Answer 1:

Bibliographic Information

Proteasome Inhibition Activates Epidermal Growth Factor Receptor (EGFR) and EGFR-Independent Mitogenic Kinase Signaling Pathways in Pancreatic Cancer Cells. Sloss, Callum M.; Wang, Fang; Liu, Rong; Xia, Lijun; Houston, Michael; Ljungman, David; Palladino, Michael A.; Cusack, James C., Jr. Authors' Affiliations: Division of Surgical Oncology, Harvard Medical School, Boston, Massachusetts General Hospital, Massachusetts and Nereus Pharmaceuticals, San Diego, CA, USA. Clinical Cancer Research (2008), 14(16), 5116-5123. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. AN 2008:976367 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

PURPOSE: In the current study, we investigate the activation of antiapoptotic signaling pathways in response to proteasome inhibitor treatment in pancreatic cancer and evaluate the use of concomitant inhibition of these pathways to augment proteasome inhibitor treatment responses. Exptl. Design: Pancreatic cancer cell lines and mouse flank xenografts were treated with proteasome inhibitor alone or in combination with chemotherapeutic compds. (gemcitabine, erlotinib, and bevacizumab), induction of apoptosis and effects on tumor growth were assessed. The effect of bortezomib (a first-generation proteasome inhibitor) and NPI-0052 (a second-generation proteasome inhibitor) treatment on key pancreatic mitogenic and antiapoptotic pathways [epidermal growth factor receptor, extracellular signal-regulated kinase, and phosphoinositide-3-kinase (PI3K)/AKT] was detd. and the ability of inhibitors of these pathways to enhance the effects of proteasome inhibition was assessed in vitro and in vivo. RESULTS: Our data showed that proteasome inhibitor treatment activates antiapoptotic and mitogenic signaling pathways (epidermal growth factor receptor, extracellular signal-regulated kinase, c-Jun-NH2-kinase, and PI3K/AKT) in pancreatic cancer. Addnl., we found that activation of these pathways impairs tumor response to proteasome inhibitor treatment and inhibition of the c-Jun-NH2-kinase and PI3K/AKT pathways increases the antitumor effects of proteasome inhibitor treatment. CONCLUSION: These preclin. studies suggest that targeting proteasome inhibitor-induced antiapoptotic signaling pathways in combination with proteasome inhibition may augment treatment response in highly resistant solid organ malignancies. Further evaluation of these novel treatment combinations in clin. trials is warranted.

Answer 2:

Bibliographic Information

Short preoperative treatment with erlotinib inhibits tumor cell proliferation in hormone receptor-positive breast cancers. Guix, Matta; Granja, Nara de Matos; Meszoely, Ingrid; Adkins, Theresa B.; Wieman, Bobbye M.; Frierson, Kerek E.; Sanchez, Violeta; Sanders, Melinda E.; Grau, Ana M.; Mayer, Ingrid A.; Pestano, Gary; Shyr, Yu; Muthuswamy, Senthil; Calvo, Benjamin; Krontiras, Helen; Krop, Ian E.; Kelly, Mark C.; Arteaga, Carlos L. Departments of Medicine, Pathology, Biostatistics, Surgery, and Cancer Biology, Breast Research Program, Vanderbilt-Ingram Comprehensive Cancer Center, Vanderbilt University School of Medicine, Nashville, TN, USA. Journal of Clinical Oncology (2008), 26(6), 897-906. Publisher: American Society of Clinical Oncology, CODEN: JCONDN ISSN: 0732-183X. Journal written in English. CAN 148:462669 AN 2008:313641 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

To administer the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor erlotinib to patients with operable untreated breast cancer during the immediate preoperative period and to measure an antiproliferative and/or a proapoptotic effect in the post-therapy specimen and det. a biomarker profile assocd. with evidence of erlotinib-mediated cellular activity. Newly diagnosed patients with stages I to IIIA invasive breast cancer were treated with erlotinib 150 mg/d orally for 6 to 14 days until the day before surgery. Erlotinib plasma levels were measured by tandem mass spectrometry the day of surgery. Drug-induced changes in tumor cell proliferation and apoptosis were assessed by Ki67 immunohistochem. and terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate-biotin nick-end labeling anal., resp., in biopsies from the pretherapy and surgical specimens. Biopsies were also evaluated for P-EGFR, P-HER-2, P-MAPK, P-Akt, P-S6, and S118 P-ERα. In drug-sensitive PC9 xenografts, 5 days of treatment with erlotinib were enough to induce a maximal inhibition of cell proliferation and induction of apoptosis. Forty-one patients completed preoperative treatment with erlotinib. Grade $\leq$ 2 rash and diarrhea were the main toxicities. Erlotinib inhibited tumor cell proliferation

(Ki67), P-EGFR, and P-HER-2. The inhibition of proliferation occurred in estrogen receptor (ER) -pos. but not in human epidermal growth factor receptor 2 (HER-2) -pos. or triple-neg. cancers. Treatment was assocd. with a significant redn. of P-MAPK, P-Akt, P-S6, and S118 P-ERα in hormone receptor-pos. cancers. A presurgical approach to evaluate cellular responses to new drugs is feasible in breast cancer. EGFR inhibitors are worthy of testing against ER-pos. breast cancers but are unlikely to have clin. activity against HER-2-pos. or triple-neg. breast cancers.

Answer 3:

Bibliographic Information

Of mice and (Wo) men: is this any way to test a new drug? Haddad, Tufia C.; Yee, Douglas. University of Minnesota Cancer Center, Minneapolis, MN, USA. Journal of Clinical Oncology (2008), 26(6), 830-832. Publisher: American Society of Clinical Oncology, CODEN: JCONDN ISSN: 0732-183X. Journal; General Review written in English. CAN 148:462354 AN 2008:313626 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A review. The research of Guix et al. (2008) entitled, "Short preoperative treatment with erlotinib inhibits tumor cell proliferation in hormone receptor-pos. breast cancers" is reviewed with commentary and refs. The authors reported a clin. study based on acquired information from a pre-clin. mouse xenograft study using erlotinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors. They revealed that erlotinib influences estrogen receptor-phosphorylation on ser118, a mitogen-activated protein kinase phosphorylation site. Their study gave evidence for the application of a short course of neoadjuvant treatment to classify a surrogate marker of response (Ki67) that may best predict clin. response. The drawbacks of using model systems in defining predictive biomarkers for response are described as well.

Answer 4:

Bibliographic Information

Induction of BIM is essential for apoptosis triggered by EGFR kinase inhibitors in mutant EGFR-dependent lung adenocarcinomas. Gong, Yixuan; Somwar, Romel; Politi, Katerina; Balak, Marissa; Chmielecki, Juliann; Jiang, Xuejun; Pao, William. Pao Laboratory, Human Oncology and Pathogenesis Program, Memorial Sloan-Kettering Cancer Center, New York, NY, USA. PLoS Medicine (2007), 4(10), 1655-1668. Publisher: Public Library of Science, CODEN: PMLEAC ISSN: 1549-1277. http://medicine.plosjournals.org/archive/1549-1676/4/10/pdf/10.1371_1549-1676_4_10_complete.pdf Journal; Online Computer File written in English. CAN 148:253493 AN 2007:1398568 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: Mutations in the epidermal growth factor receptor (EGFR) gene are assocd. with increased sensitivity of lung cancers to kinase inhibitors like erlotinib. Mechanisms of cell death that occur after kinase inhibition in these oncogene-dependent tumors have not been well delineated. We sought to improve understanding of this process in order to provide insight into mechanisms of sensitivity and/or resistance to tyrosine kinase inhibitors and to uncover new targets for therapy. Methods and Findings: Using a panel of human lung cancer cell lines that harbor EGFR mutations and a variety of biochem., mol., and cellular techniques, we show that EGFR kinase inhibition in drug-sensitive cells provokes apoptosis via the intrinsic pathway of caspase activation. The process requires induction of the proapoptotic BH3-only BCL2 family member BIM (i.e., BCL2-like 11, or BCL2L11); erlotinib dramatically induces BIM levels in sensitive but not in resistant cell lines, and knockdown of BIM expression by RNA interference virtually eliminates drug-induced cell killing in vitro. BIM status is regulated at both transcriptional and posttranscriptional levels and is influenced by the extracellular signal-regulated kinase (ERK) signaling cascade downstream of EGFR. Consistent with these findings, lung tumors and xenografts from mice bearing mutant EGFR-dependent lung adenocarcinomas display increased concns. of Bim after erlotinib treatment. Moreover, an inhibitor of antiapoptotic proteins, ABT-737, enhances erlotinib-induced cell death in vitro. Conclusions: In drug-sensitive EGFR mutant lung cancer cells, induction of BIM is essential for apoptosis triggered by EGFR kinase inhibitors. This finding implies that the intrinsic pathway of caspase activation may influence sensitivity and/or resistance of EGFR

mutant lung tumor cells to EGFR kinase inhibition. Manipulation of the intrinsic pathway could be a therapeutic strategy to enhance further the clin. outcomes of patients with EGFR mutant lung tumors.

Answer 5:

Bibliographic Information

Inhibition of the T790M Gatekeeper Mutant of the Epidermal Growth Factor Receptor by EXEL-7647. Gendreau, Steven B.; Ventura, Richard; Keast, Paul; Laird, A. Douglas; Yakes, F. Michael; Zhang, Wentao; Bentzien, Frauke; Cancilla, Belinda; Lutman, Jeffery; Chu, Felix; Jackman, Lisa; Shi, Yongchang; Yu, Peiwen; Wang, Jing; Aftab, Dana T.; Jaeger, Christopher T.; Meyer, Stephanie M.; De Costa, Anushka; Engell, Kelly; Chen, Jason; Martini, Jean-Francois; Joly, Alison H. Exelixis, Inc., South San Francisco, CA, USA. Clinical Cancer Research (2007), 13(12), 3713-3723. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 147:377850 AN 2007:654995 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

PURPOSE: Agents inhibiting the epidermal growth factor receptor (EGFR) have shown clin. benefit in a subset of non-small cell lung cancer patients expressing amplified or mutationally activated EGFR. However, responsive patients can relapse as a result of selection for EGFR gene mutations that confer resistance to ATP competitive EGFR inhibitors, such as erlotinib and gefitinib. We describe here the activity of EXEL-7647 (XL647), a novel spectrum-selective kinase inhibitor with potent activity against the EGF and vascular endothelial growth factor receptor tyrosine kinase families, against both wild-type (WT) and mutant EGFR in vitro and in vivo. Exptl. DESIGN: The activity of EGFR inhibitors against WT and mutant EGFRs and their effect on downstream signal transduction was examd. in cellular assays and in vivo using A431 and MDA-MB-231 (WT EGFR) and H1975 (L858R and T790M mutant EGFR) xenograft tumors. RESULTS: EXEL-7647 shows potent and long-lived inhibition of the WT EGFR in vivo. In addn., EXEL-7647 inhibits cellular proliferation and EGFR pathway activation in the erlotinib-resistant H1975 cell line that harbors a double mutation (L858R and T790M) in the EGFR gene. In vivo efficacy studies show that EXEL-7647 substantially inhibited the growth of H1975 xenograft tumors and reduced both tumor EGFR signaling and tumor vessel d. Addnl., EXEL-7647, in contrast to erlotinib, substantially inhibited the growth and vascularization of MDA-MB-231 xenografts, a model which is more reliant on signaling through vascular endothelial growth factor receptors. CONCLUSIONS: These studies provide a preclin. basis for clin. trials of XL647 in solid tumors and in patients bearing tumors that are resistant to existing EGFR-targeted therapies.

Answer 6:

Bibliographic Information

Antitumor activity of HER1/EGFR tyrosine kinase inhibitor erlotinib, alone and in combination with CPT-11 (irinotecan) in human colorectal cancer xenograft models. Chen, Jianping; Smith, Melissa; Kolinsky, Kenneth; Adames, Violeta; Mehta, Nila; Fritzky, Luke; Rashed, Mohammad; Wheeldon, Eric; Linn, Michael; Higgins, Brian. Department of Oncology, Hoffmann-La Roche, Inc., Nutley, NJ, USA. Cancer Chemotherapy and Pharmacology (2007), 59(5), 651-659. Publisher: Springer, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 146:513936 AN 2007:183174 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Erlotinib (Tarceva, OSI-774) is a potent, orally available, small-mol. inhibitor of HER1/EGFR tyrosine-kinase activity. In this study, the antitumor activity of erlotinib was evaluated in two human colorectal tumor xenograft models (LoVo and HCT116) in athymic mice. When erlotinib was administered as monotherapy, significant tumor growth inhibition (TGI) was seen in the LoVo model at both 100 mg/kg [TGI > 100%, P < 0.001; 6/10 partial regressions (PRs)] and 25 mg/kg (TGI = 79%, P < 0.001) doses. However, the HCT116 xenograft model was not responsive to any dose of erlotinib tested. The differential response to erlotinib of these two tumor models was not a result of differences in HER1/EGFR expression levels since these were similar in both cell lines. However, it was demonstrated that resistance to erlotinib in the HCT116 model may be a result of persistent activation of ERK in these tumors. Based

on the single agent activity of erlotinib in LoVo tumors, a combination study with CPT-11 (Camptosar, irinotecan) was performed. CPT-11 at the optimal dose of 60 mg/kg or a lower dose of 15 mg/kg resulted in significant TGI (TGI > 100%, P < 0.001, and TGI = 93%, P < 0.001, resp.) in LoVo-bearing mice. Combination treatment with erlotinib (25 mg/kg) and CPT-11 (15 mg/kg) produced significantly greater antitumor activity (TGI > 100%, P < 0.001; 10/10 PRs) than either agent alone (P < 0.05), with no increase in toxicity. These data indicate that erlotinib can enhance the antitumor activity of CPT-11, without enhanced toxicity, in the LoVo human colorectal tumor xenograft model.

Answer 7:

Bibliographic Information

Signaling interactions of rapamycin combined with erlotinib in cervical carcinoma xenografts. Birle, Diana C.; Hedley, David W. Division of Applied Molecular Oncology, Ontario Cancer Institute, University of Toronto, Toronto, ON, Can. Molecular Cancer Therapeutics (2006), 5(10), 2494-2502. Publisher: American Association for Cancer Research, CODEN: MCTOCF ISSN: 1535-7163. Journal written in English. CAN 146:74800 AN 2006:1075792 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Clin. trials using rapamycin analogs or HER1/epidermal growth factor receptor (EGFR) inhibitors show that each class of agent has activity against a range of human solid tumors. Because blockade of mitogen-activated protein kinase signaling occurs following HER1/EGFR inhibition in some cell types, we tested the combination of rapamycin and erlotinib in SiHa, Me180, and CaSki human cervical carcinomas xenografts in severe combined immunodeficient mice. In tissue culture, all three cell lines showed decreased phosphorylated S6 ribosomal protein and decreased phosphorylated extracellular signal-regulated kinase (ERK) following treatment with rapamycin and erlotinib, resp. In SiHa tumors, suppression of phosphorylated S6 was induced by either drug alone, whereas phosphorylated ERK decreased with erlotinib, and enhancement of these effects was obtained with the combination. Continuous treatment of xenografts for 3 wk led to significant tumor growth delay compared with vehicle control for rapamycin as single agent (P = 0.003) and greater for the combination (P = 0.04 vs. rapamycin). Significant antiangiogenic effect was obtained in SiHa xenografts using the drugs together (measured by microvascular d. and vascular endothelial growth factor plasma levels) but not for the single agents. Me180 and CaSki xenografts showed significant growth delay with rapamycin but not with erlotinib. Erlotinib treatment resulted in decreased phosphorylated ERK, assocd. with enhanced suppression of phosphorylated S6 and improved growth delay in Me180 but not in CaSki tumors. These results support the further clin. investigation of rapamycin and EGFR inhibitor combinations in anticancer therapy but highlight the problem of intertumoral heterogeneity in the prediction of in vivo response.

Answer 8:

Bibliographic Information

Antitumor activity of erlotinib in combination with capecitabine in human tumor xenograft models. Ouchi, Kaori F.; Yanagisawa, Mieko; Sekiguchi, Fumiko; Tanaka, Yutaka. Product Research Department, Chugai Pharmaceutical Company, Ltd., 200 Kajiwara Kamakura, Kanagawa, Japan. Cancer Chemotherapy and Pharmacology (2006), 57(5), 693-702. Publisher: Springer, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 145:180374 AN 2006:366769 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: To examine the antitumor activity and tolerability of a combination comprising erlotinib and capecitabine in human colorectal, breast and epidermal cancer xenograft models. Further aims of the study were to examine the effects of single-agent erlotinib therapy on tumor growth, and on thymidine phosphorylase (TP) and dihydropyrimidine dehydrogenase (DPD) levels, (enzymes which activate and deactivate capecitabine, resp.) in tumor tissue. Methods: BALB/c nu/nu mice bearing LoVo and HT-29 (colon cancer), A-431 (vulval cancer), and KPL-4 and MAXF401 (breast cancer) human tumors were treated with erlotinib 100 mg/kg/day and/or capecitabine 359 or 90 mg/kg/day, by oral administration once daily for 14 days. Results: The max. tolerated dose (MTD) of erlotinib, formulated in carboxymethylcelluose/Tween 80, was identified as 125 mg/kg/day. Erlotinib at a dose of 100 mg/kg/day achieved significant

tumor-growth inhibition in the, LoVo, KPL-4, and A-431 models. Some inhibition of MAXF401 tumor growth was obsd., but was not significant. In the HT-29 model, erlotinib showed less marked but statistically significant antitumor activity. On day 15, mean tumor-growth inhibition in HT-29, LoVo, KPL-4, MAXF401, and A-431 models was 46, 74, 71, 20, and 85%, resp. Evaluation of erlotinib/capecitabine combination therapy, at sub-optimal doses, in the three erlotinib-sensitive tumor models LoVo, KPL-4 and A-431, demonstrated at least additive activity with the combination compared with the single agents. In the A-431 and LoVo models, the combination of agents had greater antitumor activity than the single agent capecitabine alone at the MTD. Erlotinib in combination with capecitabine was not assocd. with significantly increased toxicity compared with single-agent therapy. Erlotinib 100 mg/kg/day induced significant upregulation of TP and DPD in the LoVo model, a significant upregulation of TP in the HT-29, MAXF401 and A-431 models, but had no obvious effect on TP and DPD levels in the KPL-4 model.
In the A-431 model, selective upregulation of TP by erlotinib 100 mg/kg resulted in an increased TP:DPD ratio. In the LoVo model, immunohistochem. revealed marked upregulation of TP (but not DPD by erlotinib). Conclusions: Erlotinib inhibits tumor growth in a range of human tumor xenograft models, including breast and colorectal cancer (CRC). Erlotinib and capecitabine demonstrated at least additive activity in LoVo, KPL-4 and A-431 tumor models. The antitumor activity of the combination was greater than that of capecitabine alone at the MTD. Erlotinib treatment did affect the TP in the CRC tumor models as confirmed immunohistochem. The findings of this study support clin. evaluation of erlotinib, both as a single agent and in combination with capecitabine, for the treatment of CRC and breast cancer.

Answer 9:

Bibliographic Information

C-fos Assessment as a Marker of Anti-Epidermal Growth Factor Receptor Effect. Jimeno, Antonio; Kulesza, Peter; Kincaid, Erik; Bouaroud, Nadia; Chan, Audrey; Forastiere, Arlene; Brahmer, Julie; Clark, Douglas P.; Hidalgo, Manuel. The Sidney Kimmel Comprehensive Cancer Center, The Johns Hopkins University School of Medicine, Baltimore, MD, USA. Cancer Research (2006), 66(4), 2385-2390. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 144:246770 AN 2006:152634 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Factors predicting sensitivity to epidermal growth factor receptor (EGFR) blockade are largely unknown and new strategies are being sought to individualize cancer therapy. This study evaluated the variation in the expression of the early response gene c-fos as a distal effect of EGFR inhibition and its relationship to antitumor effects. The growth-inhibitory and c-fos-modulating effects of gefitinib and erlotinib in human cancer cell lines (A431, CAL27, HN11, HuCCT1, and Hep2) were detd. Next, these cell lines were xenografted in mice and treated for 14 days with gefitinib (A431 and HuCCT1) or erlotinib (CAL27, HN11, and Hep2). Fine needle aspiration biopsy of tumors was done at baseline and after 14 days of therapy for c-fos assessment. In addn., we tested the feasibility of analyzing this marker in five paired tumor samples from a clin. trial of gefitinib in patients with solid tumors. In culture, gefitinib and erlotinib decreased c-fos mRNA levels in the susceptible cell lines A431, CAL27, and HN11; however, both drugs failed to achieve c-fos inhibition in resistant cells. Gefitinib or erlotinib abrogated the increase in c-fos expression in vivo in EGFR-sensitive A431, CAL27, and HN11 tumors but not in resistant strains. Ex vivo evaluation was feasible and predicted in vivo effects. The feasibility study in paired human tumor biopsies showed that this biomarker can be reliably measured in clin. materials. In summary, variations in c-fos expression reflect the pharmacol. actions of EGFR inhibitors in in vitro and in vivo models.

Answer 10:

Bibliographic Information

Combination Treatment with Erlotinib and Pertuzumab against Human Tumor Xenografts Is Superior to Monotherapy. Friess, Thomas; Scheuer, Werner; Hasmann, Max. Department of Pharmacology, Roche Diagnostics GmbH, Penzberg, Germany. Clinical Cancer Research (2005), 11(14), 5300-5309. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 143:399051 AN 2005:629991 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

In many solid tumors, overexpression of human epidermal growth factor receptors (e.g., HER1/EGFR and HER2) correlates with poor prognosis. Erlotinib (Tarceva) is a potent HER1/EGFR tyrosine kinase inhibitor. Pertuzumab (Omnitarg), a novel HER2-specific, recombinant, humanized monoclonal antibody, prevents heterodimerization of HER2 with other HERs. Both mechanisms disrupt signaling pathways, resulting in tumor growth inhibition. We evaluated whether inhibition of both mechanisms is superior to monotherapy in tumor cell lines expressing different HER levels. Human non-small cell lung cancer (NSCLC) cells (Calu-3: HER1/EGFR 0+, HER2 3+; QG56: HER1/EGFR 2-3+, HER2 0+) and breast cancer cells (KPL-4: HER1/EGFR 2-3+, HER2 3+) were implanted into BALB/c nu/nu mice and severe combined immunodeficient beige mice, resp. Tumor-bearing mice (n = 12 or 15 per group) were treated with vehicle (Captisol or buffer), erlotinib (orally, 50 mg/kg/d), pertuzumab (i.p. 6 mg/kg/wk with a 2-fold loading dose), or erlotinib and pertuzumab for 20 (QG56), 27 (KPL-4), or 49 (Calu-3) days. Drug monotherapy had antitumor activity in all models. Tumor vol. treatment-to-control ratios (TCR) with erlotinib were 0.36 (Calu-3), 0.79 (QG56), and 0.51 (KPL-4). Pertuzumab TCR values were 0.42, 0.51, and 0.64 in Calu-3, QG56, and KPL-4 models, resp. Combination treatment resulted in additive (QG56: TCR 0.39; KPL-4: TCR 0.38) or greater than additive (Calu-3: TCR 0.12) antitumor activity. Serum tumor markers for NSCLC (Cyfra 21.1) and breast cancer (sol. HER2) were markedly inhibited by combination treatment (80-97% in Calu-3 and QG56; 92% in KPL-4), correlating with decreased tumor vol. Overall, erlotinib and pertuzumab are active against various human xenograft models, independently of HER1/EGFR or HER2 expression. A combination of these HER-targeted agents resulted in additive or greater than additive antitumor activity.

Answer 11:

Bibliographic Information

Enhanced sensitivity to the HER1/epidermal growth factor receptor tyrosine kinase inhibitor erlotinib hydrochloride in chemotherapy-resistant tumor cell lines. Dai, Qun; Ling, Yi-He; Lia, Marie; Zou, Yi-Yu; Kroog, Glenn; Iwata, Kenneth K.; Perez-Soler, Roman. Department of Oncology, Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, NY, USA. Clinical Cancer Research (2005), 11(4), 1572-1578. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 143:37988 AN 2005:180845 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Erlotinib (Tarceva, OSI-774) is a potent and specific inhibitor of the HER1/epidermal growth factor receptor (EGFR) tyrosine kinase. In phase II clin. studies, oral erlotinib monotherapy has shown antitumor activity in patients with advanced non-small cell lung cancer, head and neck cancer, and ovarian cancer after the failure of std. chemotherapy. We hypothesized that some tumors treated with multiple cytotoxic therapies may become more dependent on the HER1/EGFR signaling pathways for survival. The growth-inhibitory effect of erlotinib was tested on 10 pairs of chemosensitive, parental, and chemoresistant tumor cell lines. Enhanced sensitivity to erlotinib was obsd. in the doxorubicin-resistant human breast cancer cell line MCF-7, paclitaxel-resistant human ovarian carcinoma cell line A2780, and cisplatin-resistant human cervical carcinoma cell line ME180. The IC50 values of erlotinib in the resistant cell lines were 2- to 20-fold lower than those in the corresponding parental cell lines. This enhanced sensitivity to erlotinib correlated with higher HER1/EGFR and phospho-HER1/EGFR expression when compared with the corresponding parental cell lines. Acquired resistance to cytotoxic agents was not assocd. with cross-resistance to erlotinib. AE-ME180/CDDP-resistant xenografts showed greater sensitivity to erlotinib than parental ME180 xenografts did. Our findings suggest that acquired resistance to cytotoxic therapy in some tumors is assocd. with enhanced sensitivity to HER1/EGFR inhibitors, which correlates with increased HER1/EGFR expression. These data may explain some of the obsd. clin. activity of HER1/EGFR inhibitors in patients previously treated with multiple therapies. HER1/EGFR tyrosine kinase inhibitors may be more effective as second- or third-line treatment for certain patients with tumors that were previously treated with multiple chemotherapy regimens.

Answer 12:

Bibliographic Information

Antitumor activity of erlotinib (OSI-774, Tarceva) alone or in combination in human non-small cell lung cancer tumor xenograft models. Higgins, Brian; Kolinsky, Kenneth; Smith, Melissa; Beck, Gordon; Rashed, Mohammad; Adames, Violeta; Linn, Michael; Wheeldon, Eric; Gand, Laurent; Birnboeck, Herbert; Hoffmann, Gerhard. Department of Oncology, In Vivo Section,

Hoffmann-La Roche Inc, Nutley, NJ, USA. Anti-Cancer Drugs (2004), 15(5), 503-512. Publisher: Lippincott Williams & Wilkins, CODEN: ANTDEV ISSN: 0959-4973. Journal written in English. CAN 141:684 AN 2004:432009 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Our objective was the preclin. assessment of the pharmacokinetics, monotherapy, and combined antitumor activity of the epidermal growth factor receptor (HER1/EGFR) Tyr kinase inhibitor erlotinib in athymic nude mice bearing non-small cell lung cancer (NSCLC) xenograft models. Immunohistochem. detd. the HER1/EGFR status of the NSCLC tumor models. Pharmacokinetic studies assessed blood plasma drug concns. of erlotinib in tumor- and non-tumor-bearing athymic nude mice. These were followed by max. tolerated dose (MTD) studies for erlotinib and each chemotherapy. Erlotinib was then assessed alone and in combination with these chemotherapies in the NSCLC xenograft models. Complete necropsies were performed on most of the animals in each study to further assess antitumor or toxic effects. Erlotinib monotherapy dose-dependently inhibited tumor growth in the H460a tumor model, correlating with circulating levels of drug. There was antitumor activity at the MTD with each agent tested in both the H460a and A549 tumor models (erlotinib 100 mg/kg: 71 and 93% tumor growth inhibition; gemcitabine 120 mg/kg: 93 and 75% tumor growth inhibition; cisplatin 6 mg/kg: 81 and 88% tumor growth inhibition). When each compd. was given at a fraction of the MTD, tumor growth inhibition was suboptimal. Combinations of gemcitabine or cisplatin with erlotinib were assessed at 25% of the MTD to det. efficacy. In both NSCLC models, doses of gemcitabine (30 mg/kg) or cisplatin (1.5 mg/kg) with erlotinib (25 mg/kg) at 25% of the MTD were well tolerated. For the slow growing A549 tumor, there was significant tumor growth inhibition in the gemcitabine/erlotinib and cisplatin/erlotinib combinations (above 100 and 98%, resp.), with partial regressions. For the faster growing H460a tumor, there was significant but less remarkable tumor growth inhibition in these same combinations (86 and 53% resp.).

These results show that in NSCLC xenograft tumors with similar levels of EGFR expression, the antitumor activity of erlotinib is robust both as monotherapy and in combination with chemotherapies.

Answer 13:

Bibliographic Information

Synergistic inhibition of head and neck tumor growth by green tea (-)-epigallocatechin-3-gallate and EGFR tyrosine kinase inhibitor. Zhang Xin; Zhang Hongzheng; Tighiouart Mourad; Lee John E; Shin Hyung J; Khuri Fadlo R; Yang Chung S; Chen Zhuo ' Georgia '; Shin Dong M Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA 30322, USA International journal of cancer. Journal international du cancer (2008), 123(5), 1005-14. Journal code: 0042124. E-ISSN:1097-0215. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, N.I.H., EXTRAMURAL); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 18546267 AN 2008406532 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

One of the mechanisms of the antitumor activity of green tea (-)-epigallocatechin-3-gallate (EGCG) is associated with its effect on epidermal growth factor receptor (EGFR)-mediated signaling transduction pathways. We investigated whether combining EGCG with the EGFR-tyrosine kinase inhibitor (EGFR-TKI) erlotinib may augment erlotinib-induced cell growth inhibition of squamous cell carcinoma of the head and neck (SCCHN) in a mouse xenograft model. In vitro studies with 5 head and neck cancer cell lines revealed that synergistic cell growth inhibition by the combination of EGCG and erlotinib was associated with significantly greater inhibition of pEGFR and pAKT, increased activation of caspases 9, 3 and PARP compared to the inhibition induced by EGCG or erlotinib alone. Erlotinib inhibited phosphorylation of EGFR, stabilizing EGFR at the plasma membrane, whereas EGCG induced EGFR internalization and ubiquitin-degradation, ultimately undermining EGFR signaling. The efficacy of the combination treatment was investigated with nude mice (n = 25) orally gavaged with vehicle control, EGCG, erlotinib or the combination at the same doses for 7 days, followed by subcutaneous injection with Tu212 cells. Animals were continuously administered the agents 5 days weekly for 7 weeks. The combined treatment resulted in significantly greater inhibition of tumor growth and delayed tumor progression as a result of increased apoptosis, decreased cell proliferation and reduced pEGFR and pAKT compared to the single agent treatment groups. Our results suggest a synergistic antitumor effect of a combined treatment with EGCG and erlotinib, and provide a promising regimen for future chemoprevention and treatment of SCCHN.

Answer 14:

Bibliographic Information

Induction of BIM is essential for apoptosis triggered by EGFR kinase inhibitors in mutant EGFR-dependent lung adenocarcinomas. Gong Yixuan; Somwar Romel; Politi Katerina; Balak Marissa; Chmielecki Juliann; Jiang Xuejun; Pao William Pao Laboratory, Human Oncology and Pathogenesis Program, Memorial Sloan-Kettering Cancer Center, New York, New York, United States of America PLoS medicine (2007), 4(10), e294. Journal code: 101231360. E-ISSN:1549-1676. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, N.I.H., EXTRAMURAL); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 17927446 AN 2007648124 MEDLINE
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Abstract

BACKGROUND: Mutations in the epidermal growth factor receptor (EGFR) gene are associated with increased sensitivity of lung cancers to kinase inhibitors like erlotinib. Mechanisms of cell death that occur after kinase inhibition in these oncogene-dependent tumors have not been well delineated. We sought to improve understanding of this process in order to provide insight into mechanisms of sensitivity and/or resistance to tyrosine kinase inhibitors and to uncover new targets for therapy. METHODS AND FINDINGS: Using a panel of human lung cancer cell lines that harbor EGFR mutations and a variety of biochemical, molecular, and cellular techniques, we show that EGFR kinase inhibition in drug-sensitive cells provokes apoptosis via the intrinsic pathway of caspase activation. The process requires induction of the proapoptotic BH3-only BCL2 family member BIM (i.e., BCL2-like 11, or BCL2L11); erlotinib dramatically induces BIM levels in sensitive but not in resistant cell lines, and knockdown of BIM expression by RNA interference virtually eliminates drug-induced cell killing in vitro. BIM status is regulated at both transcriptional and posttranscriptional levels and is influenced by the extracellular signal-regulated kinase (ERK) signaling cascade downstream of EGFR. Consistent with these findings, lung tumors and xenografts from mice bearing mutant EGFR-dependent lung adenocarcinomas display increased concentrations of Bim after erlotinib treatment. Moreover, an inhibitor of antiapoptotic proteins, ABT-737, enhances erlotinib-induced cell death in vitro. CONCLUSIONS: In drug-sensitive EGFR mutant lung cancer cells, induction of BIM is essential for apoptosis triggered by EGFR kinase inhibitors. This finding implies that the intrinsic pathway of caspase activation may influence sensitivity and/or resistance of EGFR mutant lung tumor cells to EGFR kinase inhibition.

Manipulation of the intrinsic pathway could be a therapeutic strategy to enhance further the clinical outcomes of patients with EGFR mutant lung tumors.