-2, adapter proteins (p-Shc and Grb2), and the signaling proteins in the mitogen-activated protein kinase (MAPK) cascade were increased compared with MCF-7Ca cells. Growth was inhibited in LTLT-Ca cells but not in MCF-7Ca cells treated with MAPK kinase 1/2 inhibitors U0126, and PD98059 (IC_{50} .apprx.25 $\mu\text{mol/L}$). PD98059 (5 $\mu\text{mol/L}$) also reduced MAPK activity and increased $\text{ER}\alpha$ to the levels in MCF-7Ca cells. Epidermal growth factor receptor kinase inhibitor, gefitinib (ZD1839) inhibited growth of LTLT-Ca cells (IC_{50} .apprx.10 $\mu\text{mol/L}$) and restored their sensitivity to tamoxifen and anastrozole. In xenografts, combined treatment with ER down-regulator fulvestrant and letrozole, prevented increases in erbB-2 and activation of MAPK and was highly effective in inhibiting tumor growth throughout 29 wk of treatment. These results indicate that blocking both ER- and growth factor-mediated transcription resulted in the most effective inhibition of growth of ER-pos. breast cancer cells.

Answer 2:

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: CCREFA 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 3:

Bibliographic Information

Therapeutic Strategies Using the Aromatase Inhibitor Letrozole and Tamoxifen in a Breast Cancer Model. Long, Brian J.; Jelovac, Danijela; Handratta, Venkatesh; Thiantanawat, Apinya; MacPherson, Nicol; Ragaz, Joseph; Goloubeva, Olga G.; Brodie, Angela M. Department of Pharmacology and Experimental Therapeutics, Health Sciences Facility, University of Maryland School of Medicine, Baltimore, MD, USA. *Journal of the National Cancer Institute* (2004), 96(6), 456-465. Publisher: Oxford University Press, CODEN: JNCIEQ ISSN: 0027-8874. Journal written in English. CAN 141:325248 AN 2004:238191 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: The antiestrogen tamoxifen has potent activity against estrogen receptor-pos. breast cancer, but two nonsteroidal aromatase inhibitors, letrozole and anastrozole, show considerable advantages over tamoxifen with respect to patient survival and tolerability. To det. the optimal way to use letrozole and tamoxifen, we studied their effects on a breast tumor xenograft model, MCF-7Ca, that is responsive to both antiestrogens and aromatase inhibitors. **Methods:** Female ovariectomized BALB/c athymic nude mice carrying xenograft tumors were treated daily s.c. with one of the following first-line therapies for varying durations: no drug (control), tamoxifen (100 µg/day) alone, letrozole (10 µg/day) alone, both drugs at the same time, or alternating 4-wk courses of each drug (beginning with a course of tamoxifen or beginning with a course of letrozole). Tumor vols. and wts. were estd. using linear mixed-effects models. The time to tumor doubling was calcd., and tumor wts. in the treatment groups were compared, with adjustments for multiple comparisons being made with either Tukey's or Dunnett's procedure. Second-line therapies (with tamoxifen, letrozole, or fulvestrant) were initiated when tumors doubled in size under first-line therapies. All statistical tests were two-sided. **Results:** The times for doubling of tumor vol. were as follows: control, 3-4 wk; tamoxifen alone, 16 wk; tamoxifen alternating with letrozole, 17-18 wk; tamoxifen plus letrozole, 18 wk; letrozole alternating with tamoxifen, 22 wk; letrozole alone, 34 wk. First-line treatment with letrozole was superior to treatment with tamoxifen alone or with the two drugs combined (at week 16, both $P < .001$). Alternating tamoxifen and letrozole and alternating letrozole and tamoxifen were also not as effective as letrozole alone (at week 16, $P = .002$ and $P < .001$, resp.).

Tumors progressing on tamoxifen remained sensitive to second-line therapy with letrozole compared with those remaining on tamoxifen at the end of treatment (week 28, $P < .001$), whereas tumors progressing on letrozole were unaffected by second-line treatment with the antiestrogens tamoxifen or fulvestrant. **Conclusions:** First-line letrozole therapy extends time for tumor progression in this model relative to the other treatment regimens tested. However, further studies are needed to det. the most effective second-line therapy for tumors that progress on letrozole.

Answer 4:

Bibliographic Information

Aromatase inhibitor development and hormone therapy: a perspective. Brodie, Angela. Department of Pharmacology and Experimental Therapeutics, School of Medicine and Greenbaum Cancer Center, University of Maryland, Baltimore, MD, USA. *Seminars in Oncology* (2003), 30(4, Suppl. 14), 12-22. Publisher: W. B. Saunders Co., CODEN: SOLGAV ISSN: 0093-7754. Journal; General Review written in English. CAN 139:374066 AN 2003:891141 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A review. The introduction of aromatase inhibitors as a new class of agents represents a further step in improving breast cancer treatment and possibly in preventing this disease. Although these agents are now used in the first- and second-line treatment of postmenopausal breast cancer, the heterogeneity of patients enrolled in clin. trials prevents a thorough assessment of the effectiveness of potential sequential and combination therapies. Such investigations are more easily performed in the lab., and to this end, a tumor model in nude mice was established to simulate several aspects of the postmenopausal breast cancer patient. This model showed that aromatase inhibitors are more efficient than tamoxifen at reducing tumor vol. Addnl., the combination of an

aromatase inhibitor plus tamoxifen does not improve the antiproliferative results obtained with the aromatase inhibitor alone, a finding corroborated in the Arimidex, Tamoxifen Alone or in Combination adjuvant clin. trial. To investigate the effect that potential sequences of treatment have on tumor growth, letrozole was administered in sequence with tamoxifen to nude mice bearing human xenografts. Tumor growth was significantly reduced with the sequence compared with tamoxifen alone. Addnl., when agents were alternated every 4 wk, mice started on letrozole fared better than those started on tamoxifen. Finally, letrozole alone provided the best and most sustained redn. in tumor growth. These expts. suggest the means to evaluate therapeutic combinations in the lab. to guide potential trial designs and provide the best chance of success to the patients who enter these clin. trials.