Answer 1:

Bibliographic Information

Acquired resistance to EGFR tyrosine kinase inhibitors in cancer cells is mediated by loss of IGF-binding proteins. Guix, Marta; Faber, Anthony C.; Wang, Shizhen Emily; Olivares, Maria Graciela; Song, Youngchul; Qu, Sherman; Rinehart, Cammie; Seidel, Brenda; Yee, Douglas; Arteaga, Carlos L.; Engelman, Jeffrey A. Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN, USA. Journal of Clinical Investigation (2008), 118(7), 2609-2619. Publisher: American Society for Clinical Investigation, CODEN: JCINAO ISSN: 0021-9738. Journal written in English. AN 2008:827487 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Although some cancers are initially sensitive to EGFR tyrosine kinase inhibitors (TKIs), resistance invariably develops. We investigated mechanisms of acquired resistance to the EGFR TKI gefitinib by generating gefitinib-resistant (GR) A431 squamous cancer cells. In GR cells, gefitinib reduced phosphorylation of EGFR, ErbB-3, and Erk but not Akt. These cells also showed hyperphosphorylation of the IGFI receptor (IGFIR) and constitutive assocn. of IRS-1 with PI3K. Inhibition of IGFIR signaling disrupted the assocn. of IRS-1 with PI3K and restored the ability of gefitinib to downregulate PI3K/Akt signaling and to inhibit GR cell growth. Gene expression analyses revealed that GR cells exhibited markedly reduced IGF-binding protein 3 (IGFBP-3) and IGFBP-4 RNA. Addn. of recombinant IGFBP-3 restored the ability of gefitinib to downregulate PI3K/Akt signaling and to inhibit cell growth. Finally, gefitinib treatment of mice with A431 xenografts in combination with an IGFIR-specific monoclonal antibody prevented tumor recurrence, whereas each drug given alone was unable to do so. These data suggest that loss of expression of IGFBPs in tumor cells treated with EGFR TKIs derepresses IGFIR signaling, which in turn mediates resistance to EGFR antagonists. Moreover, combined therapeutic inhibition of EGFR and IGFIR may abrogate this acquired mechanism of drug resistance and is thus worthy of prospective clin. investigation.

Answer 2:

Bibliographic Information

Epidermal Growth Factor Receptor Blockade in Combination with Conventional Chemotherapy Inhibits Soft Tissue Sarcoma Cell Growth In vitro and In vivo. Ren, Wenhong; Korchin, Borys; Zhu, Quan-Sheng; Wei, Caimiao; Dicker, Adam; Heymach, John; Lazar, Alexander; Pollock, Raphael E.; Lev, Dina. Departments of Surgical Oncology, Cancer Biology, Medical Oncology, and Pathology and Division of Quantitative Sciences, University of Texas, M. D. Anderson Cancer Center, Houston, TX, USA. Clinical Cancer Research (2008), 14(9), 2785-2795. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 149:191182 AN 2008:549995 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

PURPOSE: The epidermal growth factor receptor (EGFR) is highly expressed in many human soft tissue sarcomas (STS). However, EGFR blockade has not apparently been used for human STS therapy; therefore, we examd. the in vitro and in vivo effects and the underlying mechanisms before considering EGFR blockade as a therapy for STS patients. Exptl. Design: Human STS tissues and cell lines were used to study EGFR expression and activation. Western blot anal. was used to evaluate effects of EGFR activation on downstream signaling. Cell culture assays were used to assess the effect of EGF stimulation as well as EGFR blockade (using an EGFR tyrosine kinase inhibitor, Iressa; AstraZeneca) on STS cell growth, apoptosis, and chemosensitivity. An in vivo study (HT1080 human fibrosarcoma cell line in nude/nude mice: Iressa, doxorubicin, Iressa + doxorubicin, vehicle) was used to examine tumor growth; pEGFR, proliferating cell nuclear antigen, and terminal deoxyribonucleotide transferase-mediated nick-end labeling staining helped assess the effect of therapy in vivo on STS EGFR activation, proliferation, and apoptosis. RESULTS: EGFR was expressed and activated in STS cell lines and tumors, probably due to ligand binding rather than EGFR mutation. Stimulation caused activation of AKT and mitogen-activated protein kinase pathways. EGFR blockade inhibited these effects and also caused increased apoptosis, a p53-independent G0-G1 cell cycle arrest, and decreased cyclin D1 expression. In vivo, Iressa + doxorubicin had markedly synergistic anti-STS effects. CONCLUSION: EGFR blockade combined with conventional chemotherapy results in anti-human STS activity in

vitro and in vivo, suggesting the possibility that combining these synergistic treatments will improve anti-STS therapy.

Answer 3:

Bibliographic Information

Gefitinib cytotoxicity in non-small cell lung cancer cells is enhanced by low dose cisplatin due to ligand-independent EGFR autophosphorylation. Hosaka, Takamichi; Ohmori, Tohru; Ando, Koichi; Ishida, Hiroo; Kusumoto, Sojiro; Sugiyama, Tomohide; Shirai, Takao; Okuda, Kentaro; Hirose, Takashi; Ohnishi, Tsukasa; Horichi, Naoya; Inoue, Fumiko; Sauo, Nagahiro; Kuroki, Toshio; Nakadate, Toshio; Adachi, Mitsuru. First Department of Internal Medicine, Showa University School of Medicine, 1-5-8, Hatanodai, Shinagawa-ku, Tokyo, Japan. Showa University Journal of Medical Sciences (2007), 19(3), 155-164. Publisher: Showa Medical Association and Showa University, CODEN: SUMSEG ISSN: 0915-6380. Journal written in English. CAN 148:440466 AN 2008:247055 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Epidermal growth factor receptor (EGFR) is a transmembrane receptor tyrosine kinase overexpressed in non-small cell lung cancer (NSCLC) and many other solid tumors. EGFR is activated by specific ligands and various cell stresses, such as oxidative stress and UV irradn. The present study investigates the effect of ligand-independent EGFR activation on gefitinib mediated cytotoxicity using the NSCLC cell line, PC-9. The induction of EGFR autophosphorylation by non-cytotoxic levels of hydrogen peroxide (H2O2) and cisplatin (CDDP) is completely inhibited by 100 nM gefitinib. Pretreatment of cells with both H2O2 and CDDP enhances gefitinib cytotoxicity in vitro. The growth inhibitory effect of gefitinib was examd. in vivo using the xenografted severe combined immunodeficiency (SCID) mouse model. PC-9 cells were pretreated with/without a low dose of CDDP (1 μM) for 1h and injected s.c. into the right flank of SCID mice. Following the appearance of measurable tumors mice were treated by s.c. injection into the left flank with / without 10 mg / kg gefitinib for 4 days. Pretreatment with CDDP enhanced tumor growth by 20-30% compared to the control. Subsequent treatment with gefitinib resulted in disappearance of the tumor mass by day 10 in the CDDP-pretreated group and by day 16 in the control group. There was no reappearance of tumors in the CDDP-pretreated group. By comparison, tumors reappeared in the non-pretreated group by day 20 in 4/5 animals. These results suggest that chemotherapy may enhance tumor growth due to ligand-independent EGFR activation and that combination chemotherapy may result in enhanced sensitivity of tumors to the sequential administration of gefitinib.

Answer 4:

Bibliographic Information

Inhibition of epidermal growth factor receptor signalling reduces hypercalcaemia induced by human lung squamous-cell carcinoma in athymic mice. Lorch, G.; Gilmore, J. L.; Koltz, P. F.; Gonterman, R. M.; Laughner, R.; Lewis, D. A.; Konger, R. L.; Nadella, K. S.; Toribio, R. E.; Rosol, T. J.; Foley, J. Department of Veterinary Biosciences, Ohio State University, Columbus, OH, USA. British Journal of Cancer (2007), 97(2), 183-193. Publisher: Nature Publishing Group, CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 148:118267 AN 2007:752924 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The purpose of this study was to evaluate the role of the epidermal growth factor receptor (EGFR) in parathyroid hormone-related protein (PTHrP) expression and humoral hypercalcemia of malignancy (HHM), using two different human squamous-cell carcinoma (SCC) xenograft models. A randomized controlled study in which nude mice with RWGT2 and HARA xenografts received either placebo or gefitinib 200 mg kg-1 for 3 days after developing HHM. Effectiveness of therapy was evaluated by measuring plasma calcium and PTHrP, urine cAMP/creatinine ratios, and tumor vols. The study end point was at 78 h. The lung SCC lines, RWGT2 and HARA, expressed high levels of PTHrP mRNA as well as abundant EGFR protein, but very little erbB2 or erbB3. Both lines expressed high transcript levels for the EGFR ligand, amphiregulin (AREG), as well as, substantially lower levels of transforming growth factor-α (TGF-α), and heparin binding-epidermal growth factor (HB-EGF) mRNA. Parathyroid hormone-related protein gene expression in both lines was reduced 40-80% after treatment with 1 μM of EGFR tyrosine kinase inhibitor PD153035 and pptg. antibodies to AREG.

Gefitinib treatment of hypercalcemia mice with RWGT2 and HARA xenografts resulted in a significant redn. of plasma total calcium concns. by 78 h. Autocrine AREG stimulated the EGFR and increased PTHrP gene expression in the RWGT2 and HARA lung SCC lines. Inhibition of the EGFR pathway in two human SCC models of HHM by an anilinoquinazoline demonstrated that the EGFR tyrosine kinase is a potential target for antihypercalcemic therapy.

Answer 5:

Bibliographic Information

Dual inhibition of EGFR and VEGFR pathways in combination with irradiation: antitumor supra-additive effects on human head and neck cancer xenografts. Bozec, A.; Formento, P.; Lassalle, S.; Lippens, C.; Hofman, P.; Milano, G. Oncopharmacology Unit, Centre Antoine-Lacassagne, Nice, Fr. British Journal of Cancer (2007), 97(1), 65-72. Publisher: Nature Publishing Group, CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 147:398147 AN 2007:689511 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The aim of this study was to investigate the effects of combining antiangiogenic treatment, epidermal growth factor receptor (EGFR) targeting and irradn. (RT). We evaluated AZD2171, a highly potent, orally active, vascular endothelial growth factor (VEGF) signaling inhibitor, gefitinib, an EGFR tyrosine kinase inhibitor and RT. The antitumor efficacy of these treatments, administered alone and in combination for 2 wk, was assessed in a VEGF-secreting human head and neck tumor cell line, CAL33 that highly expresses EGFR, established as xenografts (250 mm3) in nude mice. The median time to reach a tumor vol. of 1000 mm3 was significantly increased for AZD2171 or gefitinib alone compared with the control. Greater inhibition of tumor growth was seen with the combination of AZD2171 + gefitinib compared with either drug alone, and the triple combination compared with either AZD2171 + gefitinib or RT alone. The intensity of endothelial cell staining was slightly reduced by each agent given alone, and markedly diminished by the double or triple combination. The triple combination almost completely abolished cell proliferation. The marked RT-induced enhancement in the DNA-repair enzyme ERCC1 expression was totally abolished by the triple combination. This observation could help to explain the supra-additive antitumor effect produced by this combination and could provide a basis for future innovative clin. trials.

Answer 6:

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 7:

Bibliographic Information

Treatment of human epidermal growth factor receptor 2-overexpressing breast cancer xenografts with multiagent HER-targeted therapy. Arpino, Grazia; Gutierrez, Carolina; Weiss, Heidi; Rimawi, Mothaffar; Massarweh, Suleiman; Bharwani, Lavina; De Placido, Sabino; Osborne, C. Kent; Schiff, Rachel. Breast Center and the Dan L. Duncan Cancer Center, Baylor College of Medicine, Houston, TX, USA. Journal of the National Cancer Institute (2007), 99(9), 694-705. Publisher: Oxford University Press, CODEN: JNCIEQ ISSN: 0027-8874. Journal written in English. CAN 148:393927 AN 2007:652807 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Human epidermal growth factor receptor 2 (HER2) is a member of the HER signaling pathway. HER inhibitors partially block HER signaling and tumor growth in preclin. breast cancer models. We investigated whether blockade of all HER homo- and heterodimer pairs by combined treatment with several inhibitors could more effectively inhibit tumor growth in such models. Mice carrying xenograft tumors of HER2-overexpressing MCF7/HER2-18 (HER2-transfected) or BT474 (HER2-amplified) cells were treated with estrogen supplementation or estrogen withdrawal, alone or combined with tamoxifen. One to three HER inhibitors (pertuzumab, trastuzumab, or gefitinib) could also be added ($n \geq 8$ mice per group). Tumor vols., HER signaling, and tumor cell proliferation and apoptosis were assessed. Results were analyzed with the t test or Wilcoxon rank sum test and survival anal. methods. All statistical tests were two-sided. Median time to tumor progression was 21 days for mice receiving estrogen and 28 days for mice receiving estrogen and pertuzumab (difference = 7 days; P = .001; hazard ratio [HR] of progression in mice receiving estrogen and pertuzumab vs. mice receiving estrogen = 0.27, 95% confidence interval [CI] = 0.09 to 0.77). Addn. of gefitinib and trastuzumab to estrogen and pertuzumab increased this time to 49 days (difference = 21 days; P = .004; HR of progression = 0.28, 95% CI = 0.10 to 0.76). MCF7/HER2-18 tumors disappeared completely and did not progress (for ≥189 days) after combination treatment with pertuzumab, trastuzumab, and gefitinib plus tamoxifen (19 of 20 mice) or plus estrogen withdrawal (14 of 15 mice). Both combination treatments induced apoptosis and blocked HER signaling and proliferation in tumor cells better than any single agent or dual combination. All BT474 tumors treated with pertuzumab, trastuzumab, and gefitinib disappeared rapidly, regardless of endocrine therapy, and no tumor progression was obsd. for 232 days.

Combined treatment with gefitinib, trastuzumab, and pertuzumab to block signals from all HER homo- and heterodimers inhibited growth of HER2-overexpressing xenografts statistically significantly better than single agents and dual combinations.

Answer 8:

Bibliographic Information

Effect of Epidermal Growth Factor Receptor Inhibitor Class in the Treatment of Head and Neck Cancer with Concurrent Radiochemotherapy In vivo. Feng, Felix Y.; Lopez, Carlos A.; Normolle, Daniel P.; Varambally, Sooryanarayana; Li, Xiaoxin; Chun, Patrick Y.; Davis, Mary A.; Lawrence, Theodore S.; Nyati, Mukesh K. Department of Radiation Oncology, University of Michigan Medical Center, Ann Arbor, MI, USA. Clinical Cancer Research (2007), 13(8), 2512-2518. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 147:180771 AN 2007:423505 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: To optimally integrate epidermal growth factor receptor (EGFR) inhibitors into the clin. treatment of head and neck cancer, two important questions must be answered: (a) does EGFR inhibition add to the effects of radiochemotherapy, and (b) if so, which method of inhibiting EGFR is superior (an EGFR antibody vs. a small mol. tyrosine kinase inhibitor) We designed an in vivo study to address these questions. Exptl. Design: Nude mice with UMSCC-1 head and neck cancer xenografts received either single, double, or triple agent therapy with an EGFR inhibitor (either cetuximab or gefitinib), gemcitabine, and/or radiation for 3 wk. Tumor vols. and animal wts. were measured for up to 15 wk. Immunoblotting and immunofluorescent staining were done on tumors treated with either cetuximab or gefitinib alone. Results: The addn. of an EGFR inhibitor significantly delayed the tumor vol. doubling time, from a median of 40 days with radiochemotherapy (gemcitabine and radiation) alone, to 106 days with cetuximab and 66 days with gefitinib (both P < 0.005). Cetuximab resulted in significantly less wt. loss than gefitinib. Immunoblot anal. and immunofluorescent staining of tumors show that although levels of phosphorylated AKT and extracellular signal-regulated kinase were decreased similarly in response to cetuximab or gefitinib, cetuximab caused prolonged suppression of pEGFR, pSTAT3, and BclXL compared with gefitinib. Conclusions: EGFR inhibition, particularly with cetuximab, improves the effectiveness of radiochemotherapy in this model of head and neck cancer. The correlation of response with prolonged suppression of EGFR, STAT3, and BclXL offers the possibility that these may be candidate biomarkers for response.

Answer 9:

Bibliographic Information

A phase I trial of intermittent high-dose gefitinib and fixed-dose docetaxel in patients with advanced solid tumors. Fury, Matthew G.; Solit, David B.; Su, Yungpo Bernard; Rosen, Neal; Sirotnak, F. M.; Smith, Robert P.; Azzoli, Christopher G.; Gomez, Jorge E.; Miller, Vincent A.; Kris, Mark G.; Pizzo, Barbara A.; Henry, Roxanne; Pfister, David G.; Rizvi, Naiyer A. Memorial Sloan-Kettering Cancer Center, Division of Solid Tumor Oncology, Thoracic Oncology Service, Department of Medicine, Weill Medical College of Cornell University, New York, NY, USA. Cancer Chemotherapy and Pharmacology (2007), 59(4), 467-475. Publisher: Springer, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 146:394538 AN 2007:57212 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: Based on our mouse xenograft model demonstrating that intermittent high-dose gefitinib sensitizes tumors to subsequent treatment with taxanes, we initiated this phase I trial to explore docetaxel in combination with escalating doses of intermittent gefitinib (Iressa) given prior to docetaxel. Methods: This was a phase I study where patients with advanced cancer were treated with escalating doses of gefitinib (1,000, 1,500, 2,250, 3,000 mg) on days 1 and 2 followed by docetaxel (75 mg/m2) on day 3 of a 21 day cycle. Gefitinib pharmacokinetic data were obtained on days 1, 2, and 3 of cycles 1 and 2 at each dose level. Results: 18 patients were enrolled in this study with the most frequent tumor types being non-small cell lung cancer and head and neck squamous cell cancer. The dose-limiting toxicity was neutropenia (n = 1 at dose level 2, n = 2 at dose level 4). Rash, diarrhea, and fatigue were the most common grade 1-2 toxicities. Pharmacokinetic data indicated no accumulation of gefitinib between cycles 1 and 2 and no clear correlation between gefitinib plasma levels and toxicity. Partial responses were obsd. in one patient with head and neck squamous cell carcinoma and one patient with anaplastic thyroid cancer. Conclusion: The recommended dose for phase II studies is gefitinib 2,250 mg on days 1 and 2, followed by docetaxel 75 mg/m2 on day 3.

Answer 10:

Bibliographic Information

Antitumor Activity of the Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitor Gefitinib (ZD1839, Iressa) in Non-Small Cell Lung Cancer Cell Lines Correlates with Gene Copy Number and EGFR Mutations but not EGFR Protein Levels. Helfrich, Barbara A.; Raben, David; Varella-Garcia, Marileila; Gustafson, Dan; Chan, Daniel C.; Bemis, Lynne; Coldren, Chris; Baron, Anna; Zeng, Chan; Franklin, Wilbur A.; Hirsch, Fred R.; Gazdar, Adi; Minna, John; Bunn, Paul A., Jr. Tobacco Related Malignancy Program,e Medicine and Biometrics, University of Colorado Cancer Center, Denver, CO, USA. Clinical Cancer Research (2006), 12(23), 7117-7125. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 146:308588 AN 2006:1264180 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: Recognition that the epidermal growth factor receptor (EGFR) was a therapeutic target in non-small cell lung cancer (NSCLC) and other cancers led to development of the small-mol. receptor tyrosine kinase inhibitors gefitinib and erlotinib. Clin. trials established that EGFR tyrosine kinase inhibitors produced objective responses in a minority of NSCLC patients. We examd. the sensitivity of 23 NSCLC lines with wild-type or mutated EGFR to gefitinib to det. genes/proteins related to sensitivity, including EGFR and HER2 cell surface expression, phosphorylated EGFR expression, EGFR gene copy no., and EGFR mutational status. Downstream cell cycle and signaling events were compared with growth-inhibitory effects. Exptl. Design: We detd. gefitinib sensitivity by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assays, EGFR expression by fluorescence-activated cell sorting and immunohistochem., phosphorylated EGFR by Western blotting, EGFR gene copy no. by fluorescence in situ hybridization, and EGFR mutation by sequencing. The cellular effects of gefitinib on cell cycle were detd. by flow cytometry and the mol. effects of gefitinib EGFR inhibition on downstream signal proteins by Western blotting. Gefitinib in vivo effects were evaluated in athymic nude mice bearing sensitive and resistant NSCLC xenografts. Results: There was a significant correlation between EGFR gene copy no., EGFR gene mutations, and gefitinib sensitivity. EGFR protein was necessary but not sufficient for predicting sensitivity. Gefitinib-sensitive lines showed a G1 cell cycle arrest and inactivation of downstream signaling proteins; resistant cell lines had no changes. The in vivo effects mirrored the in vitro effects. Conclusions: This panel of NSCLC lines characterized for gefitinib response was used to identify predictive mol. markers of response to gefitinib. Several of these have subsequently been shown to identify NSCLC patients likely to benefit from gefitinib therapy.

Answer 11:

Bibliographic Information

Molecular basis for sensitivity and acquired resistance to gefitinib in HER2-overexpressing human gastric cancer cell lines derived from liver metastasis. Yokoyama, H.; Ikehara, Y.; Kodera, Y.; Ikehara, S.; Yatabe, Y.; Mochizuki, Y.; Koike, M.; Fujiwara, M.; Nakao, A.; Tatematsu, M.; Nakanishi, H. Division of Oncological Pathology, Aichi Cancer Center Research Institute, 1-1 Kanokoden, Chikusa-ku, Nagoya, Japan. British Journal of Cancer (2006), 95(11), 1504-1513. Publisher: Nature Publishing Group, CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 146:308561 AN 2006:1244433 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Gastric cancer metastasised to the liver was found to overexpress HER2 at a significantly higher incidence than primary gastric cancers. The purpose of the present study was to investigate the possibility of mol. therapy targeting HER2 overexpression in gastric cancer liver metastasis. We developed three new HER2-overexpressing gastric cancer cell lines (GLM-1, GLM-2, GLM-4) without epidermal growth factor receptor (EGFR) mutations derived from such liver metastasis, two of which had HER2 gene amplifications. All these GLM series of cell lines were highly sensitive to gefitinib in vitro, a specific inhibitor of EGFR tyrosine kinase (Iressa) rather than anti-HER2 antibody trastuzumab (Herceptin), whereas most of the HER2 low-expressing counterparts were not. In these HER2-overexpressing GLM series, protein kinase B (Akt), but not extracellular signal-regulated kinase 1/2 (ERK1/2), was constitutively phosphorylated, and gefitinib efficiently inhibited this Akt phosphorylation, induced strong apoptosis in vitro and exhibited antitumor activity in tumor xenografts in nude mice. This gefitinib-mediated antitumor effect in xenograft was significantly potentiated by trastuzumab treatment. On the other hand, gefitinib-resistant cells (GLM-1R) exhibited increased EGFR expression, followed by constitutive activation of mitogen-activated protein kinase (MAPK) pathway. These results suggest that the antitumor effect of gefitinib is due to the effective inhibition of HER2-driven constitutive activation of phosphatidylinositol-3-kinase (PI3K)/Akt pathway, and that the acquired resistance to gefitinib is due to the constitutive activation of Ras/MAPK pathway in compensation for PI3K/Akt pathway. Gastric cancer liver metastasis with HER2 overexpression would be a potential mol. target for gefitinib and trastuzumab.

Answer 12:

Bibliographic Information

Enhanced tumour antiangiogenic effects when combining gefitinib with the antivascular agent ZD6126. Bozec, A.; Lassalle, S.; Gugenheim, J.; Fischel, J.-L.; Formento, P.; Hofman, P.; Milano, G. Oncopharmacology Unit, Centre Antoine-Lacassagne,

Nice, Fr. British Journal of Cancer (2006), 95(6), 722-728. Publisher: Nature Publishing Group, CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 146:492712 AN 2006:932678 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Current exptl. and clin. knowledge supports the optimization of endothelial cell targeting using a strategy combining anti-EGFR drugs with antivascular agents. The purpose of the present study was to examine the effects of the assocn. of ZD6126, an antivascular microtubule-destabilizing agent, with gefitinib and irradn. on the growth of six head and neck human cancer cell lines xenografted in nude mice and to study predictive and mol. factors responsible for antitumor effects. CAL33- and Hep-2-grafted cell lines were the most sensitive to ZD6126 treatment, with VEGF levels significantly higher (P = 0.0336) in these tumor xenografts compared to Detroit 562- and CAL27-grafted cell lines with relatively low VEGF levels that were not sensitive to ZD6126. In contrast, neither IL8 levels nor EGFR expression was linked to the antitumor effects of ZD6126. ZD6126 in combination with gefitinib resulted in a synergistic cytotoxic interaction with greater antitumor effects than gefitinib alone. The synergistic interaction between ZD6126 and gefitinib was corroborated by a significant decrease in CD31 labeling. The present study may serve for future innovative clin. applications, as it suggests that VEGF tumor levels are possible predictors for ZD6126 antitumor efficacy. It also supports the notion of antitumor supra-additivity when combining gefitinib and ZD6126, and identifies neoangiogenesis as the main determinant of this synergistic combination.

Answer 13:

Bibliographic Information

YM-359445, an Orally Bioavailable Vascular Endothelial Growth Factor Receptor-2 Tyrosine Kinase Inhibitor, Has Highly Potent Antitumor Activity against Established Tumors. Amino, Nobuaki; Ideyama, Yukitaka; Yamano, Mayumi; Kuromitsu, Sadao; Tajinda, Katsuinori; Samizu, Kiyohiro; Hisamichi, Hiroyuki; Matsuhisa, Akira; Shirasuna, Kenna; Kudoh, Masafumi; Shibasaki, Masayuki. Pharmacology Laboratories, Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co. Ltd., Tsukuba, Japan. Clinical Cancer Research (2006), 12(5), 1630-1638. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 145:241062 AN 2006:205529 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: The vascular endothelial growth factor receptor-2 (VEGFR2) tyrosine kinase has been implicated in the pathol. angiogenesis assocd. with tumor growth. YM-359445 was a (3Z)-3-quinolin-2(1H)-ylidene-1,3-dihydro-2H-indol-2-one deriv. found while screening based on the inhibition of VEGFR2 tyrosine kinase. The aim of this study was to analyze the efficacy of this compd. both in vitro and in vivo. Exptl. Design: We tested the effects of YM-359445 on VEGFR2 tyrosine kinase activity, cell proliferation, and angiogenesis. The antitumor activity of YM-359445 was also tested in nude mice bearing various established tumors and compared with other VEGFR2 tyrosine kinase inhibitors (ZD6474, CP-547632, CGP79787, SU11248, and AZD2171), a cytotoxic agent (paclitaxel), and an epidermal growth factor receptor tyrosine kinase inhibitor (gefitinib). Results: The IC50 of YM-359445 for VEGFR2 tyrosine kinase was 0.0085 μmol/L. In human vascular endothelial cells, the compd. inhibited VEGF-dependent proliferation, VEGFR2 autophosphorylation, and sprout formation at concns. of 0.001 to 0.003 μmol/L. These concns. had no direct cytotoxic effect on cancer cells. In mice bearing various established tumors, including paclitaxel-resistant tumors, once daily oral administration of YM-359445 at doses of 0.5 to 4 mg/kg not only inhibited tumor growth but also reduced its vasculature. YM-359445 had greater antitumor activity than other VEGFR2 tyrosine kinase inhibitors. Moreover, in human lung cancer A549 xenografts, YM-359445 markedly regressed the tumors (73%) at a dose of 4 mg/kg, whereas gefitinib caused no regression even at 100 mg/kg. Conclusion: Our results show that YM-359445 is more potent than orally bioavailable VEGFR2 tyrosine kinase inhibitors, which leads to great expectations for clin. applicability.

Answer 14:

Bibliographic Information

Minimal contribution of desmethyl-gefitinib, the major human plasma metabolite of gefitinib, to epidermal growth factor

receptor (EGFR)-mediated tumour growth inhibition. McKillop, D.; Guy, S. P.; Spence, M. P.; Kendrew, J.; Kemp, J. V.; Bushby, N.; Wood, P. G.; Barnett, S.; Hutchison, M. AstraZeneca, Alderley Park, Macclesfield, UK. Xenobiotica (2006), 36(1), 29-39. Publisher: Taylor & Francis Ltd., CODEN: XENOBH ISSN: 0049-8254. Journal written in English. CAN 145:305800 AN 2006:186341 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Desmethyl-gefitinib is a major metabolite of gefitinib obsd. in human plasma at concns. similar to those of gefitinib. The epidermal growth factor receptor (EGFR)-related inhibitory effects of gefitinib and desmethyl-gefitinib have been compared both in vitro, using enzyme kinase assays and tumor cell growth inhibition, and in vivo by assessment of tumor xenografts growth inhibition in the mouse. Both gefitinib (IC50 = 0.022 μM) and its desmethyl metabolite (0.036 μM) inhibited subcellular EGFR tyrosine kinase activity with a similar potency and selectivity. However, desmethyl-gefitinib (IC50 = 0.76 μM) was 15 times less active than gefitinib (0.049 μM) against EGF-stimulated KB cell growth in a whole cell assay. Following a preliminary pharmacokinetic study to compare apparent oral bioavailability, gefitinib (75 mg kg-1) and desmethyl-gefitinib (150 mg kg-1) were administered orally for 15 days to female nude mice bearing LoVo tumor xenografts. Tumor concns. of gefitinib (AUC = 300 μg h g-1) were much higher than those of desmethyl-gefitinib (44.3 μg h g-1), although plasma concns. of gefitinib (48.4 μg h ml-1) and desmethyl-gefitinib (39.0 μg h ml-1) were quite similar at these dose levels. Gefitinib produced significant tumor growth inhibition throughout the course of the study ultimately resulting in a 50% decrease (compared with controls) by day 15. In contrast, although present at comparable plasma levels, desmethyl-gefitinib had little effect on tumor growth and is, therefore, considered unlikely to contribute significantly to the therapeutic activity of gefitinib in the clin. situation.

Answer 15:

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 16:

Bibliographic Information

Zoledronic acid cooperates with a cyclooxygenase-2 inhibitor and gefitinib in inhibiting breast and prostate cancer. Melisi, Davide; Caputo, Rosa; Damiano, Vincenzo; Bianco, Roberto; Veneziani, Bianca Maria; Bianco, A. Raffaele; De Placido, Sabino;

Ciardiello, Fortunato; Tortora, Giampaolo. Cattedra di Oncologia Medica, Dipartimento di Endocrinologia e Oncologia Molecolare e Clinica, Universita di Napoli Federico II, Naples, Italy. Endocrine-Related Cancer (2005), 12(4), 1051-1058. Publisher: Society for Endocrinology, CODEN: ERCAE9 ISSN: 1351-0088. Journal written in English. CAN 145:431 AN 2006:78820 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Biphosphonates (BPs) are widely used to inhibit osteoclastic activity in malignant diseases such as bone metastatic breast and prostate carcinoma. Recent studies reported that BPs could also cause a direct antitumor effect, probably due to their ability to interfere with several intracellular signaling mols. The enzyme cyclooxygenase-2 (COX-2) and the epidermal growth factor receptor (EGFR) play an important role in the control of cancer cell growth and inhibitors of COX-2 and EGFR have shown antitumor activity in vitro and in vivo in several tumor types. We, and others, have previously shown that EGFR and COX-2 may be directly related to each other and that their selective inhibitors may have a cooperative effect. In the present study we have evaluated the combined effect of zoledronic acid, the most potent nitrogen-contg. BP, with the COX-2 inhibitor SC-236 and the selective EGFR-tyrosine kinase inhibitor gefitinib, on breast and prostate cancer models in vitro and in xenografted nude mice. We show that combination of zoledronic acid with SC-236 and gefitinib causes a cooperative antitumor effect accompanied by induction of apoptosis and regulation of the expression of mitogenic factors, proangiogenic factors and cell cycle controllers both in vitro and in xenografted nude mice. The modulatory effect on protein expression and the inhibitory effect on tumor growth is much more potent when the three agents are used together. Since studies are ongoing to explore the antitumor effect of zoledronic acid, our results provide new insights into the mechanism of action of these agents and a novel rationale to translate this feasible combination treatment strategy into a clin. setting.

Answer 17:

Bibliographic Information

Synergistic Antitumor Activity of Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Gefitinib and IFN-α in Head and Neck Cancer Cells In vitro and In vivo. Bruzzese, Francesca; Di Gennaro, Elena; Avallone, Antonio; Pepe, Stefano; Arra, Claudio; Caraglia, Michele; Tagliaferri, Pierosandro; Budillon, Alfredo. Experimental Pharmacology Unit, Department of Experimental Oncology, National Cancer Institute G. Pascale, Naples, Italy. Clinical Cancer Research (2006), 12(2), 617-625. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 145:55479 AN 2006:63634 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: Epidermal growth factor receptor (EGFR) overexpression has been implicated in the development of head and neck squamous cell carcinomas (HNSCC) and represents a potential therapeutic target for this disease. We have reported previously that growth inhibitory concns. of IFN-α enhance the expression and activity of EGFR and that this effect could represent an escape mechanism to the growth inhibition and apoptotic cell death induced by IFN-α. In this study, we investigate whether the combination of IFN-α and gefitinib (Iressa, AstraZeneca Pharmaceuticals, Macclesfield, United Kingdom), a selective EGFR tyrosine kinase inhibitor, might have a cooperative antitumor effect on HNSCC-derived cell lines. Exptl. Design: The interaction of IFN-α and gefitinib was evaluated in vitro on HNSCC-derived cell lines by median drug effect anal. calcg. a combination index with CalcuSyn software and in vivo by using HNSCC xenografts in nude mice. The mechanism of gefitinib and IFN-α interactions was also studied by anal. of cell cycle kinetics, apoptosis assays, and Western blotting of EGFR signal transduction components. Results: Simultaneous exposure to gefitinib and IFN-α produced synergistic antiproliferative and proapoptotic effects compared with single drug treatment. Furthermore, daily treatment of gefitinib (50 mg/kg p.o.) in combination with an IFN-α regimen (50,000 units s.c. three times weekly) induced tumor growth delay and increased survival rate on established HNSCC xenografts in nude mice. Moreover, the concomitant treatment with gefitinib suppressed the stimulation of extracellular signal-regulated kinase phosphorylation/activity induced by IFN-α both in vitro and in vivo. Conclusion: The obsd. cooperative antitumor effects could be, at least in part, explained by the inhibition exerted by gefitinib of an IFN-α-induced EGF-dependent survival pathway, which involves extracellular signal-regulated kinase activation. These results provide a rationale for the clin.

evaluation of gefitinib in combination with IFN-α in HNSCC.

Answer 18:

Bibliographic Information

Novel Toll-Like Receptor 9 Agonist Induces Epidermal Growth Factor Receptor (EGFR) Inhibition and Synergistic Antitumor Activity with EGFR Inhibitors. Damiano, Vincenzo; Caputo, Rosa; Bianco, Roberto; D'Armiento, Francesco P.; Leonardi, Antonio; De Placido, Sabino; Bianco, A. Raffaele; Agrawal, Sudhir; Ciardiello, Fortunato; Tortora, Giampaolo. Departimento di Endocrinologia e Oncologia Molecolare e Clinica, Universita di Napoli Federico II, Naples, Italy. Clinical Cancer Research (2006), 12(2), 577-583. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 145:55475 AN 2006:63629 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: Immunostimulating Toll-like receptor 9 (TLR9) agonists cause antitumor activity interfering also with cancer proliferation and angiogenesis by mechanisms still incompletely understood. We hypothesized that modified TLR9 agonists could impair epidermal growth factor receptor (EGFR) signaling and, by this means, greatly enhance EGFR inhibitors effect, acting on both the receptor targeting and the immunol. arm. Exptl. Design: We used a novel second-generation, modified, immunomodulatory TLR9 agonist (IMO), alone and in combination with the anti-EGFR monoclonal antibody cetuximab or tyrosine kinase inhibitor gefitinib, on the growth of GEO and cetuximab-resistant derivs. GEO-CR colon cancer xenografts. We have also evaluated the expression of several proteins crit. for cell proliferation, apoptosis, and angiogenesis, including EGFR, mitogen-activated protein kinase, Akt, bcl-2, cyclooxygenase-2, vascular endothelial growth factor, and nuclear factor-κB. Results: IMO inhibited GEO growth and signaling by EGFR and the other proteins crit. for cell proliferation and angiogenesis. IMO plus the anti-EGFR antibody cetuximab synergistically inhibited tumor growth, signaling proteins, and microvessel formation. EGFR signaling inhibition by IMO is relevant because IMO cooperated also with EGFR tyrosine kinase inhibitor gefitinib in GEO tumors, while it was inactive against GEO-CR xenografts. On the other hand, IMO boosted the non-EGFR-dependent cetuximab activity, causing a cooperative antitumor effect in GEO-CR cells. Finally, combination of IMO, cetuximab and chemotherapeutic irinotecan eradicated the tumors in 90% of mice. Conclusion: IMO interferes with EGFR-related signaling and angiogenesis and has a synergistic antitumor effect with EGFR inhibitors, esp. with cetuximab, boosting both the EGFR dependent and independent activity of this agent. Moreover, this therapeutic strategy could be translated in patients affected by colorectal cancer.

Answer 19:

Bibliographic Information

Synergistic Effects of Gemcitabine and Gefitinib in the Treatment of Head and Neck Carcinoma. Chun, Patrick Y.; Feng, Felix Y.; Scheurer, Ashley M.; Davis, Mary A.; Lawrence, Theodore S.; Nyati, Mukesh K. Department of Radiation Oncology, University of Michigan Medical School, Ann Arbor, MI, USA. Cancer Research (2006), 66(2), 981-988. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 144:100392 AN 2006:55803 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Although the combination of gemcitabine and radiation produces a high frequency of complete responses in the treatment of locally advanced head and neck cancer, substantial toxicity suggests that an improvement in the therapeutic index is required. The purpose of this study was to det. if gefitinib could improve the efficacy of gemcitabine and if drug schedule is important. We hypothesized that gemcitabine followed by gefitinib would be superior to the opposite order because of both cell cycle and growth factor signaling interactions. Using UMSCC-1 cells in vitro, we confirmed that gefitinib arrested cells in G1 and suppressed phospho-epidermal growth factor receptor (pY845EGFR) and that gemcitabine arrested cells in S phase and stimulated pY845EGFR. The schedule of gemcitabine followed by gefitinib caused arrest of cells in S phase. Gefitinib suppressed gemcitabine-mediated pY845EGFR stimulation. This schedule caused decreased pS473AKT, increased poly(ADP-ribose) polymerase cleavage, and increased apoptosis compared with gemcitabine alone. The schedule of gefitinib followed by gemcitabine also caused suppression of pY845EGFR but arrested cells in G1. This schedule in which gefitinib was used first was assocd. with stable levels of pS473AKT and minimal poly(ADP-ribose) polymerase cleavage and apoptosis. These results were reflected in expts. in nude mice bearing UMSCC-1 xenografts, in which there was greater tumor regression and apoptosis when animals received gemcitabine followed by gefitinib during

the first week of therapy. These findings suggest that the schedule of gemcitabine followed by gefitinib may increase the therapeutic index over gemcitabine alone and, combined with clin. data, encourage exploration of combination of gemcitabine, EGFR inhibitors, and radiation.

Answer 20:

Bibliographic Information

Epithelial membrane protein-1 is a biomarker of gefitinib resistance. Jain, Anjali; Tindell, Charles A.; Laux, Isett; Hunter, Jacob B.; Curran, John; Galkin, Anna; Afar, Daniel E.; Aronson, Nina; Shak, Steven; Natale, Ronald B.; Agus, David B. Cedars-Sinai Medical Center, Louis Warschaw Prostate Cancer Center, Los Angeles, CA, USA. Proceedings of the National Academy of Sciences of the United States of America (2005), 102(33), 11858-11863. Publisher: National Academy of Sciences, CODEN: PNASA6 ISSN: 0027-8424. Journal written in English. CAN 143:222035 AN 2005:955379 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We describe a mol. resistance biomarker to gefitinib, epithelial membrane protein-1 (EMP-1). Gefitinib is a small-mol. inhibitor that competes for the ATP-binding site on EGF receptor (EGFR) and has been approved for patients with advanced lung cancers. Treatment with gefitinib has resulted in clin. benefit in patients, and, recently, heterozygous somatic mutations within the EGFR catalytic domain have been identified as a clin. correlate to objective response to gefitinib. However, clin. resistance to gefitinib limits the utility of this therapeutic to a fraction of patients, and objective clin. responses are rare. We aimed to assess the mol. phenotype and mechanism of in vivo gefitinib resistance in xenograft models and in patient samples. We generated in vivo gefitinib-resistance models in an adenocarcinoma xenograft model by serially passaging tumors in nude mice in presence of gefitinib until resistance was acquired. EMP-1 was identified as a surface biomarker whose expression correlated with acquisition of gefitinib resistance. EMP-1 expression was further correlated with lack of complete or partial response to gefitinib in lung cancer patient samples as well as clin. progression to secondary gefitinib resistance. EMP-1 expression and acquisition of gefitinib clin. resistance was independent of gefitinib-sensitizing EGFR somatic mutations. This report suggests the role of the adhesion mol., EMP-1, as a biomarker of gefitinib clin. resistance, and further suggests a probable cross-talk between this mol. and the EGFR signaling pathway.

Answer 21:

Bibliographic Information

Antitumor effect of gefitinib ('Iressa') on esophageal squamous cell carcinoma cell lines in vitro and in vivo. Hara, Fumikata; Aoe, Motoi; Doihara, Hiroyoshi; Taira, Naruto; Shien, Tadahiko; Takahashi, Hirotoshi; Yoshitomi, Seiji; Tsukuda, Kazunori; Toyooka, Shinichi; Ohta, Tetsuya; Shimizu, Nobuyoshi. Department of Cancer and Thoracic Surgery, Okayama University Graduate School Medicine and Dentistry, Okayama, Japan. Cancer Letters (Amsterdam, Netherlands) (2005), 226(1), 37-47. Publisher: Elsevier B.V., CODEN: CALEDQ ISSN: 0304-3835. Journal written in English. CAN 143:221982 AN 2005:593169 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

High expression of epidermal growth factor receptor (EGFR) is thought to be correlated with cell proliferation, invasion, metastasis, resistance to chemoradiotherapy, and poor prognosis in various kinds of human cancers. Blockade of EGFR signal transduction can be a promising strategy for cancer therapy. Approx. 40-70% of esophageal squamous cell carcinomas (ESCCs) show high expression of EGFR. In this study, the authors examd. the antitumor effect of gefitinib, an EGFR tyrosine kinase inhibitor, against ESCC cells in vitro and in vivo. In 3 ESCC cell lines (TE8, T.T, and T.Tn), cell proliferation had been inhibited in a dose-dependent manner and IC50 values (resp., 8.49, 18.9 and 17.3 μM). Gefitinib inhibited EGF-induced autophosphorylation of EGFR and its downstream signaling pathways, Ras/Raf/MAPK and PI3K/Akt, and caused G1 arrest of cell cycle and apoptosis confirmed with flow cytometry. The authors examd. the effect of gefitinib on nude mice bearing established TE8 and T.T xenografts. Gefitinib (100 or 200 mg/kg once-daily, p.o.) showed antitumor activity in a dose-dependent manner, resulting in a significantly improved survival of treated mice

as compared with untreated mice. Immunohistochem. examn. of the harvested tumor was performed to examine the status of phosphorylated EGFR, PCNA, Factor VIII and apoptosis. The authors found inhibition of EGFR phosphorylation, cell cycle arrest (by PCNA staining), decrease of microvessel d. (Factor VIII) and induction of apoptosis by TUNEL staining. In conclusion, the authors' findings demonstrate that gefitinib is effective for growth inhibition of ESCC cell lines in vitro and in vivo and suggest that gefitinib may be one of the new therapeutic options for ESSC.

Answer 22:

Bibliographic Information

Increase in amphiregulin and epiregulin in prostate cancer xenograft after androgen deprivation - impact of specific HERI inhibition. Torring, Niels; Hansen, Frederik Dagnaes; Sorensen, Boe Sandahl; Orntoft, Torben F.; Nexo, Ebba. Molecular Diagnostics Laboratory, Department of Clinical Biochemistry-AKH, Aarhus University Hospital, Aarhus C, Den. Prostate (Hoboken, NJ, United States) (2005), 64(1), 1-8. Publisher: Wiley-Liss, Inc., CODEN: PRSTDS ISSN: 0270-4137. Journal written in English. CAN 143:437317 AN 2005:563073 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

BACKGROUND. We investigated the expression of the epidermal growth factor (EGF) network before and after castration in the prostate cancer xenograft CWR22 implanted in nude mice, and examd. the effects of gefitinib (Iresssa, ZD1839), a new drug directed towards the EGF tyrosine kinase receptor (HER1) of the EGF network. METHODS. CWR22 prostate cancer xenografts were propagated in immunodeficient male mice. The expression of the growth factors and receptors in the EGF network was examd. by real-time PCR anal. and ELISA at 0, 7, 14, and 30 days after castration, and the tumor growth was examd. after treatment with gefitinib or placebo. RESULTS. A fraction of growth factors showed a steady increase in the mRNA expression reaching between fourfold and eightfold 30 days after castration, including amphiregulin ($P < 0.005$) and epiregulin ($P < 0.001$). ELISA for amphiregulin showed a fivefold increase 30 days after castration. Tumor bearing mice were castrated and treated with or without the HER1 tyrosine kinase inhibitor gefitinib. Tumor involution was significantly increased by castration plus gefitinib as compared to castration alone. CONCLUSIONS. Castration leads to adaptive increase in the concns. of a subset of growth factors from the EGF network in the androgen sensitive CWR22 prostate cancer xenograft. Specific inhibition of the HER1 tyrosine kinase receptor significantly increases the tumor involution, and suggests that HER1 targeted drugs could be of therapeutic relevance in the treatment of advanced prostate cancer.

Answer 23:

Bibliographic Information

Gefitinib-trastuzumab combination on hormone-refractory prostate cancer xenograft. Formento, Patricia; Hannoun-Levi, Jean-Michel; Gerard, Francoise; Mazeau, Christiane; Fischel, Jean-Louis; Etienne-Grimaldi, M. C.; Gugenheim, Jean; Milano, Gerard. Oncopharmacology Unit, Centre Antoine Lacassagne, Nice, Fr. European Journal of Cancer (2005), 41(10), 1467-1473. Publisher: Elsevier Ltd., CODEN: EJCAEL ISSN: 0959-8049. Journal written in English. CAN 143:339060 AN 2005:520841 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

New drugs and new combinations of drugs have recently shown promising clin. activity in hormone refractory prostate cancer. We studied the assocn. of gefitinib with trastuzumab on the androgen-refractory prostate cancer cell line DU145 expressing both epidermal growth factor receptor (EGFR) and HER-2. Drug combinations with radiotherapy (RT) were considered along with the anal. of factors linked to cell proliferation and apoptosis. The antitumor effects of gefitinib were more pronounced than those obsd. with trastuzumab. In mice receiving the gefitinib-trastuzumab combination, redn. in tumor vol. was inferior to that predicted by the obsd. impact of the agents alone. The presence of trastuzumab markedly attenuated the relative increase on p27 expression and the Bax:Bcl2 ratio induced by gefitinib. The combination gefitinib-RT had similar antitumor effects as those predicted by the impact of the individual treatments, whereas the effect of the trastuzumab-RT combination was inferior to that predicted by the individual effects. The present

data should be borne in mind when designing new clin. schedules for treatment of hormone-refractory prostate cancer including the use of HER inhibitors.

Answer 24:

Bibliographic Information

Tumor penetration of gefitinib (Iressa), an epidermal growth factor receptor tyrosine kinase inhibitor. McKillop, David; Partridge, Elizabeth A.; Kemp, John V.; Spence, Mike P.; Kendrew, Jane; Barnett, Sharon; Wood, Phillippa G.; Giles, Petrina B.; Patterson, Andrew B.; Bichat, Francis; Guilbaud, Nicolas; Stephens, Trevor C. AstraZeneca, Alderley Park, Cheshire, Macclesfield, UK. Molecular Cancer Therapeutics (2005), 4(4), 641-649. Publisher: American Association for Cancer Research, CODEN: MCTOCF ISSN: 1535-7163. Journal written in English. CAN 143:186137 AN 2005:313325 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The relative distribution of gefitinib-related material in nude mice bearing s.c. human tumor xenografts and in an orthotopic rat lung tumor model was investigated following oral administration (50 mg/kg) of [14C]-gefitinib. Selected tissue samples were monitored for radioactivity by liq. scintillation counting, whereas plasma and tumor exts. were assayed for gefitinib and its major metabolites (M523595 and M537194) by high-performance liq. chromatog. with tandem mass spectrometric detection. Tissue distribution was also detd. by whole body autoradiog. Gefitinib was extensively distributed into the tissues of tumor-bearing mice and unchanged gefitinib was shown to account for most of the tumor radioactivity. Concns. of gefitinib in mouse s.c. tumor xenografts were similar to skin concns. and substantially greater (up to 12-fold based on area under the concn.-time curve) than plasma. Concns. of gefitinib-related material in an orthotopic rat lung tumor were similar to those in healthy lung tissue and were much higher than corresponding blood levels. Following treatment of breast cancer patients with oral gefitinib (Iressa) 250 mg/d for ≥ 14 days, gefitinib concns. (mean, 7.5 μg/g, 16.7 μmol/L) in breast tumor tissue were 42 times higher than plasma, confirming the preferential distribution of gefitinib from blood into tumor tissue in the clin. situation. These gefitinib tumor concns. are considerably higher than those reportedly required in vitro to achieve complete inhibition of epidermal growth factor receptor autophosphorylation in both epidermal growth factor receptor mutant (0.2 μmol/L) and wild-type cells (2 μmol/L).

Answer 25:

Bibliographic Information

Efficacy of epidermal growth factor receptor-targeted molecular therapy in anaplastic thyroid cancer cell lines. Nobuhara, Y.; Onoda, N.; Yamashita, Y.; Yamasaki, M.; Ogisawa, K.; Takashima, T.; Ishikawa, T.; Hirakawa, K. Department of Surgical Oncology, Osaka City University Graduate School of Medicine, Asahi-machi, Abeno-ku, Osaka, Japan. British Journal of Cancer (2005), 92(6), 1110-1116. Publisher: Nature Publishing Group, CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 143:71110 AN 2005:248150 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Anaplastic thyroid cancer is one of the most aggressive human malignancies and the outcomes of conventional therapy have been far from satisfactory. Recently, epidermal growth factor receptor (EGFR)-targeted therapy has been introduced as an alternative therapeutic strategy for highly malignant cancers. This study was undertaken to investigate the expression of EGFR in anaplastic thyroid cancer cell lines, and to explore the potential of therapies targeting EGFR as a new therapeutic approach. EGFR was universally expressed in anaplastic cancer cell lines at a variety of levels. Specific EGFR stimulation with epidermal growth factor showed significant phosphorylation of ERK1/2 and Akt, and resulted in marked growth stimulation in an anaplastic thyroid cancer cell line, which highly expressed EGFR. This EGFR-transmitted proliferation effect of the cancer cell line was completely inhibited by gefitinib, an EGFR tyrosine kinase inhibitor. Moreover, growth of xenografts inoculated in mice was inhibited in a dose-dependent manner with 25-50 mg kg-1 of gefitinib administrated orally. Inhibition of EGFR-transmitted growth stimulation by gefitinib was clearly obsd. in anaplastic thyroid cancer cell lines. Our results suggested that EGFR-targeted therapy, such as gefitinib, might be worth

further investigation for the treatment of anaplastic thyroid cancer.

Answer 26:

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 ERβ, EGFR, and Neu but no full-length ERα. One cell line contained an EGFR mutation. Cells were exposed to 10 nmol/L estrogen and 10 ng/mL EGF and either 1 μmol/L fulvestrant or 1 μmol/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 27:

Bibliographic Information

Gefitinib in recurrent non-small-cell lung cancer: an IDEAL trial? Johnson, David H.; Arteaga, Carlos L. Division of Hematology & Oncology, Vanderbilt-Ingram Comprehensive Cancer Center, Vanderbilt University School of Medicine, Nashville, TN, USA. Journal of Clinical Oncology (2003), 21(12), 2227-2229. Publisher: American Society of Clinical Oncology, CODEN: JCONDN ISSN: 0732-183X. Journal; General Review written in English. CAN 142:308841 AN 2004:945989 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A review. Gefitinib is a synthetic anilinoquinazole capable of inhibiting the epidermal growth factor (EGF) receptor (EGFR) tyrosine kinase in vitro at nanomolar concns. Orally administered gefitinib inhibited tumor growth in mice bearing a range of human tumor-derived xenografts in a dose-dependent manner. In phase I trials, gefitinib was well tolerated at doses above that required to achieve antitumor activity in preclin. studies, and antitumor activity was obsd. in patients with non-small-cell lung cancer (NSCLC). On the basis of these preclin. and clin. data, phase II trials of single-agent gefitinib were undertaken in individuals with recurrent NSCLC. The results of one of these trials, known as Iressa Dose Evaluation in Advanced Lung Cancer (IDEAL-1), are discussed.

Answer 28:

Bibliographic Information

Combined epidermal growth factor receptor targeting with the tyrosine kinase inhibitor gefitinib (ZD1839) and the monoclonal antibody cetuximab (IMC-C225): superiority over single-agent receptor targeting. Matar, Pablo; Rojo, Federico; Cassia, Raul; Moreno-Bueno, Gema; Di Cosimo, Serena; Tabernero, Jose; Guzman, Marta; Rodriguez, Sonia; Arribas, Joaquin; Palacios, Jose; Baselga, Jose. Laboratory of Oncology Research, Medical Oncology Service, Vall d'Hebron University Hospital, Barcelona, Spain. Clinical Cancer Research (2004), 10(19), 6487-6501. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 142:190379 AN 2004:827178 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The epidermal growth factor receptor (EGFR) is abnormally activated in cancer and two classes of anti-EGFR agents, monoclonal antibodies and low-mol.-wt. tyrosine kinase inhibitors, have shown antitumor activity in patients. Because these two classes of antireceptor agents target the EGFR at different sites, we decided to explore whether the combined administration of gefitinib, a tyrosine kinase inhibitor, and cetuximab, a monoclonal antibody, had superior antitumor activity than either agent given alone. We studied the effects of the combination of gefitinib and cetuximab in a panel of human cancer cell lines and in an EGFR-dependent human tumor xenograft model (A431). The effects of these two agents on EGFR signaling, proliferation, apoptosis, and vascularization were evaluated. In addn., we analyzed, with cDNA arrays, changes in gene expression profiles induced by both agents. The combined treatment with gefitinib and cetuximab resulted in a synergistic effect on cell proliferation and in superior inhibition of EGFR-dependent signaling and induction of apoptosis. In a series of in vivo expts., single-agent gefitinib or cetuximab resulted in transient complete tumor remission only at the highest doses. In contrast, suboptimal doses of gefitinib and cetuximab given together resulted in a complete and permanent regression of large tumors. In the combination-treated tumors, there was a superior inhibition of EGFR, mitogen-activated protein kinase, and Akt phosphorylation, as well as greater inhibition of cell proliferation and vascularization and enhanced apoptosis. Using cDNA arrays, we found 59 genes that were coregulated and 45 genes differentially regulated, including genes related to cell proliferation and differentiation, transcription, DNA synthesis and repair, angiogenesis, signaling mols., cytoskeleton organization, and tumor invasion and metastasis.

Our findings suggest both shared and complementary mechanisms of action with gefitinib and cetuximab and support combined EGFR targeting as a clin. exploitable strategy.

Answer 29:

Bibliographic Information

Antitumor activity of gefitinib in malignant rhabdoid tumor cells in vitro and in vivo. Kuwahara, Yasumichi; Hosoi, Hajime; Osone, Shinya; Kita, Masakazu; Iehara, Tomoko; Kuroda, Hiroshi; Sugimoto, Tohru. Department of Pediatrics, Kyoto Prefectural University of Medicine, Kyoto, Japan. Clinical Cancer Research (2004), 10(17), 5940-5948. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 142:86043 AN 2004:738059 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Malignant rhabdoid tumor (MRT) is a rare and highly aggressive neoplasm of young children. Current treatments have had only limited success. Epidermal growth factor receptor (EGFR) was found recently to be expressed on MRT cell lines. Gefitinib (trade name Iressa) is an oral and selective EGFR-tyrosine kinase inhibitor and has been demonstrated to be effective in inhibiting the proliferation of cancer cells in vivo as well as in clin. trials. This encouraged the authors to examine the antitumor effects of gefitinib on MRT cells in vitro and in vivo. The expression of EGFR in two MRT tumors and two MRT cell lines (MP-MRT-AN and KP-MRT-NS), established from these two tumor tissues, was examd. by immunohistochem., immunofluorescence, and immunoblot. The effect of gefitinib on EGFR phosphorylation was examd. by immunoblot. The effects of gefitinib on cell growth and apoptosis were examd. by cell growth assay and terminal deoxynucleotidyl transferase-mediated nick end labeling assay. The in vivo effect of gefitinib was assessed in athymic mice that had been xenografted with MRT cells. The expression of EGFR was detected in both tumor tissues and cell lines. Gefitinib inhibited EGFR-phosphorylation (IC50 < 0.1 μmol/L) and in vitro cell growth (IC50 = approx. 10-12 μmol/L), and a high concn. of gefitinib (20 μmol/L) induced apoptosis in vitro (MP-MRT-AN, 42.9% and KP-MRT-NS, 47.2%). Furthermore, gefitinib at 150 mg/kg had a cytostatic effect on established MRT xenografts (MP-MRT-AN, and 0.0014; and KP-MRT-NS, and 0.0086). Our results demonstrate that gefitinib has antitumor effects in MRT cells in vitro and in vivo and, thus, has promise as a novel and therapeutic

strategy for MRT.

Answer 30:

Bibliographic Information

Combined targeting of epidermal growth factor receptor and MDM2 by gefitinib and antisense MDM2 cooperatively inhibit hormone-independent prostate cancer. Bianco, Roberto; Caputo, Roberta; Caputo, Rosa; Damiano, Vincenzo; De Placido, Sabino; Ficorella, Corrado; Agrawal, Sudhir; Bianco, A. Raffaele; Ciardiello, Fortunato; Tortora, Giampaolo. Dipartimento di Endocrinologia e Oncologia Molecolare e Clinica, Universita di Napoli Federico II, Naples, Italy. Clinical Cancer Research (2004), 10(14), 4858-4864. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 142:190333 AN 2004:583320 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The epidermal growth factor receptor (EGFR) may play a relevant role in the progression, hormone therapy resistance, and prognosis of prostate cancer patients. Also MDM2, a neg. p53 regulator that interacts with retinoblastoma (Rb), E2F, p19arf and the ras-mitogen-activated protein kinase(MAPK) cascade plays an important role in prostate cancer progression and prognosis. On the basis of the EGFR and MDM2 role in integrating signaling pathways crit. for prostate cancer progression, we investigated whether their selective combined blockade may have a cooperative antitumor effect in prostate cancer. For this purpose, we have used the EGFR tyrosine kinase inhibitor gefitinib (ZD1839, Iressa) and a second generation hybrid oligonucleotide antisense MDM2 (AS-MDM2), resp. Gefitinib and AS-MDM2 were administered to hormone-refractory and hormone-dependent human prostate cancer cells in vitro and to mice bearing tumor xenografts, evaluating the effects on growth, apoptosis, and protein expression, in vitro and in vivo. We demonstrated that the combination of gefitinib and AS-MDM2 synergistically inhibits the growth of hormone-independent prostate cancer cells in vitro. This effect is accompanied by the inhibition of MDM2, phosphorylated Akt (pAkt), phosphorylated MAPK (pMAPK), and vascular endothelial growth factor (VEGF) expression and by Rb hypophosphorylation. The combination of the two agents in nude mice bearing the same hormone-independent tumors caused a potent cooperative antitumor effect. Tumor samples anal. confirmed the inhibition of MDM2, pAkt, pMAPK, VEGF, and basic fibroblast growth factor expression. This study shows that EGFR and MDM2 play a crit. role in the growth of prostate cancer, esp. hormone-dependent, and that their combined blockade by gefitinib and AS-MDM2 causes a cooperative antitumor effect, supporting the clin. development of this therapeutic strategy.

Answer 31:

Bibliographic Information

Treatment of HER-2/neu overexpressing breast cancer xenograft models with trastuzumab (Herceptin) and gefitinib (ZD1839): drug combination effects on tumor growth, HER-2/neu and epidermal growth factor receptor expression, and viable hypoxic cell fraction. Warburton, Corinna; Dragowska, Wieslawa H.; Gelmon, Karen; Chia, Stephen; Yan, Hong; Masin, Dana; Denyssevych, Tetyana; Wallis, Anne E.; Bally, Marcel B. Departments of Advanced Therapeutics and Medical Oncology, British Columbia Cancer Agency, BC, Can. Clinical Cancer Research (2004), 10(7), 2512-2524. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 141:342990 AN 2004:290933 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The purpose of this research was to assess the effects of single agent and combination treatment with trastuzumab and gefitinib on tumor growth and tumor microenvironment in two HER-2/neu overexpressing breast xenograft models, MDA-MB-435/LCC6HER-2 (LCC6HER-2; estrogen receptor neg.) and MCF-7HER-2 (estrogen receptor pos.). LCC6HER-2 and MCF-7HER-2 cells, both in tissue culture and xenografts grown in SCID-Rag 2M mice, were treated with trastuzumab and gefitinib, alone or in combination. The rate of tumor growth was detd. In addn., tumor HER-2/neu and epidermal growth factor receptor expression, cell viability, cell cycle distribution, and proportion of viable hypoxic cells were detd. by flow cytometric analyses of single tumor cell suspensions. Both tumor models were very sensitive to trastuzumab and moderately sensitive to gefitinib in vivo. The combination resulted in therapeutic effects, as judged by inhibition of tumor growth, which was greater (albeit not statistically significant) than that obsd. with

trastuzumab administered as a single agent. Trastuzumab was effective in down-regulating HER-2/neu, and gefitinib mediated a redn. in epidermal growth factor receptor expression on tumor cells. In LCC6HER-2 tumors, trastuzumab significantly reduced tumor cell viability, which was not improved by the addn. of gefitinib. Gefitinib dramatically reduced the proportion of viable hypoxic cells in LCC6HER-2 and MCF-7HER-2 tumors. This effect was abrogated by the addn. of trastuzumab. Although in vivo efficacy studies in two HER-2/neu overexpressing breast xenograft models showed that the combination of trastuzumab and gefitinib was effective, analyses of various cellular parameters failed to reveal beneficial effects and argue that this drug combination may not be favorable.

Answer 32:

Bibliographic Information

Antitumor activity of ZD6474, a vascular endothelial growth factor receptor tyrosine kinase inhibitor, in human cancer cells with acquired resistance to antiepidermal growth factor receptor therapy. Ciardiello, Fortunato; Bianco, Roberto; Caputo, Roberta; Caputo, Rosa; Damiano, Vincenzo; Troiani, Teresa; Melisi, Davide; De Vita, Ferdinando; De Placido, Sabino; Bianco, A. Raffaele; Tortora, Giampaolo. Dipartimento Medico-Chirurgico di Internistica Clinica e Sperimentale "F Magrassi e A Lanzara", Cattedra di Oncologia Medica, Naples, Italy. Clinical Cancer Research (2004), 10(2), 784-793. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 141:199594 AN 2004:88615 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The epidermal growth factor receptor (EGFR) autocrine signaling pathway is involved in cancer development and progression. EGFR inhibitors such as C225 (cetuximab), a chimeric human-mouse anti-EGFR monoclonal antibody, and ZD1839 (gefitinib), a small mol. EGFR-selective tyrosine kinase inhibitor, are in advanced clin. development. The potential emergence of cancer cell resistance in EGFR-expressing cancers treated with EGFR inhibitors could det. lack of activity of these drugs in some cancer patients. Vascular endothelial growth factor (VEGF) is secreted by cancer cells and plays a key role in the regulation of tumor-induced endothelial cell proliferation and permeability. ZD6474 is a small mol. VEGF flk-1/KDR (VEGFR-2) tyrosine kinase inhibitor that also demonstrates inhibitory activity against EGFR tyrosine kinase. The antitumor activity of ZD1839, C225, and ZD6474 was tested in athymic mice bearing human GEO colon cancer xenografts. GEO cell lines resistant to EGFR inhibitors were established from GEO xenografts growing in mice treated chronically with ZD1839 or C225. Expression of EGFR was evaluated by flow cytometry. Expression of various proteins involved in intracellular cell signaling was assessed by Western blotting. Tumor growth data were evaluated for statistical significance using the Student's t test. All Ps were two-sided. Although chronic administration of optimal doses of C225 or ZD1839 efficiently blocked GEO tumor growth in the majority of mice, tumors slowly started to grow within 80-90 days, despite continuous treatment. In contrast, continuous treatment of mice bearing established GEO xenografts with ZD6474 resulted in efficient tumor growth inhibition for the entire duration of dosing (up to 150 days). ZD6474 activity was also detd. in mice pretreated with ZD1839 or C225. When GEO growth was apparent after 4 wk of treatment with EGFR inhibitors, mice were either re-treated with EGFR inhibitors or treated with ZD6474.

GEO tumor growth was blocked only in mice treated with ZD6474, whereas tumor progression was obsd. in mice re-treated with C225 or ZD1839. GEO tumors growing during treatment with C225 or with ZD1839 were established as cell lines (GEO-C225-RES and GEO-ZD1839-RES, resp.). Cell membrane-assocd. EGFR expression was only slightly reduced in these cell lines compared with parental GEO cells. Western blotting revealed no major change in the expression of the EGFR ligand transforming growth factor α of bcl-2, bcl-xL, p53, p27, MDM-2, akt, activated phospho-akt, or mitogen-activated protein kinase. However, both GEO-C225-RES and GEO-ZD1839-RES cells exhibited a 5-10-fold increase in activated phospho-mitogen-activated protein kinase and in the expression of cyclooxygenase-2 and of VEGF compared with GEO cells. GEO-C225-RES and GEO-ZD1839-RES growth as xenografts in nude mice was not significantly affected by treatment with either C225 or ZD1839 but was efficiently inhibited by ZD6474. Long-term treatment of GEO xenografts with selective EGFR inhibitors results in the development of EGFR inhibitor-resistant cancer cells. Growth of EGFR inhibitor-resistant tumors can be inhibited by ZD6474. These data indicate that inhibition of VEGF signaling has potential as an anticancer strategy, even in tumors that are resistant to EGF inhibitors.

Answer 33:

Bibliographic Information

Modulation of Tumor Growth and Tumor Induced Angiogenesis after Epidermal Growth Factor Receptor Inhibition by ZD1839 in Renal Cell Carcinoma. Asakuma, Junichi; Sumitomo, Makoto; Asano, Takako; Asano, Tomohiko; Hayakawa, Masamichi. Department of Urology, National Defense Medical College, 3-2 Namiki, Tokorozawa, Saitama, Japan. Journal of Urology (Hagerstown, MD, United States) (2004), 171(2, Pt. 1), 897-902. Publisher: Lippincott Williams & Wilkins, CODEN: JOURAA ISSN: 0022-5347. Journal written in English. CAN 141:133654 AN 2004:24969 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

ZD1839 or Iressa (AstraZeneca, Macclesfield, United Kingdom) is an orally active, selective epidermal growth factor receptor tyrosine kinase inhibitor. We evaluated the antitumor activity of ZD1839 in human renal cell carcinomas (RCC). Six established human RCC lines and surgical specimens from 10 patients with RCC were used. Protein expression was detected by Western blotting and/or immunohistochem. The concns. of vascular endothelial growth factor and interleukin-8 in the supernatants were measured by ELISA. Cell cycle progression and the apoptotic ratio were evaluated by flow cytometry. In vitro angiogenesis was measured using human umbilical vascular endothelial cells by capillary-like network formation anal. In vivo SKRC-49 cells injected s.c. into athymic nude mice were treated with various doses of ZD1839 orally. The effect of ZD1839 on tumor xenografts angiogenesis was evaluated by immunohistochem. using CD34 Ab. Epidermal growth factor receptor was activated in all RCC lines and over expressed in 7 of 10 RCC specimens (70%) compared with adjacent normal renal tissues. Treatment of SKRC-49 cells with ZD1839 (0.1 to 10 μM) for 48 h resulted in the accumulation of cells in the G1 phase and a 30% to 50% decrease in cellular proliferation compared with untreated controls ($p < 0.01$). The tumor xenograft study confirmed that ZD1839 (50 to 100 mg/kg daily) significantly inhibited SKRC-49 tumor growth compared with controls within 3 wk after treatment ($p < 0.01$). Vascular endothelial growth factor and interleukin-8 prodn. was significantly decreased in ZD1839 treated SKRC-49 cells compared with untreated controls ($p < 0.01$). Treatment of human umbilical vascular endothelial cells with SKRC-49 supernatants treated with ZD1839 for 11 days resulted in an approx. 80% decrease in tubule formation compared with untreated controls ($p < 0.01$). Immunohistochem. assays showed that ZD1839 treatment resulted in a significant decrease in CD34 pos. neovessels compared with controls in SKRC-49 xenografts.

These results suggest that the antitumor activity of ZD1839 appears to derive not only from direct inhibition of cell proliferation, but also from the inhibition of tumor angiogenesis in RCC.

Answer 34:

Bibliographic Information

Synergistic interaction between the EGFR tyrosine kinase inhibitor gefitinib ("Iressa") and the DNA topoisomerase I inhibitor CPT-11 (Irinotecan) in human colorectal cancer cells. Koizumi, Fumiaki; Kanzawa, Fumihiko; Ueda, Yutaka; Koh, Yasuhiro; Tsukiyama, Shoji; Taguchi, Fumiko; Tamura, Tomohide; Saijo, Nagahiro; Nishio, Kazuto. Support Facility of Project Ward, National Cancer Center Hospital, Tokyo, Japan. International Journal of Cancer (2003), Volume Date 2004, 108(3), 464-472. Publisher: Wiley-Liss, Inc., CODEN: IJCNAW ISSN: 0020-7136. Journal written in English. CAN 140:246369 AN 2003:1006011 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Epidermal growth factor receptor [EGFR (HER1, erbB1)] is a receptor with assocd. tyrosine kinase activity, and is expressed in colorectal cancers and many other solid tumors. We examd. the effect of the selective EGFR tyrosine kinase inhibitor (EGFR-TKI) gefitinib ("Iressa") in combination with the DNA topoisomerase I inhibitor CPT-11 (irinotecan) on human colorectal cancer cells. EGFR mRNA and protein expression were detected by RT-PCR and immunoblotting in all 7 colorectal cancer cell lines studied. Gefitinib inhibited the cell growth of the cancer cell lines in vitro with an IC50 range of 1.2-160 μM by 3,(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay. Lovo cells exhibited the highest level of protein and autophosphorylation of EGFR and were the most sensitive to gefitinib. The combination of gefitinib and CPT-11 induced supra-additive inhibitory effects in COLO320DM, WiDR and Lovo cells, assessed by an in vitro MTT assay. Administration of gefitinib and CPT-11 had a supra-additive inhibitory effect on WiDR cells and tumor shrinkage was obsd. in Lovo cell xenografts established in nude mice, whereas no additive effect of combination therapy was obsd. in COLO320DM cells. To elucidate the mechanisms of synergistic effects, the effect of CPT-11-exposure on phosphorylation of EGFR was examd. by immunopptn. CPT-11 increased phosphorylation of EGFR in Lovo and WiDR cells in time- and dose-dependent manners. This EGFR activation was completely inhibited by 5 μM

gefitinib and gefitinib-induced apoptosis was enhanced by combination with CPT-11, measured by PARP activation although no PARP activation was induced by 5 μM CPT-11 alone. These results suggested that these modification of EGFR by CPT-11, in Lovo cells, is a possible mechanism for the synergistic effect of CPT-11 and gefitinib. These findings imply that the EGFR-TKI gefitinib and CPT-11 will be effective against colorectal tumor cells that express high levels of EGFR, and support clin.
evaluation of gefitinib in combination with CPT-11, in the treatment of colorectal cancers.

Answer 35:

Bibliographic Information

Gefitinib ('Iressa', ZD1839), an epidermal growth factor receptor tyrosine kinase inhibitor, up-regulates p27KIP1 and induces G1 arrest in oral squamous cell carcinoma cell lines. Shintani, Satoru; Li, Chunnan; Mihara, Mariko; Yano, Junya; Terakado, Nagaaki; Nakashiro, Koh-ichi; Hamakawa, Hiroyuki. Department of Oral and Maxillofacial Surgery, Ehime University School of Medicine, Shigenobu-cho, Onsen-gun, Ehime, Japan. Oral Oncology (2004), 40(1), 43-51. Publisher: Elsevier Science B.V., CODEN: EJCCER ISSN: 1368-8375. Journal written in English. CAN 141:81771 AN 2003:967831 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

High expression of epidermal growth factor receptor (EGFR) is frequently obsd. in many solid tumor types including oral squamous cell carcinomas (OSCC). Recently, the results of preclin. studies and early clin. trials targeting the EGFR have shown evidence of the activity. In this study, gefitinib ('Iressa', ZD1839), an EGFR-tyrosine kinase inhibitor, inhibited cell proliferation and upregulated p27KIP1 in OSCC cells. Growth inhibition was obsd. in OSCC xenografts when mice were treated with gefitinib in vivo. A flow cytometric anal. demonstrated that treatment with gefitinib induced accumulation in G1 phase, accompanied by a decrease in the percentage of cells in S phase. Apoptosis was not seen in this study. Cell growth was inhibited by an increase of the cell cycle inhibitor p27KIP1 and a decrease of its ubiquitin ligase subunit Skp2.

Answer 36:

Bibliographic Information

Enhancement of tumor radioresponse by combined treatment with gefitinib (Iressa, ZD1839), an epidermal growth factor receptor tyrosine kinase inhibitor, is accompanied by inhibition of DNA damage repair and cell growth in oral cancer. Shintani, Satoru; Li, Chunnan; Mihara, Mariko; Terakado, Nagaaki; Yano, Junya; Nakashiro, Koh-ichi; Hamakawa, Hiroyuki. Department of Oral and Maxillofacial Surgery, Ehime University School of Medicine, Ehime, Japan. International Journal of Cancer (2003), 107(6), 1030-1037. Publisher: Wiley-Liss, Inc., CODEN: IJCNAW ISSN: 0020-7136. Journal written in English. CAN 140:299559 AN 2003:917378 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Mol. blockade of EGFR with either an EGFR MAb or an EGFR TKI enhances the radiosensitivity of human SCCs. In the present study, we investigated whether treatment with the EGFR TKI gefitinib (Iressa, ZD1839) improves the response to radiotherapy in the OSCC cell lines HSC2 and HSC3. We examd. potential mechanisms that may contribute to the enhanced radiation response induced by gefitinib. Growth inhibition was obsd. in vitro with radiation or gefitinib. A cooperative antiproliferative effect was obtained when cancer cells were treated with radiation followed by gefitinib. Cells treated with a combination of radiation and gefitinib arrested in G1 and G2-M phases, with a decrease in the S-phase population. While radiation alone did not significantly affect MEK1/2 and p38 MAPK autophosphorylation, the combination of gefitinib and radiation completely inhibited the downstream signaling of EGFR. Results from DNA damage repair anal. in cultured OSCC cells demonstrated that gefitinib had a strong inhibitory effect on DNA-PKc pathways after radiation. Tumor xenograft studies demonstrated that the combination of gefitinib and radiation caused growth inhibition and tumor regression of well-established OSCC tumors in athymic mice; tumor vol. was reduced from 1,008.2 to 231.4 mm3 in HSC2 cells ($p < 0.01$) and from 284.2 to 12.4 mm3 in HSC3 cells ($p < 0.01$). Immunohistochem. anal. of OSCC xenografts revealed that gefitinib caused a striking decrease in tumor cell proliferation when combined with radiotherapy. Overall, we conclude that gefitinib enhances

tumor radioresponse by multiple mechanisms that may involve antiproliferative growth inhibition and effects on DNA repair after exposure to radiation.

Answer 37:

Bibliographic Information

Studies with CWR22 xenografts in nude mice suggest that ZD1839 may have a role in the treatment of both androgen-dependent and androgen-independent human prostate cancer. Sirotnak, Francis M.; She, Yohung; Lee, Fei; Chen, Jing; Scher, Howard I. Program in Molecular Pharmacology and Therapeutics and Genitourinary Oncology Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA. Clinical Cancer Research (2002), 8(12), 3870-3876. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 139:143462 AN 2002:974069 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

These studies examd. the effect of the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor ZD1839 (Iressa) on CWR22 prostate tumors in nude mice. The effect of ZD1839 was also examd. in combination with either bicalutamide (Casodex) or cytotoxic agents against a hormone-dependent or -independent variant of CWR22, resp. The xenografts were grown for 4-7 days, then tumor measurements were made and therapy initiated. ZD1839 and bicalutamide were given p.o. on a once-daily, 5-day schedule for 2 successive weeks. Carboplatin and paclitaxel were given every 3-4 days for a total of four doses. Measurements of tumor vol. were made twice weekly during treatment and for 2 wk after treatment. The effect of ZD1839 on EGFR function was assessed by Western blotting of EGFR and its phosphorylated form in CWR22 and variant tumors before and after treatment with this agent. ZD1839 at its max. tolerated dose (150 mg/kg) inhibited the growth of androgen-dependent CWR22 by 54%, and the growth of two variants with different degrees of androgen independence and androgen receptor gene expression (CWR22LD1 and CWR22RV1) by 76%. The effects of ZD1839 were similar to those recorded for phosphorylation of EGFR as detd. by Western blotting. Co-administration of ZD1839 at its max. tolerated dose markedly increased the antiproliferative action of the antiandrogen bicalutamide against CWR22LD1. In fact, combining ZD1839 with a suboptimal dose of bicalutamide was more effective than a higher dose of bicalutamide alone. Co-administration of ZD1839, which required a 2-3-fold attenuation of dose to avoid toxicity, also markedly increased the therapeutic activity of carboplatin and paclitaxel against CWR22RV1, bringing about regression to a degree not seen with either agent alone. Tumor-free mice were seen only with the combination of ZD1839 and paclitaxel.

The results obtained in these related and highly relevant models of human prostate cancer suggest that ZD1839 may have a role in enhancing existing treatments of androgen-dependent and -independent forms of this disease in patients.