

Answer 1:

Bibliographic Information

Mutant FLT3: a direct target of sorafenib in acute myelogenous leukemia. Zhang, Weiguo; Konopleva, Marina; Shi, Yue-xi; McQueen, Teresa; Harris, David; Ling, Xiaoyang; Estrov, Zeev; Quintas-Cardama, Alfonso; Small, Donald; Cortes, Jorge; Andreeff, Michael. Section of Molecular Hematology and Therapy, Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA. Journal of the National Cancer Institute (2008), 100(3), 184-198. Publisher: Oxford University Press, CODEN: JNCIEQ ISSN: 0027-8874. Journal written in English. CAN 148:553047 AN 2008:298308 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Internal tandem duplication (ITD) mutations in the juxtamembrane domain-coding sequence of the Fms-like tyrosine kinase 3 (FLT3) gene have been identified in 30% of acute myeloid leukemia (AML) patients and are assocd. with a poor prognosis. The kinase inhibitor sorafenib induces growth arrest and apoptosis at much lower concns. in AML cell lines that harbor FLT3-ITD mutations than in AML cell lines with wild-type FLT3. The antileukemic activity of sorafenib was investigated in isogenic murine Ba/F3 AML cell lines that expressed mutant (ITD, D835G, and D835Y) or wild-type human FLT3, in primary human AML cells, and in a mouse leukemia xenograft model. Effects of sorafenib on apoptosis and signaling in AML cell lines were investigated by flow cytometry and immunoblot anal., resp., and the in vivo effects were detd. by monitoring the survival of leukemia xenograft-bearing mice treated with sorafenib (groups of 15 mice). In a phase 1 clin. trial, 16 patients with refractory or relapsed AML were treated with sorafenib on different dose schedules. We detd. their FLT3 mutation status by a polymerase chain reaction assay and analyzed clin. responses by std. criteria. All statistical tests were two-sided. Sorafenib was 1000- to 3000-fold more effective in inducing growth arrest and apoptosis in Ba/F3 cells with FLT3-ITD or D835G mutations than in Ba/F3 cells with FLT3-D835Y mutant or wild-type FLT3 and inhibited the phosphorylation of tyrosine residues in ITD mutant but not wild-type FLT3 protein. In a mouse model, sorafenib decreased the leukemia burden and prolonged survival (median survival in the sorafenib-treated group vs the vehicle-treated group = 36.5 vs 16 days, difference = 20.5 days, 95% confidence interval = 20.3 to 21.3 days; P = .0018). Sorafenib reduced the percentage of leukemia blasts in the peripheral blood and the bone marrow of AML patients with FLT3-ITD (median percentages before and after sorafenib: 81% vs. 7.5% [P = .016] and 75.5% vs.

34% [P = .05], resp.) but not in patients without this mutation. Sorafenib may have therapeutic efficacy in AML patients whose cells harbor FLT3-ITD mutations.

Answer 2:

Bibliographic Information

Cell Cycle-Dependent and Schedule-Dependent Antitumor Effects of Sorafenib Combined with Radiation. Plataras, John P.; Kim, Seok-Hyun; Liu, Yingqiu Y.; Dicker, David T.; Dorsey, Jay F.; McDonough, James; Cerniglia, George; Rajendran, Ramji R.; Gupta, Anjali; Rustgi, Anil K.; Diehl, J. Alan; Smith, Charles D.; Flaherty, Keith T.; El-Deiry, Wafik S. Laboratory of Molecular Oncology and Cell Cycle Regulation, Departments of Medicine (Hematology/Oncology), Genetics, and Pharmacology, Institute for Translational Medicine and Therapeutics, and Abramson Cancer Center, Univ. Pennsylvania Sch. Med., Philadelphia, PA, USA. Cancer Research (2007), 67(19), 9443-9454. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 147:400605 AN 2007:1104851 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The antineoplastic drug sorafenib (BAY 43-9006) is a multikinase inhibitor that targets the serine-threonine kinase B-Raf as well as several tyrosine kinases. Given the numerous mol. targets of sorafenib, there are several potential anticancer mechanisms of action, including induction of apoptosis, cytostasis, and antiangiogenesis. We obsd. that sorafenib has broad activity in viability assays in several human tumor cell lines but selectively induces apoptosis in only some lines. Sorafenib was found to decrease Mcl-1 levels in most cell lines tested, but this decrease did not correlate with apoptotic sensitivity. Sorafenib slows cell cycle progression and prevents irradiated cells from reaching and accumulating at G2-M. In synchronized cells, sorafenib causes a reversible G1 delay,

which is assocd. with decreased levels of cyclin D1, Rb, and phosphorylation of Rb. Although sorafenib does not affect intrinsic radiosensitivity using in vitro colony formation assays, it significantly reduces colony size. In HCT116 xenograft tumor growth delay expts. in mice, sorafenib alters radiation response in a schedule-dependent manner. Radiation treatment followed sequentially by sorafenib was found to be assocd. with the greatest tumor growth delay. This study establishes a foundation for clin. testing of sequential fractionated radiation followed by sorafenib in gastrointestinal and other malignancies.

Answer 3:

Bibliographic Information

Sorafenib inhibits the angiogenesis and growth of orthotopic anaplastic thyroid carcinoma xenografts in nude mice. Kim, Seungwon; Yazici, Yasemin D.; Calzada, Gabriel; Wang, Zhuo-Ying; Younes, Maher N.; Jasser, Samar A.; El-Naggar, Adel K.; Myers, Jeffrey N. Department of Head and Neck Surgery, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA. *Molecular Cancer Therapeutics* (2007), 6(6), 1785-1792. Publisher: American Association for Cancer Research, CODEN: MCTOCF ISSN: 1535-7163. Journal written in English. CAN 147:250094 AN 2007:654896 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Anaplastic thyroid carcinoma (ATC) remains one of the most lethal human cancers. We hypothesized that sorafenib, a multikinase inhibitor of the BRAf, vascular endothelial growth factor receptor-2, and platelet-derived growth factor receptor- β kinase, would decrease tumor growth and angiogenesis in an orthotopic model of ATC. The in vitro antiproliferative and proapoptotic effects of sorafenib on ATC cell lines were examd. To study the in vivo effects of sorafenib on orthotopic ATC tumors in nude mice, sorafenib was given p.o. at 40 or 80 mg/kg daily. Intratumoral effects were studied using immunohistochem. anal. The effect of sorafenib on survival of the mice was also studied. Sorafenib inhibited the in vitro proliferation of ATC cell lines. Sorafenib also significantly inhibited tumor angiogenesis via the induction of endothelial apoptosis in an orthotopic model of thyroid cancer. As result, the growth of orthotopic ATC xenografts was reduced and the survival of the test animals was improved. Sorafenib exerts significant antitumor activity in an orthotopic xenograft model of ATC via a potent antiangiogenic effect. The antiangiogenic effects of sorafenib suggest that its use in clin. setting may not depend on the BRAF mutational status of thyroid tumors. Given the lack of curative options for patients with ATC, sorafenib warrants further study as a therapeutic agent against ATC.

Answer 4:

Bibliographic Information

Sorafenib Blocks the RAF/MEK/ERK Pathway, Inhibits Tumor Angiogenesis, and Induces Tumor Cell Apoptosis in Hepatocellular Carcinoma Model PLC/PRF/5. Liu, Li; Cao, Yichen; Chen, Charles; Zhang, Xiaomei; McNabola, Angela; Wilkie, Dean; Wilhelm, Scott; Lynch, Mark; Carter, Christopher. Department of Cancer Biology, Bayer HealthCare Pharmaceuticals, West Haven, CT, USA. *Cancer Research* (2006), 66(24), 11851-11858. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 146:243471 AN 2006:1323939 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Angiogenesis and signaling through the RAF/mitogen-activated protein/extracellular signal-regulated kinase (ERK) kinase (MEK)/ERK cascade have been reported to play important roles in the development of hepatocellular carcinomas (HCC). Sorafenib (BAY 43-9006, Nexavar) is a multikinase inhibitor with activity against Raf kinase and several receptor tyrosine kinases, including vascular endothelial growth factor receptor 2 (VEGFR2), platelet-derived growth factor receptor (PDGFR), FLT3, Ret, and c-Kit. In this study, we investigated the in vitro effects of sorafenib on PLC/PRF/5 and HepG2 HCC cells and the in vivo antitumor efficacy and mechanism of action on PLC/PRF/5 human tumor xenografts in severe combined immunodeficient mice. Sorafenib inhibited the phosphorylation of MEK and ERK and down-regulated cyclin D1 levels in these two cell lines. Sorafenib also reduced the phosphorylation level of eIF4E and down-regulated the antiapoptotic protein Mcl-1 in a MEK/ERK-independent manner. Consistent with the effects on both

MEK/ERK-dependent and MEK/ERK-independent signaling pathways, sorafenib inhibited proliferation and induced apoptosis in both HCC cell lines. In the PLC/PRF/5 xenograft model, sorafenib tosylate dosed at 10 mg/kg inhibited tumor growth by 49%. At 30 mg/kg, sorafenib tosylate produced complete tumor growth inhibition. A dose of 100 mg/kg produced partial tumor regressions in 50% of the mice. In mechanism of action studies, sorafenib inhibited the phosphorylation of both ERK and eIF4E, reduced the microvessel area (assessed by CD34 immunohistochem.), and induced tumor cell apoptosis (assessed by terminal deoxynucleotidyl transferase-mediated nick end labeling) in PLC/PRF/5 tumor xenografts. These results suggest that the antitumor activity of sorafenib in HCC models may be attributed to inhibition of tumor angiogenesis (VEGFR and PDGFR) and direct effects on tumor cell proliferation/survival (Raf kinase signaling-dependent and signaling-independent mechanisms).

Answer 5:

Bibliographic Information

BRAF Is a Therapeutic Target in Aggressive Thyroid Carcinoma. Salvatore, Giuliana; De Falco, Valentina; Salerno, Paolo; Nappi, Tito Claudio; Pepe, Stefano; Troncone, Giancarlo; Carlomagno, Francesca; Melillo, Rosa Marina; Wilhelm, Scott M.; Santoro, Massimo. Dipartimento di Biologia e Patologia Cellulare e Molecolare, Istituto di Endocrinologia ed Oncologia Sperimentale del Consiglio Nazionale delle Ricerche, Naples, Italy. *Clinical Cancer Research* (2006), 12(5), 1623-1629. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 145:224395 AN 2006:205528 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: Oncogenic conversion of BRAF occurs in .apprx.44% of papillary thyroid carcinomas and 24% of anaplastic thyroid carcinomas. In papillary thyroid carcinomas, this mutation is assocd. with an unfavorable clinicopathol. outcome. Our aim was to exploit BRAF as a potential therapeutic target for thyroid carcinoma. **Exptl. Design:** We used RNA interference to evaluate the effect of BRAF knockdown in the human anaplastic thyroid carcinoma cell lines FRO and ARO carrying the BRAF V600E (V600EBRAF) mutation. We also exploited the effect of BAY 43-9006 [N-(3-trifluoromethyl-4-chlorophenyl)-N'-(4-(2-methylcarbamoyl pyridin-4-yl)oxyphenyl)urea], a multikinase inhibitor able to inhibit RAF family kinases in a panel of six V600EBRAF-pos. thyroid carcinoma cell lines and in nude mice bearing ARO cell xenografts. Statistical tests were two sided. **Results:** Knockdown of BRAF by small inhibitory duplex RNA, but not control small inhibitory duplex RNA, inhibited the mitogen-activated protein kinase signaling cascade and the growth of ARO and FRO cells ($P < 0.0001$). These effects were mimicked by thyroid carcinoma cell treatment with BAY 43-9006 ($IC_{50} = 0.5-1 \mu\text{mol/L}$; $P < 0.0001$), whereas the compd. had negligible effects in normal thyrocytes. ARO cell tumor xenografts were significantly ($P < 0.0001$) smaller in nude mice treated with BAY 43-9006 than in control mice. This inhibition was assocd. with suppression of phospho-mitogen-activated protein kinase levels. **Conclusions:** BRAF provides signals crucial for proliferation of thyroid carcinoma cells spontaneously harboring the V600EBRAF mutation and, therefore, BRAF suppression might have therapeutic potential in V600EBRAF-pos. thyroid cancer.