

Answer 1:

Bibliographic Information

Enhanced efficiency of thermally targeted taxanes delivery in a human xenograft model of gastric cancer. Liu, Baorui; Yang, Mi; Li, Xiaolin; Qian, Xiaoping; Shen, Zetian; Ding, Yitao; Yu, Lixia. Department of Oncology, Drum Tower Hospital Affiliated to Medical School of Nanjing University, Nanjing, Peop. Rep. China. *Journal of Pharmaceutical Sciences* (2008), 97(8), 3170-3181. Publisher: Wiley-Liss, Inc., CODEN: JPMSAE ISSN: 0022-3549. Journal written in English. AN 2008:947820 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Since successful chemotherapy with taxanes requires an improvement in their therapeutic index, esp. by the redn. in unwanted systemic toxicity of either drug or adjuvants, we have investigated and are reporting results from an investigation of the use of a novel polymeric thermosensitive micellar delivery system for docetaxel and paclitaxel. Here we reported a novel metastable thermosensitive polymeric micelle for docetaxel and paclitaxel delivery [poly(N-isopropylacrylamide-co-acrylamide)-b-poly(DL-lactide), Poly(IPAAm-co-AAm)-b-PDLLA]. Previous in vitro efficacy studies indicated that, with hyperthermia, docetaxel-loaded micelles showed stronger cytotoxicity to different tumor cell lines than conventional docetaxel formulation while exhibiting slighter toxicity to normal cells. Present in vivo studies indicated that at the same dose level of docetaxel (paclitaxel), hyperthermia greatly enhanced the antitumor effect of micellar docetaxel (paclitaxel) in human gastric BGC mouse xenograft model by showing an extraordinary tumor vol. and wt. growth percentage inhibition of more than 80%. Meanwhile, acute toxicity tests features the lower LD50 of the combination of hyperthermia and micellar docetaxel (paclitaxel) compared to that of the control group. The present results suggest that poly(IPAAm-co-AAm)-b-PDLLA micelles could be a clin. useful chemotherapeutic formulation and merit further research to evaluate the feasibility of clin. application.

Answer 2:

Bibliographic Information

Chemotherapeutic drugs induce PPAR- γ expression and show sequence-specific synergy with PPAR- γ ligands in inhibition of non-small cell lung cancer. Reddy, Raju C.; Srirangam, Anjaiah; Reddy, Kaunteya; Chen, Jun; Gangireddy, Srinivasareddy; Kalemkerian, Gregory P.; Standiford, Theodore J.; Keshamouni, Vekateshwar G. Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine, University of Michigan Medical Center, Ann Arbor, MI, USA. *Neoplasia* (Ann Arbor, MI, United States) (2008), 10(6), 597-603. Publisher: Neoplasia Press Inc., CODEN: NEOPFL ISSN: 1522-8002. <http://www.neoplasia.com/pdf/manuscript/v10i06/neo08134.pdf> Journal; Online Computer File written in English. AN 2008:871375 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Preclin. studies have shown that peroxisome proliferator-activated receptor γ (PPAR- γ) ligands can exert antitumor effects against non-small cell lung cancer (NSCLC) and a variety of other cancers. In this study, we investigate the potential use of a PPAR- γ ligand, troglitazone (Tro), in combination with either of two chemotherapeutic agents, cisplatin (Cis) or paclitaxel (Pac), for the treatment of NSCLC. In vitro, treatment of NSCLC cell lines with Tro potentiated Cis- or Pac-induced growth inhibition. The potentiation of growth inhibition was obsd. only when Cis or Pac treatment was followed by Tro and not vice versa, demonstrating a sequence-specific effect. Median effect anal. revealed a synergistic interaction between Tro and Cis in the inhibition of NSCLC cell growth and confirmed the sequence-specific effect. We also found that Cis or Pac up-regulated the expression of PPAR- γ protein, accounting for the obsd. sequence-specific synergy. Similarly, expts. performed using a NSCLC xenograft model demonstrated enhanced effectiveness of combined treatment with Cis and PPAR- γ ligands, Tro or pioglitazone. Tumors from Cis-treated mice also demonstrated enhanced PPAR- γ expression. Together, our data demonstrate a novel sequence-specific synergy between PPAR- γ ligands and chemotherapeutic agents for lung cancer treatment.

Answer 3:

Bibliographic Information

Antitumor effects of paclitaxel-loaded liposome on S180 ascites-tumor bearing mice. Chen, Ning; Yang, Mi; Qian, Xiaoping; Yu, Lixia; Liu, Baorui. Department of Oncology, The Affiliated Drum Tower Hospital of Medical School, Nanjing University, Nanjing, Jiangsu Province, Peop. Rep. China. Nanjing Yike Daxue Xuebao (2007), 27(7), 706-710, C3. Publisher: Nanjing Yike Daxue Xuebao Bianjibu, CODEN: NYDXFS ISSN: 1007-4368. Journal written in Chinese. AN 2008:811618 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Antitumor effect of paclitaxel-loaded liposomes with paclitaxel on S180 ascites-tumor bearing mice was compared. The paclitaxel-loaded liposomes were prepd. by reverse evapn. and sonication techniques. The particle diams. were measured by dynamic light scattering (DLS) measurement and the entrapment efficiency was measured by the reverse-phase high-pressure liq. chromatograph (RP-HPLC) method. Twenty Kunming mice bearing ascites tumor xenografts were distributed into four groups at random: control, empty-liposome group, free paclitaxel group and paclitaxel-loaded liposome group. Treatments were started after 24 h of implantation. Two groups bearing S180 xenograft were treated i.p. with 10 mg/kg of paclitaxel (free drug or liposome encapsulated). The other two groups were given i.p. with saline or empty-liposomes. All the treatments were given 4 times and the interval was 72 h. The av. diam. of the paclitaxel-loaded liposome was 282.4 ± 8.94 nm. The entrapment efficiency was 91%. There were much ascites in the three groups of the control, empty-liposomes and free paclitaxel. While in the group of paclitaxel-loaded liposomes, there was little ascites. In addn., there were dramatically little metastasis in abdominal cavity with the group of the paclitaxel-loaded liposomes other than the other three groups. Ascites and metastasis in abdominal cavity could be inhibited by paclitaxel-loaded liposomes to S180 ascites-tumor bearing mice remarkably.

Answer 4:

Bibliographic Information

A Paclitaxel-Hyaluronan Bioconjugate Targeting Ovarian Cancer Affords a Potent In vivo Therapeutic Activity. Banzato, Alessandra; Bobisse, Sara; Rondina, Maria; Renier, Davide; Bettella, Fabio; Esposito, Giovanni; Quintieri, Luigi; Melendez-Alafort, Laura; Mazzi, Ulderico; Zanovello, Paola; Rosato, Antonio. Departments of Oncology and Surgical Sciences, University of Padua, Padua, Italy. Clinical Cancer Research (2008), 14(11), 3598-3606. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. AN 2008:678356 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

PURPOSE: This study was designed to evaluate the pharmacol. and biol. properties of a paclitaxel-hyaluronan bioconjugate (ONCOFID-P) against IGROV-1 and OVCAR-3 human ovarian cancer xenografts following i.p. administration. **Exptl. Design:** In vitro tumor sensitivity to ONCOFID-P was analyzed by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay, whereas bioconjugate interaction with cells was studied cytofluorimetrically and by confocal microscopy. In vivo toxicity was assessed by a single-dose max.-tolerated dose, peripheral blood cell count detn. and by histol. anal. Biodistribution of the compd. was evaluated with a small animal-dedicated scintigraphy gamma camera following injection of ^{99m}Tc -labeled ONCOFID-P. Pharmacokinetic anal. was also carried out. Female severe combined immunodeficiency mice implanted with ovarian cancer cells underwent treatment with ONCOFID-P or free paclitaxel starting from day 7 or 14 after tumor injection, and survivals were compared. **RESULTS:** ONCOFID-P interacted with CD44, entered cells through a receptor-mediated mechanism, and exerted a concn.-dependent inhibitory effect against tumor cell growth. After i.p. administration, the bioconjugate distributed quite uniformly within the peritoneal cavity, was well-tolerated, and was not assocd. with local histol. toxicity. Pharmacokinetic studies revealed that blood levels of bioconjugate-derived paclitaxel were much higher and persisted longer than those obtained with the unconjugated free drug. I.p. treatment of tumor-bearing mice with the bioconjugate revealed that ONCOFID-P exerted a relevant increase in therapeutic activity compared with free drug. **CONCLUSIONS:** ONCOFID-P significantly improved results obtained with conventional paclitaxel, in terms of in vivo tolerability and therapeutic efficacy; these data strongly support its development for locoregional treatment of ovarian cancer.

Answer 5:

Bibliographic Information

Dexamethasone inhibits the therapeutic effect of paclitaxel against human ovarian xenograft tumors. Hou, Wen-jing; Liu, Yan. Department of Obstetrics and Gynecology, Changzheng Hospital, Second Military Medical University, Shanghai, Peop. Rep. China. Shanghai Yixue (2008), 31(4), 275-277, C3. Publisher: Shanghai Yixue Bianji Weiyuanhui, CODEN: SIHSD8 ISSN: 0253-9934. Journal written in Chinese. AN 2008:662716 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Objective To explore the influence of dexamethasone (DEX) on the anti-tumor effect of paclitaxel (PTX) in vivo. **Methods** Human ovarian xenograft models were established with nude mice and were randomly divided into 4 groups (n = 10), namely, the control group, dexamethasone (1 mg/kg, i.p.) group, paclitaxel (20 mg/kg, iv) group, and a combination (dexamethasone and paclitaxel; dexamethasone was administered 12 h before paclitaxel treatment; drugs were given once every 3 days for 6 cycles) group. The vols. and wt. of tumor mass were detected and the tumor inhibitory rates were calcd. Immunohistochem. assay was used to examine the expression of bcl-xl and cleaved caspase-3 protein. **Results** The tumor wt. was (1.43 ± 0.13)g in the control group, (1.53 ± 0.16)g in the Dex group, (0.79 ± 0.09)g in the DEX+PTX group, and (0.52 ± 0.06)g in PTX group, with those of the latter 2 groups significantly lower than that of the control group (both P < 0.01). The inhibitory rate of DEX+PTX group was 44.76%, which was significantly lower than that of the PTX group (63.64%). The expression of bcl-xl protein in DEX+PTX group was significantly higher than that of the PTX group (P < 0.00714); the expression of Caspase-3 protein was lower in the Dex+PTX group compared with that in the PTX group (P < 0.00714). **Conclusions** Pretreatment of human ovarian cell lines SKOV-3 with dexamethasone can inhibit paclitaxel-induced tumor cell apoptosis through inhibiting caspase-3 activity via bcl-xl pathway, thus decreases the therapeutic efficacy of paclitaxel.

Answer 6:

Bibliographic Information

Preclinical investigations with epothilones in breast cancer models. Burris, Howard A., III. Sarah Cannon Research Institute, Nashville, TN, USA. Seminars in Oncology (2008), 35(2, Suppl. 2), S15-S21. Publisher: Elsevier Inc., CODEN: SOLGAV ISSN: 0093-7754. Journal; General Review written in English. CAN 149:69269 AN 2008:617844 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A review. The epothilones constitute a novel class of microtubule inhibitors that act like the taxanes by hyperstabilizing tubulin polymn., thus disrupting functioning of the mitotic spindle. Natural epothilones produced by mycobacteria, and second- or third-generation partially or fully synthesized analogs, have been explored as cancer chemotherapy agents to replace or follow the taxanes. For those epothilones that have gone on to clin. development (epothilone B, ixabepilone, BMS-310705, ZK-EPO, KOS-862, and KOS-1584), preclin. investigations in breast cancer models are reviewed. All of these epothilones improve upon the cytotoxic activity of paclitaxel in various human breast cancer cell lines in vitro, but are also highly active in lines that are resistant to paclitaxel. Comparable antitumor activity has been demonstrated against nude mouse xenografts of paclitaxel-sensitive and -resistant breast cancer lines. Addnl., some analogs have reduced toxicity or increased water soly. that may permit oral administration, while others with enhanced tissue penetration show promise in animal models of breast cancer brain or bone metastasis and may provide benefits in patients with poor-prognosis advanced breast cancer.

Answer 7:

Bibliographic Information

Preparation of paclitaxel loaded PLGA microspheres and its efficacy in Hep-2 laryngeal squamous cell carcinoma-bearing nude mice. Xie, Ming; Zhou, Liang; Gao, Zhaobing; Yao, Ming. Department of Otolaryngology, Eye and ENT Hospital, Fudan University, Shanghai, Peop. Rep. China. Fudan Xuebao, Yixueban (2007), 34(1), 51-56. Publisher: Fudan Xuebao, Yixueban

Bianji Weiyuanhui, CODEN: FXYUAO ISSN: 1672-8467. Journal written in Chinese. CAN 149:112143 AN 2008:511705
CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Poly (lactic-co-glycolic acid) (PLGA) was used to develop paclitaxel loaded sustained-release microspheres and the efficacy of the polymer delivered intratumorally against Hep-2 xenografts in nude mice was investigated. PLGA microspheres contg. paclitaxel were prepd. by modified solvent evapn. method. The in vitro characteristics were evaluated. Tumor nodules were treated by multiple i.p. or a single intratumoral administration of paclitaxel injection or a single intratumoral injection of paclitaxel loaded PLGA microspheres. Spherical microspheres with smooth surface were obtained. The drug loading, encapsulation efficiency, mean diam. and span of disparity were 1.53%, 97.29%, 42.72 μm and 0.95, resp. The cumulative release from microspheres was 53.53% during 30-day period. Compared with the physiol. saline control group, the tumor size and the tumor wt. of the groups treated with paclitaxel injection or microspheres was significantly reduced ($P<0.05$) and the tumor vol. tripling time(TT) was significantly prolonged ($P<0.01$). The TT of the group receiving intratumoral injection of paclitaxel microspheres at low dose was significantly increased compared with the paclitaxel injection groups by intratumoral or i.p. administration ($P<0.05$). The TT of the group treated with paclitaxel microspheres at high dose was significantly increased compared to other paclitaxel treated groups ($P<0.01$). The tumor inhibition rates of groups treated with i.p. paclitaxel injection, it paclitaxel injection, it paclitaxel-loaded PLGA microspheres at low and high doses were 35.99%, 39.37%, 47.83% and 59.90%, resp. PLGA blank microspheres had no effect on the tumor growth. No significant toxic reactions were obsd. in the expt. Paclitaxel loaded sustained-release microspheres were successfully prepd. Intratumoral administration of the polymer delivery system enhances the efficacy of paclitaxel against laryngeal squamous cell carcinoma.

Answer 8:

Bibliographic Information

Luteolin induces apoptosis in oral squamous cancer cells. Yang, S.-F.; Yang, W.-E.; Chang, H.-R.; Chu, S.-C.; Hsieh, Y.-S. Institute of Medicine, Chung Shan Medical University, Taichung, Taiwan. Journal of Dental Research (2008), 87(4), 401-406. Publisher: International Association for Dental Research, CODEN: JDREAF ISSN: 0022-0345. Journal written in English. CAN 149:44537 AN 2008:506317 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Oral squamous cell carcinoma is the most common malignancy of the oral cavity, and treatment approaches are inadequate. Luteolin, a natural flavonoid compd., has been shown to have anti-tumorigenic properties on various types of tumors. Therefore, we hypothesized that luteolin has anti-tumorigenic properties for oral squamous cell carcinoma, and may provide effective chemotherapy. Results revealed that luteolin reduced the viability of SCC-4 cells and induced apoptosis by decreasing the expression of cyclin-dependent kinase (CDKs), cyclins, and phosphor-retinoblastoma (p-Rb) anti-apoptotic protein, but increased the expression of pro-apoptotic proteins and activated caspase 9 and 3, with a concomitant increase in the levels of cleaved poly-ADP-ribose polymerase (PARP). Combination treatment of luteolin with paclitaxel enhanced the cytotoxic effect of paclitaxel in SCC-4 cells, and continuous administration of luteolin suppressed the growth of xenograft tumors in nude mice. These results suggest that luteolin could be an effective chemotherapeutic agent for the treatment of oral squamous cell carcinoma.

Answer 9:

Bibliographic Information

Combination of all-trans retinoic acid and paclitaxel-induced differentiation and apoptosis in human glioblastoma U87MG xenografts in nude mice. Karmakar, Surajit; Banik, Naren L.; Ray, Swapan K. Department of Neurosciences, Medical University of South Carolina, Charleston, SC, USA. Cancer (Hoboken, NJ, United States) (2008), 112(3), 596-607. Publisher: John Wiley & Sons, Inc., CODEN: CANCAR ISSN: 0008-543X. Journal written in English. CAN 148:440472 AN 2008:274492 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: Glioblastoma, which is the most malignant brain tumor, remains incurable and almost always causes death. As a new treatment strategy, the combination of all-trans retinoic acid (ATRA) and paclitaxel was explored for controlling the growth of glioblastoma U87MG xenografts. Methods: Human glioblastoma U87MG xenografts were developed in athymic nude mice for treatments with ATRA, paclitaxel, and ATRA plus paclitaxel. The efficacy of treatments in controlling tumor growth was assessed by histol. examn., Western blot anal., and immunofluorescent labelings. Results: Astrocytic differentiation in U87MG xenografts was assocd. with increased GFAP expression and decreased telomerase expression. The combination of ATRA and paclitaxel was found to cause more apoptosis than paclitaxel alone. Apoptosis occurred with down-regulation of MEK-2 and overexpression of p-ERK, p-JNK, and p-p38 MAPK. Down-regulation of both Akt and p-Akt also favored the apoptotic process. Combination therapy activated the receptor-mediated pathway of apoptosis with induction of TNF- α , activation of caspase-8, and cleavage of Bid to tBid. Combination therapy also induced the mitochondria-mediated pathway of apoptosis with an increase in the Bax:Bcl-2 ratio and mitochondrial release of cytochrome c and Smac/Diablo into the cytosol. In addn., combination therapy promoted phosphorylation of Bcl-2 for its inactivation and down-regulated NF- κ B and BIRC proteins, indicating suppression of several cell survival factors. Western blot anal. demonstrated that activation of cysteine proteases such as calpain, caspase-12, caspase-9, and caspase-3 contributed to apoptosis. Immunofluorescent labelings confirmed overexpression of cysteine proteases in apoptosis. Conclusions: Treatment of U87MG xenografts with a combination of ATRA and paclitaxel induced differentiation and also multiple mol. mechanisms for apoptosis.

Answer 10:

Bibliographic Information

Effect of E1A gene on the chemosensitivity to transplantation tumor in nude mice. Guo, Zheng-yu; Zhang, Rong; Xie, Yun; Shen, Liang-fang. The First Affiliated Hospital of Hunan University of Traditional Chinese Medicine, Changsha, Hunan, Peop. Rep. China. Zhongguo Xiandai Yixue Zazhi (2007), 17(8), 917-920, 925. Publisher: Zhongguo Xiandai Yixue Zazhishe, CODEN: ZXYZAL ISSN: 1005-8982. Journal written in Chinese. AN 2008:259145 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

[Objective] This study is to investigate the chemosensitivity of E1A gene on human cervical carcinoma xenografts in nude mice and the correlative mechanism. [Methods] Chemosensitivity of E1A gene on human cervical carcinoma xenografts in nude mice was obsd. by the expt. imitating chemotherapy on nude mice with E1A gene. The expression of E1A gene and its effect on HER-2/neu expression was detected by RT-PCR. [Results] The expt. imitating chemotherapy on nude mice with E1A gene showed that the tumor vol. in E1A group deflated most obviously, the tumor quality was evidently lower than control group and blank-vector group ($P < 0.05$); and there is no statistical difference between the last two groups ($P > 0.05$). RT-PCR demonstrated that E1A gene had a stable transfection in Hela cells and obviously down-regulated HER-2/neu expression. [Comclusion] E1A gene can effectively enhance the chemosensitivity of human cervical carcinoma xenografts in nude mice to paclitaxel and the mechanism of action may relate to the down-regulation of the HER-2/neu expression by E1A gene.

Answer 11:

Bibliographic Information

Methylseleninic Acid Enhances Taxane Drug Efficacy against Human Prostate Cancer and Down-Regulates Antiapoptotic Proteins Bcl-XL and Survivin. Hu, Hongbo; Li, Guang-xun; Wang, Lei; Watts, Jennifer; Combs, Gerald F., Jr.; Lu, Junxuan. The Hormel Institute, University of Minnesota, Austin, MN, USA. Clinical Cancer Research (2008), 14(4), 1150-1158. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 148:576032 AN 2008:199425 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

PURPOSE: Our previous work has shown that methylseleninic acid (MSeA) sensitized hormone refractory prostate cancer (HRPCa)

cells to apoptosis induced by paclitaxel (Taxol) through enhancing multiple caspases. This study aimed to (a) det. the general applicability of the sensitization effect for taxane drugs in vitro, (b) establish the enhancement of paclitaxel efficacy by MSeA in vivo, and (c) investigate Bcl-XL and survivin as mol. targets of MSeA to augment apoptosis. Exptl. design: DU145 and PC-3 HRPcCa cell lines were used to evaluate the in vitro apoptosis effects of paclitaxel, docetaxel and their combination with MSeA, and the mol. mechanisms. DU145 xenograft growth in athymic nude mice was used to evaluate the in vivo efficacy of paclitaxel and its combination with MSeA. The tumor samples were used to examine Bcl-XL and survivin protein abundance. RESULTS: MSeA combination with paclitaxel or docetaxel exerted a greater than additive apoptosis effect on DU145 and PC-3 cells. In nude mice, paclitaxel and MSeA combination inhibited growth of DU145 s.c. xenograft with the equiv. efficacy of a four-time higher dose of paclitaxel alone. MSeA decreased the basal and paclitaxel-induced expression of Bcl-XL and survivin in vitro and in vivo. Ectopic expression of Bcl-XL or survivin attenuated MSeA/paclitaxel-induced apoptosis. CONCLUSIONS: MSeA enhanced the efficacy of paclitaxel against HRPcCa in vitro and in vivo, at least in part, by down-regulating the basal and paclitaxel-induced expression of both Bcl-XL and survivin to increase caspase-mediated apoptosis. MSeA may be a novel agent to improve taxane combination therapy.

Answer 12:

Bibliographic Information

STX140 Is Efficacious In vitro and In vivo in Taxane-Resistant Breast Carcinoma Cells. Newman, Simon P.; Foster, Paul A.; Stengel, Chloe; Day, Joanna M.; Ho, Yaik T.; Judde, Jean-Gabriel; Lassalle, Myriam; Prevost, Gregoire; Leese, Mathew P.; Potter, Barry V. L.; Reed, Michael J.; Purohit, Atul. Endocrinology and Metabolic Medicine, Faculty of Medicine, Imperial College London, Sterix, Ltd., St Mary's Hospital, London, UK. Clinical Cancer Research (2008), 14(2), 597-606. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. AN 2008:106247 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

PURPOSE: The aim of these studies was to characterize the action of STX140 in a P-glycoprotein-overexpressing tumor cell line both in vitro and in vivo. In addn., its efficacy was detd. against xenografts derived from patients who failed docetaxel therapy. Exptl. Design: The effects of STX140, Taxol, and 2-methoxyestradiol (2-MeOE2) on cell proliferation, cell cycle, and apoptosis were assessed in vitro in drug-resistant cells (MCF-7DOX) and the parental cell line (MCF-7WT). Mice bearing an MCF-7DOX tumor on one flank and an MCF-7WT tumor on the other flank were used to assess the in vivo efficacy. Furthermore, the responses to STX140 of three xenografts, derived from drug-resistant patients, were assessed. RESULTS: In this study, STX140 caused cell cycle arrest, cyclin B1 induction, and subsequent apoptosis of both MCF-7DOX and MCF-7WT cells. Taxol and 2-MeOE2 were only active in the MCF-7WT parental cell line. Although both STX140 and Taxol inhibited the growth of xenografts derived from MCF-7WT cells, only STX140 inhibited the growth of tumors derived from MCF-7DOX cells. 2-MeOE2 was ineffective at the dose tested against both tumor types. Two out of the three newly derived docetaxel-resistant xenografts, including a metastatic triple-neg. tumor, responded to STX140 but not to docetaxel treatment. CONCLUSIONS: STX140 shows excellent efficacy in both MCF-7WT and MCF-7DOX breast cancer xenograft models, in contrast to Taxol and 2-MeOE2. The clin. potential of STX140 was further highlighted by the efficacy seen in xenografts recently derived from patients who had failed on taxane therapy.

Answer 13:

Bibliographic Information

A study on antitumor effect of liposome encapsulated paclitaxel in vivo and in vitro. Yang, Aizhen; Li, Jun; Xu, Haijun; Chen, Huiying. PLA Cancer Center, The 81st Hospital, Nanjing, Jiangsu Province, Peop. Rep. China. Zhongguo Zhongliu (2006), 15(12), 862-864. Publisher: Zhejiang Sheng Zhongliu Yiyuan, CODEN: ZZHHCY ISSN: 1004-0242. Journal written in Chinese. CAN 148:345982 AN 2008:81006 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The cytotoxic effect of paclitaxel liposome for injection in vitro was studied, and the antitumor activity and toxicity in vivo were obsd.

The cytotoxic effect of paclitaxel liposome on human lung adenocarcinoma cell line SPC-A1 in vitro was detected by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay. The model of mice solid S180 sarcoma was established, and 50 mice were divided into 5 groups: 5% glucose soln. group (the control group), 10 mg/kg and 15 mg/kg paclitaxel injection groups, 10 mg/kg and 15mg/kg paclitaxel liposome groups. The antitumor activity of each group and general condition of mice was obsd., and the myelogram and the hepatic function index of S180 mice were detected. The inhibitory rate of paclitaxel liposome on human lung adenocarcinoma cell line SPC-A1 was 39.0%, 51.9% and 55.8% at the concns. of 2.5 ng/mL, 5.0 ng/mL and 10.0 ng/mL, resp. Under the doses of 10 mg/(kg-d) and 15 mg/(kg-d) for 3 days, the inhibitory rate of paclitaxel liposome against xenograft of solid S180 tumor in mice was 31.12% and 45.29%, resp., and there were no significant difference among those of the paclitaxel injection groups. Comparing with the paclitaxel injection groups, the animal behavior and mice wt. variable rate of paclitaxel liposome groups were similar to the control group, and less myelosuppression. It suggested that paclitaxel liposome possessed the same anti-tumor activities in vitro and in vivo but its toxicity was lower than that of paclitaxel injection under the same dosage.

Answer 14:

Bibliographic Information

Paclitaxel enhanced radiation sensitization for the suppression of human prostate cancer tumor growth via a p53 independent pathway. Zhang, An Ling; Russell, Pamela J.; Knittel, Tony; Milross, Chris. Oncology Research Centre, Prince of Wales Hospital, Randwick, NSW, Australia. Prostate (Hoboken, NJ, United States) (2007), 67(15), 1630-1640. Publisher: Wiley-Liss, Inc., CODEN: PRSTDS ISSN: 0270-4137. Journal written in English. CAN 148:115641 AN 2007:1388605 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

This study investigated the influence of p53 status on treatment using combined paclitaxel and irradiation for human prostate cancer (PC) in vitro and in vivo. Enhancement of the radiation response by paclitaxel was detected by MTT and clonogenic assays in four sublines of the human PC cell line, LNCaP, stably transfected to express different p53 mutations found in PC patients. Suppression of xenograft growth by combined paclitaxel and radiation was assessed in NOD.SCID mice in vivo. Expression of p53 and downstream functional proteins, p21 and Bax, was assessed by Western blotting. Paclitaxel (8-10 nM) suppressed cell proliferation by 50% by inducing G2M mitotic arrest in LNCaP cell lines transfected to overexpress wild-type or mutant p53. Exposure to 20 nM paclitaxel before radiation therapy enhanced cytotoxicity in clonogenic assays. The dose and duration of paclitaxel exposure were important in inducing both G2M arrest and cell growth suppression and were critical factors in paclitaxel/irradiation combination therapy. Western blotting indicated that combination therapy increased p21 protein expression to varying degrees in all cell lines. In vivo studies indicated that paclitaxel pre-treatment followed by irradiation significantly suppressed tumor growth compared with either treatment alone. Pre-treatment with paclitaxel enhances radiation efficacy on cell killing and suppression of growth of human PC cell lines in vitro and in vivo via p53 independent pathways. Paclitaxel has potential for use as a radiosensitizer in the treatment of patients with PC with either wild-type or mutant p53 genetic status.

Answer 15:

Bibliographic Information

In vivo study for the controlled delivery of paclitaxel from electro-hydrodynamic atomized microparticles for the post-surgical treatment of glioma blastoma multiforme. Sheng, Benjamin Ong Yung; Xie, Jingwei; Wang, Chi-Hwa; Lee, How-Sung; Lu, Fan. Department of Chemical and Biomolecular Engineering, National University of Singapore, Singapore, Singapore. AIChE Annual Meeting, Conference Proceedings, San Francisco, CA, United States, Nov. 12-17, 2006 (2006), 543d/1-543d/5. Publisher: American Institute of Chemical Engineers, New York, N. Y. CODEN: 69KANW Conference; Computer Optical Disk written in English. CAN 148:85383 AN 2007:1371373 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The release behavior of 20% paclitaxel loaded microparticles fabricated by electro-hydrodynamic atomization (EHDA) in an in vivo

environment was established. Microparticles were fabricated by subjecting a soln. of poly(DL-lactic-co-glycolic acid 50:50) and paclitaxel through EHDA. The results showed that there is no sign of bulk failure and presented the tumor suppression response of the microparticles over the com. Taxol.

Answer 16:

Bibliographic Information

Tumor-host interaction in the optimization of paclitaxel-based combination therapies with vascular targeting compounds.

Giavazzi, Raffaella; Bani, Maria Rosa; Tarabozetti, Giulia. Laboratory of Biology and Treatment of Metastasis, Department of Oncology, Mario Negri Institute for Pharmacological Research, Bergamo, Italy. *Cancer and Metastasis Reviews* (2007), 26(3/4), 481-488. Publisher: Springer, CODEN: CMRED4 ISSN: 0167-7659. Journal; General Review written in English. CAN 148:369014 AN 2007:1287689 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A review. Targeting of the tumor stroma, including the tumor vasculature, represents a new frontier in the treatment of malignancy. Preclin. studies and clin. experiences have established that stroma-directed novel agents must be combined with conventional therapies in order to achieve relevant therapeutic efficacy. Here we review our preclin. experience on combinations of paclitaxel with a tyrosine kinase receptor inhibitor of angiogenesis (SU6668) and a vascular disrupting agent (VDA, ZD6126), and discuss the crit. factors that det. the outcome of these treatments. We also analyze the relevance of the intrinsic sensitivity of the tumor to the drugs, as well as the possibility that the two combined agents synergistically affect the vasculature or independently target the host and the tumor compartments. Finally, we discuss the need to carefully optimize scheduling and sequencing, through the use of reliable end points, in order to avoid neg. pharmacol. interactions and to improve the antineoplastic efficacy of paclitaxel-based combination treatments.

Answer 17:

Bibliographic Information

Distinct pharmacological properties of second generation HDAC inhibitors with the benzamide or hydroxamate head group.

Beckers, Thomas; Burkhardt, Carmen; Wieland, Heike; Gimmich, Petra; Ciossek, Thomas; Maier, Thomas; Sanders, Karl. Therapeutic Area Oncology, ALTANA Pharma, Konstanz, Germany. *International Journal of Cancer* (2007), 121(5), 1138-1148. Publisher: Wiley-Liss, Inc., CODEN: IJCNW ISSN: 0020-7136. Journal written in English. CAN 147:514632 AN 2007:1152971 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Advanced second generation inhibitors of histone deacetylases (HDAC) are currently used in clin. development. This study aimed at comparing the pharmacol. properties of selected second generation HDAC inhibitors with the hydroxamate and benzamide head group, namely SAHA, LAQ824/LBH589, CI994, MS275 and MGCD0103. In biochem. assays using recombinant HDAC1, 3, 6 and 8 isoenzymes, SAHA and LAQ824/LBH589 behave as quite unselective HDAC inhibitors. In contrast, the benzamides CI994, MS275 and MGCD0103 are more selective, potent inhibitors of at least HDAC1 and HDAC3. All HDAC inhibitors induce histone H3 hyperacetylation, correlating with inhibition of proliferation, induction of cell differentiation and apoptosis. A broad cytotoxicity is seen across cell lines from different tumor entities with LAQ824/LBH589 being the most potent agents. The apoptosis inducing activity is evident in arrested and proliferating RKO colon cancer cells with inducible, heterologous p21waf1 expression, indicative for a cell-cycle independent mode-of-action. Differentiation of MDA-MB468 breast cancer cells is induced by benzamide and hydroxamate analogs. The reversibility of drug action was evaluated by pulse treatment of A549 lung cancer cells. Whereas paclitaxel induced irreversible cell cycle alterations already after 6 h treatment, HDAC inhibitor action was retarded and irreversible after >16 h treatment. Interestingly, pulse treatment was equally effective as continuous treatment. Finally, the efficacy of LAQ824, SAHA and MS275 in A549 nude mice xenografts was comparable to that of paclitaxel at well tolerated doses. We conclude that despite a different HDAC isoenzyme inhibition profile, hydroxamate and benzamide analogs as studied display similar cellular profiles.

Answer 18:

Bibliographic Information

The effects of various chemotherapy regimens on the expression of PCNA and Bcl-2 in human breast cancer xenograft (MCF-7) transplanted in nude mice. Wang, Yu-dong; Liu, Wei; Ji, Zhi-min; Zhang, Zhi-gang; Lv, Ya-lei; Wang, Shu-qin. Department of Medical Oncology, The 4th Hospital of Hebei Medical University, Shijiazhuang, Peop. Rep. China. *Linchuang Zhongliuxue Zazhi* (2007), 12(3), 173-176. Publisher: Institution of Chinese Clinical Oncology Journal, CODEN: LZZIA5 ISSN: 1009-0460. Journal written in Chinese. CAN 148:205626 AN 2007:1152600 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The objective of the paper is to investigate the effects of various chemotherapy regimens on the expression of PCNA and Bcl-2 of breast cancer, to assess the relationships between chemotherapy and two markers, and to evaluate the value of them to predict the response of chemotherapy. Forty-eight nude mice models of human breast cancer xenograft (MCF-7) were established, and then were randomly divided into control and 5 chemotherapy groups (each group, n = 8). Among 5 chemotherapy groups, mice were treated i.p. or orally by 5 chemotherapy regimens (CMF, CAF, NP, TP, Xeloda) resp. at two-thirds LD10 (dose lethal to 10% of the mice). Control animals were administered i.p. with normal saline. The pathol. feature of transplanted tumor was studied by HE stain, and the expression of Bcl-2 and PCNA was studied by SP immunohistochem. method. The expression of PCNA in 5 chemotherapy group was significantly lower than that of control ($P < 0.05$), and the expression of PCNA in NP, TP and Xeloda groups was significantly lower than that of CMF and CAF groups ($P < 0.05$). Moreover, the expression of PCNA was significantly correlated with pathol. therapeutic response ($P = 0.001$). The expression of Bcl-2 in CAF, NP, TP, Xeloda groups was significantly higher than that of control ($P < 0.05$). Moreover, the expression of Bcl-2 in TP group was significantly higher than that of CMF and CAF groups ($P < 0.05$). The expression of Bcl-2 was not significantly correlated with the pathol. therapeutic response ($P = 0.093$). Chemotherapy can increase the expression of PCNA, and decrease the expression of Bcl-2. Different chemotherapy regimens have different effects on PCNA and Bcl-2. PCNA can become a factor to evaluate the response to chemotherapy, and become possibly the prospective factor of chemoselect.

Answer 19:

Bibliographic Information

Combination of all-trans retinoic acid and taxol regressed glioblastoma T98G xenografts in nude mice. Karmakar, Surajit; Banik, Naren L.; Patel, Sunil J.; Ray, Swapan K. Department of Neurosciences, Medical University of South Carolina, Charleston, SC, USA. *Apoptosis* (2007), 12(11), 2077-2087. Publisher: Springer, CODEN: APOPFN ISSN: 1360-8185. Journal written in English. CAN 148:205530 AN 2007:1108452 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Glioblastoma is the most prevalent and highly malignant brain tumor that continues to defy current treatment strategies. This investigation used all-trans retinoic acid (ATRA) and taxol (TXL) as a combination therapy for controlling the growth of human glioblastoma T98G xenografted in athymic nude mice. Histopathol. examn. revealed that ATRA induced differentiation and combination of ATRA and TXL caused more apoptosis than either treatment alone. Combination therapy decreased expression of telomerase, nuclear factor kappa B (NF κ B), and inhibitor-of-apoptosis proteins (IAPs) indicating suppression of survival factors while upregulated Smac/Diablo. Combination therapy also changed expression of Bax and Bcl-2 proteins leading to increased Bax:Bcl-2 ratio, mitochondrial release of cytochrome c and apoptosis-inducing factor (AIF), and activation of caspase-9. Increased activities of calpain and caspase-3 degraded 270 kD α -spectrin at the specific sites to generate 145 kD spectrin breakdown product (SBDP) and 120 kD SBDP, resp. Further, increased activity of caspase-3 cleaved inhibitor-of-caspase-activated DNase (ICAD). In situ double immunofluorescent labelings showed overexpression of calpain, caspase-12, caspase-3, and AIF during apoptosis, suggesting involvement of both caspase-dependent and caspase-independent pathways for apoptosis. Our investigation revealed that treatment of glioblastoma T98G xenografts with the combination of ATRA and TXL induced differentiation and multiple mol. mechanisms for apoptosis.

Answer 20:

Bibliographic Information**Clinical and mechanistic aspects of glucocorticoid-induced chemotherapy resistance in the majority of solid tumors.**

Zhang, Chengwen; Wenger, Till; Mattern, Juergen; Ilea, Septimia; Frey, Christian; Gutwein, Paul; Altevogt, Peter; Bodenmueller, Wolfram; Gassler, Nikolaus; Schnabel, Philipp A.; Dienemann, Hendrik; Marme, Alexander; Hohenfellner, Markus; Haferkamp, Axel; Pfitzenmaier, Jesco; Groene, Hermann-Josef; Kolb, Armin; Buechler, Peter; Buechler, Markus W.; Friess, Helmut; Rittgen, Werner; Edler, Lutz; Debatin, Klaus-Michael; Krammer, Peter H.; Rutz, Hans P.; Herr, Ingrid. Research Group Molecular OncoSurgery, University of Heidelberg, Heidelberg, Germany. *Cancer Biology & Therapy* (2007), 6(2), 278-287. Publisher: Landes Bioscience, CODEN: CBTAAO ISSN: 1538-4047. Journal written in English. CAN 147:479951 AN 2007:1039338 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Glucocorticoids have been used widely in conjunction with cancer therapy due to their ability to induce apoptosis in hematol. cells and to prevent nausea and emesis. However, recent data including ours, suggest induction of therapy-resistance by glucocorticoids in solid tumors, although it is unclear whether this happens only in few carcinomas or is a more common cell type specific phenomenon. We performed an overall statistical anal. of our new and recent data obtained with 157 tumor probes evaluated in vitro, ex vivo and in vivo. The effect of glucocorticoids on apoptosis, viability and cell cycle progression under diverse clin. important questions was examd. New in vivo results demonstrate glucocorticoid-induced chemotherapy resistance in xenografted prostate cancer. In an overall statistical anal. we found glucocorticoid-induced resistance in 89% of 157 analyzed tumor samples. Resistance is common for several cytotoxic treatments and for several glucocorticoid-derivs. and due to an inhibition of apoptosis, promotion of viability and cell cycle progression. Resistance occurred at clin. achievable peak plasma levels of patients under anti-emetic glucocorticoid therapy and below, lasted for a long time, after one single dose, but was reversible upon removal of glucocorticoids. Two nonsteroidal alternative anti-emetic agents did not counteract anticancer treatment and may be sufficient to replace glucocorticoids in cotreatment of carcinoma patients. These data demonstrate the need for prospective clin. studies as well as for detailed mechanistic studies of GC-induced cell-type specific pro- and anti-apoptotic signaling.

Answer 21:

Bibliographic Information

Novel biocompatible intraperitoneal drug delivery system increases tolerability and therapeutic efficacy of paclitaxel in a human ovarian cancer xenograft model. Vassileva, Vessela; Grant, Justin; De Souza, Raquel; Allen, Christine; Piquette-Miller, Micheline. Department of Pharmaceutical Sciences, Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Can. *Cancer Chemotherapy and Pharmacology* (2007), 60(6), 907-914. Publisher: Springer, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 148:127898 AN 2007:1019783 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: We compared the safety, toxicity, biocompatibility and anti-tumor efficacy of a novel chitosan-egg phosphatidylcholine (ePC) implantable drug delivery system that provides controlled and sustained release of paclitaxel (PTXePC) vs. com. paclitaxel formulated in Cremophor EL (PTXCrEL). Methods: Toxicity studies were conducted in healthy CD-1 female mice, whereas efficacy studies were performed in the SKOV-3 xenograft model of ovarian cancer. Treatments consisted of i.p. (IP) implantation of drug-free or PTXePC formulations, IP bolus PTXCrEL, or Cremophor EL (CrEL) vehicle. Toxicity was assessed as no. of deaths, wt. loss, serum hepatic enzyme levels and histopathol. changes. Results: Mice implanted with drug-free or PTXePC formulations did not exhibit observable toxicities, local inflammation or fibrous encapsulation of the implant. In contrast, mice receiving PTXCrEL or CrEL encountered significant toxicity, lethality, abnormal peritoneal organ morphol. and hepatic inflammation. The max. tolerable dose (MTD) of PTXCrEL was 20 mg/kg/wk, whereas PTX doses of up to 280 mg/kg/wk were well tolerated when administered as PTXePC. Enhanced anti-tumor efficacy was achieved with PTXePC in contrast to PTXCrEL with the same total dose of 60 mg/kg PTX. Conclusions: The novel PTXePC formulation is a safer and better tolerated method for PTX administration, with significant increase in MTD and enhanced anti-tumor efficacy, suggesting improved therapeutic index with possible clin. implications in the treatment of ovarian tumors.

Answer 22:

Bibliographic Information

Antitumor activity of capecitabine and bevacizumab combination in a human estrogen receptor-negative breast adenocarcinoma xenograft model. Higgins, Brian; Kolinsky, Kenneth; Linn, Michael; Adames, Violeta; Zhang, Yu-E.; Moisa, Carlos; Dugan, Ute; Heimbrook, David; Packman, Kathryn. Department of Discovery Oncology, Hoffmann-La Roche Inc., Nutley, NJ, USA. *Anticancer Research* (2007), 27(4B), 2279-2287. Publisher: International Institute of Anticancer Research, CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 147:439706 AN 2007:994186 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: Capecitabine and bevacizumab have each been shown to inhibit tumor growth. Their combination failed to improve survival in a phase III trial of metastatic breast cancer (MBC), although it should be noted patients had been heavily pretreated with anthracyclines and taxanes. Our aim was to evaluate whether combination treatment would increase tumor growth inhibition and survival in a breast cancer model. Materials and Methods: Mice bearing KPL-4 human estrogen receptor-neg. breast adenocarcinoma xenografts were given capecitabine orally daily for 14 days at the max. tolerated dose (MTD) or half MTD, alone or with 5 mg/kg i.p. bevacizumab twice weekly. Results: Tumor growth inhibition (TGI) and increased life span (ILS) were superior in the combination groups vs. monotherapy ($p < 0.05$). TGI and ILS were significantly improved in the high- vs. low-dose capecitabine combination ($p < 0.05$). Conclusion: Capecitabine in combination with bevacizumab provides a basis for pursuing the combination for first-line treatment of MBC.

Answer 23:

Bibliographic Information

Combination chemotherapy including combretastatin A4 phosphate and paclitaxel is effective against anaplastic thyroid cancer in a nude mouse xenograft model. Yeung, Sai-Ching J.; She, Miaorong; Yang, Huiling; Pan, Jingxuan; Sun, Lily; Chaplin, David. Departments of Endocrine Neoplasia and Hormonal Disorders, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA. *Journal of Clinical Endocrinology and Metabolism* (2007), 92(8), 2902-2909. Publisher: Endocrine Society, CODEN: JCEMAZ ISSN: 0021-972X. Journal written in English. CAN 147:226423 AN 2007:939208 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Context: Anaplastic thyroid cancer (ATC) is extremely aggressive, and no effective treatment is available. Combretastatin A4 phosphate (CA4P), a vascular disrupting agent, has limited activity against ATC in a clin. trial, and so does paclitaxel. Objective: We hypothesized that a triple-drug combination including CA4P and paclitaxel would improve efficacy against ATC. Therefore, we evaluated two such combinations in vivo. Setting: We used a nude mouse xenograft model with ARO and KAT-4 cells. Interventions: The first combination consisted of CA4P, paclitaxel, and manumycin A (a farnesyltransferase inhibitor), and the second, CA4P, paclitaxel, and carboplatin. Main Outcome Measures: Main outcome measures included tumor growth curves and tumor wts. Results: Tumor growth curve anal. (linear mixed models, $P < 0.05$) and xenograft wt. anal. (Kruskal-Wallis one-way ANOVA on ranks, post hoc pairwise comparison, Dunn's test, $P < 0.05$) demonstrated that both triple-drug combinations were significantly better than placebo for both cell lines. Anti-bromodeoxyuridine immunostaining of xenograft sections from animals injected with bromodeoxyuridine before being killed showed that CA4P alone did not inhibit DNA synthesis, but manumycin A and paclitaxel did. CA4P decreased the depth of the viable outer rim of tumor cells on xenograft sections. Using electron microscopy, we found blebbing/budding of endothelial cells into capillary lumens and autophagy of tumor cells in CA4P-treated xenografts. Conclusions: Both triple-drug combinations demonstrated excellent antineoplastic activity against ATC. The correlative findings in xenografts were consistent with vascular disruption but not direct inhibition of cell proliferation as the primary antineoplastic mechanism contributed by CA4P. These regimens warrant further investigation in clin. trials for ATC.

Answer 24:

Bibliographic Information

Inhibitory effects of combined low-dose chemotherapy on angiogenesis and growth of Lewis lung carcinoma xenografts in mice. Qiu, Meng; Yi, Cheng; Hou, Mei. West China Hospital, Sichuan University, Chengdu, Peop. Rep. China. Sichuan Daxue Xuebao, Yixueban (2006), 37(4), 534-537. Publisher: Sichuan Daxue Xuebao, Yixueban Bianjibu, CODEN: SDXYAY ISSN: 1672-173X. Journal written in Chinese. CAN 147:398005 AN 2007:852362 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Antiangiogenic and antitumor effects of combined low-dose cyclophosphamide (CTX) and paclitaxel (PTX) were investigated. In this expt., Lewis lung carcinoma model was established in C57BIL6 mice. Forty mice were randomly divided into four groups: control group, cyclophosphamide (170 mg/kg, q6d) group, paclitaxel (10 mg/kg, q7d) group and cyclophosphamide plus paclitaxel group. The growth of tumor and side effect of each therapy were investigated. Microvessel d. (MVD) was assessed by CD31 immunostaining, and immunohistochem. (IHC) image anal. was performed for semiquantification of vascular endothelial growth factor (VEGF). The combined low-dose therapy with cyclophosphamide and paclitaxel was most effective for antagonizing tumor-assocd. angiogenesis, and the mice of this group had the lowest MVD and VEGF expression, compared with mice of the other groups ($P < 0.005$). The combination therapy also brought about higher antitumor rate, lower tumor vol. and lower tumor wt. than did the single therapies ($P < 0.005$). The paclitaxel (10 mg/kg, q7d) therapy had the slightest side-effects, and the other therapies had similar acceptable side effects. The combined use of low dose cyclophosphamide and paclitaxel has synergistic antiangiogenic effect on mouse model of Lewis lung carcinoma, and the combination of these two agents is clearly more effective for inhibiting angiogenesis and growth of tumor.

Answer 25:

Bibliographic Information

Anti-tumor effects of bevacizumab in combination with paclitaxel on head and neck squamous cell carcinoma. Fujita, Kyoko; Sano, Daisuke; Kimura, Machiko; Yamashita, Yukiko; Kawakami, Mariko; Ishiguro, Yukari; Nishimura, Goshi; Matsuda, Hideki; Tsukuda, Mamoru. Department of Biology and Function in Head and Neck, City University Graduate School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama, Japan. Oncology Reports (2007), 18(1), 47-51. Publisher: Oncology Reports, CODEN: OCRPEW ISSN: 1021-335X. Journal written in English. CAN 147:320967 AN 2007:826593 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Human tumors are dependent on angiogenesis for growth, and the vascular endothelial growth factor (VEGF) is a major regulator of this process. Bevacizumab (Avastin), a monoclonal antibody directed against VEGF, has shown promise in treating a variety of cancers. In this study, we first examd. the anti-tumor effects of bevacizumab on head and neck squamous cell carcinoma (HNSCC). Then we examd. the effects of bevacizumab combined with paclitaxel, a chemotherapeutic agent, in HNSCC. This is the first demonstration of the anti-tumor effects of bevacizumab on HNSCC. In vitro, bevacizumab did not show any antiproliferative effects against the HNSCC cell lines. However, in vivo, bevacizumab showed dramatic anti-tumor effects against HNSCC tumor xenografts in mice. In addn., treatment with a bevacizumab-paclitaxel combination resulted in a remarkable inhibition of the HNSCC tumor xenografts, compared to the effects of each agent sep. A decreased blood vessel d. and an increased apoptotic index were seen in the shrunken tumors. These results suggest that bevacizumab in combination with paclitaxel could have useful clin. application in HNSCC.

Answer 26:

Bibliographic Information

Tumor priming enhances delivery and efficacy of nanomedicines. Lu, Dan; Wientjes, M. Guillaume; Lu, Ze; Au, Jessie L.-S. Division of Pharmaceutics, College of Pharmacy, Ohio State University, Columbus, OH, USA. Journal of Pharmacology and Experimental Therapeutics (2007), 322(1), 80-88. Publisher: American Society for Pharmacology and Experimental Therapeutics,

CODEN: JPETAB ISSN: 0022-3565. Journal written in English. CAN 147:307740 AN 2007:739041 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The authors have shown that high epithelial cell density is a major barrier to the distribution of protein-bound drugs in solid tumors, and tumor priming (expansion of interstitial space using an apoptosis-inducing pretreatment) can promote drug delivery. This study evaluated the optimal conditions of paclitaxel tumor priming (time window, particle size) and its effects on the delivery and efficacy of nanomedicines. Paclitaxel tumor priming was applied to mice bearing human xenograft tumors. The kinetics of paclitaxel-induced apoptosis was evaluated to identify the time window of tumor priming. The effects of tumor priming on the tumor delivery and interstitial dispersion of fluorescence-labeled nanoparticles of various sizes, the perfusion of tumor and normal tissues, the delivery of doxorubicin HCl liposomes to tumor and host tissues, and the antitumor activity and host toxicity were studied. Tumor priming by a single i.v. injection of paclitaxel induced apoptosis, expanded the interstitial space, vessel diameter and blood-perfused area, and promoted the delivery and interstitial dispersion of nanoparticles (100- and 200-nm diameter, administered 48 h after paclitaxel) in a tumor-selective manner. Tumor priming also enhanced the tumor delivery and antitumor activity of doxorubicin HCl liposomes (85 nm) without affecting the delivery to noncancerous host tissues or enhancing host toxicity. Tumor priming represents a potentially useful means to promote tumor-selective delivery and efficacy of nanomedicines. The current study will have significant impact on enhancing delivery and efficacy of nanomedicines and dosing regimen optimization of combination chemotherapy in the clinical setting.

Answer 27:

Bibliographic Information

Treatment parameters modulating regression of human melanoma xenografts by an antibody-drug conjugate

(CR011-vcMMAE) targeting GPNMB. Pollack, Vincent A.; Alvarez, Enrique; Tse, Kam Fai; Torgov, Michael Y.; Xie, Sam; Shenoy, Suresh G.; MacDougall, John R.; Arrol, Sharon; Zhong, Haihong; Gerwien, Robert W.; Hahne, William F.; Senter, Peter D.; Jeffers, Michael E.; Lichenstein, Henri S.; LaRochelle, William J. Department of Preclinical Development, CuraGen Corporation, Branford, CT, USA. Cancer Chemotherapy and Pharmacology (2007), 60(3), 423-435. Publisher: Springer, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 147:377815 AN 2007:646994 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

To investigate the pharmacological properties of the CR011-vcMMAE fully human antibody-drug conjugate (ADC), such as dose titration, quantitation of the time (days) to complete regression, pharmacokinetics, and schedule dependency. The prior study characterized a fully human antibody to GPNMB covalently linked to monomethylauristatin E, CR011-vcMMAE, and further demonstrated cell surface staining of melanoma lines susceptible to the immunoconjugate's cytotoxicity (Clin Cancer Res 2005; 12(4): 1373-1382). The human SK-MEL-2 and SK-MEL-5 melanoma xenografts were used in athymic mice to assess anti-tumor efficacy. After subcutaneous implantation, tumors became established (60-100 mg), and treatment commenced by intravenous injection of the immunoconjugate or vinblastine or paclitaxel. Short-term anti-tumor effects (inhibition of tumor growth) and long-term effects (complete regression) were observed. CR011-vcMMAE induced regression of established human SK-MEL-2 and SK-MEL-5 xenografts at doses from 1.25 to 80 mg/kg treatment when administered intravenously every 4 days (4 treatments); strikingly, regressions were not associated with re-growth during the observation period (200 days). The disappearance rate of implants was dose dependent (minimum time, 18.5 days). Detectable serum CR011-vcMMAE ≥ 1 $\mu\text{g/mL}$ (approximately 0.01 μM) was observed for >30 days post-dose; CR011-vcMMAE showed an elimination half-life of 10.3 days. A low volume of distribution suggested that CR011-vcMMAE was confined to blood and interstitial fluid. CR011-vcMMAE could be delivered by either a single bolus dose or by intermittent dosing (i.e., every 1, 2, 4, 8, or 16 days) with no discernible differences in the proportion of tumor-free survivors, indicating a lack of schedule dependency. The antibody-drug conjugate produced complete regressions, but the equivalent doses of free monomethylauristatin E or unconjugated antibody did not show anti-tumor effects. In addition, decreases in plasma tumor-derived human interleukin-8 coincided with tumor nodule disappearance.

Short-term anti-tumor effects and long-term effects (complete regression) were observed with CR011-vcMMAE, but not with the reference agents. These results suggest that CR011-vcMMAE may provide therapeutic benefit in malignant melanoma.

Answer 28:

Bibliographic Information

Kushen flavonoids induce apoptosis in tumor cells by inhibition of NF- κ B activation and multiple receptor tyrosine kinase activities. Han, Jun; Sun, Mingyu; Cui, Yumin; Wang, Tao; Zhang, Weihai; Guo, Mingchuan; Zhou, Yuan; Liu, Wei; Zhang, Meifang; Duan, Jifeng; Xiong, Sidong; Yao, Minghui; Yan, Xiaoqiang. Departments of Biology and Pharmacology, Hutchison Medipharma Ltd., Shanghai, Peop. Rep. China. *Phytotherapy Research* (2007), 21(3), 262-268. Publisher: John Wiley & Sons Ltd., CODEN: PHYREH ISSN: 0951-418X. Journal written in English. CAN 147:157687 AN 2007:530355 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

In this report, the mechanism of the antitumor activities of Kushen flavonoids (KS-Fs) were explored. KS-Fs and kurarinone (Kur), a single flavonoid compd., were able to induce apoptosis of H460 and Eca-109 cells in vitro and H460 cells in vivo. The apoptosis inducing effect was enhanced in the presence of Taxol. In H460 xenograft mice treated with Kur, down-regulation of Bcl-2 and up-regulation of caspase 8 and caspase 3 in tumors were obsd. by immunohistochem. staining. In addn., KS-Fs and Kur were able to inhibit TNF α -induced NF- κ B activation in 293 cells mediated by the decreased I κ B α phosphorylation. Further the effects of KS-Fs and Kur on multiple receptor tyrosine kinase activities were explored. In cell-based assays, KS-Fs and Kur inhibited the EGF-induced EGF receptor phosphorylation in A431 cells and a constitutively activated Her-2 in MDA-MB-453s cells. In enzymic assays, KS-Fs and Kur inhibited KDR, but not PDGF BR activities. In A431 xenograft mice treated with Kur, an inhibition of EGF receptor phosphorylation in tumors was obsd. These results reveal a novel mechanism by which KS-Fs induces apoptosis in tumors by acting on multiple cellular targets including the inhibition of NF- κ B activation and multiple receptor tyrosine kinase activities.

Answer 29:

Bibliographic Information

A Phase 1 Study of Pralatrexate in Combination with Paclitaxel or Docetaxel in Patients with Advanced Solid Tumors. Azzoli, Christopher G.; Krug, Lee M.; Gomez, Jorge; Miller, Vincent A.; Kris, Mark G.; Ginsberg, Michelle S.; Henry, Roxanne; Jones, Jessica; Tyson, Leslie; Dunne, Megan; Pizzo, Barbara; Farmer, Amy; Venkatraman, Ennapadam; Steffen, Robert; Sirotnak, F. M. Thoracic Oncology Service, Division of Solid Tumor Oncology, Department of Medicine, Weill Medical College, Cornell University, New York, NY, USA. *Clinical Cancer Research* (2007), 13(9), 2692-2698. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 147:250068 AN 2007:477281 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Pralatrexate is a rationally designed antifolate with greater preclin. antitumor activity than methotrexate. Pralatrexate was synergistic with paclitaxel and with docetaxel in mouse xenograft expts. This phase 1 study was designed to det. the max. tolerated dose and toxicity of pralatrexate plus paclitaxel or docetaxel in patients with advanced cancer. Pralatrexate was administered i.v. every 2 wk (days 1 and 15) in a 4-wk cycle. Depending on the taxane used and dose being tested, the taxane was administered on days 1 and 15; days 2 and 16; or days 1, 8, and 15. In the latter part of the study, patients in the docetaxel arm were treated with vitamin B12 and folic acid supplementation to mitigate toxicity and allow pralatrexate dose escalation. For the combination of pralatrexate plus paclitaxel without vitamin supplementation, dose-limiting stomatitis and peripheral neuropathy were encountered at the lowest dose levels tested. For pralatrexate plus docetaxel plus vitamin supplementation, pralatrexate 120 mg/m² plus docetaxel 35 mg/m² administered on the same day every other week was defined as the max. tolerated dose and schedule, with dose-limiting toxicities at higher dose combinations including stomatitis and asthenia. Significant antitumor activity was obsd. for this combination in patients with non-small-cell lung cancer. Pralatrexate (120 mg/m²) plus docetaxel (35 mg/m²) plus vitamin supplementation is well tolerated with signs of efficacy against non-small-cell lung cancer that merit phase 2 testing.

Answer 30:

Bibliographic Information

Selective inhibition of ADAM metalloproteases as a novel approach for modulating ErbB pathways in cancer. Fridman, Jordan S.; Caulder, Eian; Hansbury, Michael; Liu, Xiangdong; Yang, Genjie; Wang, Qian; Lo, Yvonne; Zhou, Bin-Bing; Pan, Maxwell; Thomas, Sufi M.; Grandis, Jennifer R.; Zhuo, Jincong; Yao, Wenqing; Newton, Robert C.; Friedman, Steven M.; Scherle, Peggy A.; Vaddi, Kris. Drug Discovery, Incyte Corporation, Wilmington, DE, USA. Clinical Cancer Research (2007), 13(6), 1892-1902. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 147:86515 AN 2007:289375 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

ErbB receptor signaling pathways are important regulators of cell fate, and their dysregulation, through (epi)genetic alterations, plays an etiol. role in multiple cancers. ErbB ligands are synthesized as membrane-bound precursors that are cleaved by members of the ADAM family of zinc-dependent metalloproteases. This processing, termed ectodomain shedding, is essential for the functional activation of ErbB ligands. Recent studies suggest that elevated levels of ErbB ligands may circumvent the effectiveness of ErbB-targeted therapeutics. Here, we describe the discovery and preclin. development of potent, selective inhibitors of ErbB ligand shedding. A series of biochem. and cell-based assays were established to identify selective inhibitors of ErbB ligand shedding. The therapeutic potential of these compds. was assessed in multiple in vivo models of cancer and matrix metalloprotease-related toxicity. NCB3619 was identified as a representative selective, potent, orally bioavailable small-mol. inhibitor of a subset of ADAM proteases that block shedding of ErbB ligands. Administration of INCB3619 to tumor-bearing mice reduced ErbB ligand shedding in vivo and inhibited ErbB pathway signaling (e.g., phosphorylation of Akt), tumor cell proliferation, and survival. Further, INCB3619 synergized with clin. relevant cancer therapeutics and showed no overt or compounding toxicities, including fibroplasia, the dose-limiting toxicity assocd. with broad-spectrum matrix metalloprotease inhibitors. Inhibition of ErbB ligand shedding offers a potentially novel and well-tolerated therapeutic strategy for the treatment of human cancers and is currently being evaluated in the clinic.

Answer 31:

Bibliographic Information

Complete regression of xenografted human carcinomas by a paclitaxel-carboxymethyl dextran conjugate (AZ10992). Sugahara, Shu-Ichi; Kajiki, Masahiro; Kuriyama, Hiroshi; Kobayashi, To-Ru. The Second Research Department of Central Technology, Asahi Kasei Corporation, Fuji, Shizuoka, Japan. Journal of Controlled Release (2007), 117(1), 40-50. Publisher: Elsevier B.V., CODEN: JCREEC ISSN: 0168-3659. Journal written in English. CAN 146:301926 AN 2007:124496 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Clin. available taxanes, such as paclitaxel and docetaxel, represent one of the most promising classes of anticancer agents, despite their toxicity. To improve their pharmacol. profiles, AZ10992 was synthesized based on the concept that a rational design of a polymer-drug conjugate would increase the efficacy of the parent drug. This prodrug is a paclitaxel-carboxymethyl dextran conjugate (mol. wt. 150,000 g/mol) via a gly-gly-phe-gly linker. The in vivo antitumor study using AZ10992 against colon26 carcinoma cells, resistant to paclitaxel, supported this concept. Addnl., the comparative efficacy studies of AZ10992 and paclitaxel using a panel of human tumor xenografts in nude mice showed the advantages of drug-polymer conjugation. The max. tolerated dose of AZ10992 was more than twice as high as the MTD of paclitaxel. A repeated i.v. administration of AZ10992 at 30 mg/kg/day (five injections for 4-days) showed complete regression of MX-1 mammary carcinoma xenografts. Also, HT-29 colorectal tumor xenografts, which are highly refractory to paclitaxel, showed complete regression after AZ10992 administered at 30 mg/kg/day (seven injections for 4-days). Pharmacokinetic studies showed that there were significant increases in the amt. and the exposure time of total paclitaxel in the tumors after i.v. administration of AZ10992, which explains the enhanced efficacy of AZ10992.

Answer 32:

Bibliographic Information

A recombinant human RNASET2 glycoprotein with antitumorigenic and antiangiogenic characteristics: expression,

purification, and characterization. Smirnov, Patricia; Roiz, Levava; Angelkovitch, Boaz; Schwartz, Betty; Shoseyov, Oded. Institute of Biochemistry, Food Science, and Nutrition, Faculty of Agricultural, Food, and Environmental Quality Sciences, The Hebrew University of Jerusalem, Jerusalem, Israel. *Cancer* (Hoboken, NJ, United States) (2006), 107(12), 2760-2769. Publisher: John Wiley & Sons, Inc., CODEN: CANCAR ISSN: 0008-543X. Journal written in English. CAN 146:220439 AN 2007:89905 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: Human RNASET2 is a T2-RNase glycoprotein encoded by the RNASET2 gene, which is located on chromosome 6 (6q27). Deletion in 6q27 is assocd. with several human malignancies. Methods: A synthetic RNASET2 gene that was optimized for expression in the yeast *Pichia pastoris* was designed according to the cDNA sequence and was cloned under the control of the methanol-induced promoter fused to the α -mating secretion peptide. The recombinant protein was purified from the culture supernatant of transformed *P. pastoris* through an affinity Sepharose-Con A column. Actin-binding activity was examd. by membrane blotting using monoclonal mouse antiactin IgM and by crosslinking in soln. to G-actin using 1-[3-(dimethylamino)propyl]-3-ethyl-carboimide methiodide. The antiangiogenic activity of RNASET2 (from 0.5 μ M to 10 μ M) was assessed by a human umbilical vein endothelial (HUVE) cell assay in the presence of 1 μ g/mL angiogenin, basic fibroblast growth factor (bFGF), or recombinant human vascular endothelial growth factor (VEGF). Cell colony formation was examd. in human colon HT29 cancer cells to assess the antitumorigenic activity of RNASET2 or the enzymic-inactivated RNASET2 (EI-RNASET2) (1 μ M each). In an athymic mouse xenograft model, LS174T human cancer cells were injected s.c. When tumors were palpable, the mice were treated for 3 wk with RNASET2 (1 mg/kg), paclitaxel (10 mg/kg or 15 mg/kg), or a combination of the 2 drugs. Results: The recombinant RNASET2 was identified as a 27-kilodalton glycoprotein that possessed the ability to bind actin in vitro. RNASET2 significantly inhibited clonogenicity in HT29 cells. EI-RNASET2 produced a similar effect, suggesting that its antitumorigenic activity is unrelated to its RNase activity. In HUVE cells, RNASET2 inhibited angiogenin-, bFGF-, and VEGF-induced tube formation in a dose-dependent manner. In athymic mice, RNASET2 inhibited the development of an LS174T-derived xenograft by 40%.

A synergistic effect was obtained with combined RNASET2 and paclitaxel treatments. Conclusions: The current results suggested that RNASET2 represents a new class of antitumorigenic and antiangiogenic drugs, and the findings of this study emphasize the advantage of using agents like RNASET2 in combined therapy.

Answer 33:

Bibliographic Information

Hsp27 knockdown using nucleotide-based therapies inhibit tumor growth and enhance chemotherapy in human bladder cancer cells. Kamada, Masayuki; So, Alan; Muramaki, Mototsugu; Rocchi, Palma; Beraldi, Eliana; Gleave, Martin. Prostate Centre, Vancouver General Hospital, Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Can. *Molecular Cancer Therapeutics* (2007), 6(1), 299-308. Publisher: American Association for Cancer Research, CODEN: MCTOCF ISSN: 1535-7163. Journal written in English. CAN 146:394545 AN 2007:64269 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Heat shock protein 27 (Hsp27) is a cytoprotective chaperone that is phosphoactivated during cell stress that prevents aggregation and/or regulate activity and degrdn. of certain client proteins. Recent evidence suggests that Hsp27 may be involved in tumor progression and the development of treatment resistance in various tumors, including bladder cancer. The purpose of this study was to examine, both in vitro and in vivo, the effects of overexpression of Hsp27 and, correspondingly, the down-regulation of Hsp27 using small interfering (si) RNA and OGX-427, a second-generation antisense oligonucleotide targeting Hsp27. Hsp27 overexpression increased UMUC-3 cell growth and resistance to paclitaxel. Both OGX-427 and Hsp27 siRNA decreased Hsp27 protein and mRNA levels by >90% in a dose- and sequence-specific manner in human bladder cancer UMUC-3 cells. OGX-427 or Hsp27 siRNA treatment induced apoptosis and enhanced sensitivity to paclitaxel in UMUC-3 cells. In vivo, OGX-427 significantly inhibited tumor growth in mice, enhanced sensitivity to paclitaxel, and induced significantly higher levels of apoptosis compared with xenografts treated with control oligonucleotides. Collectively, these findings suggest that Hsp27 knockdown with OGX-427 and combined therapy with paclitaxel could be a novel strategy to inhibit the progression of bladder cancer.

Answer 34:

Bibliographic Information

Poly(ethylene oxide)-modified poly(beta-amino ester) nanoparticles as a pH-sensitive system for tumor-targeted delivery of hydrophobic drugs: part 3. Therapeutic efficacy and safety studies in ovarian cancer xenograft model. Devalapally, Harikrishna; Shenoy, Dinesh; Little, Steven; Langer, Robert; Amiji, Mansoor. Department of Pharmaceutical Sciences, School of Pharmacy, Northeastern University, Boston, MA, USA. *Cancer Chemotherapy and Pharmacology* (2007), 59(4), 477-484. Publisher: Springer, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 146:365355 AN 2007:57209 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: The objective of this study was to evaluate the anti-tumor efficacy and lack of systemic toxicity of paclitaxel when administered in pH-sensitive poly(ethylene oxide) (PEO)-modified poly(beta-amino ester) (PbAE) nanoparticles in mice bearing human ovarian adenocarcinoma (SKOV-3) xenograft. **Methods:** Paclitaxel-encapsulated PEO-modified PbAE (PEO-PbAE) nanoparticles were prepd. by the solvent displacement method. PEO-modified poly(epsilon-caprolactone) (PCL) (PEO-PCL) nanoparticles were used as a non pH-responsive control formulation. Efficacy studies were conducted in SKOV-3 tumor-bearing athymic (Nu/Nu) mice at an equiv. paclitaxel dose of 20 mg/kg with the control and nanoparticle formulations. Safety of the drug when administered in the control and nanoparticle formulation was detd. from blood cell counts and changes in body wt. of the animals. **Results:** The formulated paclitaxel-contg. PEO-PbAE and PEO-PCL nanoparticles had a particle size in the range of 100-200 nm and a surface charge of + 39.0 and - 30.8 mV, resp. After i.v. administration of paclitaxel in these formulations, the tumor growth was inhibited significantly. Both of the formulated nanoparticles tested have shown improved therapeutic efficacy as compared to the paclitaxel aq. soln. Addnl., significantly lower toxicity profile of paclitaxel was obsd. with PEO-modified nanoparticles as compared to the aq. soln. formulation. **Conclusion:** PEO-modified PbAE nanoparticles are a unique pH-sensitive drug delivery system that elicits enhanced efficacy and safety profile in solid tumor therapy.

Answer 35:

Bibliographic Information

Predicting chemotherapy response to paclitaxel with 18F-fluoropaclitaxel and PET. Hsueh, Wei-Ann; Kesner, Amanda L.; Gangloff, Anne; Pegram, Mark D.; Beryt, Malgorzata; Czernin, Johannes; Phelps, Michael E.; Silverman, Daniel H. S. Ahmanson Biological Imaging Division, Department of Molecular and Medical Pharmacology, David Geffen School of Medicine, University of California, Los Angeles, CA, USA. *Journal of Nuclear Medicine* (2006), 47(12), 1995-1999. Publisher: Society of Nuclear Medicine, CODEN: JNMEAQ ISSN: 0161-5505. Journal written in English. CAN 147:136616 AN 2007:45635 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Paclitaxel is used as a chemotherapy drug for the treatment of various malignancies, including breast, ovarian, and lung cancers. To evaluate the potential of a noninvasive prognostic tool for specifically predicting the resistance of tumors to paclitaxel therapy, we examd. the tumoral uptake of 18F-fluoropaclitaxel (18F-FPAC) in mice bearing human breast cancer xenografts by using small-animal-dedicated PET and compared 18F-FPAC uptake with the tumor response to paclitaxel treatment. **Methods:** PET data were acquired after tail vein injection of approx. 9 MBq of 18F-FPAC in anesthetized nude mice bearing breast cancer xenografts. Tracer uptake in reconstructed images was quantified by region-of-interest analyses and compared with the tumor response, as measured by changes in tumor vol., after treatment with paclitaxel. **Results:** Mice with tumors that progressed demonstrated lower tumoral uptake of 18F-FPAC than mice with tumors that did not progress or that regressed ($r = 0.55$, $P < 0.02$; $n = 19$), indicating that low 18F-FPAC uptake was a significant predictor of chemoresistance. Conversely, high 18F-FPAC uptake predicted tumor regression. This relationship was found for mice bearing xenografts from cell lines selected to be either sensitive or intrinsically resistant to paclitaxel in vitro. **Conclusion:** PET data acquired with 18F-FPAC suggest that this tracer holds promise for the noninvasive quantification of its distribution in vivo in a straightforward manner. In combination with approaches for examg. other aspects of resistance, such quantification could prove useful in helping to predict subsequent resistance to paclitaxel chemotherapy of breast cancer.

Answer 36:

Bibliographic Information

Dexamethasone decreases xenograft response to paclitaxel through inhibition of tumor cell apoptosis. Pang, Diana; Kocherginsky, Masha; Krausz, Thomas; Kim, So-Young; Conzen, Suzanne D. Department of Medicine and Committee on Cancer Biology, University of Chicago, Chicago, IL, USA. *Cancer Biology & Therapy* (2006), 5(8), 933-940. Publisher: Landes Bioscience, CODEN: CBTAAO ISSN: 1538-4047. Journal written in English. CAN 146:309496 AN 2006:1343789 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Glucocorticoid receptor (GR) activation has recently been implicated in the initiation of anti-apoptotic signaling pathways in epithelial cell lines grown in culture. However, the evidence that GR-mediated inhibition of tumor cell apoptosis is the mechanism that diminishes chemotherapy effectiveness in vivo is limited. We therefore initiated a breast cancer xenograft study to examine whether or not pretreatment with glucocorticoids (GCs) decreases tumor response to chemotherapy by inhibiting tumor cell apoptosis. Here we report a significant decrease in paclitaxel-induced apoptosis in xenografts from mice pretreated with dexamethasone (Dex). A significant difference in apoptosis in xenografts from Dex/paclitaxel vs. paclitaxel treated animals was seen eight days following initiation of chemotherapy. Nine days later, mice treated with Dex/paclitaxel had significantly larger tumors compared with those that received paclitaxel alone ($p = 0.032$). Dex pretreatment did not significantly affect tumor cell proliferation rates. Taken together, these results demonstrate that systemic Dex administration results in significantly reduced breast cancer xenograft apoptosis in the context of chemotherapy treatment. We also found that systemic Dex treatment results in upregulation of the anti-apoptotic gene MKP-1 and downregulation of pro-apoptotic Bid and TRAIL genes in tumor cells six hours following Dex treatment. These in vivo gene expression changes correlated with significant inhibition of chemotherapy-induced apoptosis. Interestingly, the decreased chemotherapeutic response of Dex-pretreated tumors persisted for several weeks following treatment. These data suggest that GR-mediated transcriptional regulation of pro- and anti-apoptotic genes contributes to the mechanism through which GCs decrease paclitaxel-induced apoptosis.

Answer 37:

Bibliographic Information

Novel in vivo imaging shows up-regulation of death receptors by paclitaxel and correlates with enhanced antitumor effects of receptor agonist antibodies. Gong, Jing; Yang, David; Kohanim, Saady; Humphreys, Robin; Broemeling, Lyle; Kurzrock, Razelle. Department of Experimental Therapeutics, Univ. of Texas M.D. Anderson Cancer Center, Houston, TX, USA. *Molecular Cancer Therapeutics* (2006), 5(12), 2991-3000. Publisher: American Association for Cancer Research, CODEN: MCTOCF ISSN: 1535-7163. Journal written in English. CAN 146:308598 AN 2006:1323335 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Susceptibility to apoptosis by tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is mediated through cognate death receptor signaling. We hypothesized that auto-amplification of this app. would enhance antitumor effects in vivo and could be optimized using the results obtained from novel imaging techniques. We therefore imaged mice bearing human colorectal cancer (Colo205) tumor xenografts with HGS-ETR1 and HGS-ETR2 agonist antibodies to TRAIL receptor-1 (TRAIL-R1) and TRAIL-R2, resp., after radiolabeling the antibodies. Paclitaxel significantly increased in vivo expression of TRAIL-R1 and TRAIL-R2 in a time-dependent manner. The imaging results were confirmed by immunoblots for steady-state protein levels (>20-fold increase in TRAIL-R1 and TRAIL-R2 levels in tumor xenografts by 48 h after paclitaxel administration). TRAIL-R1 and TRAIL-R2 mRNA expression did not change, suggesting that these effects were posttranscriptional. Sequential treatment with paclitaxel followed by HGS-ETR1 or HGS-ETR2 after 48 h resulted in markedly enhanced antitumor activity against Colo205 mouse xenografts. Our expts. suggest that sequential taxane treatment followed by TRAIL-R agonist antibodies could be applied in the clinic, and that novel imaging techniques using radiolabeled receptor antibodies may be exploitable to optimize sequence timing and patient selection.

Answer 38:

Bibliographic Information

Effects of combined chemotherapy of S-1 plus paclitaxel on gene expressions of fluoropyrimidine related enzymes.

Sakurai, Yoichi; Yoshida, Ikuo; Masui, Toshihiko; Tonomura, Shuhei; Shoji, Mitsutaka; Nakamura, Yasuko; Uyama, Ichiro; Komori, Yoshiyuki; Kamoshida, Shingo; Tsutsumi, Yutaka; Ochiai, Masahiro. Department of Surgery and Pathology, Fujita Health University School of Medicine, Toyoake Aichi, Japan. Editor(s): Kitajima, Masaki; Otani, Yoshihide. Proceedings of the International Gastric Cancer Congress, 6th, Yokohama, Japan, May 4-7, 2005 (2005), 217-224. Publisher: Monduzzi Editore, Bologna, Italy CODEN: 69IQWB Conference written in English. CAN 146:92871 AN 2006:1233587 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Gene expressions of thymidine phosphorylase (TP), thymidylate synthase (TS), dihydropyrimidine dehydrogenase (DPD), orotate phosphoribosyltransferase were examd. after the administration of S-1, paclitaxel alone and their combination in gastric carcinoma xenografts. MKN-45 and TMK-1, serially transplanted into nude mice, were used to examine anticancer effects, toxic effects. Nude mice were assigned into 4 exptl. groups, and the mice received S-1 alone for 14 days orally, weekly paclitaxel alone at day 1, 8, 15 i.p., and S-1 plus paclitaxel. The gene expressions of tumors after chemotherapies were examd. using a real-time PCR method. Administration of S-1 combined with weekly paclitaxel showed addnl. anticancer effects on both gastric cancer xenografts, compared with S-1 or paclitaxel alone without significant increase in toxic effects. The expressions of TP and DPD were significantly increased after the administration of S-1 alone, while the expression of TS gene was significantly decreased after the administration of paclitaxel alone. These results provide some insight into the enhancement of the combination of these agents and the rationale of the mechanism of resistance usually appeared during the repeated administration.

Answer 39:

Bibliographic Information

Synergistic effects of combined therapy using paclitaxel and [90Y-DOTA]776.1 on growth of OVCAR-3 ovarian carcinoma xenografts.

Masters, Gregg R.; Berger, Marc A.; Albone, Earl F. Immunotherapeutics Department, Purdue Pharma, Cranbury, NJ, USA. Gynecologic Oncology (2006), 102(3), 462-467. Publisher: Elsevier, CODEN: GYNOA3 ISSN: 0090-8258. Journal written in English. CAN 146:513873 AN 2006:961524 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Objective: 776.1 is a monoclonal antibody prepd. against the human ovarian cancer antigen CA 125 that demonstrates preferential binding to the cell-assocd. form of the antigen and has shown promising results as an yttrium-90-labeled antibody in pre-clin. studies examg. the effects on tumor growth in a murine xenograft model of human ovarian cancer. The purpose of the present study was to examine the effects of combined therapy with [90Y-DOTA]776.1 and paclitaxel compared with monotherapy with either agent on the growth of OVCAR-3 xenografts in nude mice. Methods: Mice bearing OVCAR-3 xenografts were treated with paclitaxel alone, 50 μ Ci or 150 μ Ci [90Y-DOTA]776.1 alone, or a combination of both treatments. Control groups were included which consisted of a nonspecific antibody, MOPC-21, labeled to a similar degree, administered as monotherapy or in combination with paclitaxel. The effects of administration of radioimmunotherapy prior to or following chemotherapy were also examd. Results: Treatment with paclitaxel and [90Y-DOTA]776.1 had a synergistic anti-tumor effect on the growth of OVCAR-3 xenografts. Synergy was only obsd. when a tumor-specific antibody was used in radioimmunotherapy. While no difference in tumor growth was obsd. with order of dosing, reduced toxicity was seen when paclitaxel was administered prior to radioimmunotherapy. Conclusion: The combination of radioimmunotherapy using an anti-CA 125 monoclonal antibody and chemotherapy with paclitaxel was shown to be effective in an in vivo model of ovarian cancer and may hold promise as a treatment regimen for patients with ovarian cancer.

Answer 40:

Bibliographic Information

Cardenolide-induced lysosomal membrane permeabilization demonstrates therapeutic benefits in experimental human non-small cell lung cancers. Mijatovic, Tatjana; Mathieu, Veronique; Gaussin, Jean-Francois; De Neve, Nancy; Ribaucour, Fabrice; Van Quaquebeke, Eric; Dumont, Patrick; Darro, Francis; Kiss, Robert. Laboratory of Toxicology, Institute of Pharmacy, Free University of Brussels, Brussels, Belg. Neoplasia (Ann Arbor, MI, United States) (2006), 8(5), 402-412. Publisher: Neoplasia Press Inc., CODEN: NEOPFL ISSN: 1522-8002. <http://www.ingentaconnect.com/content/neo/neo/2006/00000008/00000005> Journal; Online Computer File written in English. CAN 146:308537 AN 2006:886718 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Non-small cell lung cancers (NSCLCs) are the leading cause of cancer deaths in most developed countries. Targeting heat shock protein 70 (Hsp70) expression and function, together with the induction of lysosomal membrane permeabilization (LMP), could overcome the multiple anti-cell death mechanisms evidenced in NSCLCs that are responsible for the failure of currently used chemotherapeutic drugs. Because cardenolides bind to the sodium pump, they affect multiple signaling pathways and thus have a no. of marked effects on tumor cell behavior. The aim of the present study was to characterize in vitro and in vivo the antitumor effects of a new cardenolide (UNBS1450) on exptl. human NSCLCs. UNBS1450 is a potent source of in vivo antitumor activity in the case of paclitaxel and oxaliplatin-resistant s.c. human NCI-H727 and orthotopic A549 xenografts in nude mice. In vitro UNBS1450-mediated antitumor activity results from the induction of nonapoptotic cell death. UNBS1450 mediates the decrease of Hsp70 at both mRNA and protein levels, and this is at least partly due to UNBS1450-induced downregulation of NFAT5/TonEBP (a factor responsible for the transcriptional control of Hsp70). These effects were paralleled by the induction of LMP, as evidenced by acridine orange staining and immunofluorescence anal. for cathepsin B accumulation.

Answer 41:

Bibliographic Information

Increased Antitumor Activity, Intratumor Paclitaxel Concentrations, and Endothelial Cell Transport of Cremophor-Free, Albumin-Bound Paclitaxel, ABI-007, Compared with Cremophor-Based Paclitaxel. [Erratum to document cited in CA145:159173]. Desai, Neil; Trieu, Vuong; Yao, Zhiwen; Louie, Leslie; Ci, Sherry; Yang, Andrew; Tao, Chunlin; De, Tapas; Beals, Bridget; Dykes, Donald; Noker, Patricia; Yao, Rosie; Labao, Elizabeth; Hawkins, Michael; Soon-Shiong, Patrick. American BioScience, Inc., Santa Monica, CA, USA. Clinical Cancer Research (2006), 12(12), 3869. Publisher: American Association for Cancer Research, CODEN: CCREFA ISSN: 1078-0432. Journal written in English. CAN 145:224510 AN 2006:825224 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

On page 1319, right column, "Results" section, line 10 should read: "MTD's were 30/mg/kg/d and 13/4 mg/kg/d for ABI007 and Cremophor-based paclitaxel, resp.; these doses were also eqitoxic doses (4% mortality for both)."

Answer 42:

Bibliographic Information

Reversal of multidrug resistance by two nordihydroguaiaretic acid derivatives, M4N and maltose-M3N, and their use in combination with doxorubicin or paclitaxel. Chang, Chih-Chuan; Liang, Yu-Chuan; Klutz, Athena; Hsu, Chuan-I.; Lin, Chien-Fu; Mold, David E.; Chou, Ting-Chao; Lee, Yuan Chuan; Huang, Ru Chih C. Department of Biology, Johns Hopkins University, Baltimore, MD, USA. Cancer Chemotherapy and Pharmacology (2006), 58(5), 640-653. Publisher: Springer, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 146:372014 AN 2006:760533 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: Multidrug resistance (MDR) continues to be a major obstacle for successful anticancer therapy. One of the principal factors implicated in MDR is the over expression of P-glycoprotein (Pgp), the product of the MDR1 gene. **Methods:** Here we explore the possibility of using the transcription inhibitor tetra-O-Me nordihydroguaiaretic acid (M4N) to inhibit Sp1-regulated MDR1 gene expression and restore doxorubicin and paclitaxel sensitivity to multidrug resistant human cancer cells in vitro and in vivo. **Results:** We found that M4N acted synergistically with doxorubicin and paclitaxel in inhibiting the growth of the cells in culture allowing significant dose redns. of both drugs. We obsd. no such synergism when M4N was used in combination with cisplatin, another chemotherapeutic agent, but not a Pgp substrate, as analyzed by the combination index and isobologram methods. Anal. of MDR1 mRNA and Pgp levels revealed that at sublethal doses, M4N inhibited MDR1 gene expression in the multidrug resistant NCI/ADR-RES cells and reversed the MDR phenotype as measured by Rhodamine-123 retention. In addn., M4N was found to inhibit doxorubicin-induced MDR1 gene expression in drug sensitive MCF-7 breast cancer cells. **Conclusions:** M4N and maltose-tri-O-Me nordihydroguaiaretic acid (maltose-M3N), a water-sol. deriv. of NDGA, were also able to reverse the MDR phenotype of the tumor cells in a xenograft model system and combination therapy with M4N or maltose-M3N and paclitaxel was effective at inhibiting growth of these tumors in nude mice.

Answer 43:

Bibliographic Information

Influence of Formulation Vehicle on Metronomic Taxane Chemotherapy: Albumin-Bound versus Cremophor EL-Based Paclitaxel. Ng, Sylvia S. W.; Sparreboom, Alex; Shaked, Yuval; Lee, Christina; Man, Shan; Desai, Neil; Soon-Shiong, Patrick; Figg, William D.; Kerbel, Robert S. Molecular and Cellular Biology Research, Sunnybrook Health Sciences Centre, Toronto, ON, Can. Clinical Cancer Research (2006), 12(14, Pt. 1), 4331-4338. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 146:148640 AN 2006:710532 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

PURPOSE: Low-dose metronomic chemotherapy treatments, esp. when combined with dedicated¹ antiangiogenic agents, can induce significant antitumor activity without serious toxicity in various preclin. models. It remains unclear, however, whether some cytotoxic drugs are better suited for metronomic regimens than others. Paclitaxel appears to be a strong candidate for metronomic chemotherapy given its ability to inhibit endothelial cell functions relevant to angiogenesis in vitro at extraordinarily low concns. and broad-spectrum antitumor activity. Clin. relevant concns. of the formulation vehicle cremophor EL in Taxol, however, were previously reported to nullify the antiangiogenic effect of paclitaxel, the result of which would hamper its usefulness in metronomic regimens. We hypothesized that ABI-007, a cremophor EL-free, albumin-bound, 130-nm form of paclitaxel, could potentially alleviate this problem. **Exptl. Design:** The antiangiogenic activity of ABI-007 was assessed by multiple in vitro assays. The in vivo optimal dose of ABI-007 for metronomic chemotherapy was detd. by measuring circulating endothelial progenitors in peripheral blood. The antitumor effects of metronomic and max. tolerated dose ABI-007 and Taxol were then evaluated and compared in severe combined immunodeficient mice bearing human MDA-MD-231 breast cancer and PC3 prostate cancer xenografts. **RESULTS:** ABI-007 significantly inhibited rat aortic microvessel outgrowth, human endothelial cell proliferation, and tube formation. The optimal metronomic dose of ABI-007 was detd. to be between 3 and 10 mg/kg. Metronomic ABI-007 but not Taxol, significantly suppressed tumor growth in both xenograft models. Furthermore, the antitumor effect of minimally toxic metronomic ABI-007 approximated that of the max. tolerated dose of Taxol. **CONCLUSIONS:** Our results underscore the influence of formulation vehicles on the selection of cytotoxic drugs for metronomic chemotherapy.

Answer 44:

Bibliographic Information

Molecular determinants of differential sensitivity to docetaxel and paclitaxel in human pediatric cancer models. Izbicka, Elzbieta; Campos, David; Marty, Jennifer; Carrizales, Gilbert; Mangold, Gina; Tolcher, Anthony. Cancer Therapy and Research Center, The Institute for Drug Development, San Antonio, TX, USA. Anticancer Research (2006), 26(3A), 1983-1988. Publisher:

International Institute of Anticancer Research, CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 146:19546 AN 2006:709477 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The differential sensitivity of some tumors to paclitaxel and docetaxel raises questions regarding the specific mechanisms responsible for the discrepant sensitivity to these taxanes. Docetaxel and paclitaxel were evaluated and compared at max. tolerated doses (MTD) and 0.5 MTDs against the human pediatric tumor xenograft models SK-N-MC and IMR32 (neuroblastoma), RH1 and RH30 (rhabdomyosarcoma) and KHOS/NP (osteosarcoma), with 8-10 animals per group. The drug effects on the expression of the β -tubulin isotypes, Bcl-2, Bax, Bcl-XL and proteomic profiles were evaluated by immunoblotting and SELDI mass spectrometry in tumor xenografts dosed at 0.5 MTDs. At MTDs, docetaxel was superior in neuroblastoma and osteosarcoma, while paclitaxel was more active in the rhabdomyosarcoma models. Docetaxel showed remarkable efficacy in KHOS/NP even at 0.5 MTD. The drugs had significantly different, yet highly heterogeneous effects on the tumor levels of β I-tubulin (RH30), β III-tubulin (IMR32, KHOS/NP, RH1), Bax (IMR32, SK-N-MC) and Bcl-XL (KHOS/NP). In contrast, six protein species identified by proteomic profiling were consistently and differentially regulated by docetaxel and paclitaxel in all KHOS/NP xenografts. Anticancer activity showed no apparent correlation with drug effects on β -tubulin isotypes and apoptotic markers. The mass spectrometry approach has potential for the discovery of proteomic biomarkers for drug sensitivity.

Answer 45:

Bibliographic Information

Combining a matrix metalloproteinase inhibitor, a farnesyltransferase inhibitor, and a taxane improves survival in an anaplastic thyroid cancer model. She, Miaorong; Jim Yeung, Sai-Ching. Department of General Internal Medicine, Ambulatory Treatment and Emergency Care, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA. Cancer Letters (Amsterdam, Netherlands) (2006), 238(2), 197-201. Publisher: Elsevier B.V., CODEN: CALEDQ ISSN: 0304-3835. Journal written in English. CAN 145:284327 AN 2006:595902 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We previously showed that the in vivo anticancer effects of a combination of manumycin (a farnesyltransferase inhibitor) and paclitaxel (a microtubule inhibitor) against anaplastic thyroid carcinoma (ATC) were partially due to inhibition of angiogenesis. In this study, we investigated the effect of adding minocycline (a matrix metalloproteinase inhibitor) to manumycin and paclitaxel against human ATC cells xenografted in nude mice. The triple-drug combination resulted in the lowest av. tumor growth rate, and it conferred significantly better survival than manumycin alone, paclitaxel alone, or manumycin plus paclitaxel. In conclusion, this novel combination deserves further investigation in the treatment of ATC.

Answer 46:

Bibliographic Information

Preclinical Pharmacologic Evaluation of MST-997, an Orally Active Taxane with Superior In vitro and In vivo Efficacy in Paclitaxel- and Docetaxel-Resistant Tumor Models. Sampath, Deepak; Greenberger, Lee M.; Beyer, Carl; Hari, Malathi; Liu, Hao; Baxter, Michelle; Yang, Sharon; Rios, Carol; Discafani, Carolyn. Department of Oncology, Wyeth Research, Pearl River, NY, USA. Clinical Cancer Research (2006), 12(11, Pt. 1), 3459-3469. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 145:448686 AN 2006:518124 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: Because resistance to paclitaxel and docetaxel is frequently obsd. in the clinic, new anti-microtubule agents have been sought. The aim of this study was to evaluate the efficacy and oral activity of a novel taxane (MST-997) in paclitaxel- and

docetaxel-resistant tumor models in vitro and in vivo. Exptl. Design: Tubulin polymn. assays, immunohistochem., and cell cycle anal. was used to evaluate mechanism of action of MST-997. The effect of MST-997 on growth inhibition in a panel of paclitaxel- and docetaxel-resistant cell lines that overexpressed P-glycoprotein (MDR1) or harbored β -tubulin mutations were assayed in vitro and in murine xenografts. Results: MST-997 induced microtubule polymn. ($EC_{50} = 0.9 \mu\text{mol/L}$) and bundling, resulting in G2-M arrest and apoptosis. In addn., MST-997 was a potent inhibitor of paclitaxel- and docetaxel-sensitive tumor cell lines that did not have detectable P-glycoprotein ($IC_{50} = 1.8 \pm 1.5 \text{ nmol/L}$). Minimal resistance (1- to 8-fold) to MST-997 was found in cell lines that either overexpressed MDR1 or harbored point mutations in β -tubulin. Most notable, MST-997 displayed superior in vivo efficacy as a single i.v. or p.o. dose either partially or completely inhibited tumor growth in paclitaxel- and docetaxel-resistant xenografts. Conclusions: MST-997 represents a potent and orally active microtubule-stabilizing agent that has greater pharmacol. efficacy in vitro and in vivo than the currently approved taxanes. Our findings suggest that MST-997, which has entered phase I clin. trials, may have broad therapeutic value.

Answer 47:

Bibliographic Information

Effects of 12-O-Tetradecanoylphorbol-13-acetate (TPA) in Combination with Paclitaxel (Taxol) on Prostate Cancer LNCaP Cells Cultured In vitro or Grown as Xenograft Tumors in Immunodeficient Mice. Zheng, Xi; Chang, Richard L.; Cui, Xiao-Xing; Avila, Gina E.; Hebbar, Vidya; Garzotto, Mark; Shih, Weichung Joe; Lin, Yong; Lu, Shou-En; Rabson, Arnold B.; Kong, Ah Ng Tony; Conney, Allan H. Susan Lehman Cullman Laboratory for Cancer Research, Departments of Chemical Biology and Pharmaceutics, Ernest Mario School of Pharmacy, The State University of New Jersey, Rutgers, USA. *Clinical Cancer Research* (2006), 12(11, Pt. 1), 3444-3451. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 145:448684 AN 2006:518122 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: To investigate the effects of 12-O-tetradecanoylphorbol-13-acetate (TPA) in combination with paclitaxel (Taxol) on prostate cancer cells cultured in vitro or grown as tumors in immunodeficient mice. Exptl. Design: Human prostate cancer LNCaP cells in culture were treated with TPA alone or in combination with paclitaxel. NCr immunodeficient mice with well-established LNCaP tumors received i.p. injections with vehicle or with TPA, paclitaxel, or TPA in combination with paclitaxel. The animals either received daily treatment for 5 consecutive days followed by a 2-day intermission, which was repeated for a total of 28 days (expt. 1), or continuous daily treatment for 28 days (expt. 2). Results: Treatment of LNCaP cells with a combination of TPA and paclitaxel synergistically inhibited the growth and induced apoptosis in cultured LNCaP cells, and this treatment also induced a marked increase in phosphorylated c-Jun-NH₂-kinase (JNK). In animal expts., tumor growth occurred in all mice treated with vehicle. When treated with TPA alone, the percentage of animals with some tumor regression was 33% in expt. 1 and 100% in expt. 2. Treatment of animals with paclitaxel alone caused some tumor regression in 17% and 57% of the animals in expts. 1 and 2, resp. All animals treated with TPA + paclitaxel in both expts. had some tumor regression. Conclusions: TPA and paclitaxel in combination had a stronger inhibitory effect on the growth of LNCaP cells in culture or as xenograft tumors in immunodeficient mice than either agent alone. Clin. trials with TPA alone or in combination with paclitaxel in patients with prostate cancer may be warranted.

Answer 48:

Bibliographic Information

Dual Epidermal Growth Factor Receptor and Vascular Endothelial Growth Factor Receptor Inhibition with NVP-AEE788 for the Treatment of Aggressive Follicular Thyroid Cancer. Younes, Maher N.; Yazici, Yasemin D.; Kim, Seungwon; Jasser, Samar A.; El-Naggar, Adel K.; Myers, Jeffrey N. Departments of Head and Neck Surgery, Pathology, and Cancer Biology, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA. *Clinical Cancer Research* (2006), 12(11, Pt. 1), 3425-3434. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 145:448683 AN 2006:518120 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: Patients with radioiodine-resistant follicular thyroid cancer (FTC) have a poor prognosis, if metastasized, with currently available treatment modalities. Epidermal growth factor (EGF) and vascular endothelial growth factor (VEGF) and their receptors (EGFR and VEGFR) have been reported to be overexpressed in FTC and have been implicated in FTC development. We hypothesized that inhibiting the phosphorylation of EGFR and VEGFR by treatment with NVP-AEE788 (AEE788), a novel dual specific EGFR and VEGFR inhibitor, either alone or in combination with paclitaxel, would inhibit the growth of FTC xenografts in an orthotopic nude mouse model. **Exptl. Design:** To confirm previous reports, EGF and EGFR expression and vascularity were analyzed in human samples of FTC, Huerthle cell carcinoma, and normal thyroid tissues. EGFR expression in four FTC cell lines was measured using Western blotting. The antitumor effect of AEE788 on FTC cells in vitro was evaluated using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assays and Western blotting. The effect of AEE788, alone and in combination with paclitaxel, on FTC tumor growth in an orthotopic nude mouse model was also investigated. **Immunohistochem. anal.** of EGFR and VEGFR signaling status, cell proliferation, apoptosis, and microvessel d. was done. **Results:** EGF, EGFR, and vascularity were increased in human thyroid tumor samples and EGFR was increased in FTC cells. AEE788 inhibited FTC cell growth in vitro and reduced the phosphorylation status of EGFR, VEGFR, and two downstream targets, AKT and mitogen-activated protein kinase, in FTC cells. AEE788 alone and, to a greater extent, AEE788 plus paclitaxel suppressed FTC tumor growth in the thyroids of nude mice. **Conclusion:** Dual inhibition of EGFR and VEGFR by AEE788 could represent a novel approach to the treatment of radioiodine-resistant FTC.

Answer 49:

Bibliographic Information

Activation of membrane androgen receptors potentiates the antiproliferative effects of paclitaxel on human prostate cancer cells. Kampa, Marilena; Kogia, Christina; Theodoropoulos, Panayiotis A.; Anezinis, Ploutarchos; Charalampopoulos, Ioannis; Papakonstanti, Evangelia A.; Stathopoulos, Efstathios N.; Hatzoglou, Anastassia; Stournaras, Christos; Gravanis, Achille; Castanas, Elias. Departments of Experimental Endocrinology and Biochemistry, Univ. Crete, Sch. Med., Heraklion, Greece. *Molecular Cancer Therapeutics* (2006), 5(5), 1342-1351. Publisher: American Association for Cancer Research, CODEN: MCTOCF ISSN: 1535-7163. Journal written in English. CAN 145:262650 AN 2006:501531 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Genomic signaling mechanisms require a relatively long time to get into action and represent the main way through which steroid hormones affect target cells. In addn., steroids may rapidly activate cellular functions by non-genomic signaling mechanisms involving membrane sites. Understanding in depth the mol. mechanisms of the non-genomic action represents an important frontier for developing new and more selective pharmacol. tools for endocrine therapies. In the present study, we report that membrane-impermeable testosterone-bovine serum albumin (BSA) acts synergistically with paclitaxel in modifying actin and tubulin cytoskeleton dynamics in LNCaP (androgen sensitive) and DU-145 (androgen insensitive) human prostate cancer cell lines. In addn., cocubation of either cell line with testosterone-BSA and paclitaxel induced inhibition of cell proliferation and apoptosis. Finally, in vivo expts. in LNCaP and DU-145 tumor xenografts in nude mice showed that both agents decrease tumor mass, whereas testosterone-BSA enhances the effect of paclitaxel. Our findings suggest that chronic activation of membrane androgen receptors in vitro and in vivo facilitates and sustains for a longer time the antitumoral action of cytoskeletal acting agents.

Answer 50:

Bibliographic Information

Potential of the antitumoral activity of gemcitabine and paclitaxel in combination on human breast cancer cells. Zupi, Gabriella; Scarsella, Marco; D'Angelo, Carmen; Biroccio, Annamaria; Paoletti, Giancarlo; Lopez, Massimo; Leonetti, Carlo. Experimental Chemotherapy Laboratory, Regina Elena Cancer Institute, Rome, Italy. *Cancer Biology & Therapy* (2005), 4(8), 866-871. Publisher: Landes Bioscience, CODEN: CBTAAO ISSN: 1538-4047. Journal written in English. CAN 145:347983 AN 2006:480435 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The purpose of this study was to evaluate the antitumoral activity of different gemcitabine-based combination on an exptl. model of human breast cancer, in order to identify the most effective treatment and to provide a rationale for clin. investigations. To this end, CG5 breast cancer cells were treated in vitro with gemcitabine followed by epirubicin, doxorubicin, docetaxel or paclitaxel. The reversed sequence was also investigated. Results, analyzed by multiple drug effect/combination index (CI) isobologram, demonstrated that the combination gemcitabine/paclitaxel was the most active showing synergism with a CI of about 0.5 in the two sequences employed. Moreover, the synergistic interaction of gemcitabine and paclitaxel was correlated to a block of the cells in the G0/G1 compartment of cell cycle and to an increase of apoptotic cells compared to each drug. Based on these evidences, the antitumoral efficacy of gemcitabine/paclitaxel combination has been studied in vivo. Mice bearing CG5 human breast xenografts treated with paclitaxel and gemcitabine in combination showed a significant higher inhibition of tumor growth (.apprx.70%) compared to that with either agent alone (25%). In conclusion, this study suggests that paclitaxel is the most promising agent for combination protocols with gemcitabine and supports the use of gemcitabine/paclitaxel combination in the clin. management of advanced breast cancer.

Answer 51:

Bibliographic Information

Enhanced efficacy of 90Y-radiolabeled anti-Lewis Y humanized monoclonal antibody hu3S193 and paclitaxel combined-modality radioimmunotherapy in a breast cancer model. Kelly, Marcus P.; Lee, Fook T.; Smyth, Fiona E.; Brechbiel, Martin W.; Scott, Andrew M. Tumour Targeting Program, Ludwig Institute for Cancer Research, Austin Hospital, Heidelberg, Victoria, Australia. *Journal of Nuclear Medicine* (2006), 47(4), 716-725. Publisher: Society of Nuclear Medicine, CODEN: JNMEAQ ISSN: 0161-5505. Journal written in English. CAN 145:58311 AN 2006:427103 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Radioimmunotherapy (RIT) of solid tumor is often limited in efficacy because of restrictions in achieved tumor dose. In an effort to overcome this, the combination of RIT with other therapeutic modalities was investigated in an animal model of breast carcinoma. The rationale for this combined-modality RIT (CMRIT) was to increase the therapeutic efficacy of RIT through the use of paclitaxel to arrest cells in the radiosensitive G2/M phase of the cell cycle. Methods: In this study, the biodistribution and therapeutic efficacy of 90Y-radiolabeled humanized anti-Lewis Y hu3S193 monoclonal antibody (90Y-hu3S193) RIT in combination with paclitaxel chemotherapy was explored in a Lewis Y-expressing MCF-7 tumor xenografted BALB/c nude mouse model of breast cancer. Results: Biodistribution studies demonstrated excellent tumor targeting and limited normal tissue uptake by 90Y-hu3S193. A therapeutic study with established tumors assessed 90Y-hu3S193 as a single agent and demonstrated significant antitumor effects in all animals receiving a single i.v. 1.85 or 3.70 MBq dose of this treatment compared with phosphate-buffered saline placebo controls ($P = 0.0008$ vs. $P < 0.0001$). Complete responses were obsd. in all animals in the 3.70 MBq study arm for the duration of the study. Single-dose 90Y-hu3S193 plus paclitaxel (600 μ g) CMRIT displayed improved efficacy over single-modality therapies, with a significant difference ($P < 0.0001$) between the mean percentage change in tumor vol. in mice receiving 0.46 MBq 90Y-hu3S193 alone and when combined with 600 μ g paclitaxel. Conclusion: The significant efficacy of 90Y-hu3S193 and paclitaxel CMRIT at low radiation doses in this model of breast carcinoma indicates its therapeutic potential and warrants further investigation into this promising therapeutic approach.

Answer 52:

Bibliographic Information

The Vascular Targeting Property of Paclitaxel Is Enhanced by SU6668, a Receptor Tyrosine Kinase Inhibitor, Causing Apoptosis of Endothelial Cells and Inhibition of Angiogenesis. Naumova, Elitza; Ubezio, Paolo; Garofalo, Angela; Borsotti, Patrizia; Cassis, Linda; Riccardi, Elena; Scanziani, Eugenio; Eccles, Suzanne A.; Bani, Maria R.; Giavazzi, Raffaella. Laboratory of Biology and Treatment of Metastasis, Department of Oncology, Mario Negri Institute for Pharmacological Research, Bergamo, Italy. *Clinical Cancer Research* (2006), 12(6), 1839-1849. Publisher: American Association for Cancer Research, CODEN: CCREFF4 ISSN: 1078-0432. Journal written in English. CAN 145:284196 AN 2006:264029 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: Different antiangiogenic approaches have been proposed in cancer treatment where therapeutic efficacy has been shown with the addn. of cytotoxic agents. Here, we used SU6668, a small-mol. receptor tyrosine kinase inhibitor, to investigate the combinatorial effect with paclitaxel on the cellular populations of the developing vasculature. Exptl. Design: The effect of this combination was evaluated in vitro in a 72-h proliferation assay on human umbilical vein endothelial cells (HUVEC) and human microvascular endothelial cells derived from lungs, endothelial cells, aortic smooth muscle cells, and human ovarian carcinoma cells sensitive (1A9) and resistant (1A9-PTX22) to paclitaxel. Combination data were assessed by isobologram anal. Cell survival was detd. by terminal deoxyribonucleotide transferase-mediated nick-end labeling and Annexin V staining. The activity of the combination in vivo was evaluated in fibroblast growth factor-2-induced angiogenesis in Matrigel plugs s.c. implanted in mice. The 1A9-PTX22, paclitaxel-resistant xenograft model was used to evaluate tumor response. Results: Combination index values and isobologram anal. showed synergy in inhibition of proliferation of HUVEC, human microvascular endothelial cells derived from lungs, and aortic smooth muscle cells. The combination induced greater apoptosis in HUVEC than the single agents. The addn. of paclitaxel to the treatment with SU6668 significantly decreased the Hb content and the no. of CD31-pos. vessels in Matrigel plugs in vivo. The combination of the drugs was more active than either single agent against 1A9-PTX22 xenografts; the tumor growth delay was accompanied by a significant redn. of vascular d. Conclusions: These findings show that the activity of angiogenesis inhibitors on vascular cells could be potentiated when administered in combination with chemotherapeutic agents that themselves have vascular targeting properties.

Answer 53:

Bibliographic Information

PWT-458, a novel pegylated-17-hydroxywortmannin, inhibits phosphatidylinositol 3-kinase signaling and suppresses growth of solid tumors. Yu, Ker; Lucas, Judy; Zhu, Tianmin; Zask, Arie; Gaydos, Christine; Toral-Barza, Lourdes; Gu, Jianxin; Li, Fangbiao; Chaudhary, Inder; Cai, Ping; Lotvin, Jason; Petersen, Roseann; Ruppen, Mark; Fawzi, Mahdi; Ayril-Kaloustian, Semiramis; Skotnicki, Jerauld; Mansour, Tarek; Frost, Philip; Gibbons, James. Department of Oncology Research, Wyeth Research, Pearl River, NY, USA. *Cancer Biology & Therapy* (2005), 4(5), 538-545. Publisher: Landes Bioscience, CODEN: CBTAAO ISSN: 1538-4047. Journal written in English. CAN 145:202135 AN 2006:239882 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Deregulated phosphatidylinositol 3-kinase (PI3K) signaling pathway is widely implicated in tumor growth and resistance to chemotherapy. While a strong rationale exists for pharmacol. targeting of PI3K, only a few proof-of-principle in vivo efficacy studies are currently available. PWT-458, pegylated-17-hydroxywortmannin, is a novel and highly potent inhibitor of PI3K in animal models. Upon in vivo cleavage of its poly(ethyleneglycol) (PEG), PWT-458 releases its active moiety 17-hydroxywortmannin (17-HWT), the most potent inhibitor in its class. Here we show that a single i.v. injection of PWT-458 rapidly inhibited PI3K signaling, as measured by a complete loss of AKT (Ser-473) phosphorylation in xenograft tumors grown in nude mice. Following a daily X5 dosing regimen, PWT-458 demonstrated single-agent antitumor activity in nude mouse xenograft models of U87MG glioma, nonsmall cell lung cancer (NSCLC) A549, and renal cell carcinoma (RCC) A498. Efficacious doses ranged from 0.5 mg/kg to 10 mg/kg, achieving a superior therapeutic index over 17-HWT. PWT-458 augmented anticancer efficacy of a suboptimal dose of paclitaxel against A549 and U87MG tumors. Combination treatment of PWT-458 and an mTOR inhibitor, Pegylated-Rapamycin (Peg-Rapa), resulted in an enhanced antitumor efficacy in U87MG. Finally, PWT-458 in combination with interferon- α (Intron-A) caused a dramatic regression of RCC A498, which was not achieved by either agent alone. These studies identify PWT-458 as an effective anticancer agent and provide strong proof-of-principle for targeting the PI3K pathway as novel anticancer therapy.

Answer 54:

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, Katsunori; 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 $\mu\text{mol/L}$. In human vascular endothelial cells, the compd. inhibited VEGF-dependent proliferation, VEGFR2 autophosphorylation, and sprout formation at concns. of 0.001 to 0.003 $\mu\text{mol/L}$. 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 55:

Bibliographic Information

Recombinant epoetins do not stimulate tumor growth in erythropoietin receptor-positive breast carcinoma models.

LaMontagne, Kenneth R.; Butler, Jeannene; Marshall, Deborah J.; Tullai, Jennifer; Gechtman, Ze'ev; Hall, Chassidy; Meshaw, Alan; Farrell, Francis X. Johnson and Johnson Pharmaceutical Research and Development, Raritan, NJ, USA. *Molecular Cancer Therapeutics* (2006), 5(2), 347-355. Publisher: American Association for Cancer Research, CODEN: MCTOCF ISSN: 1535-7163. Journal written in English. CAN 144:305710 AN 2006:183622 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We investigated the significance of erythropoietin receptor (EPOR) expression following treatment with recombinant human erythropoietin (rHuEPO; epoetin α) and the effect of recombinant epoetins (epoetin α , epoetin β , and darbepoetin α) alone or in combination with anticancer therapy on tumor growth in two well-established preclin. models of breast carcinoma (MDA-MB-231 and MCF-7 cell lines). Expression and localization of EPOR under hypoxic and normoxic conditions in MDA-MB-231 and MCF-7 cells were evaluated by immunoblotting, flow cytometry, and immunohistochem. EPOR binding was evaluated using [125I]rHuEPO. Proliferation, migration, and signaling in MDA-MB-231 and MCF-7 cells following treatment with rHuEPO were evaluated. Tumor growth was assessed following administration of recombinant epoetins alone and in combination with paclitaxel (anticancer therapy) in orthotopically implanted MDA-MB-231 and MCF-7 breast carcinoma xenograft models in athymic mice. EPOR expression was detected in both tumor cell lines. EPOR localization was found to be exclusively cytosolic and no specific [125I]rHuEPO binding was obsd. There was no stimulated migration, proliferation, or activation of mitogen-activated protein kinase and AKT following rHuEPO treatment. In mice, treatment with recombinant epoetins alone and in combination with paclitaxel resulted in equiv. tumor burdens compared with vehicle-treated controls. Results from our study suggest that although EPOR expression was obsd. in two well-established breast carcinoma cell lines, it was localized to a cytosolic distribution and did not transduce a signaling cascade in tumors that leads to tumor growth. The addn. of recombinant epoetins to paclitaxel did not affect the outcome of paclitaxel therapy in breast carcinoma xenograft models. These results show that recombinant epoetins do not evoke a physiol. response on EPOR-bearing tumor cells as assessed by numerous variables, including growth, migration, and cytotoxic challenge in preclin. in vivo tumor models.

Answer 56:

Bibliographic Information

Molecular mechanism of phenoxodiol-induced apoptosis in ovarian carcinoma cells. Alvero, Ayesha B.; O'Malley, David; Brown, David; Kelly, Graham; Garg, Manish; Chen, Wei; Rutherford, Thomas; Mor, Gil. Department of Obstetrics & Gynecology, Yale University School of Medicine, New Haven, CT, USA. Cancer (Hoboken, NJ, United States) (2006), 106(3), 599-608. Publisher: John Wiley & Sons, Inc., CODEN: CANCAR ISSN: 0008-543X. Journal written in English. CAN 145:76157 AN 2006:155201 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Previously, it was demonstrated that phenoxodiol induces apoptosis in epithelial ovarian carcinoma (EOC) cells and that it is capable of sensitizing these cells to Fas-mediated apoptosis. The objectives of this study were to det. whether phenoxodiol can also act as chemosensitizer to chemotherapeutic agents and to characterize the mol. mechanism behind its sensitizing effect. Ten EOC cell lines were used in this study. The effect of phenoxodiol on the inhibitory concn. 50% (IC50) of carboplatin, paclitaxel, and gemcitabine was detd. by the CellTiter 96 Assay. The in vivo effect of combination treatments with phenoxodiol and the above-mentioned agents was detd. in animal xenograft models. Apoptosis was measured using the Caspase-Glo Assay and the apoptotic cascade was characterized by Western blot analyses. The results showed that phenoxodiol is able to sensitize EOC cells to carboplatin, paclitaxel, and gemcitabine both in vitro and in vivo. In addn., it was demonstrated that phenoxodiol is capable of inducing apoptosis by: (1) the activation of the mitochondrial pathway through caspase-2 and Bid signaling, and (2) the proteasomal degrdn. of the anti-apoptotic protein XIAP. Understanding the components of the apoptotic pathway activated by phenoxodiol, which allows it to sensitize EOC cells to chemotherapeutic agents, will provide valuable information on the characteristic mode of action of a chemosensitizer. This will help in the identification of novel drugs and in the design of better strategies for combination therapy in patients with recurrent ovarian carcinoma.

Answer 57:

Bibliographic Information

Increased Antitumor Activity, Intratumor Paclitaxel Concentrations, and Endothelial Cell Transport of Cremophor-Free, Albumin-Bound Paclitaxel, ABI-007, Compared with Cremophor-Based Paclitaxel. Desai, Neil; Trieu, Vuong; Yao, Zhiwen; Louie, Leslie; Ci, Sherry; Yang, Andrew; Tao, Chunlin; De, Tapas; Beals, Bridget; Dykes, Donald; Noker, Patricia; Yao, Rosie; Labao, Elizabeth; Hawkins, Michael; Soon-Shiong, Patrick. American BioScience, Inc., Santa Monica, CA, USA. Clinical Cancer Research (2006), 12(4), 1317-1324. Publisher: American Association for Cancer Research, CODEN: CCREFF4 ISSN: 1078-0432. Journal written in English. CAN 145:159173 AN 2006:152678 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

ABI-007, an albumin-bound, 130-nm particle form of paclitaxel, was developed to avoid Cremophor/ethanol-assocd. toxicities in Cremophor-based paclitaxel (Taxol) and to exploit albumin receptor-mediated endothelial transport. We studied the antitumor activity, intratumoral paclitaxel accumulation, and endothelial transport for ABI-007 and Cremophor-based paclitaxel. Antitumor activity and mortality were assessed in nude mice bearing human tumor xenografts [lung (H522), breast (MX-1), ovarian (SK-OV-3), prostate (PC-3), and colon (HT29)] treated with ABI-007 or Cremophor-based paclitaxel. Intratumoral paclitaxel concns. (MX-1-tumored mice) were compared for radiolabeled ABI-007 and Cremophor-based paclitaxel. In vitro endothelial transcytosis and Cremophor inhibition of paclitaxel binding to cells and albumin was compared for ABI-007 and Cremophor-based paclitaxel. Both ABI-007 and Cremophor-based paclitaxel caused tumor regression and prolonged survival; the order of sensitivity was lung > breast .simeq. ovary > prostate > colon. The LD50 and max. tolerated dose for ABI-007 and Cremophor-based paclitaxel were 47 and 30 mg/kg/d and 30 and 13.4 mg/kg/d, resp. At equitoxic dose, the ABI-007-treated groups showed more complete regressions, longer time to recurrence, longer doubling time, and prolonged survival. At equal dose, tumor paclitaxel area under the curve was 33% higher for ABI-007 vs. Cremophor-based paclitaxel, indicating more effective intratumoral accumulation of ABI-007. Endothelial binding and transcytosis of paclitaxel were markedly higher for ABI-007 vs. Cremophor-based paclitaxel, and this difference was abrogated by a known inhibitor of endothelial gp60 receptor/caveolar transport. In addn., Cremophor was found to inhibit binding of paclitaxel to endothelial cells and albumin. Enhanced endothelial cell binding and transcytosis for ABI-007 and inhibition by Cremophor in Cremophor-based paclitaxel may account in part for the greater efficacy and intratumor delivery of ABI-007.

Answer 58:

Bibliographic Information

Antitumor effects of IDN5109 on head and neck squamous cell carcinoma. Sano, Daisuke; Matsuda, Hideki; Ishiguro, Yukari; Nishimura, Goshi; Kawakami, Mariko; Tsukuda, Mamoru. Department of Biology and Function in the Head and Neck, Yokohama City University Graduate School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama, Japan. *Oncology Reports* (2006), 15(2), 329-334. Publisher: Oncology Reports, CODEN: OCRPEW ISSN: 1021-335X. Journal written in English. CAN 145:95904 AN 2006:150821 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Taxanes, a new class of antitumor drugs, are effective against a large no. of human tumors, although there are problems with drug resistance. The novel taxane, IDN5109, is characterized by its high tolerability, antitumor efficacy, ability to overcome multidrug resistance, and oral bioavailability. We investigated the cellular response of IDN5109 to head and neck squamous cell carcinoma (HNSCC), and compared the antitumor activity of IDN5109 with that of paclitaxel. This is the first demonstration of antitumor effects of IDN5109 on HNSCC. In in vitro expts., IDN5109 showed antiproliferative effects against HNSCC cell lines. After treatment with IDN5109, Bcl-2 and Bcl-XL were down-regulated, Bax was up-regulated, and caspase-3 was activated. After treatment with IDN5109, concns. of both VEGF and IL-8 in the culture supernatant of HNSCC cells decreased. In in vivo expts., the oral administration of IDN5109 showed antitumor effects against HNSCC tumor xenografts. Immunohistochem. showed that IDN5109 inhibited tumor angiogenesis and induced apoptosis in HNSCC cells, producing a decreased blood vessel d. and increased apoptosis index. On the basis of these results, IDN5109 is useful as a chemotherapeutic agent against HNSCC.

Answer 59:

Bibliographic Information

Tweaking microtubules to treat scleroderma. van Laar, Jacob M.; Huizinga, Tom W. J. Department of Rheumatology, Leiden University Medical Center, Leiden, Neth. *PLoS Medicine* (2005), 2(12), 1230-1231. Publisher: Public Library of Science, CODEN: PMLEAC ISSN: 1549-1277.

http://medicine.plosjournals.org/archive/1549-1676/2/12/pdf/10.1371_1549-1676_2_12_complete.pdf Journal; General Review; Online Computer File written in English. CAN 145:100553 AN 2006:143236 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A review. Systemic sclerosis (SSc) is a rare but debilitating disease characterized by skin thickening and signs and symptoms of vasculopathy, which can involve the heart, lungs, kidneys, and gut. The disease poses a challenge for the treating clinician, since no proven therapy exists that improves outcome. A recent study shows that in a hybrid human SSc skin-severe combined immunodeficient mouse xenotransplant model, stabilizing microtubules using paclitaxel reduced the prodn. of phosphorylated Smad 2/3 and expression of COLIA2, to lessen fibrosis histol.

Answer 60:

Bibliographic Information

Optimal classes of chemotherapeutic agents sensitized by specific small-molecule inhibitors of Akt in vitro and in vivo.

Shi, Yan; Liu, Xuesong; Han, Edward K.; Guan, Ran; Shoemaker, Alexander R.; Oleksijew, Anatol; Woods, Keith W.; Fisher, John P.; Klinghofer, Vered; Lasko, Loren; McGonigal, Thomas; Li, Qun; Rosenberg, Saul H.; Giranda, Vincent L.; Luo, Yan. Departments of R47S, Abbott Laboratories, Abbott Park, IL, USA. *Neoplasia* (Ann Arbor, MI, United States) (2005), 7(11), 992-1000. Publisher: Neoplasia Press Inc., CODEN: NEOPFL ISSN: 1522-8002. Journal written in English. CAN 145:444 AN 2006:84249 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Akt is a serine/threonine kinase that transduces survival signals from survival/growth factors. Deregulation and signal imbalance in cancer cells make them prone to apoptosis. Upregulation or activation of Akt to aid the survival of cancer cells is a common theme in human malignancies. We have developed small-mol. Akt inhibitors that are potent and specific. These Akt inhibitors can inhibit Akt activity and block phosphorylation by Akt on multiple downstream targets in cells. Synergy in apoptosis induction was obsd. when Akt inhibitors were combined with doxorubicin or camptothecin. Akt inhibitor-induced enhancement of topoisomerase inhibitor cytotoxicity was also evident in long-term cell survival assay. Synergy with paclitaxel in apoptosis induction was evident in cells pretreated with paclitaxel, and enhancement of tumor delay by paclitaxel was demonstrated through cotreatment with Akt inhibitor Compd. A (A-443654). Combination with other classes of chemotherapeutic agents did not yield any enhancement of cytotoxicity. These findings provide important guidance in selecting appropriate classes of chemotherapeutic agents for combination with Akt inhibitors in cancer treatment.

Answer 61:

Bibliographic Information

Discovery and Structure-Activity Relationship of Antagonists of B-Cell Lymphoma 2 Family Proteins with Chemopotiation Activity in Vitro and in Vivo. Wendt, Michael D.; Shen, Wang; Kunzer, Aaron; McClellan, William J.; Bruncko, Milan; Oost, Thorsten K.; Ding, Hong; Joseph, Mary K.; Zhang, Haichao; Nimmer, Paul M.; Ng, Shi-Chung; Shoemaker, Alexander R.; Petros, Andrew M.; Oleksijew, Anatol; Marsh, Kennan; Bauch, Joy; Oltersdorf, Tilman; Belli, Barbara A.; Martineau, Darlene; Fesik, Stephen W.; Rosenberg, Saul H.; Elmore, Steven W. Cancer Research, Global Pharmaceutical R & D, Abbott Laboratories, Abbott Park, IL, USA. Journal of Medicinal Chemistry (2006), 49(3), 1165-1181. Publisher: American Chemical Society, CODEN: JMCMAR ISSN: 0022-2623. Journal written in English. CAN 144:100384 AN 2006:35355 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Development of a rationally designed potentiator of cancer chemotherapy, via inhibition of Bcl-XL function, is described. Lead compds. generated by NMR screening and directed parallel synthesis displayed sub- μ M binding but were strongly deactivated in the presence of serum. The dominant component of serum deactivation was identified as domain III of human serum albumin (HSA); NMR soln. structures of inhibitors bound to both Bcl-XL and HSA domain III indicated two potential optimization sites for sepn. of affinities. Modifications at both sites resulted in compds. with improved Bcl-XL binding and greatly increased activity in the presence of human serum, culminating in 73R, which bound to Bcl-XL with a K_i of 0.8 nM. In a cellular assay 73R reversed the protection afforded by Bcl-XL overexpression against cytokine deprivation in FL5.12 cells with an EC_{50} of 0.47 μ M. 73R showed little effect on the viability of the human non small cell lung cancer cell line A549. However, consistent with the proposed mechanism, 73R potentiated the activity of paclitaxel and UV irradiation in vitro and potentiated the antitumor efficacy of paclitaxel in a mouse xenograft model.

Answer 62:

Bibliographic Information

Poly(Ethylene Oxide)-Modified Poly(β -Amino Ester) Nanoparticles as a pH-Sensitive System for Tumor-Targeted Delivery of Hydrophobic Drugs: Part 2. In Vivo Distribution and Tumor Localization Studies. Shenoy, Dinesh; Little, Steven; Langer, Robert; Amiji, Mansoor. Department of Pharmaceutical Sciences, School of Pharmacy, Northeastern University, Boston, MA, USA. Pharmaceutical Research (2005), 22(12), 2107-2114. Publisher: Springer, CODEN: PHREEB ISSN: 0724-8741. Journal written in English. CAN 144:239618 AN 2005:1335780 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

This study was carried out to det. the biodistribution profiles and tumor localization potential of poly(ethylene oxide) (PEO)-modified poly(β -amino ester) (PbAE) as a novel, pH-sensitive biodegradable polymeric nanoparticulate system for tumor-targeted drug delivery.

The biodistribution studies of PEO-modified PbAE and PEO-modified poly(ϵ -caprolactone) (PCL), a non-pH-sensitive polymer, nanoparticle systems were carried out in normal mice using ^{111}In -oxine [^{111}In] as a lipophilic radiolabel encapsulated within the polymeric matrix, and the distribution of the nanoparticles was studied in plasma and all the vital organs following i.v. administration. Solid tumors were developed on nude mice using human ovarian carcinoma xenograft (SKOV-3) and the change in concns. of tritium [^3H]-labeled paclitaxel encapsulated in polymeric nanoparticles was examd. in blood, tumor mass, and liver. Study in normal mice with a gamma-emitting isotope [^{111}In] provided a thorough biodistribution anal. of the PEO-modified nanoparticulate carrier systems, whereas ^3H -paclitaxel was useful to understand the change in concn. and tumor localization of anticancer compd. directly in major sites of distribution. Both PEO-PbAE and PEO-PCL nanoparticles showed long systemic circulating properties by virtue of surface modification with PEO-contg. triblock block copolymer (Pluronic) stabilizer. Although the PCL nanoparticles showed higher uptake by the reticuloendothelial system, the PbAE nanoparticles effectively delivered the encapsulated payload into the tumor mass. PEO-modified PbAE nanoparticles showed considerable passive tumor targeting potential in early stages of biodistribution via the enhanced permeation and retention (EPR) mechanism. This prompts a detailed biodistribution profiling of the nanocarrier for prolonged periods to provide conclusive evidence for superiority of the delivery system.

Answer 63:

Bibliographic Information

Pharmacodynamics of antitumor activity of paclitaxel in monolayers and histocultures of human NSCLC cells. Park, Jong-Kook; Kim, Seong-Yun; Kuh, Hyo-Jeong. Catholic Research Institutes of Medical Science, The Catholic University, Seoul, S. Korea. *Yakche Hakhoechi* (2005), 35(5), 361-367. Publisher: Korean Society of Pharmaceutical Sciences and Technology, CODEN: YAHAEX ISSN: 0259-2347. Journal written in English. CAN 144:266750 AN 2005:1277319 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

In this study, we evaluated and compared the pharmacodynamics of paclitaxel (PTX) in human A549 NSCLC cells grown as monolayers or as three-dimensional histocultures. Growth inhibitory effects were detd. after incubating cells in drug free medium until 96 h post drug exposure initiation. Cell cycle arrest and apoptosis were measured by flow cytometry. The growth inhibition induced by PTX was significantly different in monolayers and histocultures, and PTX showed significantly less cytotoxicity in histocultures where large resistant fractions were obsd. Moreover, although PTX induced significant G2/M arrest followed by apoptosis in monolayers in a drug concn.-dependant manner, G2/M arrest was not elicited in histocultures. However, apoptotic cells appeared from the G2/M phase in histocultures. In this study, we provide first evidence that PTX in three-dimensional histocultures, does not induce G2/M arrest, but rather that it induces G2/M phase specific apoptosis. Overall, our data demonstrate different pharmacodynamics of PTX in traditional monolayer and three-dimensional histocultures.

Answer 64:

Bibliographic Information

Targeted therapy against Bcl-2-related proteins in breast cancer cells. Emi, Manabu; Kim, Ryungsa; Tanabe, Kazuaki; Uchida, Yoko; Toge, Tetsuya. Department of Surgical Oncology, Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan. *Breast Cancer Research* (2005), 7(6), R940-R952. Publisher: BioMed Central Ltd., CODEN: BRCRFS ISSN: 1465-542X. <http://breast-cancer-research.com/content/pdf/bcr1323.pdf> Journal; Online Computer File written in English. CAN 144:403854 AN 2005:1215059 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Introduction Bcl-2 and Bcl-xL confer resistance to apoptosis, thereby reducing the effectiveness of chemotherapy. We examd. the relationship between the expression of Bcl-2 and Bcl-xL and chemosensitivity of breast cancer cells, with the aim of developing specific targeted therapy. Methods Four human breast cancer cell lines were examd., and the effects of antisense (AS) Bcl-2 and AS Bcl-xL phosphorothioate oligodeoxynucleotides (ODNs) on chemosensitivity were tested in vitro and in vivo. Chemosensitivity was

evaluated by the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide) assay, and the antitumor effect was assessed in vivo by the success of xenograft transplantation into athymic mice. Results Treatment with AS Bcl-2 and Bcl-xL ODNs resulted in a sequence-specific decrease in protein expression, compared with controls. Treatment of BT-474, ZR-75-1, and MDA-MB-231 cells with AS Bcl-2 increased chemosensitivity to doxorubicin (DOX), mitomycin C (MMC), paclitaxel (TXL), and docetaxel (TXT). Transfection of the Bcl-2 gene into MDA-MB-453 cells decreased sensitivity to DOX and MMC. Treatment of MDA-MB-231, BT-474, and ZR-75-1 cells with AS Bcl-xL increased chemosensitivity to DOX, MMC and taxanes to a smaller extent than AS Bcl-2. This occurred in the setting of increased Bax and cleaved poly(ADP-ribose) polymerase, as well as decreased Bcl-2 and pAkt. AS Bcl-2 ODNs induced splenomegaly in assocn. with increased serum IL-12, which was attenuated by methylation of the CpG motifs of AS Bcl-2; however, methylated CpG failed to negate the increased antitumor effect of AS Bcl-2. Bcl-2 and Bcl-xL, to a smaller extent, are major determinants of chemosensitivity in breast cancer cells. Conclusion Targeted therapy against Bcl-2 protein with the use of AS ODNs might enhance the effects of chemotherapy in patients with breast cancer.

Answer 65:

Bibliographic Information

Curcumin Suppresses the Paclitaxel-Induced Nuclear Factor- κ B Pathway in Breast Cancer Cells and Inhibits Lung Metastasis of Human Breast Cancer in Nude Mice. Aggarwal, Bharat B.; Shishodia, Shishir; Takada, Yasunari; Banerjee, Sanjeev; Newman, Robert A.; Bueso-Ramos, Carlos E.; Price, Janet E. Cytokine Research Laboratory, University of Texas M.D. Anderson Cancer Center, Houston, TX, USA. *Clinical Cancer Research* (2005), 11(20), 7490-7498. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 144:205256 AN 2005:1128760 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Currently, there is no effective therapy for metastatic breast cancer after surgery, radiation, and chemotherapy have been used against the primary tumor. Because curcumin suppresses nuclear factor- κ B (NF- κ B) activation and most chemotherapeutic agents activate NF- κ B that mediates cell survival, proliferation, invasion, and metastasis, we hypothesized that curcumin would potentiate the effect of chemotherapy in advanced breast cancer and inhibit lung metastasis. We tested this hypothesis using paclitaxel (Taxol)-resistant breast cancer cells and a human breast cancer xenograft model. As examd. by electrophoretic mobility gel shift assay, paclitaxel activated NF- κ B in breast cancer cells and curcumin inhibited it; this inhibition was mediated through inhibition of I κ B α kinase activation and I κ B α phosphorylation and degrdn. Curcumin also suppressed the paclitaxel-induced expression of antiapoptotic (XIAP, IAP-1, IAP-2, Bcl-2, and Bcl-xL), proliferative (cyclooxygenase 2, c-Myc, and cyclin D1), and metastatic proteins (vascular endothelial growth factor, matrix metalloproteinase-9, and intercellular adhesion mol.-1). It also enhanced apoptosis. In a human breast cancer xenograft model, dietary administration of curcumin significantly decreased the incidence of breast cancer metastasis to the lung and suppressed the expression of NF- κ B, cyclooxygenase 2, and matrix metalloproteinase-9. Overall, our results indicate that curcumin, which is a pharmacol. safe compd., has a therapeutic potential in preventing breast cancer metastasis possibly through suppression of NF- κ B and NF- κ B-regulated gene products.

Answer 66:

Bibliographic Information

Does Paclitaxel (Taxol) Given after ¹¹¹In-Labeled Monoclonal Antibodies Increase Tumor-Cumulated Activity in Epithelial Cancers? Miers, Laird; Lamborn, Kathleen; Yuan, Aina; Richman, Carol; Natarajan, Arutselvan; DeNardo, Sally; DeNardo, Gerald. School of Medicine, University of California Davis, San Francisco, CA, USA. *Clinical Cancer Research* (2005), 11(19, Pt. 2), 7158s-7163s. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 144:163634 AN 2005:1061882 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: Paclitaxel synergized radiolabeled monoclonal antibodies, enhancing therapeutic effect in studies in mice with human

xenografts. Paclitaxel was also obsd. to increase tumor uptake in imaging studies of ^{111}In -DOTA-Gly3Phe-m170 in patients with breast and prostate cancers. Further evaluations of tissue-cumulated activities, therapeutic indexes, and pharmacokinetics were done using data for patients with breast and prostate cancer and for mice with human breast cancer xenografts. Exptl. Design: In radioimmunotherapy trials, 12 patients with breast or prostate cancer were given two imaging doses (5 mCi each) of ^{111}In -DOTA-Gly3Phe-m170 1 wk apart. Five of these patients were given a single dose of paclitaxel i.v. (75 mg/m²) 2 days after the second dose of ^{111}In . In a subsequent study, athymic mice with human breast cancer xenografts were given ^{111}In -DOTA-Gly3Phe-ChL6 alone, or in combination with daily paclitaxel i.p. (300 μg) one or more times. Pharmacokinetics were studied for at least 6 days in patients and 5 days in mice. Cumulated activities were detd. for tumors and normal tissues. Results: Tumor-cumulated activity for every patient in the paclitaxel-treated group increased for the second dose of ^{111}In -DOTA-Gly3Phe-m170. The median ratio of cumulated activities in tumors for imaging dose 2 to those for dose 1 was 1.0 (0.8-1.3) in patients that were not given paclitaxel and 1.3 (1.2-1.4) in patients given paclitaxel. Normal tissue-cumulated activities were not different for the two doses. Mice given paclitaxel 1 day after ^{111}In -DOTA-Gly3Phe-ChL6 also showed an increase in tumor-cumulated activity, 22.9 (\pm 1.3) vs. 19.4 (\pm 3.3) $\mu\text{Ci h/g}/\mu\text{Ci}$ ($P = 0.05$). Cumulated activities of normal tissues were similar for all groups of mice. Conclusions: Paclitaxel given 1 to 2 days after ^{111}In -DOTA-Gly3Phe-monoconal antibody increased the tumor-cumulated activity in patients and in mice with epithelial cancers and did not alter cumulated activities in normal tissues.

Answer 67:

Bibliographic Information

Phospholipid nanosomes. Castor, Trevor P. Aphios Corporation, Woburn, MA, USA. *Current Drug Delivery* (2005), 2(4), 329-340. Publisher: Bentham Science Publishers Ltd., CODEN: CDDUBJ ISSN: 1567-2018. Journal; General Review written in English. CAN 144:40452 AN 2005:1007517 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A review. Phospholipid nanosomes are small, uniform liposomes manufd. utilizing supercrit. fluid technologies. Supercrit. fluids are first used to solvate phospholipid raw materials, and then decompressed to form phospholipid nanosomes that can encapsulate hydrophilic mols. such as proteins and nucleic acids. Hydrophobic therapeutics are co-solvated with phospholipid raw materials in supercrit. fluids that, when decompressed, form phospholipid nanosomes encapsulating these drugs in their lipid bilayers. Math. modeling and semi-empirical expts. indicate that the size and character of phospholipid nanosomes depend on the several process parameters and material properties including the size and design of decompression nozzle, bubble size, pressure and the rate of decompression, interfacial forces, charge distribution and the nature of compd. being encapsulated. Examples are presented for the encapsulation of a protein and hydrophobic drugs. In vitro and in vivo data on breast cancer cells and xenografts in nude mice indicate that paclitaxel nanosomes are less toxic and much more effective than paclitaxel in Cremophor EL (Taxol). Camptothecin nanosomes demonstrate that the normally very water-insol. camptothecin can be formulated in a biocompatible aq. medium while retaining in vivo efficacy against lymphoma xenografts in nude mice. In vitro data for betulinic acid nanosomes demonstrate enhanced efficacy against HIV-1 (EC₅₀ of 1.01 $\mu\text{g}/\text{mL}$ vs. 6.72 $\mu\text{g}/\text{mL}$ for neat betulinic acid). Phospholipid nanosomes may find utility in the enhanced delivery of hydrophilic drugs such as recombinant proteins and nucleic acid as well as hydrophobic anticancer and anti-HIV drugs.

Answer 68:

Bibliographic Information

Adenovirus-mediated inhibition of survivin expression sensitizes human prostate cancer cells to paclitaxel in vitro and in vivo. Zhang, Min; Mukherjee, Neelanjan; Bermudez, R. Scott; Latham, Douglas E.; Delaney, Meaghan A.; Zietman, Anthony L.; Shipley, William U.; Chakravarti, Arnab. Department of Radiation Oncology, Massachusetts General Hospital/Harvard Medical School Boston, MA, USA. *Prostate* (Hoboken, NJ, United States) (2005), 64(3), 293-302. Publisher: Wiley-Liss, Inc., CODEN: PRSTDS ISSN: 0270-4137. Journal written in English. CAN 143:399122 AN 2005:810563 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Improvements in the response rates to chemotherapy would represent an important advancement in the care of patients with metastatic prostate cancer. There is accumulating evidence that Survivin, a member of the inhibitor of apoptosis (IAP) family, is associated with both cancer progression and drug resistance. The purpose of this study is to investigate the role of Survivin in paclitaxel-resistance and whether the targeting of Survivin sensitizes prostate cancer cells to paclitaxel. Human prostate cell lines PC-3, DU-145, and LNCaP were infected with replication-deficient adenoviruses encoding either wild-type Survivin [pAd-S(WT)], to examine Survivin overexpression effects, or a phosphorylation-defective Survivin Thr34→Ala dominant neg. mutant [pAd-S(T34A)], to examine Survivin inactivation effects. The effects of wild-type or mutant Survivin on spontaneous and paclitaxel-induced apoptosis were investigated both in vitro and in vivo. Forced overexpression of wild-type Survivin with pAd-S(WT) increased resistance to paclitaxel in all cell lines, both in vitro and in vivo. Inhibition of Survivin using pAd-S(T34A) resulted in a significant increase in the rate of spontaneous and paclitaxel-induced apoptosis in all cell lines, both in vitro and in vivo. This effect was abolished by co-treatment with VAD-CHO (Calbiochem, San Diego, CA), a pan-caspase inhibitor, indicating that Survivin normally mediates resistance to paclitaxel through suppression of caspase-mediated apoptosis. Survivin mediates paclitaxel-resistance in prostate cancer cells. The inhibition of Survivin sensitizes prostate cancer cells to paclitaxel-induced apoptosis through a caspase-dependant mechanism in vitro and in vivo.

Answer 69:

Bibliographic Information

Enhancement of antitumor activity of 5'-deoxy-5-fluorouridine (Furtulon) by taxane in human gastric cancer xenografts.

Sawada, Noriaki; Nose, Taeko; Ishikawa, Tohru; Yutaka, Tanaka. Product Research Department, Chugai Pharmaceutical Co., Ltd., Kamakura, Kanagawa, Japan. *Oncology Reports* (2005), 14(1), 53-57. Publisher: Oncology Reports, CODEN: OCRPEW ISSN: 1021-335X. Journal written in English. CAN 143:146059 AN 2005:624270 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

5'-Deoxy-5-fluorouridine (5'-DFUR, Furtulon) is activated to 5-fluorouracil (5-FU) by thymidine phosphorylase (dThdPase) highly expressed in many types of tumors. In previous studies, we demonstrated that taxanes (paclitaxel or docetaxel) up-regulated the tumor levels of dThdPase and enhanced the efficacy of 5'-DFUR in human colon and mammary xenograft models. In the present study, combination therapy of 5'-DFUR with taxanes in human gastric cancer xenograft models also showed, at the least, additive antitumor activity without significant augmentation of toxicity. Furthermore, paclitaxel up-regulated dThdPase expression in the tumor tissues as confirmed with ELISA and immunohistochem. These results suggest taxanes would potentiate the efficacy of 5'-DFUR by up-regulating-the tumor levels of dThdPase in gastric xenograft models. Clin. trials of 5'-DFUR in combination with taxane against gastric cancer are warranted.

Answer 70:

Bibliographic Information

Timing is everything: preclinical evidence supporting simultaneous rather than sequential chemohormonal therapy for prostate cancer.

Eigl, Bernhard J. C.; Eggener, Scott E.; Baybik, Jenny; Ettinger, Susan; Chi, Kim N.; Nelson, Colleen; Wang, Zhou; Gleave, Martin E. The Prostate Centre at Vancouver General Hospital and BC Cancer Agency, Vancouver, BC, Can. *Clinical Cancer Research* (2005), 11(13), 4905-4911. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 143:472831 AN 2005:585328 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Androgen ablation is the mainstay of systemic therapy for prostate cancer, with cytotoxic therapies reserved for hormone-refractory disease. It is not clear, however, that this is the most appropriate sequence of interventions for this disease. This study addresses the ideal timing of systemic treatments in the Shionogi and LNCaP xenograft models. We explored the hypothesis that stress-induced gene expression changes after chemotherapy can induce a hormone-independent phenotype. Three groups of mice bearing either

Shionogi or LNCaP xenografts were treated with (a) initial castration and delayed paclitaxel, (b) initial paclitaxel and delayed castration, or (c) simultaneous castration plus paclitaxel. End points were time to tumor progression and time to sacrifice. Microarray and reverse transcription-PCR analyses were carried out to assess changes in gene expression induced by paclitaxel. Mice receiving simultaneous therapy showed a significant improvement in median time to progression (TTP: Shionogi, 65 vs. 38 days; LNCaP, 105 vs. 70 days) and time to sacrifice (Shionogi, 83 vs. 66 days) vs. best sequential therapy. A marked lack of response to castration was obsd. after initial paclitaxel therapy. Gene expression and reverse transcription-PCR studies confirmed that several genes known to play a role in androgen independence were up-regulated in response to paclitaxel exposure. In lab. models of prostate cancer, simultaneous androgen deprivation plus paclitaxel is more effective than sequential treatments. These findings provide preclin. proof-of-principle for ongoing clin. trials addressing the role and timing of systemic therapies in prostate cancer.

Answer 71:

Bibliographic Information

Taltobulin: oncolytic drug tubulin polymerization inhibitor antimetabolic drug. Ayral-Kaloustian, S.; Zask, A. Wyeth Research, Pearl River, NY, USA. *Drugs of the Future* (2005), 30(3), 254-260. Publisher: Prous Science, CODEN: DRFUD4 ISSN: 0377-8282. Journal; General Review written in English. CAN 143:108821 AN 2005:563126 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A review. Antimicrotubule agents are among the most effective drugs for the treatment of breast, ovarian and other forms of cancer. Two classes of antimicrotubule drugs are commonly used: the taxanes, which accelerate tubulin polymn. by stabilizing assembled microtubules and obstructing depolymn., and the Vinca alkaloids, which bind to the tubulin α/β -heterodimer, block the formation of normal microtubules and lead to the depolymn. of microtubules and/or the formation of abnormal tubulin polymers. While these drugs inhibit tumor progression, their cytotoxic effects on rapidly proliferating normal tissues and other significant side effects are limiting factors. In addn., inherent resistance to antimicrotubule agents is encountered in many tumor types, or acquired resistance may occur during multiple cycles of therapy. Thus, there is great interest in and an unmet need for identifying novel antimicrotubule drugs. Taltobulin (HTI-286, SPA-110) is a novel antimetabolic agent that inhibits the polymn. of tubulin, disrupts microtubule dynamics in cells and induces mitotic arrest and apoptosis. Relative to the antimicrotubule drugs in use, taltobulin exhibits significantly less interaction with the multidrug resistance protein (P-glycoprotein) and is effective in inhibiting human tumor xenografts in nude mouse models where paclitaxel and vincristine are ineffective. Taltobulin administered i.v. or p.o. in saline inhibits the growth of numerous human tumors without the side effects assocd. with formulations. Taltobulin is in clin. development.

Answer 72:

Bibliographic Information

From deep-sea sponge to pilot plant: The large scale total synthesis of the marine natural product (+)-Discodermolide. Mickel, Stuart J. Novartis Pharma AG, 4002 Basel, Switz. Abstracts, 37th Middle Atlantic Regional Meeting of the American Chemical Society, New Brunswick, NJ, United States, May 22-25, 2005 (2005), GENE-142. Publisher: American Chemical Society, Washington, D. C. CODEN: 69GVWG Conference; Meeting Abstract written in English. AN 2005:542562 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A small, but structurally diverse collection of naturally occurring non-taxane microtubule stabilizing agents (MTS) has been discovered over the last decade. These include the epothilones (EPO), eleutherobin, laulimalide, and discodermolide. (+)-Discodermolide (1) is a novel polyketide natural product first isolated from exts. of the marine sponge *Discodermia dissoluta* by researchers at Harbor Branch Oceanog. Institution (HBOI). Discodermolide stabilizes microtubules faster and more potently than any of the other known MTS agents, is a potent inhibitor of tumor cell growth in vitro including paclitaxel- (PTX) and EPO-resistant cells. Discodermolide also demonstrates significant human tumor growth inhibition in hollow fiber and xenograft mouse models (including paclitaxel-resistant

tumors). Discodermolide is currently undergoing Phase 1 clin. trials. This presentation will discuss in some detail the strategy and tactics that lead to a large scale synthesis. Several of the key steps in the synthesis will also be presented with respect to scalability and problems encountered. Some workable solns. to the difficulties will be presented.

Answer 73:

Bibliographic Information

Chemosensitization by STI571 targeting the platelet-derived growth factor/platelet-derived growth factor receptor-signaling pathway in the tumor progression and angiogenesis of gastric carcinoma. Kim, Ryungsa; Emi, Manabu; Arihiro, Koji; Tanabe, Kazuaki; Uchida, Yoko; Toge, Tetsuya. International Radiation Information Center, Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan. *Cancer* (New York, NY, United States) (2005), 103(9), 1800-1809. Publisher: John Wiley & Sons, Inc., CODEN: CANCAR ISSN: 0008-543X. Journal written in English. CAN 143:19476 AN 2005:415435 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

BACKGROUND: Autocrine and paracrine growth mediated by the platelet-derived growth factor (PDGF)/PDGF receptor (PDGFR)-signaling pathway plays an important role in the progression of solid tumors. The authors assessed the effect of STI571 on the tumor growth of gastric carcinoma in combination with 5-fluorouracil (5-FU) or paclitaxel targeting the PDGF/PDGFR-signaling pathway. **METHODS:** In MKN-45 gastric carcinoma cells, the cytotoxic effect was evaluated by 3-(4,5 dimethylazol-2-yl)-2,5-diphenyl tetrazolium bromide assay, and the in vivo antitumor effect was evaluated in a nude mouse xenograft. Both STI571 and an antitumor drug were administered i.p. Gene expression was assessed by Western blot anal. and immunohistochem. staining. Apoptotic cell death was evaluated by the terminal deoxyuridine triphosphate-biotin nick-end labeling assay, and tumor angiogenesis was evaluated by microvessel d. anal. **RESULTS:** Treatment with STI571 alone was not effective in vitro, as assessed by a 50% inhibitory concn. value of 24.3 μ M. Combination treatment with STI571 and 5-FU or paclitaxel enhanced the cytotoxic effect somewhat when the concn. of STI571 was increased to 10 μ M. Combination treatment with STI571 and 5-FU or paclitaxel enhanced the antitumor effect of the antitumor drug significantly in vivo. The enhanced antitumor effect was assocd. with increased apoptotic cell death and inhibition of tumor angiogenesis. Treatment with STI571 down-regulated the expression of PDGF-BB and PDGFR- β in tumor cells and decreased the prodn. of phosphorylated PDGFR- β and phosphorylated Akt. Furthermore, treatment with STI571 inhibited the expression of PDGFR- β in stromal cells. **CONCLUSIONS:** STI571 was an effective chemosensitizer of antitumor drugs, such as 5-FU and paclitaxel for gastric carcinoma, targeting the PDGF/PDGFR-signaling pathway of tumor cells and stromal cells in disease progression and angiogenesis.

Answer 74:

Bibliographic Information

Opioid growth factor enhances tumor growth inhibition and increases the survival of paclitaxel-treated mice with squamous cell carcinoma of the head and neck. Jaglowski, Jeffrey R.; Zagon, Ian S.; Stack, Brendan C., Jr.; Verderame, Michael F.; Leure-duPree, Alphonse E.; Manning, Jeffrey D.; McLaughlin, Patricia J. Department of Neural and Behavioral Sciences H109, Pennsylvania State University, Hershey, PA, USA. *Cancer Chemotherapy and Pharmacology* (2005), 56(1), 97-104. Publisher: Springer GmbH, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 143:205869 AN 2005:396835 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Paclitaxel is used as a single agent, and in combination with other drugs, as a std. of care in the treatment of squamous cell carcinoma of the head and neck (SCCHN). However, the use of paclitaxel for therapy of SCCHN may be accompanied by serious side effects. Paclitaxel is a known cytotoxic inhibitor of cell proliferation that acts by stabilizing microtubules and inducing apoptosis. Opioid growth factor (OGF), [Met5]-enkephalin, is an endogenous peptide that has tonically active inhibitory effects on the growth of SCCHN in vitro and in vivo. OGF action is rapid, reversible, mediated by the nuclear-assocd. OGF receptor (OGFr), and is not cytotoxic (nor

apoptotic related). The present study was designed to examine whether a combination of chemotherapy with paclitaxel and biotherapy with OGF is more effective than either agent alone in inhibiting tumor growth. Moreover, focus was placed on whether there are changes in the side effects known to occur with paclitaxel alone, following this combined therapy. Human SCC-1 cells, derived from a well differentiated SCCHN, were transplanted into athymic mice. The mice were randomized to receive i.p. injections of sterile saline (controls), OGF (10 mg/kg, daily), paclitaxel (8 mg/kg, every other day), or both paclitaxel (8 mg/kg, every other day) and OGF (10 mg/kg, daily) beginning on the day of tumor inoculation. OGF, but not paclitaxel, delayed measurable and visible tumor appearance of mice with SCCHN. Treatment with paclitaxel, but not with other agents, had a marked effect on the body wts. Survival only was reduced in the paclitaxel group, with an av. life span of 34.3 ± 3.1 days recorded, in comparison to the 50-day survival (date of termination) for all other groups. Beginning after week 4 of tumor inoculation and drug treatment, the tumor wt. of the paclitaxel/OGF group was significantly reduced from the control, OGF, and paclitaxel-exposed mice. The OGFr no.

of the SCCHN tumors was 2.1-fold greater in the animals exposed to OGF or paclitaxel, and elevated 38% in the paclitaxel/OGF group; significant differences from the control group were found for the OGF and paclitaxel groups. These data suggest that combined chemotherapy (i.e., paclitaxel) and biotherapy (OGF) provides a valuable alternative to the std. of care for SCCHN patients.

Answer 75:

Bibliographic Information

Targeted molecular therapy of anaplastic thyroid carcinoma with AEE788. Kim, Seungwon; Schiff, Bradley A.; Yigitbasi, Orhan G.; Doan, Dao; Jasser, Samar A.; Bekele, B. Nebiyou; Mandal, Mahitosh; Myers, Jeffrey N. Departments of Head and Neck Surgery, University of Texas M.D. Anderson Cancer Center, Houston, TX, USA. *Molecular Cancer Therapeutics* (2005), 4(4), 632-640. Publisher: American Association for Cancer Research, CODEN: MCTOCF ISSN: 1535-7163. Journal written in English. CAN 143:90368 AN 2005:313324 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Anaplastic thyroid carcinoma (ATC) is one of the most aggressive human malignancies with a mean survival of only 6 mo. The poor prognosis of patients with ATC reflects the current lack of curative therapeutic options and the need for development of novel therapeutic strategies. In this study, we report the results of a preclin. study of AEE788, a dual inhibitor of epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR) tyrosine kinases, against ATC. AEE788 was able to inhibit the proliferation and induce apoptosis of ATC cell lines in vitro. Administration of AEE788, alone and in combination with paclitaxel, to athymic nude mice bearing s.c. ATC xenografts inhibited the growth of ATC xenografts by 44% and 69%, resp., compared with the control group. Furthermore, tumors from mice treated with AEE788, alone and in combination with paclitaxel, showed increase in apoptosis of tumor cells by .apprx. 6- and 8-fold, resp., compared with the control group. The microvessel d. within the ATC xenografts was decreased by > 80% in the mice treated with AEE788 alone and in combination with paclitaxel compared with the control group. Lastly, immunofluorescence microscopy showed the inhibition of EGFR autophosphorylation on the tumor cells as well as the inhibition of VEGFR-2 autophosphorylation on tumor endothelium. Considering the fact that curative options seldom exist for patients with ATC, concurrent inhibition of EGFR and VEGFR tyrosine kinases seems to be a valid and promising anticancer strategy for these patients.

Answer 76:

Bibliographic Information

Enhancement of the therapeutic efficacy of taxol by the mitogen-activated protein kinase kinase inhibitor CI-1040 in nude mice bearing human heterotransplants. McDaid, Hayley M.; Lopez-Barcons, Lluís; Grossman, Aaron; Lia, Marie; Keller, Steven; Perez-Soler, Roman; Horwitz, Susan Band. Departments of Molecular Pharmacology and Medicine, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY, USA. *Cancer Research* (2005), 65(7), 2854-2860. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 142:403728 AN 2005:303948 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Taxol may contribute to intrinsic chemoresistance by activating the mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinase (ERK) cytoprotective pathway in human cancer cell lines and tumors. We have previously shown additivity between Taxol and the MEK inhibitor, U0126 in human cancer cell lines. Here, the combination of Taxol with an orally bioavailable MEK inhibitor, CI-1040, was evaluated in human lung tumors heterotransplanted into nude mice. Unlike xenograft models that are derived from cells with multiple genetic alterations due to prolonged passage, heterotransplanted tumor models are more clin. relevant. Combined treatment with both drugs resulted in inhibition of tumor growth in all models and tumor regressions in three of four models tested, supporting our previous observation that Taxol's efficacy is potentiated by MEK inhibition. Concurrent administration was superior to intermittent dosing. Pharmacodynamic assessments of tumors indicated that suppression of MEK was assocd. with induction of S473 phosphorylated Akt and reduced proliferation in the combination groups relative to single agents, in addn. to suppression of fibroblast growth factor-mediated angiogenesis and reduced expression of vascular endothelial growth factor. These findings are significant and indicate that this combination may have broad therapeutic applications in a diverse range of lung tumors with different intrinsic chemosensitivities.

Answer 77:

Bibliographic Information

Potential antagonism of tubulin-binding anticancer agents in combination therapies. Taraboletti, Giulia; Micheletti, Gianluca; Dossi, Romina; Borsotti, Patrizia; Martinelli, Michele; Fiordaliso, Fabio; Ryan, Anderson J.; Giavazzi, Raffaella. Laboratory of Biology and Treatment of Metastasis, Department of Oncology, Mario Negri Institute for Pharmacological Research, Bergamo, Italy. *Clinical Cancer Research* (2005), 11(7), 2720-2726. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 143:145913 AN 2005:296125 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

ZD6126 is a vascular targeting agent, developed for the treatment of solid tumors. In vivo, ZD6126 is rapidly converted into the tubulin-binding agent N-acetylcolchicol. We have previously reported that in vitro N-acetylcolchicol disrupts microtubules and induces rapid changes in endothelial cell morphol., which in a tumor would lead to a rapid loss of tumor vessel integrity and subsequent extensive tumor necrosis. The aim of this study was to investigate the effect of cytotoxic antineoplastic drugs-cisplatin, doxorubicin, vincristine, paclitaxel, and docetaxel-on endothelial cell response to N-acetylcolchicol. We found that cisplatin and doxorubicin did not interfere with the ability of N-acetylcolchicol to cause morphol. changes in human umbilical vein endothelial cells, whereas vincristine showed additive effects. In contrast, the microtubule-stabilizing agents paclitaxel (1-10 $\mu\text{mol/L}$) and docetaxel (0.1-1 $\mu\text{mol/L}$) prevented the morphol. changes induced by N-acetylcolchicol in human umbilical vein endothelial cells. The effect was obsd. when cells were exposed to paclitaxel and N-acetylcolchicol together or when paclitaxel was given shortly before N-acetylcolchicol. Paclitaxel and N-acetylcolchicol interacted at the level of microtubule organization, as shown in immunofluorescence anal. of the cytoskeleton. The protective effect was reversible because 4 h after paclitaxel wash out, cells recovered the sensitivity to N-acetylcolchicol. In vivo, pretreatment of mice with paclitaxel inhibited the vascular targeting activity of ZD6126 on newly formed vessels in the Matrigel plug assay and ZD6126-induced necrosis in tumors. These findings indicate that paclitaxel, depending on the timing and schedule of administration, can affect the vascular targeting activity of ZD6126, which may have an effect on the optimal scheduling of therapies based on the combined use of microtubule-stabilizing and microtubule-destabilizing agents.

Answer 78:

Bibliographic Information

Preclinical evaluation of the pharmacodynamic properties of 2,5-diaziridinyl-3-hydroxymethyl-6-methyl-1,4-benzoquinone. Ward, Timothy H.; Danson, Sarah; McGown, Alan T.; Ranson, Malcolm; Coe, Nic A.; Jayson, Gordon C.; Cummings, Jeff; Hargreaves, Robert H. J.; Butler, John. Clinical and Experimental Pharmacology Group, Christie Hospital, Manchester, UK. *Clinical Cancer Research* (2005), 11(7), 2695-2701. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 143:145910 AN 2005:296122 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The purpose of our study was to investigate the cellular accumulation, DNA crosslinking ability, and cellular toxicity of RH1 (2,5-diaziridinyl-3-[hydroxymethyl]-6-methyl-1,4-benzoquinone)], a novel DNA alkylating agent currently in clin. trials. In addn., the in vivo efficacy of RH1 formulated in different vehicles was also compared. RH1 is activated by the two-electron reducing enzyme NQO1 [NAD(P)H:quinone oxidoreductase] forming a potent cytotoxic agent that cross-links DNA. We have used whole blood, cell lines, and primary explanted tumor cultures to measure both the cellular accumulation, DNA crosslinking, and cytotoxicity of RH1. Furthermore, the pharmacokinetic and pharmacodynamic characteristics of RH1 formulated in different vehicles were measured in vivo using the validated comet-X assay in mice bearing human tumor xenografts. Accumulation of RH1 was shown to be both time and concn. dependent, reaching a max. after 2 h and correlated well with DNA crosslinking measurements. DNA crosslinking in vitro could be detected at low (1-10 nmol/L) concns. after as little as 2 h exposure. In primary tumor cultures, RH1 induces much higher levels of DNA cross-links at lower doses than either mitomycin C or cisplatin. In vivo efficacy testing using polyvinyl pyrrolidone, saline, or cyclodextrin as vehicles showed DNA cross-links readily detectable in all tissues examd. and was enhanced when given in cyclodextrin compared with polyvinyl pyrrolidone or saline. RH1 represents a potent bioreductive anticancer drug, which may prove effective in the treatment of cancers, particularly those that overexpress NQO1. DNA crosslinking can be reliably measured in tissue using the validated comet-X assay.

Answer 79:

Bibliographic Information

Herceptin down-regulates HER-2/neu and vascular endothelial growth factor expression and enhances taxol-induced cytotoxicity of human Ewing's sarcoma cells in vitro and in vivo. Guan, Hui; Jia, Shu-Fang; Zhou, Zhichao; Stewart, John; Kleinerman, Eugenie S. Division of Pediatrics and Department of Pathology, University of Texas M.D. Anderson Cancer Center, Houston, TX, USA. Clinical Cancer Research (2005), 11(5), 2008-2017. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 143:19402 AN 2005:206837 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We have previously shown that high levels of HER-2/neu protein were overexpressed in human Ewing's sarcoma cells (TC71, SK-ES1) relative to normal human osteoblasts. The purpose of this study was to det. whether herceptin alone or in combination with chemotherapeutic agents could inhibit the growth of Ewing's sarcoma in vitro and in vivo. Western blot anal. showed that the protein levels of HER-2/neu were decreased following herceptin treatment. Cell growth was also inhibited by herceptin in a dose-dependent manner with an IC50 of 4 mg/mL in TC71 and SK-ES1 cell line, whereas human immunoglobulin had no effect. Northern blot and ELISA showed the RNA expression and protein levels of vascular endothelial growth factor were also inhibited by herceptin treatment with no alteration in HIF-1 α protein and topoisomerase II α expression. Furthermore, Ewing's sarcoma tumor growth was significantly delayed by 100 mg/kg herceptin treatment in our Ewing's sarcoma xenograft mouse model. Combining taxol with herceptin resulted in additive cytotoxicity, whereas herceptin-etoposide, doxorubicin, and 9-nitrocamptothecin combinations did not. Taxol-herceptin enhanced growth inhibition in TC71 cells in vitro compared with either agent alone. Ewing's sarcoma growth was also delayed in vivo and mean tumor size was significantly lower in mice treated with herceptin plus taxol than in those receiving taxol or herceptin alone. These data suggest that herceptin in combination with taxol may be a therapeutic option in the treatment of Ewing's sarcoma.

Answer 80:

Bibliographic Information

From deep-sea sponge to pilot plant: The large scale total synthesis of the marine natural product (+)-Discodermolide. Mickel, Stuart J. Novartis Pharma AG, 4002 Basel, Switz. Abstracts of Papers, 229th ACS National Meeting, San Diego, CA, United States, March 13-17, 2005 (2005), MEDI-577. Publisher: American Chemical Society, Washington, D. C CODEN: 69GQMP Conference; Meeting Abstract written in English. AN 2005:191909 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A small, but structurally diverse collection of naturally occurring non-taxane microtubule stabilizing agents (MTS) has been discovered over the last decade. These include the epothilones (EPO), eleutherobin, laulimalide, and discodermolide. (+)-Discodermolide (1) is a novel polyketide natural product first isolated from exts. of the marine sponge *Discodermia dissoluta* by researchers at Harbor Branch Oceanog. Institution (HBOI). Discodermolide stabilizes microtubules faster and more potently than any of the other known MTS agents, is a potent inhibitor of tumor cell growth in vitro including paclitaxel- (PTX) and EPO-resistant cells. Discodermolide also demonstrates significant human tumor growth inhibition in hollow fiber and xenograft mouse models (including paclitaxel-resistant tumors). Discodermolide is currently undergoing Phase 1 clin. trials. This presentation will discuss in some detail the strategy and tactics that lead to the prodn. of 60 g of (+)-discodermolide for phase 1 clin. trials. Several of the key steps in the synthesis will also be presented with respect to scalability and problems encountered. Some workable solns. to the difficulties will be presented.

Answer 81:

Bibliographic Information**Synergism between the anticancer actions of 2-methoxyestradiol and microtubule-disrupting agents in human breast cancer.**

Han, Gui-Zhen; Liu, Zhi-Jian; Shimoi, Kayoko; Zhu, Bao Ting. Department of Basic Pharmaceutical Sciences, College of Pharmacy, University of South Carolina, Columbia, SC, USA. *Cancer Research* (2005), 65(2), 387-393. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 142:170236 AN 2005:76681 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

2-Methoxyestradiol (2-MeO-E2), a well-known nonpolar endogenous metabolite of 17 β -estradiol, has strong antiproliferative, apoptotic, and antiangiogenic actions in vitro and in vivo at pharmacol. concns. We detd. in the present study whether 2-MeO-E2 can enhance the anticancer actions of paclitaxel or vinorelbine (two commonly used microtubule-disrupting agents) in several human breast cancer cell lines, including the estrogen receptor-pos. MCF-7 and T-47D cells and the receptor-neg. MDA-MB-435s and MDA-MB-231 cells. 2-MeO-E2 in combination with paclitaxel or vinorelbine exhibited a synergistic anticancer effect in these human breast cancer cells in vitro, and this synergistic effect was more pronounced when each of the drugs was used at relatively low concns. Addnl. expts. using female athymic BALB/c nu/nu mice showed that p.o. administration of 2-MeO-E2 at 30 mg/kg body wt., once a week for 6 wk, markedly enhanced the activity of paclitaxel or vinorelbine against the growth of the estrogen receptor-neg. MDA-MB-231 human breast cancer xenografts in these animals. By contrast, combination of 2-MeO-E2 with 5-fluorouracil only had a partial additive effect against the growth of these cell lines in culture, and no synergistic effect was obsd. Interestingly, when doxorubicin was used in combination with 2-MeO-E2, the antiproliferative effect of 2-MeO-E2 was somewhat antagonized by doxorubicin when it was present at high concns. Our results showed that 2-MeO-E2 at nontoxic or subtoxic doses selectively enhanced the effects of certain microtubule-disrupting agents (such as paclitaxel and vinorelbine) against the growth of the receptor-neg. human breast cancer cells in culture and also in athymic nude mice.

Answer 82:

Bibliographic Information**Expression of Bcl-xL in ovarian carcinoma is associated with chemoresistance and recurrent disease.**

Williams, Jennifer; Lucas, Peter C.; Griffith, Kent A.; Choi, Milheon; Fogoros, Sarah; Hu, Yuan Yuan; Liu, J. Rebecca. Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA. *Gynecologic Oncology* (2005), 96(2), 287-295. Publisher: Elsevier, CODEN: GYNOA3 ISSN: 0090-8258. Journal written in English. CAN 143:37973 AN 2005:66520 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Objective: The long-term survival of patients with epithelial ovarian cancer is limited by the emergence of tumor cells that are resistant

to chemotherapy. We hypothesized that expression of Bcl-xL, a homolog of Bcl-2 that confers protection from chemotherapy-induced apoptosis, may be predictive of patients' clin. response to treatment, and that treatment with chemotherapy may result in the selection of tumor cells that overexpress this protein. Methods: We detd. the expression of Bcl-xL in epithelial ovarian cancers from 28 patients at the time of initial staging laparotomy and in recurrent tumors in the same patients following treatment with platinum-based chemotherapy. The data were analyzed to det. whether Bcl-xL expression was predictive of clin. outcome. A2780 ovarian cancer cells were stably transfected with Bcl-xL or control plasmid. Chemotherapy-induced apoptosis in these cell lines was detd. in vitro and in a xenograft model. Results: Bcl-xL expression in primary tumors was assocd. with a significantly shorter disease-free interval as compared to patients whose tumors did not express Bcl-xL (1.6 mo as compared to 7.7 mo). We found that Bcl-xL expression conferred resistance to chemotherapy-induced apoptosis resulting from treatment with cisplatin, paclitaxel, topotecan, and gemcitabine in vitro. In a xenograft model, Bcl-xL expressing tumors continued to grow following treatment with cisplatin, paclitaxel, topotecan, and gemcitabine, in contrast to control tumors, which disappeared. Conclusions: These results portray an important role for Bcl-xL as a key factor assocd. with chemotherapy failure in the treatment of ovarian cancer.

Answer 83:

Bibliographic Information

2-Methoxyestradiol inhibits hypoxia-inducible factor 1 α , tumor growth, and angiogenesis and augments paclitaxel efficacy in head and neck squamous cell carcinoma. Ricker, Justin L.; Chen, Zhong; Yang, Xin Ping; Pribluda, Victor S.; Swartz, Glenn M.; Van Waes, Carter. Tumor Biology Section, Head and Neck Surgery Branch, National Institute on Deafness and Other Communication Disorders, National Institutes of Health, Bethesda, MD, USA. Clinical Cancer Research (2004), 10(24), 8665-8673. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 142:309342 AN 2004:1150207 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Head and neck squamous cell carcinomas have been reported to overexpress hypoxia-inducible factor (HIF)-1 α , a transcription factor that promotes expression of angiogenesis factors and resistance to programmed and therapy-induced cell death. 2-Methoxyestradiol (2ME2) is a natural compd. with HIF-1 α inhibitory activity that is currently being evaluated in phase 1 and 2 clin. trials for advanced solid tumors and multiple myeloma. To our knowledge, this is the first study to evaluate the effects of 2ME2 in head and neck squamous cell carcinoma. In the present study, we investigated the effects of 2ME2 alone and in combination with paclitaxel, an active agent in recurrent or advanced head and neck squamous cell carcinoma. 2ME2 exhibited antiproliferative and cytotoxic effects in a panel of five head and neck squamous cell carcinoma cell lines in the 0.5 to 10 μ mol/L range, including induction of G2-M blockade, caspase-3/7 activation, and apoptosis at 48 h. 2ME2 resulted in decreased nuclear HIF-1 α -binding activity and affected the expression of downstream genes, such as bid, a proapoptotic bcl-2 family member, and vascular endothelial growth factor, a proangiogenic cytokine. The up-regulation of Bid (57.5% at 12 h, $P < 0.0006$) and inhibition of vascular endothelial growth factor secretion (57.7% at 24 h, $P < 0.015$; and 50.3% at 48 h, $P < 0.0006$) could be partially attributed to the effects on HIF-1 α , because HIF-1 α small interfering RNAs produced similar effects. Finally, in vivo, in a xenograft model of head and neck squamous cell carcinoma using UM-SCC-11A cells, 2ME2 exhibited antitumor and antiangiogenic activity, as measured by CD31 immunostaining. These results provide support for the use of 2ME2 in combination with paclitaxel for the treatment of recurrent or advanced head and neck squamous cell carcinoma.

Answer 84:

Bibliographic Information

A selective fetinoid X receptor agonist bexarotene (targretin) prevents and overcomes acquired paclitaxel (taxol) resistance in human non-small cell lung cancer. Yen, Wan-Ching; Corpuz, Manny R.; Prudente, Rene Y.; Cooke, Tracy A.; Bissonnette, Reid P.; Negro-Vilar, Andres; Lamph, William W. Department of Molecular Oncology, Ligand Pharmaceuticals, Inc., San Diego, CA, USA. Clinical Cancer Research (2004), 10(24), 8656-8664. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 142:329067 AN 2004:1150205 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Paclitaxel is an important anticancer agent for the treatment of non-small cell lung cancer (NSCLC). However, its use in cancer therapy is limited by development of acquired drug resistance. The goal of this study was to det. the effect of bexarotene on development of acquired paclitaxel resistance in NSCLC. Human NSCLC Calu3 cells were repeatedly treated in culture with intermittent paclitaxel alone or in combination with continuous bexarotene for 3 mo. Thereafter, cells were isolated and characterized for their drug sensitivity in vitro and in vivo. Repeat exposure to paclitaxel alone resulted in development of paclitaxel resistance with cross-resistance to multidrug resistance P-glycoprotein substrates, whereas the bexarotene/paclitaxel combination prevented the development of drug resistance and the cells remained chemosensitive. Furthermore, paclitaxel resistance could be overcome when the resistant cells were treated with the combination regimen. Fluctuation anal. showed that treatment with bexarotene decreased the rate of spontaneous development of paclitaxel resistance. In vivo, the bexarotene/paclitaxel combination regimen produced a statistically significant decrease in tumor growth in a Calu3 NSCLC xenograft model compared with the single agents (two-tailed, $P < 0.05$). In addn., paclitaxel-resistant Calu3 tumors treated with the bexarotene/paclitaxel combination showed greater delay in tumor growth compared with those treated with paclitaxel alone. Our results suggest that bexarotene may offer a novel approach to prevent and overcome paclitaxel resistance in patients with NSCLC.

Answer 85:

Bibliographic Information

Preclinical evaluation of antisense bcl-2 as a chemosensitizer for patients with gastric carcinoma. Kim, Ryungsa; Emi, Manabu; Tanabe, Kazuaki; Toge, Tetsuya. Department of Surgical Oncology, Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan. *Cancer* (New York, NY, United States) (2004), 101(10), 2177-2186. Publisher: John Wiley & Sons, Inc., CODEN: CANCAR ISSN: 0008-543X. Journal written in English. CAN 142:253981 AN 2004:1061374 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

BACKGROUND: Because bcl-2 is a crit. factor for anticancer drug-induced apoptosis, the authors conducted a preclin. evaluation of antisense (AS) bcl-2 as an enhancer of the chemotherapeutic effect in the treatment of patients with gastric carcinoma. **METHODS:** AS bcl-2 was used with 18-mer phosphorothiated oligonucleotides in the MKN-45 gastric carcinoma cell line. Drug sensitivity in vitro was evaluated using the methyl-thiazoldiphenyl tetrazolium assay, and antitumor effects in vivo were evaluated using the nude mouse xenograft. Apoptosis was detd. with the terminal deoxyuridine triphosphate nick-end labeling assay. AS bcl-2 in vitro was treated with lipofectin, whereas it was administered i.p. for 6 consecutive days twice every 2 wk in vivo. Anticancer drugs were administered i.p. four times per wk. **RESULTS:** bcl-2 was down-regulated to 60% of its initial value after treatment with 1.0 μ M AS bcl-2 compared with the controls of random and mismatched oligonucleotides. Drug sensitivity to doxorubicin, cisplatin, and paclitaxel (TXL) was increased 3-4-fold when used in combination with AS bcl-2, which was detd. with 50% inhibitory concn. values, compared with the control group. Increased drug sensitivity was assocd. with apoptosis, which increased in Bax and poly-ADP (ADP-ribose) polymerase and decreased in phosphorylated Akt (pAkt). The antitumor effect of cisplatin and TXL in vivo was enhanced significantly in combination with AS bcl-2. Down-regulation of bcl-2 was obsd. on Day 4 after the treatment with AS bcl-2. **CONCLUSIONS:** Combination treatment with AS bcl-2 and anticancer drugs, including cisplatin and TXL, may be a new strategy for enhancing chemotherapeutic effects in the treatment of gastric carcinoma.

Answer 86:

Bibliographic Information

Reversal of multidrug resistance of cancer through inhibition of P-glycoprotein by 5-bromotetrandrine. Jin, Jing; Wang, Feng-Peng; Wei, Huailing; Liu, Gengtao. Department of Pharmacology, University of Cambridge, Cambridge, UK. *Cancer Chemotherapy and Pharmacology* (2005), 55(2), 179-188. Publisher: Springer GmbH, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 142:253974 AN 2004:1053627 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: The present study aimed to evaluate the MDR reversal activity of bromotetrandrine (BrTet), a bromized deriv. of tetrandrine (Tet), in vitro and in vivo. **Methods:** Drug sensitivity was detd. using the MTT assay. The in vivo effect of Tet was investigated using nude mice grafted with sensitive and resistant KB human epidermoid cancer cells. Doxorubicin (Dox) accumulation was analyzed by fluorospectrophotometry and the protein and mRNA levels of P-glycoprotein (P-gp) were detd. by immunocytochem. and RT-PCR, resp. **Results:** BrTet at 0.25, 0.5 and 1 μ M reversed Dox resistance in MDR human breast cancer MCF-7/Dox cells dose-dependently and its potency was greater than that of Tet at the same concns. BrTet reversed vincristine (VCR), Dox and paclitaxel resistance in MDR human oral epidermoid carcinoma KBv200 cells as well as innate VCR and Dox resistance in human hepatocellular carcinoma Bel7402 cells. However, BrTet showed no effect on the IC50 values of the above-mentioned anticancer drugs in sensitive MCF-7 and KB cells. No reversal effect of BrTet on the cytotoxicity of 5-fluorouracil and cisplatin, non-P-gp substrates, was obsd. In nude mice bearing KBv200 xenografts on the left flank and KB xenografts on the right flank, i.p. injection of 5 mg/kg and 10 mg/kg BrTet significantly enhanced the antitumor activity of Dox against KBv200 xenografts with inhibitory rates of 33.0 and 39.2, while Dox alone inhibited the growth of KBv200 xenografts by only 11.6. No enhancement by BrTet was seen in KB xenografts. Moreover, BrTet at 5 mg/kg reversed paclitaxel resistance in KBv200 xenografts. Fluorospectrophotometric assay showed that BrTet significantly increased the intracellular accumulation of Dox in MCF-7/Dox cells in a dose-dependent manner. BrTet also inhibited the overexpression of P-gp in MCF-7/Dox cells, but had no effect on *mdr1* expression. **Conclusions:** BrTet showed significant MDR reversal activity in vitro and in vivo.

Its activity may be related to the inhibition of P-gp overexpression and the increase in intracellular accumulation of anticancer drugs. BrTet may be a promising MDR modulator for eventual assessment in the clinic.

Answer 87:

Bibliographic Information

Targeting mammalian target of rapamycin synergistically enhances chemotherapy-induced cytotoxicity in breast cancer cells. Mondesire, Wallace H.; Jian, Weiguo; Zhang, Haixia; Ensor, Joe; Hung, Mien-Chie; Mills, Gordon B.; Meric-Bernstam, Funda. Department of Surgical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA. *Clinical Cancer Research* (2004), 10(20), 7031-7042. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 142:190488 AN 2004:975688 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The serine-threonine kinase mammalian target of rapamycin has emerged as a potential target for cancer therapy. Rapamycin and rapamycin analogs are undergoing clin. trials and have induced clin. responses in a subgroup of patients. Rapamycin has also been reported to enhance the efficacy of several cytotoxic agents. The aim of this study was to det. the nature of the interactions between rapamycin and chemotherapeutic agents used as first- and second-line agents against breast cancer. We performed a multiple drug effect/combination index isobologram anal. in cells sensitive and resistant to rapamycin alone in vitro, and we evaluated the in vivo efficacy of combination therapy in a rapamycin-sensitive model. In vitro, synergistic interactions were obsd. in combinations with paclitaxel, carboplatin, and vinorelbine. Additive effects were obsd. in combinations with doxorubicin and gemcitabine. Rapamycin dramatically enhanced paclitaxel- and carboplatin-induced apoptosis. This effect was sequence dependent and mediated at least partly through caspase activation. Furthermore, rapamycin enhanced chemosensitivity to paclitaxel and carboplatin in HER2/neu-overexpressing cells, suggesting a potential approach to these poorly behaving tumors. Cell lines that are resistant to the growth-inhibitory effect of rapamycin were also resistant to rapamycin-mediated chemosensitization. In vivo, rapamycin combined with paclitaxel resulted in a significant redn. in tumor vol. compared with either agent alone in rapamycin-sensitive tumors. Rapamycin potentiates the cytotoxicity of selected chemotherapeutic agents in cell lines sensitive to the effects of rapamycin due to aberrations in the phosphatidylinositol 3'-kinase/Akt pathway, suggesting that combination therapy may be effective in patients selected for aberrations in this pathway.

Answer 88:

Bibliographic Information

Antitumor Activity of Hydrophilic Paclitaxel Copolymer Prodrug Using Locoregional Delivery in Human Orthotopic Non-Small Cell Lung Cancer Xenograft Models. Zou, Yiyu; Fu, Hao; Ghosh, Sukhen; Farquhar, David; Klostergaard, Jim. Department of Oncology, Albert Einstein College of Medicine, Bronx, NY, USA. *Clinical Cancer Research* (2004), 10(21), 7382-7391. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 142:232569 AN 2004:946695 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Paclitaxel (Taxol) has demonstrated clin. activity in non-small-cell lung cancer (NSCLC), but its use has not led to marked improvements in survival. This ineffectiveness can in part be attributed to inadequate delivery of effective drug levels to the lung via systemic administration and to drug resistance mechanisms. Locoregional drug administration and the use of drug copolymers are possible approaches to address these issues. In this study, we evaluated the activity of a poly(L-glutamic acid)-paclitaxel (PGA-TXL) formulation administered by intratracheal injection to mice bearing orthotopic human NSCLC tumors (H460, H358). H460 cells were found to be sensitive to paclitaxel and PGA-TXL in vitro, in a time- and concn.-dependent manner. In preliminary acute toxicity studies, PGA-TXL administered by intratracheal injection was found to be much less toxic than paclitaxel, as anticipated. Mice into which H460 cells had been implanted by intratracheal injection were given single-dose intratracheal treatments with paclitaxel (1.2 or 2.4 mg/kg) or with PGA-TXL (15 mg/kg, paclitaxel equiv.) 1 wk later. When the mice were sacrificed at up to 65 days after tumor implantation, they were evaluated grossly for tumor at bronchial, neck, and lung sites. Control mice had tumors in 60% of all three sites, and all of the control mice had tumors in at least one site. The low- and high-dose Taxol groups had fewer incidences at these three sites (27-33%) and 60-80% of these mice had tumors in at least one site. The PGA-TXL mice displayed a low (13%) incidence at these sites, and only 40% had detectable tumors. In a subsequent survival study with the intratracheal H358 model, control mice had a mean life span of 95 days, whereas both the intratracheal Taxol (2.5 mg/kg, every 7th day for three doses) and the intratracheal PGA-TXL (20 mg/kg, paclitaxel equiv., every 7th day for three doses) groups had improved survival (mean life spans: 133.5 and 136.5 days, resp.).

In pilot studies intended to compare the feasibility of the development of paclitaxel aerosols suitable for clin. application, based either on Cremophor solns. or on PGA backbones, only the latter gave acceptable particle size distributions and flow rates. These results encourage the development and application of Cremophor-free copolymer formulations of paclitaxel for locoregional treatment (e.g., as aerosol) of endobronchial malignant diseases.

Answer 89:

Bibliographic Information

Development of a chemoresistant orthotopic human nonsmall cell lung carcinoma model in nude mice: analyses of tumor heterogeneity in relation to the immunohistochemical levels of expression of cyclooxygenase-2, ornithine decarboxylase, lung-related resistance protein, prostaglandin E synthetase, and glutathione-S-transferase (GST)- α , GST- μ , and GST- π Mathieu, Anne; Rimmelink, Myriam; D'Haene, Nicky; Penant, Stanislas; Gaussin, Jean-Francois; van Ginckel, Rob; Darro, Francis; Kiss, Robert; Salmon, Isabelle. Pathology Laboratory, Erasmus University Hospital, Universite Libre de Bruxelles, Brussels, Belg. *Cancer* (New York, NY, United States) (2004), 101(8), 1908-1918. Publisher: John Wiley & Sons, Inc., CODEN: CANCAR ISSN: 0008-543X. Journal written in English. CAN 142:169276 AN 2004:936957 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

BACKGROUND: Nonsmall cell lung carcinomas (NSCLCs) are assocd. with very dismal prognoses, and adjuvant chemotherapy, including irinotecan, taxanes, platin, and vinca alkaloid derivs., offer patients only slight clin. benefits. Part of the chemoresistance of NSCLC results from the expression in NSCLC cells of a very large set of endogenous proteins, which antagonize chemotherapy-mediated attacks on these tumor cells. **METHODS:** The authors set up an orthotopic model of a human NSCLC by grafting A549 cells into the lungs of nude mice. They tried treating these A549 NSCLC orthotopic xenograft-bearing nude mice on the basis of various chemotherapeutic protocols, including chronic administrations of taxol, oxaliplatin, and irinotecan. A cyclooxygenase-2 (COX-2) inhibitor (NS-398) also was assayed in combination with taxol. The immunohistochem. expression levels of COX-2, prostaglandin E synthetase (PGES), ornithine decarboxylase (ODC), the lung-related resistance protein (LRP), and glutathione-S-transferase- α (GST- α), GST-P μ , and GST- π were quant. detd. by means of computer-assisted microscopy in control and drug-treated NSCLC orthotopic xenografts. **RESULTS:** The orthotopic A549 xenograft model developed in 100% of the grafted mice,

leading to brain metastases in approx. 61% mice and to liver metastases in approx. 40% of mice. The model was resistant to taxol and oxaliplatin and was only weakly sensitive to irinotecan. High levels of chemoresistant markers (i.e., COX-2, PGES, ODC, LRP, GST- α , GST- μ , and GST- π) were obsd. in the nontreated A549 xenografts, although with dramatic variations in individual expression. Taxol and oxaliplatin significantly increased the levels of expression of COX-2, PGES, GST- μ , and GST- π in a no. of different exptl. protocols. CONCLUSIONS: The A549 orthotopic xenograft model could be used to evaluate investigational chemotherapeutic agents to identify drugs rapidly that are more active than the drugs currently in use in hospitals.

Answer 90:

Bibliographic Information

Fluoxetine inhibits multidrug resistance extrusion pumps and enhances responses to chemotherapy in syngeneic and in human xenograft mouse tumor models. Peer, Dan; Dekel, Yaron; Melikhov, Dina; Margalit, Rimona. Department of Biochemistry, the George S. Wise Life Science Faculty, Tel Aviv University, Tel Aviv-Jaffa, Israel. *Cancer Research* (2004), 64(20), 7562-7569. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 141:343083 AN 2004:858494 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Multidrug resistance (MDR) operated by extrusion pumps such as P-glycoprotein and multidrug-resistance-assocd.-proteins, is a major reason for poor responses and failures in cancer chemotherapy. MDR modulators (chemosensitizers) were found among drugs approved for noncancer indications and their derivs. Yet toxicity, adverse effects, and poor soly. at doses required for MDR reversal prevent their clin. application. Among newly designed chemosensitizers, some still suffer from toxicity and adverse effects, whereas others progressed to clin. trials. Diversities among tumors and among MDR pumps indicate a need for several clin. approved MDR modulators. Here we report for the first time that fluoxetine (Prozac), the well-known antidepressant, is a highly effective chemosensitizer. In vitro, fluoxetine enhanced (10- to 100-fold) cytotoxicity of anticancer drugs (doxorubicin, mitomycin C, vinblastine, and paclitaxel) in drug-resistant but not in drug-sensitive cells (5 and 3 lines, resp.). Fluoxetine increased drug accumulation within MDR-cells and inhibited drug efflux from those cells. In vivo, fluoxetine enhanced doxorubicin accumulation within tumors (12-fold) with unaltered pharmacokinetics. In four resistant mouse tumor models of both syngeneic and human xenograft, combination treatment of fluoxetine and doxorubicin generated substantial ($P < 0.001$) improvements in tumor responses and in survivals (2- to 3-fold). Moreover, fluoxetine reversed MDR at doses that are well below its human safety limits, free of the severe dose-related toxicity, adverse effects, and poor soly. that are obstacles to other chemosensitizers. This low-dose range, together with the findings reported here, indicate that fluoxetine has a high potential to join the arsenal of MDR reversal agents that may reach the clinic.

Answer 91:

Bibliographic Information

Low-dose suramin enhanced paclitaxel activity in chemotherapy-naive and paclitaxel-pretreated human breast xenograft tumors. Song, SaeHeum; Yu, Bei; Wei, Yong; Wientjes, M. Guillaume; Au, Jessie L.-S. College of Pharmacy, The Ohio State University, Columbus, OH, USA. *Clinical Cancer Research* (2004), 10(18, Pt. 1), 6058-6065. Publisher: American Association for Cancer Research, CODEN: CCREFA ISSN: 1078-0432. Journal written in English. CAN 142:147996 AN 2004:787002 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We reported induction of broad-spectrum chemoresistance by acidic and basic fibroblast growth factors and chemosensitization by their nonspecific inhibitor suramin at nontoxic and subtherapeutic doses. This study evaluated whether low-dose suramin enhances paclitaxel activity in chemotherapy-naive and paclitaxel-pretreated human MCF7 breast xenograft tumors in mice. Suramin, 10 mg/kg, and/or paclitaxel, 15 mg/kg, were administered i.v., twice weekly for 2 to 3 wk. In addn. to conventional end points [tumor size change, median survival time (MST)], we also used clin. relevant end points [partial (PR) and complete response rates (CR); progressive

disease (PD); stable disease (SD); time to tumor progression (TTP)]. In chemotherapy-naive mice, the control and suramin groups showed identical TTP (3 days) and MST (21 days). Single-agent paclitaxel produced 47% PR and 24% CR, and prolonged both TTP and MST to 73 days. The addn. of suramin further improved the total response rate to 100% with a dramatically greater 63% CR, shortened the time to attain PR and CR, and prolonged TTP and MST to ≥ 136 days. In the paclitaxel-pretreated group, single-agent paclitaxel resulted in 67% SD and 33% PD, whereas the combination produced 50% PR and 50% SD. Suramin also significantly enhanced the apoptotic effect of paclitaxel in tumors. In conclusion, suramin improved the activity of paclitaxel in both chemotherapy-naive and paclitaxel-pretreated animals, without enhancing host toxicity ($\leq 10\%$ body wt. loss in all groups). These data have led to the initiation of phase I/II trials of paclitaxel and low-dose suramin combination in advanced metastatic breast cancer patients.

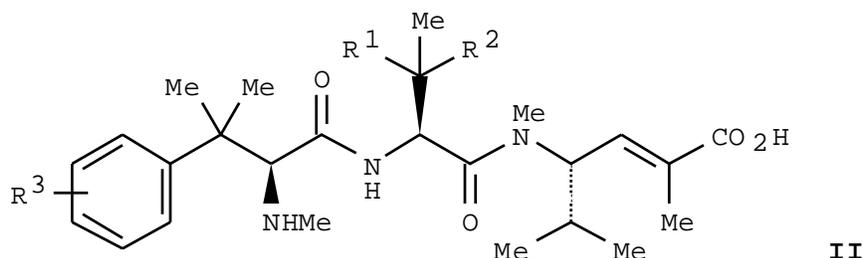
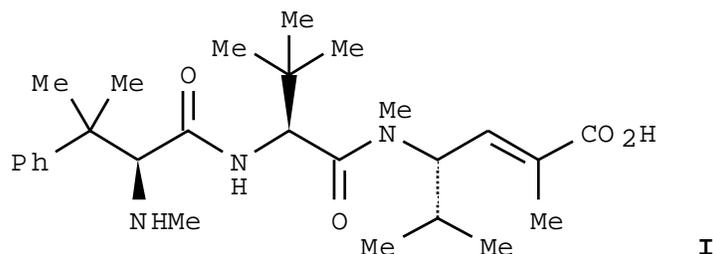
Answer 92:

Bibliographic Information

Tubulin inhibitors. Synthesis and biological activity of HTI-286 analogs with B-segment heterosubstituents. Niu, Chuan; Smith, Daniel; Zask, Arie; Loganzo, Frank; Discafani, Carolyn; Beyer, Carl; Greenberger, Lee; Ayral-Kaloustian, Semiramis. Chemical and Screening Sciences, Discovery Medicinal Chemistry, Wyeth Research, Pearl River, NY, USA. *Bioorganic & Medicinal Chemistry Letters* (2004), 14(16), 4329-4332. Publisher: Elsevier Science B.V., CODEN: BMCLE8 ISSN: 0960-894X. Journal written in English. CAN 141:277875 AN 2004:581057 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Modifications of the B-segment of HTI-286 (I) produced a class of analogs, peptides II [R1 = Me, H; R2 = SMe, S(:O)Me, SO2Me, SCH2C6H4OMe-4, C6H4OMe-4, OH, OMe; R3 = H, OMe] contg. heteroatom-substituents. Majority of II strongly inhibited tubulin polymn., and structure-activity relationship of II towards tubulin polymn. was evaluated. In addn., in vivo assays of II (R1 = Me, R2 = SMe, R3 = H; R1 = Me, R2 = SMe, R3 = OMe) revealed that these two compds. effectively inhibited the growth of human tumor xenografts in athymic mice, including tumors resistant to paclitaxel.



Answer 93:

Bibliographic Information

Selective modulation of the therapeutic efficacy of anticancer drugs by selenium containing compounds against human

tumor xenografts. Cao, Shousong; Durrani, Farukh A.; Rustum, Youcef M. Department of Pharmacology and Therapeutics, Roswell Park Cancer Institute, Buffalo, NY, USA. *Clinical Cancer Research* (2004), 10(7), 2561-2569. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 141:360262 AN 2004:290939 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Studies were carried out in athymic nude mice bearing human squamous cell carcinoma of the head and neck (FaDu and A253) and colon carcinoma (HCT-8 and HT-29) xenografts to evaluate the potential role of selenium-contg. compds. as selective modulators of the toxicity and antitumor activity of selected anticancer drugs with particular emphasis on irinotecan, a topoisomerase I poison. Antitumor activity and toxicity were evaluated using nontoxic doses (0.2 mg/mouse/day) and schedule (14-28 days) of the selenium-contg. compds., 5-methylselenocysteine and seleno-L-methionine, administered orally to nude mice daily for 7 days before i.v. administration of anticancer drugs, with continued selenium treatment for 7-21 days, depending on anticancer drugs under evaluation. Several doses of anticancer drugs were used, including the max. tolerated dose (MTD) and toxic doses. Although many chemotherapeutic agents were evaluated for toxicity protection by selenium, data on antitumor activity were primarily obtained using the MTD, 2 x MTD, and 3 x MTD of weekly x4 schedule of irinotecan. Selenium was highly protective against toxicity induced by a variety of chemotherapeutic agents. Furthermore, selenium increased significantly the cure rate of xenografts bearing human tumors that are sensitive (HCT-8 and FaDu) and resistant (HT-29 and A253) to irinotecan. The high cure rate (100%) was achieved in nude mice bearing HCT-8 and FaDu xenografts treated with the MTD of irinotecan (100 mg/kg/wk x 4) when combined with selenium. Administration of higher doses of irinotecan (200 and 300 mg/kg/wk x 4) was required to achieve high cure rate for HT-29 and A253 xenografts. Administration of these higher doses was possible due to selective protection of normal tissues by selenium. Thus, the use of selenium as selective modulator of the therapeutic efficacy of anticancer drugs is new and novel.

We demonstrated that selenium is a highly effective modulator of the therapeutic efficacy and selectivity of anticancer drugs in nude mice bearing human tumor xenografts of colon carcinoma and squamous cell carcinoma of the head and neck. The obsd. in vivo synergic interaction is highly dependent on the schedule of selenium.

Answer 94:

Bibliographic Information

Chemosensitization and radiosensitization of human cancer by antisense anti-MDM2 oligonucleotides: In vitro and in vivo activities and mechanisms. Wang, Hui; Oliver, Patsy; Zhang, Zhuo; Agrawal, Sudhir; Zhang, Ruiwen. Departments of Pharmacology and Toxicology, Division of Clinical Pharmacology, Comprehensive Cancer Center, and Gene Therapy Center, University of Alabama at Birmingham, Birmingham, AL, USA. *Annals of the New York Academy of Sciences* (2003), 1002(Therapeutic Oligonucleotides), 217-235. Publisher: New York Academy of Sciences, CODEN: ANYAA9 ISSN: 0077-8923. Journal; General Review written in English. CAN 141:253336 AN 2004:256226 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A review. MDM2 oncogene is overexpressed in many human cancers including breast, colon, and prostate cancer, and MDM2 levels are assocd. with poor prognosis in patients with cancer. Here, we summarize the investigation of the functions of MDM2 oncogene in human cancer growth and the value of MDM2 as a drug target for prostate cancer therapy by using antisense to inhibit MDM2 expression. Antisense anti-human-MDM2 oligonucleotides and mismatch controls were tested in in vitro and in vivo human cancer models for antitumor activity. Targeted gene products and related proteins were analyzed and the antitumor activity was detd. when the oligonucleotides were used alone or in combination with cancer chemotherapeutics and radiation therapy. The antisense oligonucleotide specifically inhibited MDM2 expression in a dose- and time-dependent manner, resulting in significant antitumor activity in vitro and in vivo. The antisense oligonucleotides also potentiated the effects of p53 activation and p21 induction by chemotherapeutic agents 10-hydroxycamptothecin, adriamycin, 5-fluorouracil, and paclitaxel. In a dose-dependent manner, the antisense oligonucleotide showed antitumor activity in nude mice bearing human cancer xenografts and increased therapeutic effectiveness of the chemotherapeutic agents irinotecan, paclitaxel, and Rituxan and radiation therapy. These results indicate that MDM2 has a role in various tumor growth through both p53-dependent and p53-independent mechanisms, indicating that MDM2 inhibitors have a broad spectrum of antitumor activities in human cancers regardless of p53 status. These results provide a basis for

clin. evaluation of antisense anti-MDM2 oligonucleotides as chemosensitizer and radiosensitizer.

Answer 95:

Bibliographic Information

Synthesis and evaluation of novel fatty acid-2nd-generation taxoid conjugates as promising anticancer agents.

Kuznetsova, Larissa; Wu, Xinyuan; Chen, Jin; Pepe, Antonella; Sun, Liang; Veith, Jean M.; Bernacki, Ralph J.; Ojima, Iwao. Department of Chemistry, State University of New York at Stony Brook, Stony Brook, NY, USA. Abstracts of Papers, 227th ACS National Meeting, Anaheim, CA, United States, March 28-April 1, 2004 (2004), MEDI-110. Publisher: American Chemical Society, Washington, D. C CODEN: 69FGKM Conference; Meeting Abstract written in English. AN 2004:226468 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Novel fatty acid-2nd-generation taxoid conjugates were designed and synthesized, wherein the fatty acids include docosahexaenoic acid (DHA), docosanoic acid, linolenic acid (LNA) and linoleic acid (LA). These novel conjugates were evaluated in vivo against the human ovarian tumor A121 xenografts as well as the Pgp-pos. human colon tumor DLD-1 xenografts in SCID mice. Some of these conjugates exhibited remarkable efficacy, e.g., DHA-SB-T-1213 brought about the complete regression (CR) of tumor in all surviving mice (4 of 5) implanted with the A121 xenografts. Even more impressive results were obtained against the Pgp-pos. DLD1 xenografts, e.g., the treatment with DHA-SB-T-1214 resulted in the CR in 5 of 5 mice, while DHA-paclitaxel (Taxoprexin-) and paclitaxel were practically ineffective (only 4-day and 8-day tumor growth delays, resp.). SAR and a possible mechanism of action for these novel fatty acid-taxoid conjugates will also be presented.

Answer 96:

Bibliographic Information

Gene expression correlating with response to paclitaxel in ovarian carcinoma xenografts. Bani, Maria Rosa; Nicoletti, Maria Ines; Alkharouf, Nawal W.; Ghilardi, Carmen; Petersen, David; Erba, Eugenio; Sausville, Edward A.; Liu, Edison T.; Giavazzi, Raffaella. Mario Negri Institute for Pharmacological Research, Bergamo and Milan, Italy. Molecular Cancer Therapeutics (2004), 3(2), 111-121. Publisher: American Association for Cancer Research, CODEN: MCTOCF ISSN: 1535-7163. Journal written in English. CAN 140:297066 AN 2004:154134 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We have investigated gene expression profiles of human ovarian carcinomas in vivo during Taxol (paclitaxel) treatment and obsd. a difference in expression. Nude mice bearing 1A9 or 1A9PTX22 xenografts were given 60 mg/kg of paclitaxel. Therapeutic efficacy was achieved for 1A9, while 1A9PTX22 did not respond. Tumor tissues harvested 4 and 24 h after treatment were evaluated by cDNA microarray against untreated tumors. Paclitaxel caused the modulation of more genes in 1A9 than in 1A9PTX22 tumors, in accordance to their therapeutic response. Most gene expression alterations were detected 24 h after paclitaxel administration and affected genes involved in various biol. functions including cell cycle regulation and cell proliferation (CDC2, CDKN1A, PLAB, and TOP2A), apoptosis (BNIP3 and PIG8), signal transduction and transcriptional regulation (ARF1, ATF2, FOS, GNA11, HDAC3, MADH2, SLUG, and SPRY4), fatty acid biosynthesis and sterol metab. (FDPS, IDI1, LIPA, and SC5D), and IFN-mediated signaling (G1P3, IFI16, IFI27, IFITM1, and ISG15). The modulation of two representative genes, CDKN1A and TOP2A, was validated by Northern analyses on a panel of seven ovarian carcinoma xenograft models undergoing treatment with paclitaxel. We found that the changes in expression level of these genes was strictly assocd. with the responsiveness to paclitaxel. Our study shows the feasibility of obtaining gene expression profiles of xenografted tumor models as a result of drug exposure. This in turn might provide insights related to the drugs' action in vivo that will anticipate the response to treatment manifested by tumors and could be the basis for novel approaches to mol. pharmacodynamics.

Answer 97:

Bibliographic Information

ZD1839 modulates paclitaxel response in renal cancer by blocking paclitaxel-induced activation of the epidermal growth factor receptor-extracellular signal-regulated kinase pathway. Sumitomo, Makoto; Asano, Tomohiko; Asakuma, Junichi; Asano, Takako; Horiguchi, Akio; Hayakawa, Masamichi. Department of Urology, National Defense Medical College, Tokorozawa, Saitama, Japan. *Clinical Cancer Research* (2004), 10(2), 794-801. Publisher: American Association for Cancer Research, CODEN: CCRE4 ISSN: 1078-0432. Journal written in English. CAN 141:199595 AN 2004:88616 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We evaluated the antitumor activity of ZD1839, a selective epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor, in combination with paclitaxel in human renal cell carcinomas (RCCs). Eight human RCC lines and the surgical specimens obtained from 10 RCC patients were used. The protein expression was detected by Western blotting, immunohistochem. and/or flow cytometry. Apoptosis was evaluated by flow cytometry and fragmented DNA ELISA. SKRC-49 tumor xenografts in athymic nude mice were treated with ZD1839 and/or paclitaxel, and tumor vol. was detd. EGFR protein was expressed and phosphorylated in eight RCC lines and EGFR expression was markedly increased in RCC specimens compared with adjacent normal renal tissues. Treatment of SKRC-49 with 1 μ M ZD1839 resulted in a marked decrease in the phosphorylation of EGFR but not of HER-2. Treatment of SKRC-49 with ZD1839 in combination with 5 nM paclitaxel resulted in a significant increase in apoptotic cell no. compared with paclitaxel alone, whereas ZD1839 alone failed to induce apoptosis. Although administration of ZD1839 or paclitaxel resulted in a transient growth inhibition in SKRC-49 xenografts, significant tumor regrowth delay was obsd. when paclitaxel was combined with ZD1839. Paclitaxel phosphorylated extracellular signal-regulated kinase through EGFR activation predominantly in cancer cells. ZD1839 promoted paclitaxel-induced Bcl-2 down-regulation resulting in promoting apoptosis by blocking paclitaxel-induced activation of the EGFR-extracellular signal-regulated kinase antiapoptotic pathway independent of Akt activity in SKRC-49. Our findings support the idea that the significant clin. benefit is obtained from ZD1839 in combination with paclitaxel for the treatment of RCC.

Answer 98:

Bibliographic Information

2-Deoxy-D-glucose Increases the Efficacy of Adriamycin and Paclitaxel in Human Osteosarcoma and Non-Small Cell Lung Cancers In Vivo. Maschek, Gregory; Savaraj, Niramol; Priebe, Waldemar; Braunschweiger, Paul; Hamilton, Kara; Tidmarsh, George F.; De Young, Linda R.; Lampidis, Theodore J. School of Medicine and Sylvester Comprehensive Cancer Center, Department of Cell Biology and Anatomy, University of Miami, Miami, FL, USA. *Cancer Research* (2004), 64(1), 31-34. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 140:228739 AN 2004:47877 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Slow-growing cell populations located within solid tumors are difficult to target selectively because most cells in normal tissues also have low replication rates. However, a distinguishing feature between slow-growing normal and tumor cells is the hypoxic microenvironment of the latter, which makes them extraordinarily dependent on anaerobic glycolysis for survival. Previously, we have shown that hypoxic tumor cells exhibit increased sensitivity to inhibitors of glycolysis in three distinct in vitro models. Based on these results, we predicted that combination therapy of a chemotherapeutic agent to target rapidly dividing cells and a glycolytic inhibitor to target slow-growing tumor cells would have better efficacy than either agent alone. Here, we test this strategy in vivo using the glycolytic inhibitor 2-deoxy-D-glucose (2-DG) in combination with Adriamycin (ADR) or paclitaxel in nude mouse xenograft models of human osteosarcoma and non-small cell lung cancer. Nude mice implanted with osteosarcoma cells were divided into four groups as follows: (a) untreated controls; (b) mice treated with ADR alone; (c) mice treated with 2-DG alone; or (d) mice treated with a combination of ADR + 2-DG. Treatment began when tumors were either 50 or 300 mm³ in vol. Starting with small or large tumors, the ADR + 2-DG combination treatment resulted in significantly slower tumor growth (and therefore longer survival) than the control, 2-DG, or ADR treatments ($P < 0.0001$). Similar beneficial effects of combination treatment were found with 2-DG and paclitaxel in the MV522 non-small cell lung cancer xenograft model. In summary, the treatment of tumors with both the glycolytic inhibitor 2-DG and ADR or

paclitaxel results in a significant redn. in tumor growth compared with either agent alone. Overall, these results, combined with our in vitro data, provide a rationale for initiating clin. trials using glycolytic inhibitors in combination with chemotherapeutic agents to increase their therapeutic effectiveness.

Answer 99:

Bibliographic Information

Antitumor efficacy of TRA-8 anti-DR5 monoclonal antibody alone or in combination with chemotherapy and/or radiation therapy in a human breast cancer model. Buchsbaum, Donald J.; Zhou, Tong; Grizzle, William E.; Oliver, Patsy G.; Hammond, Charlotte J.; Zhang, Sijian; Carpenter, Mark; LoBuglio, Albert F. Department of Radiation Oncology, University of Alabama at Birmingham, Birmingham, AL, USA. *Clinical Cancer Research* (2003), 9(10, Pt. 1), 3731-3741. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 140:419942 AN 2003:847707 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A monoclonal antibody (TRA-8) has been developed that binds to death receptor 5 (DR5), one of two death receptors bound by tumor necrosis factor-related apoptosis-inducing ligand. The purpose of this study was to evaluate in vitro the binding and cytotoxicity of TRA-8 to human breast cancer cell lines. The antitumor efficacy of TRA-8 was evaluated in a xenograft human breast cancer murine model, as a single agent and in combination with chemotherapy or radiation therapy. The binding of TRA-8 to a panel of nine human breast cancer cell lines was evaluated by indirect immunofluorescence and flow cytometry. Cytotoxicity of TRA-8 alone and in the presence of Adriamycin or paclitaxel was measured in vitro using the ATP-lite assay. Antitumor efficacy was detd. by treatment of nude mice bearing well-established s.c. DR5-pos. 2LMP human breast cancer xenografts with TRA-8 alone or in combination with Adriamycin or paclitaxel. Tumor size and regression rates were detd. In addn., a study was carried out with TRA-8 and Adriamycin in combination with 3 Gy 60Co irradiation of 2LMP xenografts on days 9 and 17. All nine human breast cancer cell lines expressed DR5 with TRA-8 reactivity varying from strongly to weakly pos. Four cell lines were sensitive to TRA-8 cytotoxicity with IC50 of 17-299 ng/mL, whereas other cell lines had weak cytotoxicity or were resistant. In vivo studies demonstrated significant inhibition of growth of 2LMP xenografts by TRA-8 treatment alone. The combination of TRA-8 + Adriamycin or paclitaxel produced significant inhibition of tumor growth as compared with controls or either agent alone. An aggregate anal.

of all 166 animals studied demonstrated that TRA-8 alone or in combination with Adriamycin, paclitaxel, or radiation produced a significant increase in tumor doubling time compared with any modality alone with mean doubling time in days of 12 (untreated), 14 (radiation), 17 (Adriamycin), 25 (paclitaxel), 39 (Adriamycin + radiation), 47 (TRA-8), 65 (TRA-8 + radiation), 71 (TRA-8 + paclitaxel), 81 (TRA-8 + Adriamycin), and > 140 (TRA-8 + Adriamycin and radiation). Complete tumor regressions occurred in 1 of 42 untreated animals, 1 of 54 animals receiving chemotherapy and/or radiation, and 28 of 68 animals receiving TRA-8 alone or TRA-8 combination regimens. Fourteen of those 28 complete regressions did not relapse over periods of follow-up between 99 and 171 days, with a mean of 146 ± 24 days. The TRA-8 anti-DR5 antibody alone or in combination with chemotherapy and/or radiation has striking antitumor efficacy in breast cancer xenograft models. Addnl. studies with other tumor types and chemotherapy agents are warranted. These studies support the generation of a humanized TRA-8 for introduction into early clin. trials.

Answer 100:

Bibliographic Information

The combination of the tyrosine kinase receptor inhibitor SU6668 with paclitaxel affects ascites formation and tumor spread in ovarian carcinoma xenografts growing orthotopically. Garofalo, Angela; Naumova, Elitza; Manenti, Luigi; Ghilardi, Carmen; Ghisleni, Gabriele; Caniatti, Mario; Colombo, Tina; Cherrington, Julie M.; Scanziani, Eugenio; Nicoletti, Maria Ines; Giavazzi, Raffaella. Laboratory of Biology and Treatment of Metastasis, Department of Oncology, Mario Negri Institute for Pharmacological Research, Bergamo, Italy. *Clinical Cancer Research* (2003), 9(9), 3476-3485. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 139:390907 AN 2003:814752 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The purpose of this study was to investigate the antitumor activity of SU6668, tyrosine kinase inhibitor of vascular endothelial growth factor receptor 2 (VEGFR2), fibroblast growth factor receptor 1 (FGFR1), and platelet-derived growth factor receptor β (PDGFR β), as single-agent therapy and in combination with paclitaxel on ovarian carcinoma xenograft models transplanted in the peritoneal cavity of nude mice. HOC22 and HOC79 ascites-producing human ovarian carcinoma xenografts were transplanted i.p. into nude mice. SU6668 was given p.o. (200 mg/kg, daily) as a single agent or in combination with paclitaxel i.v. (6 mg/kg/dose every other day or 20 mg/kg/dose weekly). Tumor burden was evaluated at the end of the treatment period as ascites vol. and tumor cells, VEGF, FGF-2, and PDGF levels in ascites, and involvement of the organ of the peritoneal cavity. Response was evaluated as percentage increment of life span (%ILS). SU6668 affected ascites formation and tumor burden in the peritoneal cavity of nude mice bearing HOC22 and HOC79 xenografts. Decreased levels of VEGF and PDGF in ascites paralleled this effect. The overall survival of the mice bearing HOC xenograft (HOC79 less response than HOC22) was significantly increased by the treatment with SU6668. The magnitude of the effects depended on the length of treatment and tumor burden at the beginning of treatment. The combination of SU6668 with paclitaxel significantly prolonged the survival of mice bearing HOC79, compared with single therapies. SU6668-based combination therapy was more effective with paclitaxel given at the optimal dose and schedule (20 mg/kg every 7 days for 3 doses) than at the same total dose but split (6 mg/kg every 2 days for 10 doses). However, a similar outcome was obsd. when giving high-dose paclitaxel (20 mg/kg every 7 days for 3 doses) in monotherapy or split low-dose paclitaxel (6 mg/kg every 2 days for 10 doses) but in combination with SU6668. The addn.

of paclitaxel, by either schedule, to SU6668 treatment inhibited tumor spread in the peritoneal organs (omentum, pancreas, and diaphragm) even at low doses of paclitaxel. A greater effect was obsd. with prolonged treatments. This study shows that SU6668 in combination with paclitaxel inhibits ovarian carcinoma progression in the peritoneal cavity, by blocking ascites formation and tumor spread. Because an adequate schedule and dose of the combination might be as effective as conventional chemotherapy, this should be considered as a therapeutic alternative. These findings provide a rationale for the clin. evaluation of combination therapies affecting multiple biol. targets in this tumor type.

Answer 101:

Bibliographic Information

Combination therapy with paclitaxel and thalidomide inhibits angiogenesis and growth of human colon cancer xenograft in mice. Fujii, Toshiyuki; Tachibana, Mitsuo; Dhar, Dipok Kumar; Ueda, Shuhei; Kinugasa, Shoichi; Yoshimura, Hiroshi; Kohno, Hitoshi; Nagasue, Naofumi. Second Department of Surgery, Shimane Medical University, Shimane, Japan. *Anticancer Research* (2003), 23(3B), 2405-2411. Publisher: International Institute of Anticancer Research, CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 140:70494 AN 2003:658866 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Combination chemotherapy is increasingly practiced for treating malignancies with greater sensitivity and less toxicity. Paclitaxel is a potent anti-tumor agent but has dose-limiting side-effects, whereas thalidomide is an orally active anti-angiogenic drug but less than sufficient to exert anti-tumor effect as a single agent. Nude mice bearing hypervascular (LS174T) and less vascular (HT29) colon carcinomas were challenged with either a noncytotoxic dose of paclitaxel, thalidomide or a combination of paclitaxel and thalidomide. Significant growth retardation was noticed only in the combination treatment group of LS174T tumors. Microvessel d. data indicated a significantly low count in the combination treatment group compared to the others. Trends of decreased expression of angiogenic growth factors and increased apoptotic index were noticed in the combination treatment group. The results of this study underscore the therapeutic efficacy of concomitant use of paclitaxel and thalidomide in the treatment of highly vascular colorectal tumors in a xenograft model.

Answer 102:

Bibliographic Information

Rho kinase and matrix metalloproteinase inhibitors cooperate to inhibit angiogenesis and growth of human prostate cancer xenotransplants. Somlyo, Avril V.; Phelps, Clayton; Dipierro, Charles; Eto, Masumi; Read, Paul; Barrett, Matthew; Gibson, Jennifer J.; Burnitz, M. Christine; Myers, Charles; Somlyo, Andrew P. Dep. of Mol. Physiol. and Biol. Phys., Univ. of Virginia, Charlottesville, VA, USA. *FASEB Journal* (2003), 17(2), 223-234. Publisher: Federation of American Societies for Experimental

Biology, CODEN: FAJOEC ISSN: 0892-6638. Journal written in English. CAN 139:46600 AN 2003:108987 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The purpose of this study was to det. the effects of inhibitors of Rho kinase (ROK) and matrix metalloproteinases (MMPs) on angiogenesis and tumor growth and to evaluate ROK activity in human prostate cancer PC3 cells and endothelial cells (HUVECs). Vacuolation by endothelial cells and lumen formation, the earliest detectable stages of angiogenesis, were inhibited by the ROK inhibitor Wf-536. Combining Wf-536 with the MMP inhibitor Marimastat greatly enhanced in vitro inhibition of endothelial vacuolation, lumen and cord formation, and VEGF- and HGF-stimulated endothelial sprout formation from aorta. Inhibition of sprout formation by the two inhibitors was synergistic. Both agents inhibited migration of HUVECs. The regulatory subunit (MYPT1) of the myosin phosphatase was phosphorylated in PC3 cells and HUVECs, and phosphorylation of MYPT1 and the myosin regulatory light chain was reduced by Wf-536, providing direct evidence of ROK activity. Early treatment of immuno-incompetent mice bearing xenotransplants of PC3 cells with a combination of Wf-536 plus Marimastat with or without Paclitaxel, significantly inhibited tumor growth, prevented tumor growth escape after discontinuation of Paclitaxel, and increased survival.

Answer 103:

Bibliographic Information

Simultaneous Targeting of Telomeres and Telomerase as a Cancer Therapeutic Approach. Mo, Yiqun; Gan, Yuebo; Song, SaeHeum; Johnston, Jeffrey; Xiao, Xiaodong; Wientjes, M. Guillaume; Au, Jessie L-S. The Ohio State University, College of Pharmacy, Columbus, OH, USA. *Cancer Research* (2003), 63(3), 579-585. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 139:46573 AN 2003:84803 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Telomeres, which are important for maintaining chromosome integrity and functions, shorten with each cell division. Telomerase, responsible for telomere synthesis, is expressed in .apprx.90% of human tumor cells but seldom in normal somatic cells. This study evaluated the hypothesis that simultaneous shortening of telomeres and inhibition of telomerase results in synergistic and tumor-selective cytotoxicity. In telomerase-pos. human pharynx FaDu tumor cells, paclitaxel caused telomere erosion (first detected at 1 h) and apoptosis. Expression of antisense to the RNA component of human telomerase (hTR) inhibited telomerase activity, shortened telomere length, reduced cell growth rate, and resulted in a significant higher sensitivity to paclitaxel. Another telomerase inhibitor, 3'-azido-3'-deoxythymidine (AZT), at a concn. that produced little or no cell detachment or apoptosis, inhibited the telomerase activity and enhanced the paclitaxel-induced cell detachment and apoptosis. AZT also enhanced the activity of paclitaxel in mice bearing well-established s.c. FaDu xenograft tumors (i.e., reduced residual tumor size, enhanced apoptotic cell fraction, and prolonged survival time), without enhancing host toxicity. In contrast, AZT did not enhance the paclitaxel activity in the telomerase-neg. osteosarcoma Saos-2 cells nor in FaDu cells where telomerase was already suppressed by antisense hTR, confirming that the AZT effect in parent FaDu cells is mediated through telomerase inhibition. These results demonstrate that combined use of agents targeting both telomere and telomerase yielded synergistic activity selective for tumors that depend on telomerase for telomere maintenance.

Answer 104:

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 CAPI US (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.

Answer 105:

Bibliographic Information

Sequence-dependent synergistic cytotoxicity of ecteinascidin-743 and paclitaxel in human breast cancer cell lines in vitro and in vivo. Takahashi, Naoto; Li, WeiWei; Banerjee, Debabrata; Guan, Yongbiao; Wada-Takahashi, Yasuko; Brennan, Murray F.; Chou, Ting-Chao; Scotto, Kathleen W.; Bertino, Joseph R. Program of Molecular Pharmacology and Therapeutics, Memorial Sloan-Kettering Cancer Center, New York, NY, USA. *Cancer Research* (2002), 62(23), 6909-6915. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 138:378756 AN 2002:942222 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Ecteinascidin 743 (ET-743) is a potent antitumor agent from the Caribbean tunicate *Ecteinascidia turbinata* and is presently in clin. trials for human cancers. The aim of this study was to assess the nature of the interaction between ET-743 and other antineoplastic agents using the combination index method of Chou and Talalay to better understand how ET-743 might be used clin. We examd. the cytotoxic effect of ET-743 combined with six other antineoplastic agents on human breast cancer cell lines, MX-1, MCF7, and P-glycoprotein overexpressing MCF7/DXR to different schedules. Pretreatment with paclitaxel for 24 h before ET-743 was the most effective combination regimen in all three breast cancer cell lines. Furthermore, sequential treatment with paclitaxel followed by ET-743 increased the antitumor effects in nude mice bearing MX-1 mammary carcinoma xenografts without increasing toxicity. These results suggest that the combination of ET-743 and paclitaxel should be assessed in clin. trials for the treatment of breast cancer.

Answer 106:

Bibliographic Information

Therapeutic advantage from combining paclitaxel with the hypoxia-selective cytotoxin NLCQ-1 in murine tumor- or human xenograft-bearing mice. Papadopoulou, Maria V.; Ji, Ming; Ji, Xinhai; Bloomer, William D.; Hollingshead, Melinda G. The Radiation Medicine Institute, Evanston Northwestern Healthcare, Evanston, IL, USA. *Cancer Chemotherapy and Pharmacology* (2002), 50(6), 501-508. Publisher: Springer-Verlag, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 139:239774 AN 2002:898866 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: The antitumor effect of paclitaxel was investigated against murine tumors and human xenografts in combination with the hypoxia-selective cytotoxin NLCQ-1. **Methods:** The tumor regrowth assay was used as the endpoint and an optimal administration schedule was followed, based on previous studies. In certain cases the hypoxia-selective cytotoxin tirapazamine (TPZ) was included for comparison. NLCQ-1 was given i.p. in saline, whereas paclitaxel was given i.p. (C3H) or i.v. (athymic mice) in an appropriately formulated vehicle. **Results:** In the SCCVII/C3H model, when NLCQ-1 (10 mg/kg) was given 90 min after paclitaxel (8 mg/kg) twice a day 4 h apart on days 0 and 9, tumor regrowth delay was increased by 10.3 days compared to paclitaxel alone, at fivefold the original tumor size. This corresponds to 1.51 log cell kill. In the same study, TPZ resulted in 4.6 days of extra delay compared to paclitaxel alone, which corresponds to 0.91 log cell kill. Paclitaxel alone resulted in 3.9 days of tumor growth delay compared to control, or 0.42 log cell kill, but this delay was not statistically significant ($P < 0.2$). In the FSaIIIC/C3H model, when NLCQ-1 (10 mg/kg) was given 90 min after paclitaxel (12 mg/kg) on day 0, tumor regrowth delay was increased by 5.8 days compared to paclitaxel alone, at 20-fold the original tumor size. In athymic nude mice bearing PC-3 prostate xenografts, NLCQ-1 (10 mg/kg) given 90 min before paclitaxel (8 mg/kg) for five consecutive days, increased tumor regrowth delay by 5.6 days compared to paclitaxel alone, at threefold the original tumor size. This corresponds to 0.95 log cell kill whereas the log cell kill for paclitaxel alone was 0.52. No improvement was obsd. in the tumor regrowth delay at any lower paclitaxel doses given in combination with NLCQ-1. No concurrent enhancement in paclitaxel-induced toxicity was obsd. in any of the combination treatments or in any of the models tested. NLCQ-1 alone was ineffective at the doses given.

Conclusions: These results suggest that an enhancement in tumor growth delay can be achieved both in murine tumors and in human xenografts due to a synergistic interaction between NLCQ-1 and paclitaxel.

Answer 107:

Bibliographic Information

Induction of thymidine phosphorylase by interferon and taxanes occurs only in human cancer cells with low thymidine phosphorylase activity. Fukushima, Masakazu; Okabe, Hiroyuki; Takechi, Teiji; Ichikawa, Wataru; Hirayama, Renzo. Institute for Applied Oncology, Taiho Pharmaceutical Co., Ltd., Hanno-city, Saitama, Japan. Cancer Letters (Shannon, Ireland) (2002), 187(1-2), 103-110. Publisher: Elsevier Science Ireland Ltd., CODEN: CALEDQ ISSN: 0304-3835. Journal written in English. CAN 138:19221 AN 2002:740453 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Thymidine phosphorylase (TP) regulates intracellular thymidine metab. It has been reported to be a prognostic factor for tumor angiogenesis and to activate some prodrugs of 5-fluorouracil (5-FU) to 5-FU. There is also evidence that TP is induced by interferons (IFNs) and xenobiotics, such as cyclophosphamide and taxanes, in exptl. human cancer cells and xenografts. We investigated the induction of TP expression by IFN α and Paclitaxel in vitro and in vivo in human tumor cells with low and with high TP activity. TP activity in KB, NUGC-3, and KOC2S cells, which had low TP activity, was increased 2 to 4 fold by IFN α , but was still lower than in non-treated SHIN-3 and HRA cells, which have high TP activity. IFN α did not promote TP activity in SHIN-3 and HRA cells, but expression of TP mRNA increased 2 to 4 fold in response to IFN α in all cells tested. These results suggest that the expression of TP protein would be regulated post-transcriptionally by another factor after IFN-induced amplification of TP mRNA. A single dose of Paclitaxel to nude mice xenografted with KB and KM20C tumors, expressing low TP activity, increased TP activity about 4 to 7 fold compared to non-treated tumors. In contrast, TP expression in MX-1 and H-31 tumors was originally high and did not change by the treatment of Paclitaxel. The activities of uridine phosphorylase in all tumors used showed no changes in response to IFN α or Paclitaxel. We detd. the level of STAT1 α , an IFN-inducible transcription factor of the TP gene, and found that it was low in low TP expressing tumor cells and markedly increased to about 4 fold by IFN, almost reaching the level in high TP expressing cells whose STAT1 α level was unchanged by IFN. When TP activity and STAT1 α expression in clin. resected colorectal cancers were simultaneously measured, almost all tumors had high expression of both TP and STAT1 α .

In conclusion, our results suggest that IFN and Paclitaxel affect human cancer cells with low TP activity but not those with high TP activity and that the STAT1 α expression may reflect TP activity, at least in exptl. human cancer cells.

Answer 108:

Bibliographic Information

Antiangiogenic and Antitumor Effects of a Protein Kinase C β Inhibitor in Human Breast Cancer and Ovarian Cancer Xenografts. Teicher, Beverly A.; Menon, Krishna; Alvarez, Enrique; Shih, Chuan; Faul, Margaret M. Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN, USA. *Investigational New Drugs* (2002), 20(3), 241-251. Publisher: Kluwer Academic Publishers, CODEN: INNDDK ISSN: 0167-6997. Journal written in English. CAN 138:247991 AN 2002:512394 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

In cell culture, the compd. 317615-2HCl, a potent inhibitor of VEGF-stimulated HUVEC proliferation, was not very effective against MX-1 breast cancer cells (IC₅₀ = 8.1 μ M) or SKOV-3 ovarian carcinoma cells (IC₅₀ = 9.5 μ M). Exposure to combinations of paclitaxel or carboplatin and 317615-2HCl with MX-1 cells in culture resulted in cell survival that reflected primarily additivity of the 2 agents. Exposure of SKOV-3 cells to paclitaxel or carboplatin along with 317615-2HCl resulted in cell survivals that reflected additivity of 317615-2HCl with paclitaxel and greater-than-additive cytotoxicity with carboplatin. Administration of 317615-2HCl orally twice daily to nude mice bearing s.c. MX-1 tumors or SKOV-3 tumors resulted in a decreased no. of intratumoral vessels as detd. by CD31 and CD105 staining with decreases of 35% and 43% in MX-1 tumors and 60% and 75% in SKOV-3 tumors, resp. 317615-2HCl was an active antitumor agent against the MX-1 xenograft and increased the tumor growth delay produced by paclitaxel by 1.7-fold and the tumor growth delay produced by carboplatin by 3.8-fold. Administration of 317615-2HCl also increased the tumor growth delay produced by fractionated radiation therapy in the MX-1 tumor. Treatment with 317615-2HCl alone increased the lifespan of animals bearing i.p. SKOV-3 xenografts by 1.9 fold compared with untreated control animals. The combination of paclitaxel and 317615-2HCl resulted in 100% 120-day survival of SKOV-3 bearing animals. Administration of 317615-2HCl along with carboplatin to animals bearing the SKOV-3 tumor produced a 1.8-fold increase in lifespan compared with carboplatin alone. 317615-2HCl is a promising new antiangiogenic agent that is in early phase clin. testing.

Answer 109:

Bibliographic Information

Antiangiogenic and antitumor activity of IDN 5390, a new taxane derivative. Taraboletti, Giulia; Micheletti, Gianluca; Rieppi, Monica; Poli, Maura; Turatto, Michele; Rossi, Cosmo; Borsotti, Patrizia; Roccabianca, Paola; Scanziani, Eugenio; Nicoletti, Maria Ines; Bombardelli, Ezio; Morazzoni, Paolo; Riva, Antonella; Giavazzi, Raffaella. Department of Oncology, Mario Negri Institute for Pharmacological Research, Bergamo, Italy. *Clinical Cancer Research* (2002), 8(4), 1182-1188. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 138:134 AN 2002:359657 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Different taxanes, seco derivs. of taxanes, and 14 β -hydroxy-10-deacetylbaicatin III derivs. were tested for their effects on the proliferation and motility of human umbilical vein endothelial cells. The antiangiogenic and antineoplastic activities of IDN 5390, the compd. selected from this screening, were further investigated in exptl. models in vitro and in vivo. IDN 5390 is a seco deriv. that showed potent antimotility activity and less cytotoxicity than paclitaxel. IDN 5390 inhibited endothelial cell migration without affecting proliferation. This compd. concn.-dependently inhibited the capacity of human umbilical vein endothelial cells plated on Matrigel to organize into a network of cords. In vivo, IDN 5390 inhibited fibroblast growth factor-2-induced angiogenesis in Matrigel implants in mice. Daily treatment with IDN 5390 in mice bearing established lung micrometastases from the B16BL6 murine melanoma caused a redn. in the size of metastases. Finally, IDN 5390 slowed the s.c. growth of the paclitaxel-resistant human ovarian carcinoma 1A9/PTX22 xenografted in nude mice. The seco deriv. IDN 5390 might represent the prototype of a new class of taxane derivs. with antiangiogenic properties.

Answer 110:

Bibliographic Information

A G-quadruplex-interactive potent small-molecule inhibitor of telomerase exhibiting in vitro and in vivo antitumor activity.

Gowan, Sharon M.; Harrison, John R.; Patterson, Lisa; Valenti, Melanie; Read, Martin A.; Neidle, Stephen; Kelland, Lloyd R. Cancer Research Campaign (CRC) Center for Cancer Therapeutics, Institute of Cancer Research, Surrey, UK. Molecular Pharmacology (2002), 61(5), 1154-1162. Publisher: American Society for Pharmacology and Experimental Therapeutics, CODEN: MOPMA3 ISSN: 0026-895X. Journal written in English. CAN 137:304373 AN 2002:335691 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The telomerase complex is responsible for telomere maintenance and represents a promising cancer therapeutic target. We describe herein the antitelomerase and antitumor properties of a small-mol. compd. designed by computer modeling to interact with and stabilize human G-quadruplex DNA, a structure that may form with telomeric DNA, thereby inhibiting access to telomerase. The 3,6,9-trisubstituted acridine 9-[4-(N,N-dimethylamino)phenylamino]-3,6-bis(3-pyrrolidinopropionamido) acridine (BRACO19) represents one of the most potent cell-free inhibitors of human telomerase yet described (50% inhibitory concn. of 115 ± 18 nM). Moreover, in contrast to G-quadruplex interactive agents described previously, BRACO19 did not cause nonspecific acute cytotoxicity at similar concns. to those required to completely inhibit telomerase activity. There exists a 90-fold differential (mean 50% inhibitory concn. for acute cell kill across seven human tumor cell lines of 10.6 ± 0.7 μ M). The exposure of 21NT human breast cancer cells, which possess relatively short telomeres, to nonacute cytotoxic concns. of BRACO19 (2 μ M) resulted in a marked redn. in cell growth after only 15 days. This was concomitant with a redn. in intracellular telomerase activity and onset of senescence as indicated by an increase in the no. of β -galactosidase pos.-staining cells. I.p. administration of non-toxic doses of BRACO19 (2 mg/kg) to mice bearing advanced stage A431 human vulval carcinoma s.c. xenografts and previously treated with paclitaxel induced a significant increase in antitumor effect compared with that obsd. with paclitaxel alone. BRACO19 thus represents the first of a "second generation" of G-quadruplex-mediated telomerase/telomere-interactive compds.

It possesses nanomolar potency against telomerase but low nonspecific cytotoxicity, growth inhibitory effects, and induction of senescence in a human breast cancer cell line and, moreover, significant antitumor activity in vivo when administered post paclitaxel to mice bearing a human tumor xenograft carcinoma.

Answer 111:

Bibliographic Information

Enhanced antitumor activity of combined pretargeted radioimmunotherapy and paclitaxel in medullary thyroid cancer xenograft. Kraeber-Bodere, Françoise; Sai-Maurel, Catherine; Campion, Loïc; Faivre-Chauvet, Alain; Mirallie, Eric; Cherel, Michel; Supiot, Stéphane; Barbet, Jacques; Chatal, Jean-François; Thedrez, Philippe. Regional Cancer Center, Institut National de la Santé et de la Recherche Médicale Research Unit 463, CEA, Nantes, Fr. Molecular Cancer Therapeutics (2002), 1(4), 267-274. Publisher: American Association for Cancer Research, CODEN: MCTOCF ISSN: 1535-7163. Journal written in English. CAN 137:72777 AN 2002:230852 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A significant antitumor effect assocd. with moderate toxicity was obtained previously with anti-carcinoembryonic antigen \times anti-diethylene-triaminepentaacetic acid (DTPA)-indium F6-734 bispecific antibody and iodine-131-labeled DTPA-indium bivalent hapten in an animal model of medullary thyroid cancer (MTC). The purpose of this study was to det. whether the cytotoxic agents doxorubicin and paclitaxel, also known as radiosensitizers, improve efficacy of pre-targeted radioimmunotherapy (RIT) in exptl. MTC. Nude mice bearing TT MTC xenograft were treated with F6-734 and iodine-131-labeled DTPA-indium bivalent hapten injected 48 h apart with or without doxorubicin or paclitaxel. The max. tolerated dose (MTD) of RIT was 92.5 MBq (as detd. previously) and that of doxorubicin and paclitaxel 200 and 1000 μ g, resp. A control group received no treatment. Animal wt., hematotoxicity, tumor vol., and serum calcitonin were monitored for 5 mo. Tumor growth inhibition induced by drugs alone, RIT alone, or combined therapy was characterized by measuring relative tumor vol. 20, 40, and 60 days after treatment to detect additivity or synergism. Mean tumor vol. doubling time (MTVDT) was 13 ± 4 days in the control group, 15 ± 8 days in the group treated with the MTD of doxorubicin, and 32 ± 13 days in the group treated with the MTD of paclitaxel. After RIT alone at 92.5 MBq, MTVDT was 86 ± 22 days. After RIT at 74 MBq (80% of MTD), MTVDT was 56 ± 10 days. MTVDT was not significantly different from this value after RIT plus doxorubicin, 60 ± 16 days (65 and 100% of the resp. single-agent MTDs). Combination of RIT with paclitaxel (65 and 100% of the resp. single-agent MTDs) prolonged the suppression of tumor growth. One complete response was obsd., and MTVDT was 114 ± 44 days. This value was significantly longer than the value

obtained with RIT alone at 74 MBq ($P < 0.05$) or with RIT combined with doxorubicin ($P < 0.02$). The change in serum calcitonin levels paralleled those in tumor vol. Anal.

of dose-response curves at days 20 and 40 showed additivity between RIT and paclitaxel, and anal. at day 60 suggested a synergistic effect. In conclusion, addn. of doxorubicin did not improve RIT efficacy, whereas paclitaxel improved RIT efficacy significantly without increasing toxicity.

Answer 112:

Bibliographic Information

Conservation of the class I β -tubulin gene in human populations and lack of mutations in lung cancers and paclitaxel-resistant ovarian cancers. Sale, Sanja; Sung, Raphael; Shen, Peidong; Yu, Kristine; Wang, Yan; Duran, George E.; Kim, Jong-Hyeok; Fojo, Tito; Oefner, Peter J.; Sikic, Branimir I. Stanford University School of Medicine, Stanford, CA, USA. *Molecular Cancer Therapeutics* (2002), 1(3), 215-225. Publisher: American Association for Cancer Research, CODEN: MCTOCF ISSN: 1535-7163. Journal written in English. CAN 136:277027 AN 2002:95274 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The goal of this study was to det. the prevalence of sequence variants in the class I β -tubulin (clone m40) gene and their occurrence in human tumors and cancer cell lines. DNA was isolated from 93 control individuals representing a wide variety of ethnicities, 49 paclitaxel-naive specimens (16 ovarian cancers, 17 non-small cell lung cancers, and 16 ovarian cancer cell lines), and 30 paclitaxel-resistant specimens (9 ovarian cancers, 9 ovarian cancer cell lines, and 12 ovarian cancer xenografts in nude mice). Denaturing high-performance liq. chromatog. and direct sequence anal. detected two silent polymorphisms in exon 4, Leu217Leu (CTG/CTA) and Gly400Gly (GGC/GGT), with minor allele frequencies of 17 and 0.5%, resp. Five nucleotide substitutions and one single-base deletion were detected in introns 1, 2, and 3 and in the 3' untranslated region. Anal. of 49 paclitaxel-naive and 30 paclitaxel-resistant specimens revealed no addnl. polymorphisms in the coding region. In addn., no amino acid replacements were found in chimpanzee, gorilla, and orangutan in comparison to human. Our data demonstrate a very high degree of sequence conservation in class I β -tubulin, suggesting that all residues are important in tubulin structure and function. Individual variation in response to treatment with paclitaxel is not likely to be caused by genetic variations in the β -tubulin drug target. Moreover, acquired mutations in class I β -tubulin are unlikely to be a clin. relevant cause of drug resistance.

Answer 113:

Bibliographic Information

Combined modality radioimmunotherapy for human prostate cancer xenografts with taxanes and ^{90}Y -DOTA-peptide-ChL6. O'Donnell, Robert T.; DeNardo, Sally J.; Miers, Laird A.; Lamborn, Kathleen R.; Kukis, David L.; DeNardo, Gerald L.; Meyers, Frederick J. Department of Internal Medicine, University of California Davis Medical Center, Sacramento, CA, USA. *Prostate (New York, NY, United States)* (2002), 50(1), 27-37. Publisher: Wiley-Liss, Inc., CODEN: PRSTDS ISSN: 0270-4137. Journal written in English. CAN 137:121682 AN 2002:58453 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Therapy for prostate cancer in the PC3 tumor-nude mouse model with ^{90}Y -DOTA-peptide-ChL6 (5.55 MBq; 150 μCi) has resulted in durable responses. To make radioimmunotherapy (RIT) more effective, the radiation-enhancing drugs Taxol (paclitaxel) and Taxotere (docetaxel) were tested for synergy with ^{90}Y -DOTA-peptide-ChL6. Nude mice bearing human prostate cancer PC3 xenografts were treated with ^{90}Y -DOTA-peptide-ChL6 (2.78 MBq; 75 μCi) and after 24 h, paclitaxel (300 or 600 μg), or docetaxel (300 μg). Tumor size, survival, blood counts, and pharmacokinetics were monitored to assess efficacy and toxicity. Docetaxel plus RIT had a 67% cure rate, whereas no mice were cured among the RIT alone, chemotherapy alone, or untreated controls. Paclitaxel (600 μg) plus RIT produced a 100% response rate with 20% cures. Av. tumor vol. was reduced to a greater degree in the combined

modality radioimmunotherapy (CMRIT) groups compared to controls and the anti-tumor response was durable. Myelotoxicity in the combined modality groups (RIT plus paclitaxel or RIT plus docetaxel) were similar to groups receiving the same dose of RIT alone. In the PC3-tumor nude mouse model, addn. of paclitaxel or docetaxel to 90Y-DOTA-peptide-ChL6, in doses clin. achievable in humans, provided therapeutic synergy without increased or excessive toxicity.

Answer 114:

Bibliographic Information

Antitumor efficacy of 26-fluoroepothilone B against human prostate cancer xenografts. Newman, Robert A.; Yang, Jun; Finlay, M. Raymond V.; Cabral, Fernando; Vourloumis, Dionisios; Stephens, L. Clifton; Troncoso, Patricia; Wu, Xiaobing; Logothetis, Christopher J.; Nicolaou, K. C.; Navone, Nora M. University of Texas M.D. Anderson Cancer Center, Pharmaceutical Development Center, Houston, TX, USA. *Cancer Chemotherapy and Pharmacology* (2001), 48(4), 319-326. Publisher: Springer-Verlag, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 137:119115 AN 2001:695788 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: Epothilone compds. (e.g., epothilones A and B) represent a new structural class of microtubule inhibitors with the remarkable ability to inhibit tumor growth of multidrug-resistant cell lines at low nanomolar or even subnanomolar concns. Unfortunately, this therapeutic efficacy has only been achieved to date with a narrow therapeutic window. Hence, other structural analogs of compds. such as epothilone B are currently being synthesized in the hope that they will demonstrate equiv. antitumor efficacy with reduced systemic toxicity. Purpose: To evaluate the relative efficacy and toxicity of selectively modified epothilone compds. Methods: Compds. were initially screened for relative cytotoxicity against the human prostate cancer cell lines PC3, LNCaP, MDA PCa 2a and MDA PCa 2b. Growth inhibitory IC50 values of 0.5 to 4 nM were obtained. From this initial screen, one epothilone compd., 26-fluoroepothilone B, was chosen for further evaluation against the growth of s.c.-implanted MDA PCa 2b- and PC3-derived prostate tumors in athymic nude mice. The compd. was administered i.v. at 2, 5 and 10 mg/kg after the tumors had reached 300 Mm3. Two control groups were used: paclitaxel (40 mg/kg) and saline. Results: Following treatment with 10 mg 26-fluoroepothilone B/kg, there was a sustained decrease in tumor size for 30 days reaching a maximal redn. of 80% when compared with tumor growth in the saline control group. Sustained suppression (>20 days) of tumor growth was obsd. following the second drug injection. Although a maximal body wt. loss of 30% occurred after the second injection, all mice completely regained their initial body wt. in 20 days. A lower dose (2 mg/kg) produced a 58% maximal redn. in tumor size and a 20% body wt. loss. Minimal inhibition of tumor growth, however, was obtained with paclitaxel at a maximally tolerated dose (40 mg/kg). Other epothilones tested were either less effective and/or more toxic than 26-fluoroepothilone B. This new fluorinated epothilone compd.

supports the growth of paclitaxel-dependent Tax-18 mutant CHO cells and produces microtubule bundles similar to those produced by paclitaxel, indicating that the two drugs share a similar mechanism of action. Conclusion: A new fluorinated epothilone compd., 26-fluoroepothilone B, has been described that stabilizes microtubule structures based on its support of growth of a mutant paclitaxel-dependent CHO cell line. Its antitumor activity against human prostate cancer in nude mice is superior to that of paclitaxel at equiv. toxic doses. Further research is required to det. optimal dosing strategies and to fully assess the compd.'s activity against other malignant diseases.

Answer 115:

Bibliographic Information

Effects of orally active taxanes on P-glycoprotein modulation and colon and breast carcinoma drug resistance. Vredenburg, Michael R.; Ojima, Iwao; Veith, Jean; Pera, Paula; Kee, Kristin; Cabral, Fernando; Sharma, Amarnath; Kanter, Peter; Greco, William R.; Bernacki, Ralph J. Department of Pharmacology and Therapeutics, Roswell Park Cancer Institute, Buffalo, NY, USA. *Journal of the National Cancer Institute* (2001), 93(16), 1234-1245. Publisher: Oxford University Press, CODEN: JNCIEQ ISSN: 0027-8874. Journal written in English. CAN 136:363342 AN 2001:667871 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The orally active paclitaxel analog IDN-5109 has been reported to overcome P-glycoprotein (Pgp)-mediated drug resistance. This work tested whether IDN-5109 acts by modulating Pgp activity. Human MDA435/LCC6mdr1 and MDA435/LCC6 breast carcinoma cells, which express and do not express Pgp, resp., were incubated with [³H]IDN-5109 and paclitaxel to det. intracellular drug accumulation. Flow cytometry was used to analyze intracellular retention of two Pgp substrates, rhodamine 123 (Rh-123) and doxorubicin, in both breast carcinoma cell lines and in human colon carcinoma cells (SW-620, DLD1, and HCT-15, whose Pgp levels vary) treated with different taxanes. The effects of IDN-5109 and paclitaxel on tumor growth in vivo were studied with the use of tumors established through xenografts of Pgp-expressing SW-620 and DLD1 cells in mice with severe combined immunodeficiency. Pgp-expressing cells treated with IDN-5109 or with the taxane-based drug-resistance-reversal agent tRA96023, which blocks Pgp activity, retained 8.1- and 9.4-fold more Rh-123, resp., and 1.7- and 1.9-fold more doxorubicin, resp., than cells treated with paclitaxel. Non-Pgp-expressing cells treated similarly demonstrated no increased retention of either substrate. MDA435/LCC6mdr1 cells retained 5.3-fold more [³H]IDN-5109 than [³H]paclitaxel after 2 h. IDN-5109 caused greater tumor growth inhibition than paclitaxel against the SW-620 xenograft. Thus, IDN-5109 modulates Pgp activity, resulting in greater tumor growth inhibition against Pgp-expressing tumors as compared with paclitaxel. IDN-5109 may broaden the spectrum of taxane use to include colon tumors.

Answer 116:

Bibliographic Information

The synthesis, discovery, and development of a highly promising class of microtubule stabilization agents: curative effects of desoxyepothilones B and F against human tumor xenografts in nude mice. Chou, Ting-Chao; O'Connor, Owen A.; Tong, William P.; Guan, Yongbiao; Zhang, Zui-Guo; Stachel, Shawn J.; Lee, Chulbom; Danishefsky, Samuel J. Preclinical Pharmacology Core Facility, Memorial Sloan-Kettering Cancer Center, New York, NY, USA. Proceedings of the National Academy of Sciences of the United States of America (2001), 98(14), 8113-8118. Publisher: National Academy of Sciences, CODEN: PNAS6 ISSN: 0027-8424. Journal written in English. CAN 135:327022 AN 2001:526491 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We have evaluated two synthetic epothilone analogs lacking the 12,13-epoxide functionality, 12,13-desoxyepothilone B (dEpoB), and 12,13-desoxyepothilone F (dEpoF). The concns. required for 50% growth inhibition (IC₅₀) for a variety of anticancer agents were measured in CCRF-CEM/VBL1000 cells (2,048-fold resistance to vinblastine). By using dEpoB, dEpoF, aza-EpoB, and paclitaxel, the IC₅₀ values were 0.029, 0.092, 2.99, and 5.17 μM, resp. These values represent 4-, 33.5-, 1,423- and 3,133-fold resistance, resp., when compared with the corresponding IC₅₀ in the parent [nonmultiple drug-resistant (MDR)] CCRF-CEM cells. We then produced MDR human lung carcinoma A549 cells by continuous exposure of the tumor cells to sublethal concns. of dEpoB (1.8 yr), vinblastine (1.2 yr), and paclitaxel (1.8 yr). This continued exposure led to the development of 2.1-, 4,848-, and 2,553-fold resistance to each drug, resp. The therapeutic effect of dEpoB and paclitaxel was also compared in vivo in a mouse model by using various tumor xenografts. DEpoB is much more effective in reducing tumor sizes in all MDR tumors tested. Anal. of dEpoF, an analog possessing greater aq. soly. than dEpoB, showed curative effects similar to dEpoB against K562, CCRF-CEM, and MX-1 xenografts. These results indicate that dEpoB and dEpoF are efficacious antitumor agents with both a broad chemotherapeutic spectrum and wide safety margins.

Answer 117:

Bibliographic Information

In vivo antitumor efficacy of MGI-114 (6-hydroxymethylacylfulvene, HMAF) in various human tumor xenograft models including several lung and gastric tumors. Sato, Y.; Kashimoto, S.; MacDonald, J. R.; Nakano, K. Discovery Research Laboratories, Department of Pharmacology II, Dainippon Pharmaceutical Co., Ltd., Suita, Osaka, Japan. European Journal of Cancer (2001), 37(11), 1419-1428. Publisher: Elsevier Science Ltd., CODEN: EJCAEL ISSN: 0959-8049. Journal written in English. CAN 136:288614 AN 2001:483139 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The in vivo antitumor efficacy of MGI-114 (a semisynthetic analog of the cytotoxic sesquiterpenoid illudins) was examd. in a panel of human tumor xenografts in mice, consisting mainly of human lung and gastric tumors, and compared with that of other antitumor drugs (irinotecan, paclitaxel, cisplatin, doxorubicin, vindesine, etoposide and 5-fluorouracil). When different administration schedules were compared, daily administration of MGI-114 was more effective than intermittent administrations. In human tumor xenograft models of nasopharyngeal, breast and colon carcinoma and melanoma, MGI-114 exerted a strong antitumor activity, with complete tumor regression occurring. Moreover, in four human lung and three gastric tumor xenografts, MGI-114 had a strong antitumor activity, with complete tumor regression occurring in some cases. The antitumor efficacy of MGI-114 was generally higher than or equiv. to that of irinotecan and paclitaxel. These results support the potential utility of MGI-114 in the treatment of a variety of human solid tumors.

Answer 118:

Bibliographic Information

Inhibition of growth factor production and angiogenesis in human cancer cells by ZD1839 (Iressa), a selective epidermal growth factor receptor tyrosine kinase inhibitor. Ciardiello, Fortunato; Caputo, Rosa; Bianco, Roberto; Damiano, Vincenzo; Fontanini, Gabriella; Cuccato, Sabina; De Placido, Sabino; Bianco, A. Raffaele; Tortora, Giampaolo. Cattedra di Oncologia Medica, Dipartimento di Endocrinologia e Oncologia Molecolare e Clinica, Universita degli Studi di Napoli "Federico II," Naples, Italy. *Clinical Cancer Research* (2001), 7(5), 1459-1465. Publisher: American Association for Cancer Research, CODEN: CCRE4 ISSN: 1078-0432. Journal written in English. CAN 136:193768 AN 2001:433622 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The transforming growth factor- α /epidermal growth factor receptor (TGF- α -EGFR) autocrine pathway, which is involved in the development and the progression of human epithelial cancers, controls, in part, the prodn. of angiogenic factors. These angiogenic factors, including vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), are secreted by cancer cells to stimulate normal endothelial cell growth through paracrine mechanisms. ZD1839 (Iressa) is a p.o.-active, selective EGFR-tyrosine kinase inhibitor (TKI) in clin. trials in cancer patients. In this study, we evaluated the antiangiogenic and antitumor activity of ZD1839 in human colon (GEO, SW480, and CaCo2), breast (ZR-75-1 and MCF-7 ADR), ovarian (OVCAR-3), and gastric (KATO III and N87) cancer cells that coexpress TGF- α and EGFR. ZD1839 treatment detd. a dose- and time-dependent growth inhibition accompanied by the decrease of VEGF, bFGF and TGF- α prodn. in vitro. Treatment of immunodeficient mice bearing well-established, palpable GEO xenografts with ZD1839 detd. a cytostatic dose-dependent tumor growth inhibition. Immunohistochem. anal. of GEO tumor xenografts after ZD1839 treatment revealed a significant dose-dependent redn. of TGF- α , bFGF, and VEGF expression in cancer cells and of neoangiogenesis, as detd. by microvessel count. Furthermore, the antitumor activity of ZD1839 was potentiated in combination with the cytotoxic drug paclitaxel in GEO tumor xenografts. Tumor regression was obsd. in all mice after treatment with ZD1839 plus paclitaxel, and it was accompanied by a significant potentiation in inhibition of TGF- α , VEGF, and bFGF expression with a few or no microvessels. Furthermore, 6 of 16 mice bearing well-established, palpable GEO xenografts had no histol. evidence of GEO tumors at the end of treatment with ZD1839 plus paclitaxel. These results demonstrate that the antitumor effect of ZD1839 is accompanied by inhibition in the prodn.

of autocrine and paracrine growth factors that sustain autonomous local growth and facilitate angiogenesis, and that this effect can be potentiated by the combined treatment with certain cytotoxic drugs, such as paclitaxel.

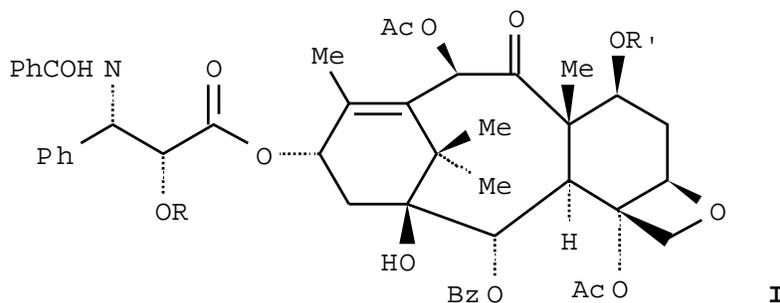
Answer 119:

Bibliographic Information

A new prodrug of paclitaxel: synthesis of Protaxel. Seligson, Allen L.; Terry, Ronald C.; Bressi, Jerome C.; Douglass, James G., III; Sovak, Milos. *Biophysica*, La Jolla, CA, USA. *Anti-Cancer Drugs* (2001), 12(4), 305-313. Publisher: Lippincott Williams & Wilkins, CODEN: ANTDEV ISSN: 0959-4973. Journal written in English. CAN 135:247101 AN 2001:400706 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

2'- And 7-Polyol carbonates of paclitaxel were synthesized and screened as potential paclitaxel prodrugs. Paclitaxel is released from 7-(2'',3''-dihydroxypropylcarbonato)paclitaxel (Protaxel) (I) at rates inversely proportional to pH, by an intramol. cyclization. Compared to paclitaxel, max. tolerated i.v. or i.p. doses (MTD) of Protaxel are about 2.5- to 3-fold higher; its efficacy is substantially higher in human cancer line xenografts in athymic mice, esp. in prostate PC-3, breast MDA-MB 468 and ovary OVCAR-1.



Answer 120:

Bibliographic Information

Study on cytotoxic Effect and antitumor effect of Paclitaxel liposome. Wei, Fengying; Cheng, Wencai. Department of Obstetrics and Gynecology, The Affiliated Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology, Wuhan, Peop. Rep. China. *Tongji Yike Daxue Xuebao* (2001), 30(1), 46-49. Publisher: Tongji Yike Daxue, CODEN: TYDXEP ISSN: 0258-2090. Journal written in Chinese. CAN 135:282772 AN 2001:254218 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The cytotoxic effect and antitumor effect of paclitaxel liposome were studied by using MTT assay method in vitro and in vivo antitumor test. The inhibitory rate of paclitaxel liposome on human ovarian cancer cell COC1 was 78.48%, 84.90%, 93.53% resp. at the concns. of 22.5 $\mu\text{g/mL}$, 45 $\mu\text{g/mL}$, 90 $\mu\text{g/mL}$ resp. Under the doses of 5 mg/ (kg d) and 10 mg/ (kg d) for 8 days, the inhibitory rate of paclitaxel liposome against xenograft of solid Ehrlich tumor in mice was 32.47 % and 54.63% resp. ($P < 0.01$). The wt. change rate of the mice was 22.11% and 21.16% resp. It was suggested that paclitaxel liposome had antitumor activities in vitro and in vivo. The toxicity of liposomal paclitaxel was lower than that of free paclitaxel.

Answer 121:

Bibliographic Information

Inhibition of human tumor cell growth in vivo by an orally bioavailable inhibitor of human farnesyltransferase, BIM-46228. Prevost, Gregoire P.; Pradines, Anne; Brezak, Marie-Christine; Lonchamp, Marie-Odile; Viossat, Isabelle; Ader, Isabelle; Toulas, Christine; Kasprzyk, Philip; Gordon, Thomas; Favre, Gilles; Morgan, Barry. Institut Henri Beaufour, Les Ulis, Fr. *International Journal of Cancer* (2001), 91(5), 718-722. Publisher: Wiley-Liss, Inc., CODEN: IJCNW ISSN: 0020-7136. Journal written in English. CAN 135:174767 AN 2001:128354 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

This work reports a novel farnesyltransferase inhibitor, BIM-46228, which gave: (1) specific inhibition of purified human farnesyltransferase enzyme, (2) inhibition of proliferation of a broad spectrum of human tumor cell lines in vitro, (3) inhibition of the growth of human tumor xenografts in athymic nude mice treated orally and (4) combination of its activity with chemotherapy (paclitaxel) or radiotherapy in vitro.

Answer 122:

Bibliographic Information

In vitro and in vivo reversal of P-glycoprotein-mediated multidrug resistance by a novel potent modulator, XR9576. Mistry, Prakash; Stewart, Alistair J.; Dangerfield, Wendy; Okiji, Sade; Liddle, Chris; Bootle, Douglas; Plumb, Jane A.; Templeton, David; Charlton, Peter. Xenova Limited, Slough, UK. Cancer Research (2001), 61(2), 749-758. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 134:305064 AN 2001:125551 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The overexpression of P-glycoprotein (P-gp) on the surface of tumor cells causes multidrug resistance (MDR). This protein acts as an energy-dependent drug efflux pump reducing the intracellular concn. of structurally unrelated drugs. Modulators of P-gp function can restore the sensitivity of MDR cells to such drugs. XR9576 is a novel anthranilic acid deriv. developed as a potent and specific inhibitor of P-gp, and in this study we evaluate the in vitro and in vivo modulatory activity of this compd. The in vitro activity of XR9576 was evaluated using a panel of human (H69/LX4, 2780AD) and murine (EMT6 AR1.0, MC26) MDR cell lines. XR9576 potentiated the cytotoxicity of several drugs including doxorubicin, paclitaxel, etoposide, and vincristine; complete reversal of resistance was achieved in the presence of 25-80 nM XR9576. Direct comparative studies with other modulators indicated that XR9576 was one of the most potent modulators described to date. Accumulation and efflux studies with the P-gp substrates, [3H]daunorubicin and rhodamine 123, demonstrated that XR9576 inhibited P-gp-mediated drug efflux. The inhibition of P-gp function was reversible, but the effects persisted for > 22 h after removal of the modulator from the incubation medium. This is in contrast to P-gp substrates such as cyclosporin A and verapamil, which lose their activity within 60 min, suggesting that XR9576 is not transported by P-gp. Also, XR9576 was a potent inhibitor of photoaffinity labeling of P-gp by [3H]azidopine implying a direct interaction with the protein. In mice bearing the intrinsically resistant MC26 colon tumors, coadministration of XR9576 potentiated the antitumor activity of doxorubicin without a significant increase in toxicity; max. potentiation was obsd. at 2.5-4.0 mg/kg dosed either i.v. or p.o.

In addn., coadministration of XR9576 (6-12 mg/kg p.o.) fully restored the antitumor activity of paclitaxel, etoposide, and vincristine against two highly resistant MDR human tumor xenografts (2780AD, H69/LX4) in nude mice. Importantly all of the efficacious combination schedules appeared to be well tolerated. Furthermore, i.v. coadministration of XR9576 did not alter the plasma pharmacokinetics of paclitaxel. These results demonstrate that XR9576 is an extremely potent, selective, and effective modulator with a long duration of action. It exhibits potent i.v. and p.o. activity without apparently enhancing the plasma pharmacokinetics of paclitaxel or the toxicity of coadministered drugs. Hence, XR9576 holds great promise for the treatment of P-gp-mediated MDR cancers.

Answer 123:

Bibliographic Information

Taxane-antibody conjugates afford potent cytotoxicity, enhanced solubility, and tumor target selectivity. Guillemard, Veronique; Saragovi, H. Uri. Departments of Pharmacology and Therapeutics, McGill University, Montreal, QC, Can. Cancer Research (2001), 61(2), 694-699. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 134:348031 AN 2001:125543 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Paclitaxel (Taxol) is a chemotherapeutic agent that prevents disassembly of microtubular polymers, causing a growth arrest in the G2-M phase of the cell cycle and leading to apoptotic death. Paclitaxel has remarkable efficacy against fast-growing tumors but possesses major drawbacks, such as poor soly. and lack of tumor selectivity. Conversely, monoclonal antibodies usually have low therapeutic efficacy but are highly sol. and selectively target tumor markers overexpressed in cancer cells. Therefore, to improve the therapeutic index of taxanes as chemotherapeutics, the high toxicity of paclitaxel was combined with the high selectivity and soly. of monoclonal antibodies as targeting agents. We report the chem. coupling and characterization of paclitaxel-antibody conjugates for treatment of neuroectoderm-derived tumors. Paclitaxel-antibody conjugates afforded selective toxicity toward cells expressing the

target marker and were more cytotoxic in vitro than equimolar concns. of free paclitaxel or free paclitaxel plus free antibody. In an in vivo model of xenografted tumors, systemic administration of paclitaxel-antibody conjugates prevented tumor growth and prolonged survival of mice better than free drugs. In addn., paclitaxel-antibody conjugates were highly sol. in water and stable at -20°C for at least 3 mo. These studies may lead to an increase or an improvement of the armamentarium and selectivity of cytotoxic agents.

Answer 124:

Bibliographic Information

Evaluation of the anti-tumor and anti-angiogenic effect of paclitaxel and thalidomide on the xenotransplanted oral squamous cell carcinoma. Myoung, H.; Hong, S.-D.; Kim, Y.-Y.; Hong, S.-P.; Kim, M.-J. College of Dentistry and Dental Research Institute, Department of Oral and Maxillofacial Surgery, Seoul National University, Chong-No gu, Seoul, S. Korea. *Cancer Letters* (Shannon, Ireland) (2001), 163(2), 191-200. Publisher: Elsevier Science Ireland Ltd., CODEN: CALEDQ ISSN: 0304-3835. Journal written in English. CAN 134:305057 AN 2001:95433 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Angiogenesis is an essential process for the growth and invasion of cancer. However, it is uncertain that anti-angiogenic effects can be a major treatment strategy of oral cancer. The aim of this study was to investigate whether thalidomide and paclitaxel, which are known to be potent inhibitors of angiogenesis, have inhibitory effects on the growth of oral squamous cell carcinoma (OSCC) xenotransplanted into nude mice and whether anti-angiogenesis can be included as a major treatment strategy of oral cancer. After human OSCC cell line, KB, was s.c. inoculated into 32 nude mice, the vol. of tumor was measured every 3 days. When the tumor mass reached 300-500 mm³, thalidomide (200 mg/kg) and paclitaxel (13 mg/kg) were administered into the animals and tumor vol. change was checked. The excised tumor masses on the 30th day after administration were frozen and processed for immunohistochem. using vascular endothelial growth factor (VEGF) and CD31, and for real-time reverse transcription-polymerase chain reaction (RT-PCR). We evaluated VEGF expression and the expression of its mRNA and CD31 for vessel d. Paclitaxel showed an inhibitory effect on the growth of transplanted human OSCC and reduced the immunohistochem. expression of VEGF and CD31 and VEGF mRNA (P<0.01). Thalidomide also lowered remarkably VEGF expression (P<0.01) and CD31 (P<0.01) as well as VEGF mRNA (P<0.05), but it did not show statistically significant inhibitory effect on the tumor growth. These results suggest that the growth of human OSCC is not simply dependent on VEGF-induced angiogenesis and that anti-angiogenic therapy alone is not likely to be effective for the treatment of OSCC, but might be regarded as adjuvant chemotherapeutic strategy.

Answer 125:

Bibliographic Information

Pharmacodynamics and pharmacokinetics of paclitaxel (Zisu). Han, Rui; He, Xiao-qing; Liu, Hong-yan; Lei, Xiao-hong; Cheng, Qing; Zhao, Wan-shou. Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, Peop. Rep. China. *Chinese Journal of Cancer Research* (2000), 12(4), 235-238. Publisher: Chinese Journal of Cancer Research, CODEN: CJCRFH ISSN: 1000-9604. Journal; General Review written in English. CAN 135:101768 AN 2001:90633 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A review, with 6 refs. Pharmacol. studies demonstrated that paclitaxel (Zisu) was very active in the inhibition of the growth of human cancer cell panel including KB cells, HCT-8, A2780, and MCF-7 cells. The IC₅₀ was as low as 0.0019, 0.0019, 0.0036 and 0.01 µg/mL, resp. Exptl. therapeutic studies indicated that paclitaxel(Zisu) significantly inhibited the growth of melanoma B-16, Walker carcinosarcoma and heterotransplanted human ovarian cancer in nude mice. Biochem. pharmacol. studies showed that paclitaxel (Zisu) could accelerate microtubule assembly and inhibit its deassembly; population in G₁ was decreased while the cell population in G₂+M phase was increased significantly. In addn., a polyploid cell population appeared. Pharmacokinetic studies demonstrated that the t_{1/2α} was 0.12 h and t_{1/2β} was 5.02 h when it was injected i.v. at a dose of 5 mg/kg in rats. The AUC, V_c and CLs were 11.82(µg·h)/mL, 0.50L/kg and 0.42 L(h·kg), resp.

Answer 126:

Bibliographic Information

Response and determinants of sensitivity to paclitaxel in human non-small cell lung cancer tumors heterotransplanted in nude mice. Perez-Soler, Roman; Kemp, Bonnie; Wu, Qing Ping; Mao, Li; Gomez, Jorge; Zeleniuch-Jacquotte, Anne; Yee, Herman; Lee, Jin Soo; Jagirdar, Jaishree; Ling, Yi He. Kaplan Comprehensive Cancer Center, New York University School of Medicine, New York, NY, USA. *Clinical Cancer Research* (2000), 6(12), 4932-4938. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 135:86679 AN 2001:83383 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The lack of tumor models that can reliably predict for response to anticancer agents remains a major deficiency in the field of exptl. cancer therapy. Although heterotransplants of certain human solid tumors can be successfully grown in nude mice, they have never been appropriately explored for prediction of in vivo chemosensitivity to anticancer agents. The authors detd. the tumor response rate and studied the influence of several biol. and mol. tumor parameters on the in vivo sensitivity to paclitaxel in a series of heterotransplanted human non-small cell lung cancer (NSCLC) tumors. One hundred consecutive resected NSCLC tumors were heterotransplanted s.c. in nude mice. The in vivo sensitivity to i.v. paclitaxel (60 mg/kg every 3 wk) was studied in 34 successfully grown heterotransplants. Treatment started when the tumors reached a size of 5 mm in diam., and strict std. clin. criteria (>50% shrinkage in tumor wt. or cross-sectional surface) were used to define tumor response. Baseline multidrug resistance protein (MRP), Her-2/neu, and epidermal growth factor receptor (EGFR) expression, and pre- and post-therapy bax and bcl-2 expression were detd. by Western blot anal. P53 status was detd. by sequencing. The overall take rate was 46% (95% confidence interval, 36-56%) and was significantly higher ($P < 0.05$) for squamous carcinoma tumors (75%) than for adenocarcinoma tumors (30%) and bronchoalveolar tumors (23%). The heterotransplants were morphol. very similar to the original tumors. The response rate to paclitaxel was 21% (95% confidence interval, 9-38%). Baseline tumor parameters assocd. with response were no Her-2/neu expression (none of the responding tumors expressed Her-2/neu vs. 48% of the nonresponding tumors, $P = 0.05$) and baseline bcl-2 expression (all responding tumors expressed bcl-2 vs. only 43% of the nonresponding tumors, $P = 0.02$). There was a trend toward a higher response rate in bax-pos. tumors, and MRP- and EGFR-neg. tumors, but it was not statistically significant.

The response was independent of baseline p53 status and baseline mitotic index. Responding tumors had a higher bax/bcl-2 ratio 24 h after therapy, but the difference was only marginally significant (2.8 for responding tumors vs. 1.1 for nonresponding tumors, $P = 0.07$). The extent of mitotic arrest at 24 h after therapy was not assocd. with response. Human NSCLC heterotransplants are morphol. identical to the original tumors and have a response rate to paclitaxel that is equiv. to that reported in Phase II studies in patients with advanced NSCLC treated with single-agent paclitaxel. NSCLC heterotransplants deserve to be explored to evaluate new agents for lung cancer and to predict clin. response on an individual basis in selected groups of patients.

Answer 127:

Bibliographic Information

Development and validation of sensitive assays to quantitate gene expression after p53 gene therapy and paclitaxel chemotherapy using in vivo dosing in tumor xenograft models. Wen, Shu Fen; Xie, Lei; McDonald, Matthew; DiGiacomo, Ruth; Chang, Alice; Gurnani, Maya; Shi, Bin; Liu, Suxing; Indelicato, Stephen R.; Hutchins, Beth; Nielsen, Loretta L. Canji, San Diego, CA, USA. *Cancer Gene Therapy* (2000), 7(11), 1469-1480. Publisher: Nature America Inc., CODEN: CGTHEG ISSN: 0929-1903. Journal written in English. CAN 134:157305 AN 2000:871902 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

SCH58500 (ACN53) is a replication-deficient, type 5 adenovirus (Ad) expressing human wild-type p53 tumor suppressor. It is currently undergoing clin. trials as a cancer therapeutic. Many SCH58500 clin. trials incorporate an arm comparing traditional chemotherapy against chemotherapy combined with SCH58500. Paclitaxel was chosen for combination therapy in the preclin. study reported here due to its extensive use as a first-line therapy in ovarian cancer, its synergy with SCH58500 in preclin. cancer models, and its

activation of p53-independent apoptosis, which might result in a "lowered threshold" for tumor cell death. SCID mice bearing human tumor xenografts were dosed with intratumoral vehicle, control Ad vector, or SCH58500, with or without paclitaxel. Real-time quant. reverse transcriptase polymerase chain reaction assays were developed and validated to quantitate expression of p53, the p53 downstream effector gene p21, and the apoptosis-related genes, bax, bcl-2, and survivin. Protein expression was confirmed using immunohistochem. assays for p53 and p21. Only tumors injected with SCH58500 had detectable levels of exogenous p53 DNA and mRNA. After SCH58500 treatment, 3-11-fold elevations of p21 expression were obsd. in tumor xenografts contg. nonfunctional p53 (MDA-MB-468, MDA-MB-231, MIAPaCa2, DU-145, and SK-OV-3), but no change in p21 mRNA in wild-type p53 PA-1 tumors. Immunohistochem. assays confirmed induction of p21 protein in MDA-MB-468 and SK-OV-3 cells, but not in PA-1 cells. Ad vector alone or paclitaxel alone had no effect on p21 mRNA levels in most tumors. However, paclitaxel suppressed p21 expression induced by SCH58500 4-fold in DU-145 and SK-OV-3 tumors. Paclitaxel also affected expression of the housekeeping gene gapdh. There was no consistent pattern to the changes in bax, bcl-2, or survivin after SCH58500 treatment with or without paclitaxel between tumor types, although there were consistent responses within individual tumor lines.

The mRNA ratios for bax/bcl-2 and bax/survivin were also not informative across tumor types. Of the genes examd., only p21 gave a predictable response 24 h after p53 gene therapy and therefore, p21 expression may be useful for confirming SCH58500 activity in human tumor biopsies.

Answer 128:

Bibliographic Information

Enhanced antitumour activity of 6-hydroxymethylacylfulvene in combination with topotecan or paclitaxel in the MV522 lung carcinoma xenograft model. Hammond, L. A.; Hilsenbeck, S. G.; Eckhardt, S. G.; Marty, J.; Mangold, G.; MacDonald, J. R.; Rowinsky, E. K.; Von Hoff, D. D.; Weitman, S. Cancer Therapy and Research Center, Institute for Drug Development, San Antonio, TX, USA. *European Journal of Cancer* (2000), 36(18), 2430-2436. Publisher: Elsevier Science Ltd., CODEN: EJCAEL ISSN: 0959-8049. Journal written in English. CAN 135:55558 AN 2000:834318 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

6-Hydroxymethylacylfulvene (HMAF; MGI 114; Irofulven) is a semisynthetic analog of the toxin illudin S, which is a product of the *Omphalotus* mushroom. MGI 114 induces cytotoxicity against a broad range of solid tumors in vivo, including the drug-refractory MV522 human lung cancer xenograft. In this study, the potential application of MGI 114 in the treatment of lung cancer was explored by evaluating the activity of MGI 114 in combination with either topotecan (TPT) or paclitaxel. Groups of eight nude mice bearing MV522 xenografts were treated with MGI 114, TPT or paclitaxel as single agents and with MGI 114 in combination with TPT or paclitaxel. MGI 114 was administered at doses of 2.5 and 5.0 mg/kg i.p. (i.p.) daily on days 1-5, while TPT and paclitaxel were administered at doses of 0.5 or 1.0 mg/kg and 20 mg/kg, resp., i.p. on days 1-5. In the single-agent studies, MGI 114, TPT and paclitaxel all resulted in decreased final tumor wts. compared with vehicle-treated controls. As single agents, TPT, at the 0.5 mg/kg dose level, and paclitaxel, at the 20 mg/kg dose level, produced partial shrinkages (PSs). All combinations of MGI 114, and either TPT or paclitaxel, produced decrements in final tumor wts. compared with monotherapy with the same doses of MGI 114, TPT and paclitaxel. Although all animals treated with the combination of MGI 114 and paclitaxel experienced PSs or complete shrinkages (CSs) (or died), anal. of the time to tumor doubling revealed that the combination of MGI 114 and TPT at 2.5 and 0.5 mg/kg, resp., was synergistic. These results suggest that cytotoxic activity is enhanced when MGI 114 is combined with either TPT or paclitaxel, and clin. trials to further evaluate these combination regimens are warranted.

Answer 129:

Bibliographic Information

Use of a surrogate marker (human secreted alkaline phosphatase) to monitor in vivo tumor growth and anticancer drug efficacy in ovarian cancer xenografts. Bao, Rudi; Selvakumaran, Muthu; Hamilton, Thomas C. Ovarian Cancer Program, Fox Chase Cancer Center, Philadelphia, PA, USA. *Gynecologic Oncology* (2000), 78(3, Pt. 1), 373-379. Publisher: Academic Press, CODEN: GYNOA3 ISSN: 0090-8258. Journal written in English. CAN 134:231600 AN 2000:714380 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A limitation to preclin. evaluation of possible anticancer therapy is the objective assessment of efficacy, esp. in the presence of small tumor burden or inaccessible disease. This study is designed to test whether human secreted alk. phosphatase (SEAP) could be used as a sol. marker for in vivo tumor burden. A SEAP expression construct under control of the CMV promoter was created. The SEAP activity in the conditioned medium was evaluated at 24 h and 48 h after the A2780 cell line was transiently transfected with the SEAP vector using Superfect reagent. Stable transfection of A2780 was accomplished by selection of transfectants in G418. SEAP activity of the stable transfectant was detd. in conditioned medium and its relationship to tumor cell no. was examd. A highly expressing stable transfectant was implanted into immunocompromised mice (2×10^6 s.c. and 5×10^6 i.p.) and peripheral blood was obtained by orbital puncture every 5 days. The relationship between blood SEAP activity and tumor burden was studied. The usefulness of this marker in preclin. assessment of anticancer drug efficacy was evaluated by studying the plasma SEAP activity in xenografted mice treated or not treated with paclitaxel. After transient transfection of the A2780 cell line (5×10^5) with the plasmid, SEAP activity was found in the medium at 24 h (482.0 ± 2.0 ng/mL) and 48 h (1296.0 ± 1.0 ng/mL). The in vitro study using a stable transfectant demonstrated that SEAP activity was linearly related to cell nos. ($r = 0.99$). The in vivo study demonstrated that SEAP was detectable in plasma one day postinjection, long before measurable tumor or detectable i.p. tumor was present. Once detectable SC tumor was present, the SEAP activity correlated well with tumor vol. ($r = 0.94-0.97$). The plasma SEAP level was reduced after xenografted mice were treated with paclitaxel (20 mg/kg, weekly $\times 5$) compared with untreated mice in both SC and IP tumor models ($P = 0.05$, $P = 0.025$, resp.).

These data suggest that the plasma SEAP activity can be used as an alternative to survival or tumor measurement in evaluating anticancer agents for efficacy, esp. in the case of minimal or inaccessible disease. (c) 2000 Academic Press.

Answer 130:

Bibliographic Information

Effects of mitomycin C and carboplatin pretreatment on multidrug resistance-associated P-glycoprotein expression and on subsequent suppression of tumor growth by doxorubicin and paclitaxel in human metastatic breast cancer-xenografted nude mice. Ihnat, Michael A.; Nervi, Angela M.; Anthony, Stephen P.; Kaltreider, Ronald C.; Warren, Amy J.; Pesce, Carrie A.; Davis, Stacey A.; Lariviere, Jean P.; Hamilton, Joshua W. Department of Pharmacology and Toxicology, Dartmouth Medical School, Hanover, NH, USA. *Oncology Research* (1999), 11(7), 303-310. Publisher: Cognizant Communication Corp., CODEN: ONREE8 ISSN: 0965-0407. Journal written in English. CAN 133:344264 AN 2000:517393 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Mitomycin C and carboplatin each suppressed cell P-glycoprotein levels in human MDA-MB-435 cells xenografted as solid tumors into the lateral mammary fat pads of female nude mice, with a similar time course as had previously been obsd. in cell culture. Pretreatment of the mice with mitomycin C or carboplatin 48-72 h prior to receiving either doxorubicin or paclitaxel caused a greater redn. of tumor growth rate than did either of the latter agents alone or given simultaneously. These data suggest that a combination chemotherapy regimen consisting of a DNA crosslinking agent given to modulate the multidrug-resistant phenotype, followed by a 2nd cytotoxic agent, may be an effective treatment for human patients with de novo or late-stage-acquired multidrug-resistant malignancies.

Answer 131:

Bibliographic Information

Study on the biodistribution of 99mTc-labeled paclitaxel liposome in xenograft-bearing nude mice. Zhang, Changying; Cheng, Wencai; Wang, Yanggong; Cui, Wuren; Zhao, Ming; Zhu, Xiaohua. Department of Obstetrics and Gynecology, Tongji Hospital, Tongji Medical University, Wuhan, Peop. Rep. China. *Tongji Yike Daxue Xuebao* (2000), 29(3), 253-255. Publisher: Tongji Yike Daxue, CODEN: TYDXEP ISSN: 0258-2090. Journal written in Chinese. CAN 133:159599 AN 2000:503968 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

S.c. xenograft tumor model was established in 20 female nude mice. ^{99m}Tc -paclitaxel liposome (^{99m}Tc -TL) 0.2 mL was injected through tail vein into the mice. Five animals were killed in each time point of 15 min, 30 min, 90 min after injection. The major organs were taken out and accurately weighed including heart, liver, spleen, lung, kidney, intestine, uterus and appendix, skeleton and tumor tissue. The remaining 5 mice were subjected to the injection of 0.2 mL ^{99m}Tc -soln. and killed 90 min after injection. Liver, spleen, lung and tumor tissue were taken out and weighed. γ -Measure device was used to measure the tissue radioactive intensity. Radioactive intensity was the highest (552.1 ± 92.8 to 260.1 ± 21.0 CPM/100 mg tissue) in spleen, liver and lung relatively, and tended to decrease with the prolongation of the time. The intensity in tumor tissue was obviously lower (3.6 ± 0.6 CPM/100 mg tissue) but kept relative stabilization and did not show a decreasing tendency. There was statistically significant difference in radioactive intensity in liver, spleen and lung tissues ($P < 0.05$), but there was no significant difference in tumor tissue ($P > 0.05$) between ^{99m}Tc -TL group and ^{99m}Tc -soln. group. Paclitaxel liposome after i.v. injection was mostly accumulated in liver, spleen, lung tissues in xenograft-bearing mice and showed a target ability. There was certain intensity in tumor tissue but it did not show target ability as compared with ^{99m}Tc -soln.

Answer 132:

Bibliographic Information

Discovery and characterization of OC144-093, a novel inhibitor of P-glycoprotein-mediated multidrug resistance. Newman, Michael J.; Rodarte, Jennifer C.; Benbatoul, Khalid D.; Romano, Suzanne J.; Zhang, Chengzhi; Krane, Sonja; Moran, Edmund J.; Uyeda, Roy T.; Dixon, Ross; Guns, Emma S.; Mayer, Lawrence D. Ontogen Corporation, Carlsbad, CA, USA. *Cancer Research* (2000), 60(11), 2964-2972. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 133:187741 AN 2000:397650 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

OC144-093 is a novel substituted diarylimidazole (Mr 495) generated using the OntoBLOCK system, a solid-phase combinatorial chem. technol., in combination with high-throughput cell-based screening. OC144-093 reversed multidrug resistance (MDR) to doxorubicin, paclitaxel, and vinblastine in human lymphoma, breast, ovarian, uterine, and colorectal carcinoma cell lines expressing P-glycoprotein (P-gp) with an av. EC₅₀ of 0.032 μM . Inhibition of MDR by OC144-093 was reversible, but the effect persisted for at least 12 h after removal of compd. from the culture medium. OC144-093 had no effect on the response to cytotoxic agents by cells in vitro lacking P-gp expression or expressing a multidrug resistance-assocd. protein (MRP-1). OC144-093 was not cytotoxic by itself against 15 normal, nontransformed, or tumor cell lines, regardless of P-gp status, with an av. cytostatic IC₅₀ of $>60 \mu\text{M}$. OC144-093 blocked the binding of [^3H]azidopine to P-gp and inhibited P-gp ATPase activity. The compd. was $>50\%$ p.o. bioavailable in rodents and dogs and did not alter the plasma pharmacokinetics of i.v.-administered paclitaxel. OC144-093 increased the life span of doxorubicin-treated mice engrafted with MDR P388 leukemia cells by $>100\%$ and significantly enhanced the in vivo antitumor activity of paclitaxel in MDR human breast and colon carcinoma xenograft models, without a significant increase in doxorubicin or paclitaxel toxicity. The results demonstrate that OC144-093 is an orally active, potent, and nontoxic inhibitor of P-gp-mediated multidrug resistance that exhibits all of the desired properties for treatment of P-gp-mediated MDR, as well as for prevention of MDR prior to selection and/or induction of refractory disease.

Answer 133:

Bibliographic Information

A peptidomimetic inhibitor of ras functionality markedly suppresses growth of human prostate tumor xenografts in mice. Prospects for long-term clinical utility. Sirotnak, F. M.; Sepp-Lorenzino, Laura; Kohl, Nancy E.; Rosen, Neal; Scher, Howard I. Laboratory for Molecular Pharmacology and Experimental Therapeutics, Memorial Sloan-Kettering Cancer Center, New York, NY, USA. *Cancer Chemotherapy and Pharmacology* (2000), 46(1), 79-83. Publisher: Springer-Verlag, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 134:13170 AN 2000:386116 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: These studies sought to evaluate the antitumor properties of an inhibitor of ras functionality, L-744832, which acts at the level of its assocd. protein farnesyltransferase. **Methods:** Studies were carried out to measure the effects of L-744832 alone and in combination with paclitaxel (PTXL) against TSU-PR1, DU-145 and PC-3 human prostate tumors xenografted to NCR-nu1 (AT) mice. Tumor-bearing mice were treated on a schedule of daily for 5 days \times 2 or 3 with the MTD of L-744832 and every 3-4 days \times 4 with the MTD of PTXL starting 3-5 days after tumor implantation. Tumor vol. in millimeters ($4/3\pi r^3$) was measured 3-5 days after cessation of treatment and the increase in tumor vol. in treated and control groups compared. Statistical anal. was carried out by the Chi-squared test. **Results:** L-744832 at its MTD markedly inhibited the growth of all three tumors (T/C) for increase in tumor mass varied from 11% to 15% and inhibition of growth had a rapid onset (within 1-2 days) and was independent of ras gene status. Estd. tumor doubling times were 8-12-fold greater in treated animals than in control animals. Treatment with L-744832 for as long as 3 wk had no untoward effects on the mice as detd. by gross examn. or necropsy. Administration of L-744832 with this same dose and schedule potentiated the growth-inhibitory effect of PTXL at its MTD and induced some regression of TSU-PR1 with no obvious deleterious effects on the mice. **Conclusions:** L-744832 could be safely administered over a protracted period of time to mice at doses which were markedly inhibitory to the growth of three human prostate tumor xenografts and in combination with PTXL was also well tolerated and brought about some regression of the TSU-PR1 tumor. Overall, these results suggest that L-744832 could be clin. useful for long-term treatment of early-stage prostate cancer in patients and as an adjunct to cytotoxic therapy for late stages of this disease.

Answer 134:

Bibliographic Information

Development of human lymphoma/leukemia xenograft models in immune-deficient mice for evaluation of potential anticancer agents. Dykes, D. J.; Hollingshead, M. G.; Camalier, R. F.; Waud, W. R.; Mayo, J. G. Southern Research Institute, Birmingham, AL, USA. Contributions to Oncology (1999), 54(Relevance of Tumor Models for Anticancer Drug Development), 295-304. Publisher: S. Karger AG, CODEN: COONEV ISSN: 0250-3220. Journal written in English. CAN 133:217399 AN 2000:242563 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Eleven human lymphoma/leukemia cell lines were assessed as in vivo xenograft models in severe combined immunodeficient (SCID) mice. In prepn. for efficacy evaluations of new antitumor agents, all eleven cell lines have been characterized for sensitivity to known clin. useful agents. The lines included in the study represent a variety of diseases including T-cell, myelogenous, and lymphoblastic leukemias, as well as histiocytic, B-cell and Burkitt's lymphomas. The selected agents for this study were representative of various chem. classes. Addnl., growth studies were performed including comparisons in athymic nude mice. These studies were designed to det. s.c. tumor vol. doubling times, graft success, latent growth periods, and other characteristics necessary to effectively implement and interpret anticancer efficacy evaluations. The various tumor lines used proved to be good models for chemotherapy trials. In the chemotherapy trials, considerable independent chemotherapeutic profiles were obsd. but there were also some similarities among the various histol. types.

Answer 135:

Bibliographic Information

Manumycin enhances the cytotoxic effect of paclitaxel on anaplastic thyroid carcinoma cells. Yeung, Sai-Ching Jim; Xu, Guangpu; Pan, Jingxuan; Christgen, Michelle; Bamiagis, Alexander. Section of General Internal Medicine, M. D. Anderson Cancer Center, University of Texas, Houston, TX, USA. Cancer Research (2000), 60(3), 650-656. Publisher: AACR Subscription Office, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 132:260329 AN 2000:125569 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Despite the current multimodal approach to treatment of anaplastic thyroid cancer (ATC), the prognosis for patients with the disease is poor. New effective therapy for ATC is desperately needed. Thus, the authors investigated the effects of manumycin (a farnesyl:protein-transferase inhibitor), alone and in combination with other drugs frequently used to treat ATC, in six human ATC cell lines: ARO, C643, DRO, Hth-74, KAT-4, and KAT-18. By a formazan dye-based spectrophotometric assay of cell viability and light microscopy, manumycin was shown to decrease the no. of viable cells in all six of the cell lines though to a lesser degree in DRO and C643 cells than in ARO, Hth-74, KAT-4, and KAT-18 cells. In combination, manumycin enhanced the effect of paclitaxel in all six of the cell lines. The mechanism of cell death was investigated by measuring caspase-3 activity, immunoblotting with anti-poly-(ADP-ribose)polymerase (PARP) antibody and electrophoresis of DNA. After an 18-h incubation, manumycin plus paclitaxel caused enhanced activation of caspase-3 activity, cleavage of PARP into Mr 89,000 and 28,000 fragments, and internucleosomal fragmentation of DNA (all of which are characteristic of apoptotic cell death). In contrast, neither manumycin alone, paclitaxel alone, doxorubicin alone, nor doxorubicin plus manumycin produced significant specific cleavage of PARP and internucleosomal DNA fragmentation after 18 h of incubation. The *in vivo* effect and toxicity of combined manumycin and paclitaxel treatments were evaluated in a nude mouse xenograft model using ARO and KAT-4 cells. Drugs were injected *i.p.* on days 1 and 3 of a 7-day cycle for three cycles. Both manumycin (7.5 mg/kg/dose) and paclitaxel (20 mg/kg/dose) had significant inhibitory effects on tumor growth. Combined manumycin and paclitaxel treatments seemed as effective as manumycin against ARO cells and more effective than either manumycin or paclitaxel alone against KAT-4 cells.

No significant morbidity or mortality was caused by the treatments. In conclusion, manumycin can inhibit the growth of ATC both *in vitro* and *in vivo*. Manumycin plus paclitaxel has enhanced cytotoxic effects and increased apoptotic cell death in ATC cells *in vitro* compared with either drug by itself. The combination of manumycin and paclitaxel is also effective *in vivo* with no significant toxicity obsd. The lack of synergy obsd. in this *in vivo* expt. may be due to a ceiling effect, and further experimentation is warranted to ascertain the optimal way to combine these two agents for maximal therapeutic effects.

Answer 136:

Bibliographic Information

Biological and pharmacological characterization of three models of human ovarian carcinoma established in nude mice: use of the CA125 tumor marker to predict antitumor activity. Burbridge, Mike F.; Kraus-Berthier, Laurence; Naze, Monique; Pierre, Alain; Atassi, Ghanem; Guilbaud, Nicolas. Institut de Recherches Servier, Division de Cancerologie Experimentale, Suresnes, Fr. *International Journal of Oncology* (1999), 15(6), 1155-1162. Publisher: International Journal of Oncology, CODEN: IJONES ISSN: 1019-6439. Journal written in English. CAN 132:288373 AN 2000:14351 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

In an attempt to improve the relevance of human tumor xenografts to the clin. situation, we have established 3 models of human ovarian carcinoma (IGROV1, A2780 and NIH:OVCAR-3) in nude mice in which progressive peritoneal carcinomatosis resulted in the death of tumor-bearing animals (median survival times: 32, 40 and 64 days, resp.). Histol. analyses revealed both common and different characteristics in growth patterns and dissemination profiles. In each case, three stages of the disease were defined (early, intermediate and late). The antitumor activities of adriamycin, cisplatin, cyclophosphamide and paclitaxel were then compared when administered at the early stage where small multifocal tumor nodules were detectable in the peritoneal cavity of the animals. Significant antitumor activities of cisplatin and particularly paclitaxel were noted in terms of increase in survival time of the treated mice (T/C values for IGROV1, A2780 and NIH:OVCAR-3 resp.: 152%, 167%, and 187% for cisplatin and 211%, 179% and >283% for paclitaxel), paclitaxel being curative against the NIH:OVCAR-3 xenograft. These results reflect the high efficacy of these two drugs in the clinic in the treatment of ovarian carcinoma. The clin. used CA125 tumor marker, not detectable in healthy mice, was measured in the serum of mice bearing IGROV1 and NIH:OVCAR-3 tumors. CA125 serum levels increased as a function of time and were well correlated to disease progression. Moreover, treatment with cisplatin and paclitaxel led to significant decreases in these levels of between 58% and 100%. This human serum marker could be used to predict early on the efficacy of chemotherapy in these two models. In conclusion, the three exptl. ovarian carcinomas possess several important characteristics of the human disease and may thus be used as a screen to select new antitumor drugs potentially active in this pathol.

Answer 137:

Bibliographic Information**Enhanced antitumor activity of paclitaxel in combination with the anticarcinoma immunoconjugate BR96-doxorubicin.**

Trail, Pamela A.; Willner, David; Bianchi, Albert B.; Henderson, Arris J.; TrailSmith, Mark D.; Girit, Emel; Lasch, Shirley; Hellstrom, Ingegerd; Hellstrom, Karl Erik. Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ, USA. *Clinical Cancer Research* (1999), 5(11), 3632-3638. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 132:260199 AN 1999:809348 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Combined therapy of athymic rats or mice bearing human tumor xenografts with an anticarcinoma immunoconjugate, BR96-doxorubicin, and the cytotoxic drug paclitaxel resulted in a significant increase in antitumor activity over that of either agent alone. Synergistic activity was seen at doses of BR96-doxorubicin that were minimally active as a single agent. A dramatic increase in regression rates was seen when a regimen that combined BR96-doxorubicin and paclitaxel was used to treat both paclitaxel-sensitive and paclitaxel-insensitive carcinomas. Combined therapy resulted in increased antitumor activity against lung, colon, and breast tumors xenografted in athymic mice and large, paclitaxel-insensitive colon tumors xenografted in athymic rats that also express the Lewisy target antigen in normal tissues.

Answer 138:

Bibliographic Information**Determinants of paclitaxel penetration and accumulation in human solid tumor.**

Kuh, Hyo-Jeong; Jang, Seong H.; Wientjes, M. Guillaume; Weaver, Jean R.; Au, Jessie L.-S. College of Pharmacy, The Ohio State University, Columbus, OH, USA. *Journal of Pharmacology and Experimental Therapeutics* (1999), 290(2), 871-880. Publisher: American Society for Pharmacology and Experimental Therapeutics, CODEN: JPETAB ISSN: 0022-3565. Journal written in English. CAN 131:237623 AN 1999:486439 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The present study examd. the determinants of the penetration and accumulation of [3H]paclitaxel (12-12,000 nM) in three-dimensional histocultures of patient tumors and of a human xenograft tumor in mice. The results showed (1) significant and saturable drug accumulation in tumors, (2) extensive drug retention in tumors, and (3) a slower penetration but a more extensive accumulation in the xenograft tumor compared with patient tumors. Drug penetration was not rate-limited by drug diffusion from medium through the matrix supporting the histocultures. The difference in the expression of the mdr1 P-glycoprotein did not fully account for the difference in the drug accumulation in xenograft and patient tumors. Autoradiog. and imaging were used to evaluate the spatial relationship between tumor architecture, tumor cell distribution, and drug distribution as a function of time and initial drug concn. in culture medium. The tumor cell d. and the kinetics of drug-induced apoptosis were also evaluated. The results indicate that a high tumor cell d. is a barrier to paclitaxel penetration and that the apoptotic effect of paclitaxel enhances its penetration in solid tumor. These factors are responsible for the time- and concn.-dependent drug penetration rate, with drug penetration confined to the periphery until apoptosis and redn. of epithelial cell d. occurred at 24 h, after which time paclitaxel penetrated the inner parts of the tumor.

Answer 139:

Bibliographic Information**MTA (LY231514) in combination treatment regimens using human tumor xenografts and the EMT-6 murine mammary carcinoma.**

Teicher, Beverly A.; Alvarez, Enrique; Liu, Pocheng; Lu, Ku; Menon, Krishna; Dempsey, Jack; Schultz, Richard M. Lilly Research Laboratories, Lilly Corporate Center, Eli Lilly and Company, Indianapolis, IN, USA. *Seminars in Oncology* (1999), 26(2, Suppl. 6), 55-62. Publisher: W. B. Saunders Co., CODEN: SOLGAV ISSN: 0093-7754. Journal written in English. CAN 131:125026 AN 1999:290814 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

An important component in the development of a new anticancer drug is an understanding of its potential for inclusion in combination treatment regimens. LY231514, a multitargeted antifolate (MTA), was tested in combination with cisplatin, methotrexate, 5-fluorouracil, paclitaxel, docetaxel, doxorubicin, LY329201 (a glycinamide ribonucleotide formyl-transferase [GARFT] inhibitor), and fractionated radiation therapy in vivo using EMT-6 mammary carcinoma, human HCT 116 colon carcinoma, and human H460 non-small cell lung carcinoma grown as xenografts in nude mice. Isobologram methodol. was used to det. the additivity or synergy of the combination regimens. MTA administered with cisplatin, paclitaxel, docetaxel, or fractionated radiation therapy produced additive to greater than additive tumor response by tumor cell survival assay and tumor growth delay. While an additive tumor response was obsd. when MTA was administered with methotrexate, synergistic tumor responses were seen when MTA was administered with the GARFT inhibitor, LY329201, or with the topoisomerase I inhibitor, irinotecan. MTA was administered in combination with full doses of each anticancer agent studied, with no evidence of increased toxicity resulting from the combination.

Answer 140:

Bibliographic Information

Recent advances in the medicinal chemistry of taxoid anticancer agents. Ojima, Iwao; Kuduk, Scott D.; Chakravarty, Subrata. Department of Chemistry, State University of New York at Stony Brook, Stony Brook, NY, USA. *Advances in Medicinal Chemistry* (1999), 4 69-124. Publisher: JAI Press Inc., CODEN: ADCHEO ISSN: 1067-5698. Journal; General Review written in English. CAN 130:282179 AN 1999:256819 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Taxol (paclitaxel) and Taxotere (docetaxel) are currently considered to be the most promising leads in cancer chemotherapy. Both paclitaxel and docetaxel exhibit significant antitumor activity against various cancers, esp. breast and ovarian cancers, which have not been effectively treated by existing chemotherapeutic drugs. The anticancer activity of these drugs is ascribed to their unique mechanism of action, i.e. causing mitotic arrest in cancer cells leading to apoptosis through inhibition of the depolymn. of microtubules. Although both paclitaxel and docetaxel possess potent antitumor activity, treatment with these drugs often results in a no. of undesired side effects as well as multidrug resistance (MDR). Therefore, it has become essential to develop new anticancer agents with fewer side effects, superior pharmacol. properties, and improved activity against various classes of tumors. This chapter describes the accounts of the authors' research on the chem. of paclitaxel and taxoid anticancer agents at the biomedical interface including: (i) the development of a highly efficient method for the semisynthesis of paclitaxel and a variety of taxoids by means of the β -Lactam Synthone Method (β -LSM), (ii) the structure-activity relationship (SAR) study of taxoids for their activities against human cancer cell lines, (iii) the discovery and development of "second-generation" taxoid anticancer agents that possess exceptional activities against drug-resistant cancer cells expressing the MDR phenotype as well as solid tumors (human cancer xenografts in mice), (iv) the development of fluorine-contg. taxoids as a series of the second-generation taxoid anticancer agents and as excellent probes for the identification of bioactive conformation(s) of paclitaxel and taxoids by means of ^{19}F NMR in soln. as well as in solid state for the microtubule-taxoid complex, (v) the development of radiolabeled photoreactive analogs of paclitaxel for photoaffinity labeling and mapping of the drug-binding domain on microtubules as well as P-glycoprotein that is responsible for MDR, and (vi) an SAR study of taxoids on their activities for inducing NO and tumor necrosis factor (TNF) through macrophage activation, which may be operative as an alternative mechanism of action. Thus, this review covers a wide range of issues assocd. with these powerful taxoid anticancer agents, discussing current status and future prospects.

Answer 141:

Bibliographic Information

Evidence of enhanced in vivo activity using tirapazamine with paclitaxel and paraplatin regimens against the MV-522 human lung cancer xenograft. Weitman, Steven; Mangold, Gina; Marty, Jennifer; Dexter, Daniel; Hilsenbeck, Susan; Rake, James; Juniewicz, Paul; Von Hoff, Daniel. Inst. Drug Development, San Antonio, TX, USA. *Cancer Chemotherapy and Pharmacology*

(1999), 43(5), 402-408. Publisher: Springer-Verlag, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 130:232120 AN 1999:191838 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The in-vivo interaction between tirapazamine with paclitaxel and paraplatin was examd. in 2- and 3-way combination studies using the MV-522 human lung carcinoma xenograft model in female nude mice. The agents were administered as a single i.p. bolus, with tirapazamine being given 3 h prior to paclitaxel, paraplatin, or their combination. Tirapazamine as a single agent was ineffective against this tumor model. A substantial increase in tumor growth inhibition was seen in animals treated with the triple-agent regimen (tirapazamine-paclitaxel-paraplatin) compared to animals treated with double-agent regimens that did not include tirapazamine. The addn. of tirapazamine to paclitaxel-paraplatin therapy resulted in a 50% complete response rate; there were no complete responses seen when only the paclitaxel-paraplatin combination was administered. Time to tumor doubling was also improved by addn. of tirapazamine to the paclitaxel and paraplatin combinations. Tirapazamine did not increase the toxicity of paclitaxel, paraplatin, or their combinations as judged by its min. impact on body wt. and the fact that no toxic deaths were obsd. with tirapazamine-contg. regimens.

Answer 142:

Bibliographic Information

Tyrosine kinase inhibitor emodin suppresses growth of HER-2/neu-overexpressing breast cancer cells in athymic mice and sensitizes these cells to the inhibitory effect of paclitaxel. Zhang, Lisha; Lau, Yiu-Keung; Xia, Weiya; Hortobagyi, Gabriel N.; Hung, Mien-Chie. Section of Molecular Cell Biology, Departments of Cancer Biology, University of Texas M. D., Houston, TX, USA. Clinical Cancer Research (1999), 5(2), 343-353. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 131:309 AN 1999:141857 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Overexpression of the HER-2/neu proto-oncogene, which encodes the tyrosine kinase receptor p185neu, has been obsd. in tumors from breast cancer patients. We demonstrated previously that emodin, a tyrosine kinase inhibitor, suppresses tyrosine kinase activity in HER-2/neu-overexpressing breast cancer cells and preferentially represses transformation phenotypes of these cells in vitro. In the present study, we examd. whether emodin can inhibit the growth of HER-2/neu-overexpressing tumors in mice and whether emodin can sensitize these tumors to paclitaxel, a commonly used chemotherapeutic agent for breast cancer patients. We found that emodin significantly inhibited tumor growth and prolonged survival in mice bearing HER-2/neu-overexpressing human breast cancer cells. Furthermore, the combination of emodin and paclitaxel synergistically inhibited the anchorage-dependent and -independent growth of HER-2/neu-overexpressing breast cancer cells in vitro and synergistically inhibited tumor growth and prolonged survival in athymic mice bearing s.c. xenografts of human tumor cells expressing high levels of p185neu. Both immunohistochem. staining and Western blot anal. showed that emodin decreases tyrosine phosphorylation of HER-2/neu in tumor tissue. Taken together, our results suggest that the tyrosine kinase activity of HER-2/neu is required for tumor growth and chemoresistance and that tyrosine kinase inhibitors such as emodin can inhibit the growth of HER-2/neu-overexpressing tumors in mice and also sensitize these tumors to paclitaxel. The results may have important implications in chemotherapy for HER-2/neu-overexpressing breast tumors.

Answer 143:

Bibliographic Information

Synergistic therapy of breast cancer with Y-90-chimeric L6 and paclitaxel in the xenografted mouse model: development of a clinical protocol. Denardo, Sally J.; Richman, Carol M.; Kukis, David L.; Shen, Sui; Lamborn, Kathleen R.; Miers, Laird A.; Kroger, Linda A.; Perez, Edith A.; Denardo, Gerald L. Section of Radiodiagnosis and Therapy, Division of Hematology/Oncology, University of California Davis Medical Center, Sacramento, CA, USA. Anticancer Research (1998), 18(6A), 4011-4018. Publisher: Anticancer Research, CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 130:278665 AN 1999:68161 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Paclitaxel (Taxol) has demonstrated synergistic enhancement of radioimmunotherapy (RIT) of breast cancer with Y-90 labeled antibody ChL6, in the xenografted mouse model. To det. the optimal sequence and timing of RIT and Taxol for a prospective clin. trial, efficacy and dosimetry in mice, and dosimetry in patients receiving RIT alone, were examd. Mice bearing human breast cancer xenografts (HBT 3477) received i.v. Y-90-DOTA-peptide-ChL6 (260 μ Ci), and i.p. Taxol (300 or 600 μ g) 72, 48, or 24 h prior to RIT, or 6, 24, 48, or 72 h after RIT. Taxol after RIT resulted in cure, CR, or PR of all mice (70/70 tumors) and demonstrated greater therapeutic enhancement ($p = 0.001$) than Taxol before RIT. Mice receiving 600 μ g Taxol 48 h after RIT achieved 88% cure (7/8 tumors). In mice, 57% and 42% of the radiation dose to tumor and marrow, resp., was delivered from 48-336 h after RIT; in patients receiving 90Y-DOTA-peptide-ChL6, the corresponding values were 56% and 22%. Taxol given approx. 48 h after RIT provides coincident peak deposition of Taxol and Y-90 in tumor, and no Taxol in the marrow during the major radiation dose to marrow, resulting in therapeutic enhancement without observable additive toxicity. A clin. trial of low dose Taxol given after RIT to patients with metastatic breast cancer is planned.

Answer 144:

Bibliographic Information

Human ovarian cancer xenografts in nude mice: chemotherapy trials with paclitaxel, cisplatin, vinorelbine and titanocene dichloride. Vellena-Heinsen, C.; Friedrich, M.; Ertan, A. K.; Farnhammer, C.; Schmidt, W. Department Obstetrics Gynecology, University Saarland, Homburg/Saar, Germany. *Anti-Cancer Drugs* (1998), 9(6), 557-563. Publisher: Lippincott-Raven Publishers, CODEN: ANTDEV ISSN: 0959-4973. Journal written in English. CAN 129:225378 AN 1998:496740 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The new cytostatics titanocene dichloride and vinorelbine were compared to cisplatin and paclitaxel using a human ovarian cancer xenografts model. Biopsy material from a native human ovarian carcinoma was expanded and transplanted into 96 nude mice. The animals were divided into six treatment groups: cisplatin 3 \times 4 mg/kg, paclitaxel 5 \times 26 mg/kg, vinorelbine 1 \times 20 mg/kg, titanocene dichloride 3 \times 30 mg/kg, titanocene dichloride 3 \times 40 mg/kg and a control group treated with 0.9% saline. Each expt. was repeated with eight mice in each treatment group. Treatment groups were evaluated in terms of av. daily increase in tumor vol. and av. daily body wt. increase of nude mice based on slopes of least-square regressions performed on individual animals. The slope factors α and β of the body wt. (α) and tumor vol. changes (β) within each group during the course of an expt. were calcd. Both a statistically significant decrease ($p < 0.05$) in the body wt. of the exptl. animals (cisplatin: $\alpha = -0.5163$, vinorelbine: $\alpha = -0.6598$, paclitaxel: $\alpha = -0.6746$, titanocene dichloride 3 \times 30 mg/kg: $\alpha = -0.6259$, titanocene dichloride 3 \times 40 mg/kg: $\alpha = -0.7758$) and a significant redn. ($p < 0.05$) of the increase in tumor vol. (cisplatin: $\beta = 12.049$, vinorelbine: $\beta = 0.504$, paclitaxel: $\beta = -1.636$, titanocene dichloride 3 \times 30 mg/kg: $\beta = -6.212$, titanocene dichloride 3 \times 40 mg/kg: $\beta = -0.685$) was shown in all treated groups compared to the control group ($\alpha = -0.1398$; $\beta = 23.056$). No significant wt. changes were obsd. between the individually treated groups. A statistically significant redn. of the tumor growth occurred under paclitaxel ($\beta = -1.636$), vinorelbine ($\beta = -0.504$) and titanocene dichloride medication 3 \times 40 mg/kg ($\beta = -0.685$), as compared to the group treated with cisplatin ($\beta = 12.049$). We found titanocene dichloride to be as effective as paclitaxel and more effective than cisplatin. Vinorelbine seems to be a very effective antineoplastic agent exhibiting a significant higher cytostatic effect than cisplatin.

Both titanocene dichloride and vinorelbine provide new therapeutic options in women with ovarian carcinoma not responding to std. chemotherapy.

Answer 145:

Bibliographic Information

Efficacy of MGI 114 (6-hydroxymethylacylfulvene, HMAF) against the mdrl/gp170 metastatic MV522 lung carcinoma xenograft. Kelner, M. J.; McMorris, T. C.; Estes, L.; Samson, K. M.; Bagnell, R. D.; Taetle, R. Department of Pathology, University of California San Diego Medical Center, San Diego, CA, USA. *European Journal of Cancer* (1998), 34(6), 908-913. Publisher: Elsevier Science Ltd., CODEN: EJCAEL ISSN: 0959-8049. Journal written in English. CAN 129:170166 AN 1998:400146 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Illudins are a novel class of agents with a chem. structure entirely different from current chemotherapeutic agents. A new semisynthetic deriv., HMAF, is markedly effective in a variety of lung, breast and colon carcinoma xenograft models. This analog, MGI 114, is currently in phase I human clin. trials, and is scheduled for 2 different phase II trials. To det. if MGI 114 could be effective in vivo against mdr tumor cells, we generated an mdr1/gp170-pos. clone of the metastatic MV522 human lung carcinoma line by transfecting a eukaryotic expression vector contg. the cDNA encoding for the human gp170 protein. This MV522/mdr1 daughter line retained the metastatic ability of parental cells. The parental MV522 xenograft is mildly responsive in vivo to mitomycin C and paclitaxel, as evidenced by partial tumor growth inhibition and a small increase in life span, whereas MV522/mdr1 xenografts were resistant to these agents. In contrast to mitomycin C and paclitaxel, MGI 114 produced xenograft tumor regressions in 32 of 32 animals and completely eliminated tumors in more than 30% of MV522/mdr1 tumor-bearing mice. Thus, MGI 114 should be effective in vivo against mdr1/gp170-pos. tumors.

Answer 146:

Bibliographic Information**Effectiveness of cisplatin, paclitaxel, and suramin against human malignant mesothelioma xenografts in athymic nude mice.**

Chahinian, A. Philippe; Mandeli, John P.; Gluck, Harry; Naim, Houshmand; Teirstein, Alvin S.; Holland, James F. Division of Neoplastic Diseases, Mount Sinai School of Medicine, New York, NY, USA. *Journal of Surgical Oncology* (1998), 67(2), 104-111. Publisher: Wiley-Liss, Inc., CODEN: JSONAU ISSN: 0022-4790. Journal written in English. CAN 128:252623 AN 1998:134707 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Malignant mesothelioma has a poor prognosis and is refractory to many agents. The antitumor effectiveness of cisplatin, paclitaxel, and suramin as single agents and in combination was evaluated in vivo against four lines of human pleural malignant mesothelioma xenografts in athymic nude mice, including one epithelial type and three fibrosarcomatous. After growth of tumors occurred by day 54 or 55, mice were randomized in groups of four each to receive either cisplatin 4 mg/kg i.p. weekly x5, or paclitaxel (Taxol) 12.5 mg/kg s.c. daily 5 days/wk for 3 consecutive weeks, or suramin 60 mg/kg i.p. daily x4, vs. controls treated with normal saline. Results: Cisplatin was very effective against one line and also to a lesser degree against another line. Paclitaxel showed antitumor effects similar to cisplatin, being very effective in one line, and also showed good activity in another line. Suramin was basically inactive in all four lines. Following the results obtained with these single agents, it was decided to evaluate the combination of cisplatin and paclitaxel, which resulted in more pronounced antitumor effect in all four cell lines. These results indicate that the combination of cisplatin and paclitaxel is superior to each agent alone in this model, and that it deserves to be evaluated in patients with malignant mesothelioma.

Answer 147:

Bibliographic Information**Anti-tumor efficacy of paclitaxel against human lung cancer xenografts.**

Yamori, Takao; Sato, Shigeo; Chikazawa, Hiroataka; Kadota, Toshihito. Division of Experimental Chemotherapy, Cancer Chemotherapy Center, Japanese Foundation for Cancer Research, Tokyo, Japan. *Japanese Journal of Cancer Research* (1997), 88(12), 1205-1210. Publisher: Japanese Cancer Association, CODEN: JJCREP ISSN: 0910-5050. Journal written in English. CAN 128:149275 AN 1998:13258 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We examd. paclitaxel for anti-tumor activity against human lung cancer xenografts in nude mice and compared its efficacy with that of cisplatin, currently a key drug for lung cancer chemotherapy. Five non-small cell lung cancers (A549, NCI-H23, NCI-H226, NCI-H460 and NCI-H522) and 2 small cell lung cancers (DMS114 and DMS273) were chosen for this study, since these cell lines have

been well characterized as regards in vitro and in vivo drug sensitivity. These cells were exposed to graded concns. of paclitaxel (0.1 to 1000 nM) for 48 h. The 50% growth-inhibitory concns. (GI50) for the cell lines ranged from 4 to 24 nM, which are much lower than the achievable peak plasma concn. of paclitaxel. In the in vivo study, 4 cell lines (A549, NCI-H23, NCI-H460, DMS-273) were grown as s.c. tumor xenografts in nude mice. Paclitaxel was given i.v. as consecutive daily injections for 5 days at the doses of 24 and 12 mg/kg/day. Against every xenograft, paclitaxel produced a statistically significant tumor growth inhibition compared to the saline control. Paclitaxel at 24 mg/kg/day was more effective than cisplatin at 3 mg/kg/day with the same dosing schedule as above, although the toxicity of paclitaxel was similar to or rather lower than that of cisplatin, in terms of body wt. loss. In addn., paclitaxel showed potent activity against 2 other lung cancer xenografts (NCI-H226 and DMS114). Therefore, paclitaxel showed more effective, wider-spectrum anti-tumor activity than cisplatin in this panel of 6 lung cancer xenografts. These findings support the potential utility of paclitaxel in the treatment of human lung cancer.

Answer 148:

Bibliographic Information

Synergistic inhibition of human cancer cell growth by cytotoxic drugs and mixed backbone antisense oligonucleotide targeting protein kinase A. Tortora, Giampaolo; Caputo, Rosa; Damiano, Vincenzo; Bianco, Roberto; Pepe, Stefano; Bianco, A. Raffaele; Jiang, Zhiwei; Agrawal, Sudhir; Ciardiello, Fortunato. Dipartimento di Endocrinologia e Oncologia Molecolare e Clinica, Universita Federico II, Naples, Italy. Proceedings of the National Academy of Sciences of the United States of America (1997), 94(23), 12586-12591. Publisher: National Academy of Sciences, CODEN: PNAS6 ISSN: 0027-8424. Journal written in English. CAN 128:84129 AN 1997:768659 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Protein kinase A type I plays a key role in neoplastic transformation, conveying mitogenic signals of different growth factors and oncogenes. Inhibition of protein kinase A type I by antisense oligonucleotides targeting its R α regulatory subunit results in cancer cell growth inhibition in vitro and in vivo. A novel mixed backbone oligonucleotide HYB 190 and its mismatched control HYB 239 were tested on soft agar growth of several human cancer cell types. HYB 190 demonstrated a dose-dependent inhibition of colony formation in all cell lines whereas the HYB 239 at the same doses caused a modest or no growth inhibition. A noninhibitory dose of each mixed backbone oligonucleotide was used in OVCAR-3 ovarian and GEO colon cancer cells to study whether any cooperative effect may occur between the antisense and a series of cytotoxic drugs acting by different mechanisms. Treatment with HYB 190 resulted in an additive growth inhibitory effect with several cytotoxic drugs when measured by soft agar colony formation. A synergistic growth inhibition, which correlated with increased apoptosis, was obsd. when HYB 190 was added to cancer cells treated with taxanes, platinum-based compds., and topoisomerase II selective drugs. This synergistic effect was also obsd. in breast cancer cells and was obtained with other related drugs such as docetaxel and carboplatin. Combination of HYB 190 and paclitaxel resulted in an accumulation of cells in late S-G2 phases of cell cycle and marked induction of apoptosis. A cooperative effect of HYB 190 and paclitaxel was also obtained in vivo in nude mice bearing human GEO colon cancer xenografts. These results are the first report of a cooperative growth inhibitory effect obtained in a variety of human cancer cell lines by antisense mixed backbone oligonucleotide targeting protein kinase A type I-mediated mitogenic signals and specific cytotoxic drugs.

Answer 149:

Bibliographic Information

Structure-activity relationships of the epothilones and the first in vivo comparison with paclitaxel. Su, Dai-Shi; Balog, Aaron; Meng, Dongfang; Bertinato, Peter; Danishefsky, Samuel J.; Zheng, Yu-Huang; Chou, Ting-Chao; He, Lifeng; Horwitz, Susan B. Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, New York, NY, USA. Angewandte Chemie, International Edition in English (1997), 36(19), 2093-2096. Publisher: Wiley-VCH, CODEN: ACIEAY ISSN: 0570-0833. Journal written in English. CAN 127:358730 AN 1997:714314 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The structure-activity relationships of the epothilones and 18 derivs. and analogs were studied. An in vivo comparison of the chemotherapeutic effect of epothilone B with that of paclitaxel was also studied. The chemotherapeutic effect of daily doses of epothilone B (0.7 mg/kg) and paclitaxel (2 mg/kg) in CB-17 SCID mice bearing drug-resistant human CCRF-CEM/VBL xenografts were T/C = 0.33 and T/C = 0.70, resp.

Answer 150:

Bibliographic Information

p53-independent apoptosis induced by paclitaxel through an indirect mechanism. Lanni, Jennifer S.; Lowe, Scott W.; Licitra, Edward J.; Liu, Jun O.; Jacks, Tyler. Center for Cancer Research and Department of Biology, Howard Hughes Med. Institute, Massachusetts Inst. of Technology, Cambridge, MA, USA. Proceedings of the National Academy of Sciences of the United States of America (1997), 94(18), 9679-9683. Publisher: National Academy of Sciences, CODEN: PNASA6 ISSN: 0027-8424. Journal written in English. CAN 127:257212 AN 1997:581033 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The efficacy of chemotherapeutic agents may be detd. by a no. of different factors, including the genotype of the tumor cell. The p53 tumor suppressor gene frequently is mutated in human tumors, and this may contribute to chemotherapeutic resistance. We tested the requirement for wild-type p53 in the response of tumor cells to treatment with paclitaxel (trade name Taxol), an antineoplastic agent that stabilizes cellular microtubules. Although paclitaxel is broadly effective against human tumor xenografts in mice, including some known to carry p53 mutations, we found that p53-contg. mouse tumor cells were significantly more sensitive to direct treatment with this drug than were p53-deficient tumor cells. In an attempt to reconcile this apparent discrepancy, we examd. the requirement for p53 in the cytotoxic effects of tumor necrosis factor α (TNF- α), a cytokine released from murine macrophages upon paclitaxel treatment. Conditioned medium from paclitaxel-treated macrophages was capable of inducing p53-independent apoptosis when applied to transformed mouse embryonic fibroblasts and was inhibitable by antibodies against TNF- α . Furthermore, in response to direct treatment with TNF- α , both wild-type and p53-deficient tumor cells underwent apoptosis to similar extents and with similar kinetics. Our results suggest that the efficacy of paclitaxel in vivo may be due not only to its microtubule-stabilizing activity, but its ability to activate local release of an apoptosis-inducing cytokine.

Answer 151:

Bibliographic Information

Activity of paclitaxel liposome formulations against human ovarian tumor xenografts. Sharma, Amarnath; Mayhew, Eric; Bolcsak, Lois; Cavanaugh, C.; Harmon, P.; Janoff, Andrew; Bernacki, Ralph J. Dep. Experimental Therapeutics, Roswell Park Cancer Inst., Buffalo, NY, USA. International Journal of Cancer (1997), 71(1), 103-107. Publisher: Wiley-Liss, CODEN: IJCNAA ISSN: 0020-7136. Journal written in English. CAN 126:308719 AN 1997:266102 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Although the current clin. formulation of paclitaxel (Taxol) is an important new anti-cancer agent, it has significant side effects, some of which are related to its formulation in Cremophor/ethanol. Paclitaxel is difficult to formulate for i.v. administration because of its poor aq. soly. Here, the authors report the therapeutic effects of 2 liposome formulations of paclitaxel against human ovarian A121 tumor growing as an s.c. xenograft in athymic nude mice. The liposome formulations used were ETL and TTL, which have 1 or 3 lipid components, resp. TTL was used as a reconstituted lyophilizate or as a stable aq. suspension. ETL was used as a reconstituted lyophilizate only. Both paclitaxel-liposome formulations were much better tolerated than Taxol after i.v. or i.p. administration. The acute reactions seen after Taxol administration did not occur when paclitaxel-liposome formulations were administered. All ETL and TTL prepns. significantly delayed A121 tumor growth similarly to Taxol at equiv. doses and schedules. Based on pharmacokinetic data, it is possible that paclitaxel rapidly dissocs. from ETL or TTL after i.v. administration and distributes in a manner similarly to Taxol. ETL and TTL formulations may be useful clin. not only for eliminating toxic effects of the Cremophor/ethanol vehicle but also for allowing

alterations in route and schedule of drug administration.

Answer 152:

Bibliographic Information

Antitumor activity of paclitaxel against human breast carcinoma xenografts serially transplanted into nude mice. Kubota, Tetsuro; Matsuzaki, Shinjiro Wilson; Hoshiya, Yasunori; Watanabe, Masahiko; Kitajima, Masaki; Asanuma, Fumiki; Yamada, Yoshinori; Koh, Jun-Ichi. Department of Surgery, School of Medicine, Keio University, Tokyo, Japan. *Journal of Surgical Oncology* (1997), 64(2), 115-121. Publisher: Wiley-Liss, CODEN: JSONAU ISSN: 0022-4790. Journal written in English. CAN 126:233249 AN 1997:192505 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Paclitaxel (BMS-181339, Taxol) is a promising agent against previously treated breast cancer. The antitumor activity of paclitaxel was evaluated using five human breast carcinoma xenografts in nude mice. Paclitaxel at 20 mg/kg dissolved in 0.2 mL ethanol/cremophor EL soln. was administered i.p. daily for 5 days. Paclitaxel showed significant antitumor activity against MCF-7 and MX-1, but only limited activity against the other three xenografts (R-27, Br-10, and T-61), suggesting its substantially different antitumor spectrum from conventional antibreast cancer drugs. The different sensitivity of xenografts to paclitaxel was successfully reproduced in vitro using MTT assay, when the cutoff concn. of paclitaxel was 20 µg/mL. Since no significant differences were obsd. in the pharmacokinetics of paclitaxel in sensitive and resistant tumor cell lines, the efficacy of this agent seemed to depend on the sensitivity of tumor cells rather than the intratumoral concn. of agent.

Answer 153:

Bibliographic Information

Continuous cell lines derived from head and neck tumors for mechanistic studies in vitro and in a nude mouse animal model. Knebel, J. W.; Eckardt, A.; Fokas, K.; Aufderheide, M.; Nolte, M. Institute of Experimental Pathology, Hannover Medical School, Hannover, Germany. *International Congress Series* (1996), 1114(Head and Neck Cancer: Advances in Basic Research), 111-119. Publisher: Elsevier, CODEN: EXMDA4 ISSN: 0531-5131. Journal written in English. CAN 126:54594 AN 1997:37414 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

In a series of expts. the authors established and characterized continuous cell lines of different squamous cell carcinomas. The isolated cells grew in epithelial clusters and expressed cytokeratin. Their differentiation pattern and capacity differ to a certain extent. Using these in vitro systems the authors studied the effects of different chemotherapeutic drugs (e.g., MTX, 5-FU, CBDCA and Taxol). Injection of HN SCC-001 cells into nude mice gave rise to serially transplantable s.c. tumors. The cell line as well as the xenotransplants showed the phenotype and genotype characteristics of the primary tumor.

Answer 154:

Bibliographic Information

Effects of amifostine and paclitaxel on growth of human ovarian carcinoma xenografts in the severe combined immune-deficient mouse: Preliminary results. Paine, Gillan D.; Taylor, Charles W.; Lopez, Marialouisa H. A.; Johnson, Cynthia S.; Capizzi, Robert L. College Medicine, University Arizona, Tucson, AZ, USA. *Seminars in Oncology* (1996), 23(4, Suppl. 8), 35-39. Publisher: Saunders, CODEN: SOLGAV ISSN: 0093-7754. Journal written in English. CAN 125:292474 AN 1996:654562 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The effects of amifostine on paclitaxel-induced tumor growth delay using in vivo human ovarian cancer models were evaluated. In some mouse strains amifostine causes hypothermia and/or vasodilation, leading to increased spleen wt. and ascites that can result in exptl. artifacts. We found, however, that amifostine alone at 100 or 200 mg/kg i.p. did not substantially alter body wt., spleen wt., or body temp. in severe combined immune-deficient (scid) mice bearing human 2780 ovarian cancer cells. In a model of minimal tumor burden (tumor cells injected s.c. day 0, drug treatment started day 1) scid mice receiving paclitaxel (27 mg/kg i.p.) with or without amifostine had increased survival at day 76 (83% to 100%) compared with mice that did not receive paclitaxel (17% to 33%). For a model of advanced ovarian cancer, mice received tumor cell injections on day 0 and did not begin drug treatment until tumors were palpable (0.2 × 0.2 cm). Paclitaxel given for five repetitive doses significantly decreased tumor growth ($P = .0001$) in the advanced ovarian cancer model, and these results were the same whether or not mice received amifostine prior to each paclitaxel dose. We conclude that the scid mouse is a good model for evaluating amifostine in vivo, and that there was no evidence of amifostine-induced tumor protection in these scid mouse human ovarian cancer models. In future studies we will evaluate whether the cytoprotective effects of amifostine will allow dose escalation of paclitaxel and result in enhanced antitumor effects.

Answer 155:

Bibliographic Information

Preclinical in vivo efficacy of two 9-dihydrotaxane analogs against human and murine tumors. Alder, J. D.; Jarvis, K. P.; Marsh, K. C.; Klein, L. L.; Clement, J.J. Department 47T, Abbott Laboratories, Abbott Park, IL, USA. *British Journal of Cancer* (1996), 73(5), 560-4. Publisher: Stockton, CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 124:332014 AN 1996:228308 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Two 9-dihydrotaxane analogs were synthesized and tested for in vitro potency and in vivo efficacy against murine and human tumor xenografts in mice. The in vitro potency of 9-dihydrotaxol (9-DH-t) and 10-deacetyl-9-dihydrotaxol (10-DeAc-9-DH-t) was generally less than that of paclitaxel against human and murine tumor cells. However, both analogs were at least 20-fold more sol. than paclitaxel in water. The analogs yielded cure rates $\geq 60\%$ against human MX-1 solid tumor xenografts in mice, compared with a cure rate of 10% for mice treated with paclitaxel. Both of the analogs were more effective than paclitaxel for treatment of murine M109 solid tumor in mice. 10-DeAc-9-DH-t was as effective as paclitaxel against murine B16 ascites tumor, while 9-DH-t was less effective. Both 10-DeAc-9-DH-t and 9-DH-t were demonstrably less toxic than paclitaxel. At equal dosages 9-DH-t produced serum concns. greater than paclitaxel, while 10-DeAc-9-DH-t yielded serum concns. less than paclitaxel. However, the decrease in toxicity of 9-DH-t and 10-DeAc-9-DH-t allowed a 4-fold increase in daily dosage. These two 9-dihydrotaxane analogs yielded favorable preclin. data and demonstrated good potential for further development.

Answer 156:

Bibliographic Information

PAK-104P, a pyridine analog, reverses paclitaxel and doxorubicin resistance in cell lines and nude mice bearing xenografts that overexpress the multidrug resistance protein. Vanhoefer, Udo; Cao, Shousong; Minderman, Hans; Toth, Karoly; Scheper, Rik J.; Slovak, Marilyn L.; Rustum, Youcef M. Dep. Exptl. Therapeutics, Roswell Park Cancer Inst., Buffalo, NY, USA. *Clinical Cancer Research* (1996), 2(2), 369-77. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 124:278265 AN 1996:182914 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Multidrug resistance (MDR) is considered multifactorial and has been assocd. with overexpression of the multidrug resistance protein (MRP). However, effective compds. for reversal of MRP-related MDR are limited. In the present study, the modulatory activity of the novel pyridine analog PAK-104P on MRP-mediated resistance to doxorubicin and paclitaxel was investigated in two

doxorubicin-selected human tumor cell lines [HT1080/DR4 (sarcoma) and HL60/ADR (leukemia)] and compared with the nonimmunosuppressive cyclosporine analog PSC-833. In cell lines HT1080/DR4 (MRP/lung resistance-related protein phenotype) and HL60/ADR (MRP phenotype), doxorubicin resistance was significantly higher (250-fold and 180-fold, resp.) than that to paclitaxel (6-fold and 9-fold, resp.). With noncytotoxic concns. of PAK-104P (1 and 5 μ M), the reversal of doxorubicin resistance was significant but partial in HT1080/DR4 and HL60/ADR cells (dose-modifying factor for 5.0 μ M PAK-104P, 25.0 and 31.2, resp.), whereas complete reversal of paclitaxel resistance was achieved in HL60/ADR cells. In contrast, PSC-833 modulation of doxorubicin and paclitaxel resistance was modest. Cellular drug uptake and retention studies by flow cytometry anal. demonstrated that PAK-104P was effective in restoring cellular doxorubicin concns. in resistant cells to levels comparable to those obtained in parental cells. In athymic nude mice, PAK-104P significantly potentiated the therapeutic efficacy of doxorubicin and paclitaxel against resistant HT1080/DR4 xenografts. Of significance is that the max. tolerated doses of doxorubicin and paclitaxel were administered in combination with PAK-104P, documenting improvement in the therapeutic index of these agents. In addn. to reversing P-glycoprotein-mediated MDR, the pyridine analog PAK-104P provides an example of an effective in vivo modulator of MRP-mediated MDR.

Answer 157:

Bibliographic Information

Comparison of paclitaxel and docetaxel activity on human ovarian carcinoma xenografts. Nicoletti, M.I.; Lucchini, V.; D'Incalci, M.; Giavazzi, R. Ist. Ric. Farmacol. 'Mario Negri', Bergamo, Italy. Eur. J. Cancer, Part A (1994), 30A(5), 691-6. CODEN: EJCTEA Journal written in English. CAN 121:195175 AN 1994:595175 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The antitumor activities of paclitaxel (NSC 125973) and docetaxel (RP 56976, NSC 628503) were evaluated and compared against human ovarian carcinoma (HOC) xenografts in nude mice. Paclitaxel and docetaxel were given i.v. at 16.6-34.5 mg/kg, once every 4 days for 3 consecutive doses, to nude mice with HOC xenografts, transplanted s.c. (HOC18 and HOC22-S) or i.p. (HOC8 and HOC22). Both paclitaxel and docetaxel, at the highest dosage, induced complete tumor regression in 80-100% of the mice bearing HOC22-S and in 67% of the mice bearing HOC18. Both drugs cured 100% of mice bearing early-stage HOC22 tumor in the peritoneal cavity, while treatment at an advanced stage increased the survival time of all the mice. Both induced a 57% cure rate in mice bearing HOC8 in the peritoneal cavity. Paclitaxel and docetaxel were more effective than cisplatin (4 mg/kg, same dose regimen as above) used as a ref. compd. These findings indicate that paclitaxel and docetaxel were highly active on four HOC xenograft models. No significant difference between them was detected in these xenografts.

Answer 158:

Bibliographic Information

Clusterin knockdown using the antisense oligonucleotide OGX-011 re-sensitizes docetaxel-refractory prostate cancer PC-3 cells to chemotherapy. Sowery Richard D; Hadaschik Boris A; So Alan I; Zoubeidi Amina; Fazli Ladan; Hurtado-Coll Antonio; Gleave Martin E The Prostate Centre at Vancouver General Hospital, Vancouver, BC, Canada BJU international (2008), 102(3), 389-97. Journal code: 100886721. E-ISSN:1464-410X. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 18336596 AN 2008518100 In-process for MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

OBJECTIVES: To characterize changes in secretory clusterin (sCLU) expression in prostate cancer cells after treatment with docetaxel and to determine whether sCLU knockdown can re-introduce chemosensitivity in a docetaxel-resistant, androgen-independent human prostate cancer model. **PATIENTS AND METHODS:** A tissue microarray was constructed for 84 radical prostatectomy (RP) specimens from a multicentre Phase II trial of neoadjuvant combined androgen ablation and docetaxel (CUOG-P01a) and assessed for changes in the expression of the cytoprotective chaperone sCLU. The

human prostate cancer cell line PC-3 was repeatedly exposed to docetaxel chemotherapy in vitro, and a docetaxel-resistant cell subline (PC-3dR) was developed and analysed. RESULTS: sCLU levels were significantly higher in RP specimens treated with neoadjuvant combined androgen ablation and docetaxel than in untreated specimens. Similarly, sCLU expression increased 2.5-fold in the newly developed docetaxel-refractory PC-3dR cell line compared with parental PC-3 cells. There was a dose-dependent and sequence-specific decrease in sCLU levels in PC-3dR cells using OGX-011, an antisense oligonucleotide against human sCLU. OGX-011 and small-interference RNA both chemosensitized PC-3dR cells to docetaxel and mitoxantrone in vitro and apoptotic rates in PC-3dR cells were significantly increased when OGX-011 was combined with docetaxel. In vivo, growth of PC-3dR xenografts in nude mice was synergistically inhibited by OGX-011 combined with paclitaxel or mitoxantrone (by 76% and 44% compared with their mismatch controls, respectively). CONCLUSION: The present findings indicate that targeted knockdown of sCLU enhances the effects of cytotoxic chemotherapy in docetaxel-refractory cells, and provide preclinical proof of principle for clinical trials testing OGX-011 in second-line chemotherapy regimens for patients with docetaxel-refractory prostate cancer.

Answer 159:

Bibliographic Information

Relationship between chemotherapy with paclitaxel, cisplatin, vinorelbine and titanocene dichloride and expression of proliferation markers and tumour suppressor gene p53 in human ovarian cancer xenografts in nude mice. Kolberg H C; Villena-Heinsen C; Deml M M; Kraemer S; Diedrich K; Friedrich M Department of Gynecology and Obstetrics, University Clinic of Schleswig-Holstein, Campus Lubeck, Germany European journal of gynaecological oncology (2005), 26(4), 398-402. Journal code: 8100357. ISSN:0392-2936. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 16122187 AN 2005455203 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

PURPOSE: In this study the relationship between therapy with paclitaxel, cisplatin, vinorelbine and titanocene dichloride and of the expression of proliferation markers (ki67 and S-phase fraction) and tumour suppressor gene p53 was analyzed using a human ovarian cancer xenograft model. **METHODS:** Biopsy material from one human ovarian cancer was expanded and transplanted into 102 nude mice. The mice were divided into six groups with different intraperitoneal treatments with paclitaxel, cisplatin, vinorelbine, titanocene dichloride and a control group treated with 0.9% saline solution. After the observation period the tumours were extracted and immunohistochemically stained with monoclonal antibodies against ki67 and p53. The S-phase-fraction was identified by flow cytometry. **RESULTS:** There were no statistically significant differences. Regarding the treatment groups, the vinorelbine-group showed the highest percentage (53.3%) and the titanocene dichloride-3x40 mg/kg-group the lowest percentage (7.1%) of ki67-positive specimens, whereas in the control group 35.7% of the specimens were positively stained for ki67. The results for the expression of p53 were similar. The vinorelbine-group had the highest percentage of p53-positive specimens (60%), in both titanocene-groups no specimen showed a positive staining for p53 and in the control group 7.1% of the specimens were positively stained for p53. The mean S-phase-fraction was 14.48% (SD +/- 3.98), no statistically significant relation between S-phase-fraction and expression of p53 ($p = 0.883$) or of ki67 ($p = 0.351$) could be shown. The change of tumour volume was independent of the results for ki67, p53 and the S-phase-fraction. **CONCLUSION:** Although, as previously published, a significant difference of tumour volume change occurred between the treatment groups, in this study we could not find a relation between this change of tumour volume and the expression of p53 or ki67.

The absolute number of p53- and ki67-positive staining specimens was too small for statistical analysis, therefore the relevance of the differences between the different treatment groups and the control remains unclear. The results for the S-phase-fraction showed no correlation between the change of tumour volume, different treatment protocols or the expression of p53- and ki67. Our findings contribute to the controversy of the influence of chemotherapy on the expression of proliferation markers and p53.

Answer 160:

Bibliographic Information

Enhancement of paclitaxel-mediated cytotoxicity in lung cancer cells by 17-allylamino geldanamycin: in vitro and in vivo analysis. Nguyen D M; Lorang D; Chen G A; Stewart J H 4th; Tabibi E; Schrupp D S Section of Thoracic Oncology and Surgical Metabolism, Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA. Dao_Nguyen@nih.gov The Annals of thoracic surgery (2001), 72(2), 371-8; discussion 378-9. Journal code: 15030100R. ISSN:0003-4975. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 11515869 AN 2001471257 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

BACKGROUND: It has previously been demonstrated that 17-allylamino geldanamycin (17-AAG) enhances paclitaxel-mediated cytotoxicity and downregulates vascular endothelial factor expression in non-small cell lung cancer. This project was designed to evaluate the tumoricidal and antiangiogenic effects of 17-AAG and paclitaxel in H358 non-small cell lung cancer cells grown as xenografts in nude mice. **METHODS:** In vitro cytotoxic drug combination effects were evaluated by (4, 5-dimethylthiazo-2-yl)-2, 5-diphenyl tetrazolium bromide-based proliferation assays. The combinations of 17-AAG and paclitaxel were administered intraperitoneally in nude mice bearing H358 tumor xenografts. Tumor volumes were measured weekly. Tumor expression of erbB2, vascular endothelial cell growth factor, von Willebrand factor (tumor microvasculature), and activated caspase 3 (apoptosis) were determined by immunohistochemistry. **RESULTS:** Five- to 22-fold enhancement of paclitaxel cytotoxicity was achieved by paclitaxel + 17-AAG combination that was paralleled with marked induction of apoptosis. This combination treatment profoundly suppressed tumor growth and significantly prolonged survival of mice bearing H358 xenografts. Immunohistochemical staining of tumor tissues indicated profound reduction of vascular endothelial cell growth factor expression associated with reduction of microvasculature in tumors treated with 17-AAG. Apoptotic cells were more abundant in tumors treated with 17-AAG + paclitaxel than in those treated with 17-AAG or paclitaxel alone. **CONCLUSIONS:** Concurrent exposure of H358 cells to 17-AAG and paclitaxel resulted in supraadditive growth inhibition effects in vitro and in vivo. Analysis of molecular markers of tumor tissues indicated that therapeutic drug levels could be achieved with this chemotherapy regimen leading to significant biological responses.

Moreover, 17-AAG-mediated suppression of vascular endothelial cell growth factor production by tumor cells may contribute to the antitumor effects of this drug combination in vivo.

Answer 161:

Bibliographic Information

Comparative antitumor efficacy of docetaxel and paclitaxel in nude mice bearing human tumor xenografts that overexpress the multidrug resistance protein (MRP). Comment in: Ann Oncol. 1997 Dec;8(12):1183-4. PubMed ID: 9496382 Vanhoefer U; Cao S; Harstrick A; Seeber S; Rustum Y M Department of Internal Medicine (Cancer Research), West German Cancer Center, University of Essen, Germany Annals of oncology : official journal of the European Society for Medical Oncology / ESMO (1997), 8(12), 1221-8. Journal code: 9007735. ISSN:0923-7534. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 9496387 AN 1998157472 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

BACKGROUND: Multidrug resistance has been associated with expression of the multidrug resistance protein (MRP). Recently, MRP-expression has been detected in human tumor samples of patients with breast cancer and non-small-cell lung cancer. Since taxoids are the most active drugs in the treatment of both tumor entities, the antitumor efficacies of paclitaxel and docetaxel were compared in nude mice bearing human tumor xenografts that express MRP. **MATERIALS AND METHODS:** Athymic nude mice (nu/nu) bearing tumor xenografts of parental human sarcoma HT1080 or MRP-expressing HT1080/DR4 cells (as confirmed by Northern blot analysis) were treated with the maximum tolerated doses (MTD) of doxorubicin ([Dx] 10 mg/kg i.v. push), paclitaxel ([PC] 50 mg/kg three-hour i.v. infusion), or docetaxel ([DC] 40 mg/kg three-hour i.v. infusion). In vitro, the activity of doxorubicin, paclitaxel and docetaxel was evaluated by

the sulphorhodamine B (SRB) assay using the pyridine analogue PAK-104P (5 microM), a potent inhibitor of MRP-function. RESULTS: At their MTDs both taxoids showed significant activity against MRP-negative HT1080 xenografts with response rates of 80% (40% CR) for PC and 100% (60% CR) for DC. In contrast, DC was significantly more active than PC in nude mice bearing doxorubicin resistant MRP-expressing HT1080/DR4 tumor xenografts (overall response rates: 100% (60% CR) for DC; 10% (0% CR) for PC; 0% for Dx). Since treatment of mice with the MTD of PC or DC yielded similar overall toxicity (maximum weight loss for HT1080: PC 8.6 +/- 2.2%; DC 7.5 +/- 2.2% and for HT1080/DR4: PC 11.6 +/- 3.0%; DC 7.6 +/- 1.8%, respectively), these results demonstrate the increase in the therapeutic index for docetaxel against MRP-expressing tumors. In vitro, HT1080/DR4 cells were 270-fold, 6.4-fold and 2.8-fold more resistant than parental cells to doxorubicin, PC and DC, respectively. Pyridine analogue PAK-104P completely restored drug sensitivity to PC and DC, while no effect of PAK-104P on parental HT1080 cells was observed.

CONCLUSIONS: Both taxoids, when given at their MTDs, showed significant efficacy against parental HT1080 tumor xenografts. However, docetaxel at its MTD was significantly more active against MRP-expressing tumor xenografts than paclitaxel. Furthermore, in vitro resistance of HT1080/DR4 cells was higher for PC (6.4-fold) than for DC (2.8-fold). Since PAK-104P completely restored sensitivity to both taxoids, the observed resistance appears to be related to MRP. These data suggest, that docetaxel is not as readily transported by MRP as paclitaxel leading to an increased therapeutic ratio in MRP-expressing tumors in vivo. Therefore, docetaxel may have therapeutic advantages in the clinical treatment of MRP-expressing tumors.

Answer 162:

Bibliographic Information

Scheduling of chemotherapy and radiotherapy in locally advanced non-small cell lung cancer. Bishop J F
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Abstract

In scheduling chemotherapy and radiotherapy for locally advanced non-small cell lung cancer (NSCLC), chemotherapy can be given pre-radiotherapy or concurrently as a single agent or in combination. Optimal scheduling has yet to be established. Optimal pre-radiotherapy for NSCLC requires further development but cisplatin with vinblastine, vindesine, etoposide or navelbine appear the best currently available. A number of new drugs show potential for enhancing radiation effects. Concurrent chemotherapy and radiotherapy has been tested in a number of experimental tumours in cell culture. In these systems cisplatin, carboplatin, 5-fluorouracil, mitomycin-C and other agents appear to improve cell kill compared to chemotherapy alone. Mouse xenograft models allow the study of various concurrent drug and radiation schedules including the effect of radiation with cisplatin, carboplatin, paclitaxel and gemcitabine. In these systems, cisplatin in divided doses shows optimal enhancement with fractionated radiotherapy. There are a number of drug candidates for concurrent chemotherapy and radiotherapy programs. Clinical studies in head and neck cancer, esophageal cancer, small cell lung cancer and NSCLC show promising results with concurrent chemotherapy and radiotherapy. Cisplatin given daily with radiotherapy improved survival in NSCLC compared to cisplatin given weekly with radiotherapy or to radiotherapy alone. To study the toxicity of radiation and concurrent carboplatin, we have studied 170 patients with unresectable locally advanced NSCLC in a 4-arm randomized trial. An analysis of the first 100 patients entered revealed significantly more neutropenia ($P < 0.0001$) and thrombocytopenia ($P < 0.004$) with the combined modality arms. Esophagitis was worse on all three experimental arms but was significantly more prolonged with accelerated radiotherapy arms.(ABSTRACT TRUNCATED AT 250 WORDS)