

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

Natural BH3 mimetic (-)-gossypol chemosensitizes human prostate cancer via Bcl-xL inhibition accompanied by increase of Puma and Noxa. Meng, Yang; Tang, Wenhua; Dai, Yao; Wu, Xiaoqing; Liu, Meilan; Ji, Qing; Ji, Min; Pienta, Kenneth; Lawrence, Theodore; Xu, Liang. Department of Radiation Oncology, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA. *Molecular Cancer Therapeutics* (2008), 7(7), 2192-2202. Publisher: American Association for Cancer Research, CODEN: MCTOCF ISSN: 1535-7163. Journal written in English. AN 2008:874405 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Antiapoptotic members of the Bcl-2 family proteins are overexpressed in prostate cancer and are promising mol. targets for modulating chemoresistance of prostate cancer. (-)-Gossypol, a natural BH3 mimetic, is a small-mol. inhibitor of Bcl-2/Bcl-xL/Mcl-1 currently in phase II clin. trials as an adjuvant therapy for human prostate cancer. Our objective is to examine the chemosensitization potential of (-)-gossypol in prostate cancer and its mol. mechanisms of action. (-)-Gossypol inhibited cell growth and induced apoptosis through mitochondria pathway in human prostate cancer PC-3 cells and synergistically enhanced the antitumor activity of docetaxel both in vitro and in vivo in PC-3 xenograft model in nude mouse. (-)-Gossypol blocked the interactions of Bcl-xL with Bax or Bad in cancer cells by fluorescence resonance energy transfer assay and overcame the Bcl-xL protection of FL5.12 model cells on interleukin-3 withdrawal. Western blot and real-time PCR studies showed that a dose-dependent increase of the proapoptotic BH3-only proteins Noxa and Puma contributed to the cell death induced by (-)-gossypol and to the synergistic effects of (-)-gossypol and docetaxel. The small interfering RNA knockdown studies showed that Noxa and Puma are required in the (-)-gossypol-induced cell death. Taken together, these data suggest that (-)-gossypol exerts its antitumor activity through inhibition of the antiapoptotic protein Bcl-xL accompanied by an increase of proapoptotic Noxa and Puma. (-)-Gossypol significantly enhances the antitumor activity of chemotherapy in vitro and in vivo, representing a promising new regime for the treatment of human hormone-refractory prostate cancer with Bcl-2/Bcl-xL/Mcl-1 overexpression. [Mol Cancer Ther 2008;7(7):2192-202].

Answer 3:

Bibliographic Information

RAD001 (Everolimus) inhibits growth of prostate cancer in the bone and the inhibitory effects are increased by combination with docetaxel and zoledronic acid. Morgan, Todd M.; Pitts, Tiffany E. M.; Gross, Ted S.; Poliachik, Sandra L.; Vessella, Robert L.; Corey, Eva. Department of Urology, University of Washington School of Medicine, Seattle, WA, USA. Prostate (Hoboken, NJ, United States) (2008), 68(8), 861-871. Publisher: Wiley-Liss, Inc., CODEN: PRSTDS ISSN: 0270-4137. Journal written in English. CAN 149:118999 AN 2008:746751 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

INTRODUCTION: mTOR activity is increased in advanced prostate cancer (CaP) as a result of a high rate of PTEN mutations. RAD001 (Everolimus) is a new orally available mTOR inhibitor. The objective of our study was to evaluate the effects of RAD001 on the growth of CaP in the bone, both alone and in combination with docetaxel and zoledronic acid. **METHODS:** C4-2 CaP cells were injected into tibia of mice and the animals were treated with RAD001, docetaxel, and zoledronic acid alone or in combination. Histomorphometrical anal., serum PSA measurements, bone mineral d. (BMD), and μ CT were used to det. the effects of treatment on tumor and bone. **RESULTS:** All three agents alone decreased tumor vol., and RAD001 and docetaxel also decreased levels of serum PSA by 68% and 65%, resp. (both $P < 0.01$). Combinations of the agents were more effective in decreasing tumor vol. than single agents. Three-drug treatment showed the greatest effect: 64% inhibition vs. control ($P < 0.01$). Treatment with RAD001 interfered with the wt. loss assocd. with growth of this tumor in the bone (non-RAD001 groups: 4.0% decrease in body wt., $P = 0.0014$; RAD001 groups: increase of 3.6% in body wt., $P = 0.0037$). **CONCLUSIONS:** RAD001 inhibited growth of C4-2 cells in bone, an effect augmented by addn. of docetaxel and zoledronic acid. Moreover RAD001 had a significant impact on maintenance of body wt. RAD001 may hold promise for its effects on both metastatic CaP and the important syndrome of tumor cachexia.

Answer 4:

Bibliographic Information

Tumor, tissue, and plasma pharmacokinetic studies and antitumor response studies of docetaxel in combination with 9-nitrocampthecin in mice bearing SKOV-3 human ovarian xenografts. Zamboni, William C.; Strychor, Sandra; Joseph, Erin; Parise, Robert A.; Egorin, Merrill J.; Eiseman, Julie L. Department of Pharmaceutical Sciences, School of Pharmacy, University of Pittsburgh, Pittsburgh, PA, USA. Cancer Chemotherapy and Pharmacology (2008), 62(3), 417-426. Publisher: Springer, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. AN 2008:723976 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose We evaluated the antitumor activity of two different schedules of docetaxel and 9-nitrocampthecin (9NC) in mice bearing human SKOV-3 ovarian carcinoma xenografts and evaluated the plasma, tissue, and tumor disposition of each agent alone and in combination. **Exptl. design** The following treatment groups were evaluated: (1) docetaxel 10 mg/kg IV on days 0 and 7; (2) 9NC 0.67 mg/kg PO qdx5dx2wk; (3) 9NC 0.67 mg/kg PO qdx5dx2wk in combination with docetaxel 10 mg/kg IV on days 0 and 7; and (4) 9NC 0.67 mg/kg PO qdx5dx2wk in combination with docetaxel 10 mg/kg IV on days 4 and 11; (5) vehicle controls for each agent; and (6) no treatment controls. **Results** All treatment regimens produced significant antitumor activity as compared with control groups ($P < 0.05$). Docetaxel administered on days 0 and 7 or on days 4 and 11 in combination with 9NC resulted in similar antitumor activity ($P > 0.05$). High docetaxel concns. in tumor were maintained at late time points as compared with plasma and tissues with the retention of docetaxel at 24 h being 132-fold and 15-fold higher in tumor than in plasma and liver, resp. After administration of 9NC alone, the ratio of the 9-aminocampthecin (9AC) area under the concn. vs. time curve (AUC) to 9NC AUC in plasma and tumor was 0.15 and 1.34, resp. **Conclusions** The combination of docetaxel and 9NC was effective against SKOV-3 xenografts. The lack of a difference in sequence-dependent antitumor activity may reflect the sensitivity of the SKOV-3 xenograft to 9NC. The factors assocd. with tumor-specific retention of docetaxel and the ratio of 9NC to 9AC in tumors is unknown.

Answer 5:

Bibliographic Information

Combined antitumor activity of cucurbitacin B and docetaxel in laryngeal cancer. Liu, Tingyan; Zhang, Meixia; Zhang, Hongliang; Sun, Chunyan; Yang, Xiaolin; Deng, Yihui; Ji, Wenyue. Department of Otolaryngology, Second Affiliated Hospital, China Medical University, Shenyang, Liaoning, Peop. Rep. China. *European Journal of Pharmacology* (2008), 587(1-3), 78-84. Publisher: Elsevier B.V., CODEN: EJPHAZ ISSN: 0014-2999. Journal written in English. CAN 149:95122 AN 2008:655718 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Combination therapy with multiple drugs is a common practice in the treatment of cancer. The promising clin. activity of docetaxel has promoted considerable interest in combining it with other antitumor agents. To det. whether cucurbitacin B can enhance chemosensitivity to docetaxel in laryngeal cancer, in the present study, we investigated the combined antitumor effect of cucurbitacin B with docetaxel on Hep-2, a human laryngeal cancer cell line. We treated Hep-2 cells with cucurbitacin B alone or in combination with docetaxel and evaluated cell growth, cell cycle distribution, and apoptosis using MTT (3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide) assay, flow cytometry, and fluorescent microscopy. Our results showed that, in comparison with single agent treatment, the combination of cucurbitacin B and docetaxel produced greater efficacy in growth inhibition, cell cycle arrest at G2/M phase, and apoptosis induction. Measuring the modulation of regulators in the cell cycle, apoptosis and signal transductions by Western blot anal. showed that the combination effect of cucurbitacin B and docetaxel was due to suppress the expression of p-STAT3 (signal transducers and activators of transcription 3), Bcl-2, and cyclin B1. Moreover, our in vivo studies were reproduced in a mouse xenograft model, where, the combination of cucurbitacin B with docetaxel synergistically inhibited tumor growth. Together, this investigation suggests that cucurbitacin B combined with docetaxel may be a feasible strategy to enhance the effects of chemotherapy in patients with laryngeal cancer.

Answer 6:

Bibliographic Information

Circulating endothelial cells as a therapeutic marker for thalidomide in combined therapy with chemotherapy drugs in a human prostate cancer model. Li, Haiqing; Raia, Valentina; Bertolini, Francesco; Price, Douglas K.; Figg, William D. Molecular Pharmacology Section, Medical Oncology Branch, Center for Cancer Research, National Cancer Institute, NIH, Bethesda, MD, USA. *BJU International* (2008), 101(7), 884-888. Publisher: Blackwell Publishing Ltd., CODEN: BJINFO ISSN: 1464-4096. Journal written in English. CAN 149:44576 AN 2008:537069 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

OBJECTIVE: To investigate how thalidomide confers its survival benefit in prostate cancer, by assessing its effect on circulating endothelial cells (CECs) and progenitors (CEPs) in a combined therapy of thalidomide and chemotherapy drugs in a human prostate cancer xenograft model, as in clin. trials patients treated with both thalidomide and docetaxel had a >50% decrease in prostate-specific antigen (PSA) levels and longer median overall survival than those treated with docetaxel monotherapy. **MATERIALS AND METHODS:** A human prostate cancer xenograft model was used to evaluate the effect of either thalidomide, docetaxel or a combination of the two drugs on circulating ECs. Drug treatment was continued for 17 days, and tumors were measured two or three times a week. Blood samples were taken at three different time points: before the treatments, 4 days and 17 days into the treatments, and CECs and CEPs were measured by flow cytometry anal. **RESULTS:** There was an increased level of apoptotic/dead CECs shortly after the i.v. injection of docetaxel, and the addn. of thalidomide further increased the apoptotic/dead CEC level, showing that thalidomide enhances the cytotoxicity of docetaxel against tumor vascular ECs. **CONCLUSION:** Thalidomide increased the apoptotic/dead CEC level and enhanced the cytotoxicity of docetaxel against tumor vascular ECs, confirming its antiangiogenic property in vivo in combined anticancer treatments. In addn., there was a correlation between the increased apoptotic/dead CEC levels early in the treatment and antitumor efficacy later, suggesting that the apoptotic/dead CEC level could be used as a marker, at an early stage, to predict tumor response to antiangiogenic therapies.

Answer 7:

Bibliographic Information

Antitumor mechanisms of systemically administered epidermal growth factor receptor antisense oligonucleotides in combination with docetaxel in squamous cell carcinoma of the head and neck. Thomas, Sufi Mary; Ogagan, Michelene Jeter; Freilino, Maria L.; Strychor, Sandy; Walsh, Dustin R.; Gooding, William E.; Grandis, Jennifer Rubin; Zamboni, William C. Department of Otolaryngology, University of Pittsburgh and the University of Pittsburgh Cancer Institute, Pittsburgh, PA, USA. *Molecular Pharmacology* (2008), 73(3), 627-638. Publisher: American Society for Pharmacology and Experimental Therapeutics, CODEN: MOPMA3 ISSN: 0026-895X. Journal written in English. CAN 148:440518 AN 2008:323300 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Squamous cell carcinoma of the head and neck (SCCHN) is one of the most common malignancies worldwide, with low 5-yr survival rates. Current strategies that block epidermal growth factor receptor (EGFR) have limited effects when administered as single agents. Targeting EGFR via intratumoral administration of phosphorothioate-modified antisense oligonucleotides has antitumor efficacy in xenograft models of SCCHN. Because intratumoral delivery of therapeutic agents has limited clin. application, the present study was undertaken to examine the therapeutic mechanisms of systemically delivered phosphorothioate-modified EGFR antisense oligonucleotides alone, or in combination with docetaxel, in a SCCHN xenograft model. EGFR antisense oligonucleotides were administered at 5 mg/kg i.p. daily in athymic mice bearing 1483 human SCCHN xenografts alone or in combination with docetaxel at 2.5 mg/kg i.p. once a week for 4 wk. Administration of EGFR antisense oligonucleotides in combination with docetaxel improved antitumor efficacy and resulted in lower expression levels of EGFR, fewer proliferating cells, and more apoptotic cells in the tumors compared with controls. Systemic administration of phosphorothioated EGFR antisense oligonucleotides for 30 days increased the retention of docetaxel in the tumor by approx. 4-fold compared with tumors treated with docetaxel alone or docetaxel and EGFR sense oligonucleotides ($P < 0.05$). Combination of EGFR antisense oligonucleotides with low doses of docetaxel has antitumor efficacy, and it may be an effective treatment strategy for SCCHN.

Answer 8:

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 HRPCa 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 HRPCa 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 9:

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 10:

Bibliographic Information

Supra-additive antitumor effect of sunitinib malate (SU11248, Sutent) combined with docetaxel. A new therapeutic perspective in hormone refractory prostate cancer. Guerin, O.; Formento, P.; Lo Nigro, C.; Hofman, P.; Fischel, J. L.; Etienne-Grimaldi, M. C.; Merlano, M.; Ferrero, J. M.; Milano, G. Nice General Hospital, Nice, Fr. Journal of Cancer Research and Clinical Oncology (2008), 134(1), 51-57. Publisher: Springer, CODEN: JCROD7 ISSN: 0171-5216. Journal written in English. CAN 148:440375 AN 2007:1268849 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: Physiol. and mol. findings indicate over-expression of HER proteins and dysregulation of neo-angiogenesis during progression of advanced prostate cancer. The aim of this study was to test a novel rational therapeutic approach by combining docetaxel with an EGFR-targeting agent (cetuximab) and with an anti-angiogenic agent (sunitinib, SUTENT). **Methods:** Mice bearing well-established PC3 prostate tumors (mean tumor vol./treatment group .apprx.250 mm³) were treated every week with vehicle alone (controls), sunitinib (40 mg/kg/day, 5 days/wk for 3 wk, 0.2 mL p.o.), cetuximab (0.2 mg/kg/day, 5 days/wk for 3 wk, 0.2 mL i.p.) and docetaxel (10 mg/kg, 1 day/wk for 3 wk, 0.2 mL i.p.). **Results:** Each drug, administered as a single-agent, demonstrated comparable and moderate effects on tumor growth with approx. 50 % inhibition at the end of the 3-wk dosing schedule. Computed combination ratio (CR) values for tumor growth detd. on days 61, 68 and 75 after cell implantation indicated supra-additive effects for the sunitinib-docetaxel (1.53, 1.15 and 1.47, resp.) and sunitinib-cetuximab combinations (1.2, 1.32 and 1.14, resp.), and suggested additive effects only for the sunitinib-cetuximab-docetaxel combination (CR = 1). The effects on tumor growth were accompanied by a parallel diminution in tumor cell proliferation (Ki 67) and tumor vascularization (von Willebrandt factor). There were significantly higher pro-apoptotic effects (caspase-3 cleavage) obsd. for the sunitinib-docetaxel and sunitinib-docetaxel-cetuximab as compared to the other conditions. **Conclusion:** The supra-additive anti-tumor effect obsd. with the sunitinib-docetaxel combination might support innovative strategies in the management of advanced prostate cancer.

Answer 11:

Bibliographic Information

MRI-measured water mobility increases in response to chemotherapy via multiple cell-death mechanisms. Morse, David L.; Galons, Jean-Philippe; Payne, Claire M.; Jennings, Dominique L.; Day, Sam; Xia, Guowei; Gillies, Robert J. Arizona Cancer Center, The University of Arizona, Tucson, AZ, USA. *NMR in Biomedicine* (2007), 20(6), 602-614. Publisher: John Wiley & Sons Ltd., CODEN: NMRBEF ISSN: 0952-3480. Journal written in English. CAN 148:112459 AN 2007:1199221 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Numerous pre-clin. and clin. reports have demonstrated that the MRI-measured apparent diffusion coeff. of water (ADC) increases early in the response to a wide variety of anti-cancer therapies. It has been proposed that this increase in ADC generally results from an increase in the tumor extracellular vol. fraction leading to a greater degree of unrestricted water motion. Furthermore, an increase in extracellular vol. has been ascribed to the cell shrinkage that occurs early in the process of programmed cell death. However, other modes of death can be initiated soon after beginning therapy. These other modes of death include mitotic catastrophe and necrosis, and may also involve changes in the fraction of water with unrestricted motion. This work examines whether MRI-measured ADC is altered in response to therapies that induce cell death via non-apoptotic mechanisms and correlates ADC changes with cell death modalities regionally within the tumor. Apoptotic responses were limited to the tumor periphery in apoptosis-proficient tumors. Apoptosis was not obsd. in deficient tumors. Mitotic catastrophe was obsd. after treatment at the periphery and deeper into the tumor. Necrosis was the predominant response in the center of the tumor. ADC changes were moderate in the periphery and larger in the center. The results indicate that early and significant changes in ADC can occur in concert with mitotic catastrophe and lytic necrosis in the absence of apoptosis. Hence, changes in ADC may be a generalized measure of cytotoxic response to chemotherapy.

Answer 12:

Bibliographic Information

Therapeutic integration of c-myc and bcl-2 antisense molecules with docetaxel in a preclinical model of hormone-refractory prostate cancer. Leonetti, Carlo; Biroccio, Annamaria; D'Angelo, Carmen; Semple, Sean C.; Scarsella, Marco; Zupi, Gabriella. Experimental Chemotherapy Laboratory, Regina Elena Cancer Institute, Rome, Italy. Prostate (Hoboken, NJ, United States) (2007), 67(13), 1475-1485. Publisher: Wiley-Liss, Inc., CODEN: PRSTDS ISSN: 0270-4137. Journal written in English. CAN 148:544 AN 2007:1124769 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: The response of hormone-refractory prostate cancer (HRPC) to chemotherapy remains modest, necessitating the search for new forms of treatment to improve the prognosis. Since an increased expression of oncogenes, including c-myc and bcl-2, accompanies the transition to HRPC, we evaluated whether the concomitant downregulation of these oncogenes by antisense strategy sensitized HRPC to chemotherapy. Methods: PC-3 prostate cancer cells were exposed in vitro to c-myc (INX-6295) and bcl-2 (G3139) antisense oligodeoxynucleotides (ODNs) and docetaxel given alone or in combination. Therapeutic efficacy of the different treatments was also evaluated in xenografts. Results: We show that the triple combination of drugs given in the sequence G3139/docetaxel/INX-6295 was the most active in reducing the survival of PC-3. Likewise, the combination triggered apoptosis in more than 80% of cells. A marked tumor wt. inhibition was obsd. in PC-3 xenografts after G3139/docetaxel/INX-6295 treatment, with a complete tumor regression being noted in half the mice. A 111% overall increase in life survival and a complete cure in two out of eight mice was also reported. This treatment remained effective even when started at a very late stage of tumor growth producing about 80% tumor wt. inhibition (TWI), with tumor regression being maintained for 1 mo. Finally, the antitumor effect resulted in a significant increase (70%) in mice survival. Conclusions: These data indicate that the combined targeting of genes involved in uncontrolled proliferation and evasion of apoptosis renders HRPC responsive to chemotherapy making this treatment a promising antineoplastic strategy.

Answer 13:

Bibliographic Information

Response of choline metabolites to docetaxel therapy is quantified in vivo by localized 31P MRS of human breast cancer xenografts and in vitro by high-resolution 31P NMR spectroscopy of cell extracts. Morse, David L.; Raghunand, Natarajan; Sadarangani, Pooja; Murthi, Shiva; Job, Constantin; Day, Sam; Howison, Christine; Gillies, Robert J. BIO5 Institute, Arizona Cancer Center, The University of Arizona, Tucson, AZ, USA. *Magnetic Resonance in Medicine* (2007), 58(2), 270-280. Publisher: Wiley-Liss, Inc., CODEN: MRMEEN ISSN: 0740-3194. Journal written in English. CAN 147:440099 AN 2007:990698 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Choline-contg. compds. (CCCs) are elevated in breast cancer, and detected in vivo by the ¹H MRS total choline (tCho) resonance (3.25 ppm) and the ³¹P MRS phosphomonoester (PME) resonance (3.8 ppm). Both the tCho and PME resonances decrease early after initiation of successful therapy. The single major component of these composite resonances, phosphocholine (PCho), also responds to therapy by decreasing. The ability to resolve and quantify PCho in vivo would thus increase the sensitivity of this biomarker for early detection of therapeutic response. Herein, the in vivo resoln. and quantification of PCho is reported in human mouse xenograft tumors of the human breast cancer cell lines MCF-7 and MDA-mb-231. Significant decreases in tumor PCho are obsd. within 2 to 4 d posttreatment with the antimicrotubule drug, docetaxel. To det. whether these decreases are a general tumor response or an intracellular metabolic response, high-resoln. NMR spectroscopy was performed on exts. of cells treated with docetaxel. Significant decreases in intracellular PCho and increases in glycerophosphocholine (GPC) were obsd. These decreases are coincident with other tumor and cellular responses such as tumor growth delay (TGD), cell-cycle arrest, and modes of cell death such as mitotic catastrophe, necrosis, and apoptosis, with mitotic catastrophe predominating.

Answer 14:

Bibliographic Information

Bevacizumab plus 5-fluorouracil induce growth suppression in the CWR-22 and CWR-22R prostate cancer xenografts. Hung, Huynh. Laboratory of Molecular Endocrinology, Division of Cellular and Molecular Research, National Cancer Centre, Singapore, Singapore. *Molecular Cancer Therapeutics* (2007), 6(8), 2149-2157. Publisher: American Association for Cancer Research, CODEN: MCTOCF ISSN: 1535-7163. Journal written in English. CAN 147:268498 AN 2007:905665 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Prostate cancer is the most common malignancy in men. Although patients with metastatic prostate cancer can benefit from androgen ablation, most of them will die of prostate cancer progression to an androgen-refractory state. In the present study, the effects of docetaxel, bevacizumab, 5-fluorouracil (5-FU), bevacizumab plus docetaxel, and bevacizumab plus 5-FU on the growth of human CWR-22 (androgen-dependent) and CWR-22R (androgen-independent) prostate carcinoma xenografts were investigated. We report that i.p. administration of 10 mg/kg docetaxel at 1-wk interval, 5 mg/kg/ bevacizumab once every 2 wk, or 12.5 mg/kg 5-FU, bevacizumab/docetaxel, or bevacizumab/5-FU weekly to severe combined immunodeficient mice bearing prostate cancer xenografts (12 mice per treatment group) for 21 days resulted in 22.5±8%, 23±7%, 31±8%, 22±6%, and 81±5% growth inhibition, resp. Greatest growth suppression was obsd. in bevacizumab/5-FU treatment. Bevacizumab/5-FU-induced growth suppression was assocd. with redn. in microvessel d., inhibition of cell proliferation; up-regulation of phosphatase and tensin homolog, p21Cip1/Waf1, p16INK4a, and p27Kip1; hypophosphorylation of retinoblastoma protein; and inhibition of Akt/mammalian target of rapamycin pathway. Our data indicate that bevacizumab/5-FU effectively inhibits angiogenesis and cell cycle progression and suggest that bevacizumab/5-FU may represent an alternative treatment for patients with prostate cancer.

Answer 15:

Bibliographic Information

Predicting the active doses in humans from animal studies: a novel approach in oncology. Rocchetti, M.; Simeoni, M.; Pesenti, E.; De Nicolao, G.; Poggesi, I. Preclinical Development, Nerviano Medical Sciences, Nerviano, Italy. *European Journal of Cancer* (2007), 43(12), 1862-1868. Publisher: Elsevier Ltd., CODEN: EJCAEL ISSN: 0959-8049. Journal written in English. CAN 147:461695 AN 2007:895461 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The success rate of clin. drug development is significantly lower in oncol. than in other therapeutic areas. Predicting the activity of new compds. in humans from preclin. data could substantially reduce the no. of failures. A novel approach for predicting the expected active doses in humans from the first animal studies is presented here. The method relies upon a PK/PD model of tumor growth inhibition in xenografts, which provides parameters describing the potency of the tested compds. Anticancer drugs, currently used in the clinic, were evaluated in xenograft models and their potency parameters were estd. A good correlation was obtained between these parameters and the exposures sustained at the therapeutically relevant dosing regimens. Based on the corresponding regression equation and the potency parameters estd. in the first preclin. studies, the therapeutically active concns. of new compds. can be estd. An early knowledge of level of exposure or doses to be reached in humans will improve the risk evaluation and decision making processes in anticancer drug development.

Answer 16:

Bibliographic Information

Determination of the optimal combination chemotherapy regimen for treatment of platinum-resistant ovarian cancer in nude mouse model. Saucier, Jenifer M.; Yu, Jiang; Gaikwad, Anjali; Coleman, Robert L.; Wolf, Judith K.; Smith, Judith A. Department of Gynecologic Oncology, Division of Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX, USA. *Journal of Oncology Pharmacy Practice* (2007), 13(1), 39-45. Publisher: Sage Publications Ltd., CODEN: JOPPFI ISSN: 1078-1552. Journal written in English. CAN 147:157549 AN 2007:740310 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Objective: The primary objective of this study was to evaluate the potential to increase the in vivo activity of liposomal doxorubicin when administered in combination with other chemotherapeutic agents such as topotecan, docetaxel, gemcitabine, capecitabine, or celecoxib in an ovarian cancer xenograft mouse model to identify new treatment options for recurrent platinum-sensitive/resistant ovarian cancer. Methods: This was a five-arm study in two xenograft ovarian cancer mouse models, ES-2 (platinum-sensitive), and OVCAR3 (platinum-resistant), to evaluate the combination of liposomal doxorubicin with the common chemotherapeutic agents. Each cell line had five mice for each treatment arm, five vehicle control mice, and five liposomal doxorubicin alone control mice. Expts. were done in duplicate. Results: The percentage tumor redn. ranged from 52% to 74.1% for the single-agent treatment arms. Tumor growth inhibition and regression (response) was improved on the combination treatment arms ranging from 76.1% to 100%. We obsd. increased activity in the liposomal doxorubicin plus topotecan arm, with a 27.3% improvement in response, compared with either agent alone. Conclusions: The addn. of liposomal doxorubicin demonstrated increased antitumor activity compared with either agent used alone. The most active combination treatment arm was liposomal doxorubicin with topotecan which is consistent with recent clin. study reports of enhanced activity with the combination of topoisomerase I and topoisomerase II agents. Addnl. studies are warranted to evaluate the efficacy and safety to optimize the combination of liposomal doxorubicin and topotecan for the treatment of recurrent or refractory ovarian cancer.

Answer 17:

Bibliographic Information

A New Model of Patient Tumor-Derived Breast Cancer Xenografts for Preclinical Assays. Marangoni, Elisabetta; Vincent-Salomon, Anne; Auger, Nathalie; Degeorges, Armelle; Assayag, Franck; de Cremoux, Patricia; de Plater, Ludmilla; Guyader, Charlotte; De Pinieux, Gonzague; Judde, Jean-Gabriel; Rebucci, Magali; Tran-Perennou, Carine; Sastre-Garau, Xavier; Sigal-Zafrani, Brigitte; Delattre, Olivier; Dieras, Veronique; Poupon, Marie-France. U612, Pharmacologie Preclinique Antitumorale, Institut National

de la Sante et de la Recherche Medicale, Fr. Clinical Cancer Research (2007), 13(13), 3989-3998. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 147:397725 AN 2007:718559 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

PURPOSE: To establish a panel of human breast cancer (HBC) xenografts in immunodeficient mice suitable for pharmacol. preclin. assays. Exptl. Design: 200 samples of HBCs were grafted into Swiss nude mice. Twenty-five transplantable xenografts were established (12.5%). Their characterization included histol., p53 status, genetic anal. by array comparative genomic hybridization, gene expression by Western blotting, and quant. reverse transcription-PCR. Biol. profiles of nine xenografts were compared with those of the corresponding patient's tumor. Chemosensitivities of 17 xenografts to a combination of Adriamycin and cyclophosphamide (AC), docetaxel, trastuzumab, and Degarelix were evaluated. **RESULTS:** Almost all patient tumors established as xenografts displayed an aggressive phenotype, i.e., high-grade, triple-neg. status. The histol. of the xenografts recapitulated the features of the original tumors. Mutation of p53 and inactivation of Rb and PTEN proteins were found in 83%, 30%, and 42% of HBC xenografts, resp. Two HBCx had an ERBB2 (HER2) amplification. Large variations were obsd. in the expression of HER family receptors and in genomic profiles. Genomic alterations were close to those of original samples in paired tumors. Three xenografts formed lung metastases. A total of 15 of the 17 HBCx (88%) responded to AC, and 8 (47%) responded to docetaxel. One ERBB2-amplified xenograft responded to trastuzumab, whereas the other did not. The drug response of HBC xenografts was concordant with that of the patient's tumor in five of seven analyzable cases. **CONCLUSIONS:** This panel of breast cancer xenografts includes 15 triple-neg., one ER pos. and 2 ERBB2 pos. This panel represents a useful preclin. tool for testing new agents and protocols and for further exploration of the biol. basis of drug responses.

Answer 18:

Bibliographic Information

Grb2-SH3 ligand inhibits the growth of HER2+ cancer cells and has antitumor effects in human cancer xenografts alone and in combination with docetaxel. Gril, Brunilde; Vidal, Michel; Assayag, Franck; Poupon, Marie-France; Liu, Wang-Qing; Garbay, Christiane. UFR Biomedicale, Laboratoire de Pharmacochimie Moleculaire et Cellulaire, Universite Paris Descartes, Paris, Fr. International Journal of Cancer (2007), 121(2), 407-415. Publisher: Wiley-Liss, Inc., CODEN: IJCNAW ISSN: 0020-7136. Journal written in English. CAN 147:250106 AN 2007:677663 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

HER2 represents an important signaling pathway in breast and other cancers. Herceptin has demonstrated clin. activity, but resistance is common. Thus, new therapeutic approaches to the HER2 pathway are needed. Grb2 is an adaptor protein involved in Ras-dependent signaling induced by HER2 receptors. A specific Grb2-SH3 ligand, designed and synthesized in our lab., called peptidimer-c, inhibited colony formation in HER2 overexpressing SKBr3 cancer cells. Combined treatment of peptidimer-c with docetaxel further inhibited both colony formation and tumor cell survival compared to docetaxel treatment alone. Efficacy of this combined treatment was correlated with a redn. in the phosphorylation of MAPK and AKT. Finally, peptidimer-c reduced the growth of a HER2+ human breast cancer (BK111) xenograft in nude mice and potentiated the antitumor effect of docetaxel in a HER2+ hormone-independent human prostate adenocarcinoma (PAC120 HID28) xenograft. These results validate Grb2 as a new target for the HER2 pathway.

Answer 19:

Bibliographic Information

3'-deoxy-3'-18F-fluorothymidine (FLT) positron emission tomography for early prediction of response to chemoradiotherapy - a clinical application model of esophageal cancer. Chao, K. S. Clifford. Department of Radiation Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA. Seminars in Oncology (2007), 34(2, Suppl. 1), S31-S36. Publisher: Elsevier Inc., CODEN: SOLGAV ISSN: 0093-7754. Journal; General Review written in English. CAN 147:294583 AN 2007:609801 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A review. Early detection of response to neoadjuvant chemoradiation in esophageal cancer may allow individualization of treatment strategies and avoidance of unnecessary treatment. Although positron emission tomog. (PET) with [18F]fluorodeoxyglucose (FDG) permits detection of changes in tumor proliferation before any change in tumor size is evident, FDG-PET may fail to distinguish between residual tumor and inflammation and between complete response and partial response with substantial residual tumor burden. PET with the nucleoside analog 3'-deoxy-3'-18F-fluorothymidine (FLT) is more accurate than FDG-PET in visualizing early changes in tumor proliferation. In a recent study in exptl. models of esophageal cancer, FLT-PET was more accurate than FDG-PET in detecting early changes in proliferation following docetaxel and radiation therapy in human SEG-1 cells and mouse SEG-1 xenografts, including having a much stronger correlation with histol. findings. Clin. studies are needed to det. if FLT-PET can distinguish among degrees of response to neoadjuvant chemoradiation in patients with esophageal cancer. The ability to visualize tumor cell proliferation may also contribute to the ability to improve precision delivery of radiation therapy.

Answer 20:

Bibliographic Information

Antitumor activity of edotecarin in breast carcinoma models. Ciomei, Marina; Croci, Valter; Stellari, Fabio; Amboldi, Nadia; Giavarini, Rosa; Pesenti, Enrico. Cell Biology/Oncology, Nerviano Medical Sciences, Nerviano (MI), Italy. Cancer Chemotherapy and Pharmacology (2007), 60(2), 229-235. Publisher: Springer, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 147:268543 AN 2007:510745 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Edotecarin (J-107088, formerly ED-749) is a potent indolocarbazole topoisomerase-I inhibitor that has the potential to treat solid tumors. The current studies evaluated the potency and antitumor activity of edotecarin, as a single agent and in combination with capecitabine or docetaxel. Antiproliferative activity was tested in vitro in a panel of 13 mammary cell lines and antitumor efficacy was tested in vivo in various breast cancer models. Edotecarin inhibited cellular proliferation in breast carcinoma cell lines: 50% inhibitory concns. ranged from 8 nmol/L in SKBR-3 cells to .apprx.30 µmol/L in BT20 cells. Single dose and weekly i.v. treatments with edotecarin 30 and 150 mg/kg produced significant antitumor activity in the SKBR-3 human breast carcinoma xenograft model, with no major toxicities, compared with vehicle solvent treatment. Daily administration of edotecarin 15 mg/kg for 10 days was not well tolerated, whereas the total dose of 150 mg/kg was safe when administered in a single injection. Edotecarin 3 and 30 mg/kg given after docetaxel in the nude mouse SKBR-3 xenograft model produced tumor growth delays that were greater than those obsd. with either agent alone and with no toxicity as evaluated on the basis of body wt. redn. (<20%). Furthermore, edotecarin 3 mg/kg in combination with capecitabine produced more than additive effects and the combination was well tolerated. However, edotecarin at a dose of 30 mg/kg in combination with capecitabine was lethal. Edotecarin also exhibited potent antitumor activity against xenografted human MX-1 cells, MMTV-v-Ha-ras oncogene-driven mouse breast tumors, and chem. induced rat mammary tumors. The data suggest that edotecarin may be useful as a single agent or a component of combination chemotherapy regimens for treating human breast cancer.

Answer 21:

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 22:

Bibliographic Information

Honokiol, a natural plant product, inhibits the bone metastatic growth of human prostate cancer cells. Shigemura, Katsumi; Arbiser, Jack L.; Sun, Shi-Yong; Zayzafoon, Majd; Johnstone, Peter A. S.; Fujisawa, Masato; Gotoh, Akinobu; Weksler, Babette; Zhau, Haiyen E.; Chung, Leland W. K. Molecular Urology and Therapeutics Program, Department of Urology, Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA, USA. *Cancer* (Hoboken, NJ, United States) (2007), 109(7), 1279-1289. Publisher: John Wiley & Sons, Inc., CODEN: CANCAR ISSN: 0008-543X. Journal written in English. CAN 147:226466 AN 2007:476164 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background. Honokiol, a sol. nontoxic natural product derived from *Magnolia* spp., has been shown to induce apoptosis in malignant cells. The effect of honokiol and the combined therapy with docetaxel on prostate cancer (PCa) growth and bone metastasis was investigated in exptl. models. **Methods.** The in vitro proapoptotic effects of honokiol on human androgen-dependent and -independent PCa, bone marrow, bone marrow-derived endothelial, and prostate stroma cells were investigated. Honokiol-induced activation of caspases was evaluated by Western blot and FACS anal. To confirm the cytotoxicity of honokiol, mice bone was inoculated in vivo with androgen-independent PCa, C4-2 cells and the effects of honokiol and/or docetaxel on PCa growth in bone were evaluated. Daily honokiol (100 mg/kg) and/or weekly docetaxel (5 mg/kg) were injected i.p. for 6 wk. PCa growth in mouse bone was evaluated by radiog., serum prostate-specific antigen (PSA) and tissue immunohistochem. **Results.** Honokiol induced apoptosis in all cell lines tested. In PCa cells honokiol induced apoptosis via the activation of caspases 3, 8, and 9 and the cleavage of poly-ADP ribose polymerase in a dose- and time-dependent manner. Honokiol was shown to inhibit the growth and depress serum PSA in mice harboring C4-2 xenografts in the skeleton and the combination with docetaxel showed additive effects that inhibited further growth without evidence of systemic toxicity. Immunohistochem. staining confirmed honokiol exhibited growth-inhibitory, apoptotic, and antiangiogenic effects on PCa xenografts. **Conclusions.** The combination of honokiol and low-dose docetaxel may be used to improve patient outcome in androgen-independent prostate cancer with bone metastasis.

Answer 23:

Bibliographic Information

Polymeric nanoparticles with controlled sizes for targeted drug delivery. Tong, Rong; Cheng, Jianjun. Department of Materials Science and Engineering, University of Illinois at Urbana-Champaign, Urbana, IL, USA. *PMSE Preprints* (2007), 96 333. Publisher: American Chemical Society, CODEN: PPMRA9 ISSN: 1550-6703. Journal; Computer Optical Disk written in English. CAN 146:323062 AN 2007:324619 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Biodegradable polymeric nanoparticles (NPs) have been widely used for drug delivery applications. In cancer drug delivery, NPs can accumulate in tumor tissues after systemic administration, and their biodistribution is largely detd. by their phys. and biochem. properties, such as particle size, nature of the encapsulated drug, and surface biochem. properties. We developed ≈ 180 nm docetaxel-encapsulated NP-Apt bioconjugates using poly(DL-lactide-co-glycolide)block-poly(ethylene glycol) (PLGA-b-PEG) copolymer that showed remarkable antitumor efficacy in vivo after a single intratumoral administration to s.c. xenograft mouse models of prostate cancer. Although intratumoral drug delivery is suitable for localized cancer therapy, patients with advanced or metastatic cancer require drugs to be administered systemically for the treatment of disseminated tumors. Systemic delivery of targeted NPs presents other challenges for developing an effective NP drug delivery vehicle with desirable pharmacol. properties capable of extended circulation in blood and targeted drug delivery. In this study, we systemically studied the formulation parameters on the size of NPs, including: (1) polymer concn., (2) drug loading, (3) water miscibility of solvent, and (4) the ratio of water to solvent. For the first time, we reported NP mean volumetric size correlates linearly with polymer concn. for NPs between 70 and 250 nm in diam. (linear coeff. = 0.99 for NPs formulated with solvents studied). We also found particle formulated using covalently bound PLA-paclitaxel in DMF soln. forms very uniform sizes with narrow distribution. These nanoparticles demonstrate excellent cytotoxicity-particle size correlations.

Answer 24:

Bibliographic Information

Tumor growth inhibition with cetuximab and chemotherapy in non-small cell lung cancer xenografts expressing wild-type and mutated epidermal growth factor receptor. Steiner, Philipp; Joynes, Christopher; Bassi, Rajiv; Wang, Su; Tonra, James R.; Hadari, Yaron R.; Hicklin, Daniel J. ImClone Systems Incorporated, New York, NY, USA. *Clinical Cancer Research* (2007), 13(5), 1540-1551. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 147:22955 AN 2007:230062 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Targeting the epidermal growth factor receptor (EGFR) is a validated approach to treat cancer. In non-small cell lung cancer (NSCLC), EGFR contains somatic mutations in 10% of patients, which correlates with increased response rates to small mol. inhibitors of EGFR. We analyzed the effects of the monoclonal IgG1 antibody Erbitux (cetuximab) in NSCLC xenografts with wild-type (wt) or mutated EGFR. NSCLC cell lines were grown s.c. in nude mice. Dose-dependent efficacy was established for cetuximab. To det. whether combination therapy produces tumor regressions, cetuximab was dosed at half-maximal efficacy with chemotherapy used at max. tolerated dose. Cetuximab showed antitumor activity in wt (A549, NCI-H358, NCI-H292) and mutated [HCC-827 (delE746-A750), NCI-H1975 (L858R, T790M)] EGFR-expressing xenografts. In the H292 model, cetuximab and docetaxel combination therapy was more potent to inhibit tumor growth than cetuximab or docetaxel alone. Cisplatin augmented efficacy of cetuximab to produce 6 of 10 regressions, whereas 1 of 10 regressions was found with cetuximab and no regression was found with cisplatin. Using H1975 xenografts, gemcitabine increased efficacy of cetuximab resulting in 12 of 12 regressions. Docetaxel with cetuximab was more efficacious with seven of nine regressions compared with single treatments. Cetuximab inhibited autophosphorylation of EGFR in both H292 and H1975 tumor lysates. Exploring the underlying mechanism for combination effects in the H1975 xenograft model, docetaxel in combination with cetuximab added to the antiproliferative effects of cetuximab but was the main component in this drug combination to induce apoptosis. Cetuximab showed antitumor activity in NSCLC models expressing wt and mutated EGFR. Combination treatments increased the efficacy of cetuximab, which may be important for the management of patients with chemorefractory NSCLC.

Answer 25:

Bibliographic Information

MEK1/2 inhibition promotes Taxotere lethality in mammary tumors in vivo. Yacoub, Adly; Gilfor, Donna; Hawkins, William; Park, Margaret A.; Hanna, David; Hagan, Michael P.; Curiel, David T.; Fisher, Paul B.; Grant, Steven; Dent, Paul. Departments of Biochemistry, Radiation Oncology, Virginia Commonwealth University, Richmond, VA, USA. *Cancer Biology & Therapy* (2006), 5(10), 1332-1339. Publisher: Landes Bioscience, CODEN: CBTAAO ISSN: 1538-4047. Journal written in English. CAN 146:350757 AN 2007:159626 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Taxol (paclitaxel) and Taxotere (docetaxel) are considered as two of the most important anti-cancer chemotherapy drugs. The cytotoxic action of these drugs has been linked to their ability to inhibit microtubule depolymn., causing growth arrest and subsequent cell death. Studies by a no. of labs. have also linked suppression of MEK1/2 signaling to enhanced Taxol toxicity in vitro and in vivo. The present study examd. the interactions of the semi-synthetic taxane Taxotere with MEK1/2 inhibitors in epithelial tumor cells. In vitro colony formation studies demonstrated that Taxotere and the MEK1/2 inhibitor PD184352 interacted in a sequence dependent fashion to synergistically kill human mammary carcinoma cells (MDA-MB-231, MCF7) as well as in other tumor cell types; e.g. prostate and renal cell carcinoma. Athymic mice were implanted in the rear flank with either MDA-MB-231 or MCF7 cells and tumors permitted to form to a vol. of .apprx.100 mm³ prior to a two day exposure of either Vehicle, PD184352 (25 mg/kg), Taxotere (15 mg/kg) or the drug combination. Tumor vol. was measured every other day and tumor growth detd. over the following .apprx.30 days. Transient exposure of MDA-MB-231 tumors or MCF7 tumors to PD184352 did not significantly alter tumor growth rate or the mean tumor vol. in vivo .apprx.15-30 days after drug administration. Transient Taxotere exposure of MDA-MB-231 or to a lesser extent MCF7, tumors modestly reduced the mean tumor vol. in vivo .apprx.15-30 days after drug administration. In contrast, combined treatment with PD184352 and Taxotere significantly reduced MDA-MB-231 and MCF7 tumor growth. The tumor control values for MDA-MB-231 cells and MCF7 cells were 0.43 and 0.71, resp. Fractionated irradiation of MDA-MB-231 tumors during drug exposure or single dose irradiation prior to drug administration did not significantly further suppress tumor growth beyond that of cells exposed to Taxotere and MEK1/2 inhibitor. Single dose irradiation

of tumors after drug exposure, however, caused a significant further suppression of tumor growth below that caused by drug exposure. These findings were also reflected in ex vivo colony formation analyses of isolated tumor cells. Collectively, these findings argue that Taxotere and MEK1/2 inhibitors have the potential to suppress mammary tumor growth in vivo which is enhanced by sequence-dependent exposure to ionizing radiation. Based on the cell lines used in these studies, our findings argue that the interaction of Taxotere and PD184352 is independent of p53 status, estrogen dependency, caspase 3 levels or oncogenic K-RAS expression.

Answer 26:

Bibliographic Information

Functional imaging for early prediction of response to chemoradiotherapy: 3'-deoxy-3'-18F-fluorothymidine positron emission tomography - a clinical application model of esophageal cancer. Chao, K. S. Clifford. Department of Radiation Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA. *Seminars in Oncology* (2006), 33(6, Suppl. 11), S59-S63. Publisher: Elsevier Inc., CODEN: SOLGAV ISSN: 0093-7754. Journal; General Review written in English. CAN 147:136477 AN 2007:140486 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A review. Pathol. complete response after neoadjuvant chemoradiation therapy is assocd. with increased survival in esophageal cancer. Early detection of response or nonresponse to neoadjuvant chemoradiation might allow individualization of treatment strategies and avoidance of unnecessary treatment. Positron emission tomog. (PET) with [18F]fluorodeoxyglucose (FDG) permits detection of changes in tumor proliferation before any change in tumor size occurs, and FDG-PET findings have been correlated with outcomes in esophageal cancer. However, FDG-PET may fail to distinguish between residual tumor and inflammation and between complete response and partial response with substantial residual tumor burden. PET with the nucleoside analog 3'-deoxy-3'-18F-fluorothymidine (FLT) has been found to be more accurate than FDG-PET in visualizing early changes in tumor proliferation. In a recent study in exptl. models of esophageal cancer, FLT-PET was more accurate than FDG-PET in detecting early changes in proliferation following docetaxel and radiation therapy in human SEG-1 cells and mouse SEG-1 xenografts, including having a much stronger correlation with histol. findings. Clin. studies are needed to det. if FLT-PET can distinguish among degrees of response to neoadjuvant chemoradiation in patients with esophageal cancer.

Answer 27:

Bibliographic Information

Potentiation of antitumor activity of docetaxel by combination with trastuzumab in a human prostate cancer xenograft model and underlying mechanisms. Legrier, M.-E.; Oudard, S.; Judde, J.-G.; Guyader, C.; de Pinieux, G.; Boye, K.; de Cremoux, P.; Dutrillaux, B.; Poupon, M.-F. Section Recherche, Institut Curie, Paris, Fr. *British Journal of Cancer* (2007), 96(2), 269-276. Publisher: Nature Publishing Group, CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 146:434377 AN 2007:81374 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Antitumor activity of docetaxel (Taxotere) in hormone-dependent (HD) and hormone-independent (HID) prostate cancer PAC120 xenograft model was previously reported, and its level was assocd. with HER2 protein expression. In the present study, we evaluate the antitumor effects of docetaxel combined with trastuzumab (Herceptin), an anti-HER2 antibody. Although trastuzumab alone had no effect on tumor growth, it potentiated the antitumor activity of docetaxel in HD tumors and more strongly in HID variants. Using the HID28 variant, we show that docetaxel treatment of tumor-bearing mice induces an increased HER2 mRNA expression of the tyrosine kinase receptor of 25-fold 24 h after docetaxel treatment, while HER2 protein and p-AKT decreased. This was followed by an increase of HER2 protein 3 days (two-fold) after docetaxel treatment and by a strong HER2 release in the serum of treated mice; expression of phospho-ERK, p27, BCL2 and HSP70 concomitantly increased. Similar mol. alterations were induced by docetaxel plus trastuzumab combination, except for that there was a transient and complete disappearance of AR and HSP90 proteins 24 h after treatment. We show that in addn. to its known effects on tubulin and mitotic spindles, docetaxel induces complex signalization pathway mechanisms in surviving cells, including HER2, which can be pharmacol. targeted. This study suggests that the docetaxel/trastuzumab combination may prove an effective therapeutic approach for HER2-expressing hormone-refractory prostate cancer.

Answer 28:

Bibliographic Information

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

Abstract

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

Answer 29:

Bibliographic Information

15-Deoxy- Δ 12,14-prostaglandin J2 enhances docetaxel anti-tumor activity against A549 and H460 non-small-cell lung cancer

cell lines and xenograft tumors. Fulzele, Suniket V.; Chatterjee, Abhijit; Shaik, Madhu Sudhan; Jackson, Tanise; Ichite, Nkechi; Singh, Mandip. College of Pharmacy and Pharmaceutical Sciences, Florida A&M University, Tallahassee, FL, USA. *Anti-Cancer Drugs* (2007), 18(1), 65-78. Publisher: Lippincott Williams & Wilkins, CODEN: ANTDEV ISSN: 0959-4973. Journal written in English. CAN 146:134825 AN 2006:1288587 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

15-Deoxy- Δ 12,14-prostaglandin J2 is a naturally occurring endogenous ligand for peroxisome proliferator-activated receptor- γ . The current study was aimed to det. the mechanism of anti-proliferative effect of 15-deoxy- Δ 12,14-prostaglandin J2 + docetaxel against A549 and H460 non-small-cell lung cancer cell lines and xenograft tumors. In-vitro cytotoxicity of 15-deoxy- Δ 12,14-prostaglandin J2 alone and in combination with docetaxel was studied against A549 and H460 cell lines. For in-vivo studies, female athymic nu/nu mice were xenografted with A549 and H460 tumors and treated with 15-deoxy- Δ 12,14-prostaglandin J2 (1 mg/kg/day; i.p.), docetaxel (10 mg/kg; i.v. on days 14, 18 and 22) and 15-deoxy- Δ 12,14-prostaglandin J2 + docetaxel. Apoptosis was measured in A549 cells and tumor tissues, following various treatments. Peroxisome proliferator-activated receptor- γ , caspases, Bcl2 and p53 family proteins or their mRNA expressions were measured by Western blotting, reverse transcription-polymerase chain reaction and real-time polymerase chain reaction in A549 tumors. A possible role of a peroxisome proliferator-activated receptor- γ -independent mechanism was studied in A549 cells treated with peroxisome proliferator-activated receptor- γ antagonist, GW9662. Isobolog. anal. demonstrated synergistic interaction (combination index <1.0) between 15-deoxy- Δ 12,14-prostaglandin J2 and docetaxel against A549 and H460 cells in vitro. 15-Deoxy- Δ 12,14-prostaglandin J2 + docetaxel significantly reduced the tumor vol. compared with control (P<0.05), 15-deoxy- Δ 12,14-prostaglandin J2 (P<0.05) and docetaxel (P<0.05, P<0.01) in both A549 and H460 tumors. 15-Deoxy- Δ 12,14-prostaglandin J2 + docetaxel showed a significant increase in apoptosis assocd. with inhibition of the Bcl2 and cyclin D1 expression and overexpression of caspase and p53 pathway genes.

Further, enhanced expression of caspase 3 and inhibition of cyclin D1 by 15-deoxy- Δ 12,14-prostaglandin J2 + docetaxel was not reversed by GW9662, thus suggesting a possible peroxisome proliferator-activated receptor- γ -independent mechanism. In conclusion, 15-deoxy- Δ 12,14-prostaglandin J2 enhanced the antitumor action of docetaxel by peroxisome proliferator-activated receptor- γ -dependent and -independent mechanisms mediated by induction of apoptosis.

Answer 30:

Bibliographic Information

Nanoparticle-aptamer bioconjugates for targeted antineoplastic drug delivery. Teply, Benjamin A.; Rocha, Flavio G.; Levy-Nissenbaum, Etgar; Langer, Robert; Farokhzad, Omid C. Department of Anesthesiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA. *American Journal of Drug Delivery* (2006), 4(3), 123-130. Publisher: Adis International Ltd., CODEN: AJDDBM ISSN: 1175-9038. Journal; General Review written in English. CAN 146:87014 AN 2006:1232132 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A review. Targeted drug delivery technologies can provide physicians with new approaches to treat and manage patients with cancer. Nucleic acid ligands (aptamers) are a novel class of targeting mol. that can be used in a similar manner to antibodies. Beyond use as drugs themselves, aptamers have the potential to serve as targeting ligands to deliver drugs, imaging agents, or other bioactive agents to the intended site of action. Bioconjugates of nanoparticles and aptamers can selectively bind and be taken up by cancer cells. In this article we review progress to date for antineoplastic drug delivery using nanoparticle-aptamer bioconjugates. Aptamers are isolated through a process of in vitro selection, also referred to as systematic evolution of ligands by exponential enrichment (SELEX). There is an increasing nos. of aptamers for cancer targeting being reported in the literature. These aptamers often interact with antigens that are overexpressed exclusively, or preferentially, on cancer cells or in the cancer microenvironment. As novel drug delivery vehicles, nanoparticle-aptamer bioconjugates may be developed to target a myriad of diseases including many cancers by delivering a variety of therapeutic agents specifically to the site of interest. The first in vivo study of antineoplastic drug delivery by a bioconjugate employed nanoparticle encapsulating docetaxel and aptamers that bind certain prostate cancer cells. In this study using a xenograft murine model of prostate cancer, these bioconjugates were shown to significantly improve tumor redn. after intratumoral injection compared with all controls. Furthermore, the docetaxel-loaded nanoparticle-aptamer bioconjugates demonstrated reduced toxicity in terms of acute bodyweight loss compared with the controls. In vitro, the efficacy of the docetaxel-loaded nanoparticle-aptamer

bioconjugate was shown to be due to intracellular delivery of the drug to the cancer cells, and the bioconjugate without the drug had no cytotoxicity.

Nanoparticle-aptamer bioconjugates may prove to be useful not only for management of cancer but also various other indications. New aptamers, multivalent targeting strategies, and multimodal treatments such as simultaneous radio- and chemotherapy may further increase the efficacy of these bioconjugates and facilitate their clin. translation for therapeutic and diagnostic applications.

Answer 31:

Bibliographic Information

Restoring chemotherapy and hormone therapy sensitivity by parthenolide in a xenograft hormone refractory prostate cancer model. Shanmugam, Rajasubramaniam; Jayaprakasan, Vetrichelvan; Gokmen-Polar, Yesim; Kelich, Stephanie; Miller, Kathy D.; Yip-Schneider, Michele; Cheng, Liang; Bhat-Nakshatri, Poomima; Sledge, George W., Jr.; Nakshatri, Harikrishna; Zheng, Qi-Huang; Miller, Michael A.; DeGrado, Timothy; Hutchins, Gary D.; Sweeney, Christopher J. Department of Medicine, Indiana University, Indianapolis, IN, USA. Prostate (Hoboken, NJ, United States) (2006), 66(14), 1498-1511. Publisher: Wiley-Liss, Inc., CODEN: PRSTDS ISSN: 0270-4137. Journal written in English. CAN 147:1016 AN 2006:1117125 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Nuclear Factor kappa B (NF κ B) is a eukaryotic transcription factor that is constitutively active in human cancers and can be inhibited by the naturally occurring sesquiterpene lactone, parthenolide (P). The in vitro effects of P were assessed using the androgen independent cell line, CWR22Rv1, and human umbilical endothelial cells (HUVECs). The in vivo activity of P as a single agent and its ability to augment the efficacy of docetaxel and the anti-androgen, bicalutamide, were detd. using the CWR22Rv1 xenograft model. Parthenolide at low micromolar concn. inhibited proliferation of CWR22Rv1 and HUVEC cells, promoted apoptosis and abrogated NF κ B-DNA binding. Parthenolide downregulated anti-apoptotic genes under NF κ B control, TRAF 1 and 2, and promoted sustained activation of c-jun-NH2 kinase (JNK). Parthenolide also augmented the in vivo efficacy of docetaxel and restored sensitivity to anti-androgen therapy. These studies demonstrate parthenolide's anti-tumor and anti-angiogenic activity, and its potential to augment the efficacy of chemotherapy and hormonal therapy.

Answer 32:

Bibliographic Information

Endothelin receptor A blockade enhances taxane effects in prostate cancer. Akhavan, Ardavan; McHugh, Kevin H.; Guruli, Georgi; Bies, Robert R.; Zamboni, William C.; Strychor, Sandra; Nelson, Joel B.; Pflug, Beth R. Department of Urology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA. Neoplasia (Ann Arbor, MI, United States) (2006), 8(9), 725-732. Publisher: Neoplasia Press Inc., CODEN: NEOPFL ISSN: 1522-8002. <http://www.neoplasia.com/pdf/manuscript/neo06388.pdf> Journal; Online Computer File written in English. CAN 147:973 AN 2006:1056777 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Endothelin (ET) 1 is important in the growth of prostate cancer cells through the activation of the endothelin A (ETA) receptor. ET receptor blockade is a new therapeutic target in treating advanced prostate cancer. This study investigates the impact of the combination of the ETA antagonist atrasentan (ABT-627) and taxane chemotherapy on prostate cancer cell survival in vitro and on the delay of prostate cancer in a xenograft mouse model. In vitro, PPC-1 cells transfected with an ETA-overexpressing vector were treated with ABT-627, paclitaxel/docetaxel, or both. Clonogenic viability and cell death assays were used to det. cell survival and apoptosis, resp. ABT-627 and docetaxel combination treatment was used in vivo to treat mice with established ETA-overexpressing PPC-1 xenograft tumors, and tumor growth rates were assessed. Cell proliferation and vascularity were detd. with KI-67 and CD31 staining, resp. Cells treated with combination therapy had significantly fewer viable cells and more programmed cell death than cells

given monotherapy. Xenograft tumor growth rates were significantly lower in mice treated with combination therapy than in animals given a single agent. Ki-67 immunostaining demonstrated significantly fewer proliferative cells following combination therapy than following monotherapy. This study demonstrates ABT-627 to have additive antitumor effects when used in combination with taxane drugs both in vitro and in vivo.

Answer 33:

Bibliographic Information

Preclinical Characterization of AEG35156/GEM 640, a Second-Generation Antisense Oligonucleotide Targeting X-Linked Inhibitor of Apoptosis. LaCasse, Eric C.; Cherton-Horvat, Gabriele G.; Hewitt, Kimberley E.; Jerome, Lori J.; Morris, Stephen J.; Kandimalla, Ekambar R.; Yu, Dong; Wang, Hui; Wang, Wei; Zhang, Ruiwen; Agrawal, Sudhir; Gillard, John W.; Durkin, Jon P. Aegera Therapeutics, Inc., Montreal, QC, Can. *Clinical Cancer Research* (2006), 12(17), 5231-5241. Publisher: American Association for Cancer Research, CODEN: CCRE4 ISSN: 1078-0432. Journal written in English. CAN 146:454298 AN 2006:899348 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

PURPOSE: Cancer cells can use X-linked inhibitor of apoptosis (XIAP) to evade apoptotic cues, including chemotherapy. The antitumor potential of AEG35156, a novel second-generation antisense oligonucleotide directed toward XIAP, was assessed in human cancer models when given as a single agent and in combination with clin. relevant chemotherapeutics. **Exptl. Design:** AEG35156 was characterized for its ability to cause dose-dependent redns. of XIAP mRNA and protein in vitro and in vivo, to sensitize cancer cell lines to death stimuli, and to exhibit antitumor activity in multiple human cancer xenograft models as a single agent or in combination with chemotherapy. **RESULTS:** AEG35156 reduced XIAP mRNA levels with an EC50 of 8 to 32 nmol/L and decreased XIAP protein levels by >80%. Loss of XIAP protein correlated with increased sensitization to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-mediated apoptosis in Panc-1 pancreatic carcinoma cells. AEG35156 exhibited potent antitumor activity relative to control oligonucleotides in three human cancer xenograft models (prostate, colon, and lung) and was capable of inducing complete tumor regression when combined with taxanes. Antitumor effects of AEG35156 correlated with suppression of tumor XIAP levels. **CONCLUSIONS:** AEG35156 reduces XIAP levels and sensitizes tumors to chemotherapy. AEG35156 is presently under clin. assessment in multiple phase I trials in cancer patients as a single agent and in combination with docetaxel in solid tumors or cytarabine/idarubicin in leukemia.

Answer 34:

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 isoforms, 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 35:

Bibliographic Information

Enhanced antitumor efficacy of telomerase-selective oncolytic adenoviral agent OBP-401 with docetaxel: preclinical evaluation of chemovirotherapy. Fujiwara, Toshiya; Kagawa, Shunsuke; Kishimoto, Hiroyuki; Endo, Yoshikatsu; Hioki, Masayoshi; Ikeda, Yoshihiro; Sakai, Ryo; Urata, Yasuo; Tanaka, Noriaki; Fujiwara, Toshiyoshi. Division of Surgical Oncology, Department of Surgery, Okayama University Graduate School of Medicine and Dentistry, Okayama, Japan. International Journal of Cancer (2006), 119(2), 432-440. Publisher: Wiley-Liss, Inc., CODEN: IJCNW ISSN: 0020-7136. Journal written in English. CAN 145:202215 AN 2006:647075 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Oncolytic adenoviruses are being developed as novel anticancer therapeutics and currently undergoing clin. trials. We previously demonstrated that telomerase-specific replication-competent adenovirus (Telomelysin: OBP-301), in which the human telomerase reverse transcriptase (hTERT) promoter regulates viral replication, efficiently killed human tumor cells. We further constructed OBP-401 (Telomelysin-GFP) that expresses the green fluorescent protein (GFP) reporter gene under the control of the cytomegalovirus promoter in the E3 region to monitor viral distribution. Here, we examd. the feasibility of a single-agent therapy with OBP-401 as well as of combining OBP-401 with chemotherapeutic agents. Infection of OBP-401 alone or followed by the treatment of a chemotherapeutic drug, docetaxel (Taxotere), resulted in a profound in vitro cytotoxicity and GFP expression in various human cancer cell lines originating from different organs (lung, colon, esophagus, stomach, liver and prostate), although the magnitude of antitumor effect varied among the cell types. Other chemotherapeutic drugs such as vinorelbine (Navelbine) and SN38 (the potent active metabolite of irinotecan) combined with OBP-401 also inhibited the growth of human cancer cells. Quant. real-time PCR anal. demonstrated that docetaxel did not affect viral replication. For in vivo evaluation, nu/nu mice xenografted with H1299 human lung tumor received intratumoral injection of OBP-401 and i.p. administration of docetaxel. Anal. of growth of implanted tumors showed a significant, therapeutic synergism, although OBP-401 alone and docetaxel alone showed modest inhibition of tumor growth. Thus, OBP-401 in combination with docetaxel efficiently enhances the antitumor efficacy both in vitro and in vivo, and the outcome has important implications for tumor-specific oncolytic chemovirotherapies for human cancers.

Answer 36:

Bibliographic Information

Antitumor effect of combination of S-1 and docetaxel on the human breast cancer xenograft transplanted into SCID mice. Suto, Akihiko; Kubota, Tetsuro; Fukushima, Masakazu; Ikeda, Tadashi; Takeshita, Toshio; Ohmiya, Harumi; Kitajima, Masaki. Department of Surgery, School of Medicine, Keio University, Shinanomachi 35, Shinjuku-ku, Tokyo, Japan. Oncology Reports (2006), 15(6), 1517-1522. Publisher: Oncology Reports, CODEN: OCRPEW ISSN: 1021-335X. Journal written in English. CAN 145:431800 AN 2006:587117 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

In vivo expts. were performed on breast cancer xenografts to examine whether the combination therapy with S-1, an oral dihydrouracil dehydrogenase (DPD) inhibitory fluoropyrimidine, plus docetaxel functions as an additive/synergistic modulator in tumor growth. The human breast cancer xenograft, MDA-MB-435SHM, was inoculated into SCID female mice. The tumor growth and thymidylate synthase (TS)/DPD activity of tumors treated with the agents were investigated. The T/C value (relative mean tumor wt. of the treated group/relative tumor wt. of the control group) of the group treated with docetaxel, S-1 and combination therapy were 45.3, 63.1 and 29.8%, resp.; suggesting the pos. antitumor effects of the combination therapy in particular. In addn., significant down-regulation

of DPD activity was also obsd. in the tumors treated with S-1, docetaxel and their combination. Down-regulation of the DPD activity of the tumors is also considered to be correlated with the antitumor effect of the treated groups, suggesting its influence on the synergistic effect of the combination therapy.

Answer 37:

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: CCREFA 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 {szligbeta}-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 {szligbeta}-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 38:

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: CBTA AO 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/combo 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 39:

Bibliographic Information

Lactandrate: a D-homo-aza-androsterone alkylator in the treatment of breast cancer. Trafalis, Dimitrios T. P.; Geromichalos, George D.; Koukoulitsa, Catherine; Papageorgiou, Athanasios; Karamanakis, Panayiotis; Camoutsis, Charalambos. Laboratory of Medicinal Chemistry, Faculty of Pharmacy, University of Patras, Patras, Greece. Breast Cancer Research and Treatment (2006), 97(1), 17-31. Publisher: Springer, CODEN: BCTRD6 ISSN: 0167-6806. Journal written in English. CAN 145:410138 AN 2006:467778 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The sensitivity of breast neoplasms to hormonal control provides the basis of novel investigational treatments with steroidal alkylators. An androsterone D-lactam steroidal ester, the 3 β -hydroxy-13 α -amino-13,17-seco-5 α -androstane-17 α -oic-13,17-lactam, p-bis(2-chloroethyl)amino Ph acetate (lactandrate) was synthesized and tested for antitumor activity against six human breast cancer cell lines in vitro and against two murine and one xenograft mammary tumors in vivo. A docking study on the binding interactions of lactandrate with the ligand-binding domain (LBD) of estrogen receptor-alpha (ER α) was inquired. In vitro testing of lactandrate cytostatic and cytotoxic activity was performed on T47D, MCF7, MDA-MB-231, BT-549, Hs578T, MDA-MB-435 breast adenocarcinoma human cell lines. In vivo testing was performed on two murine mammary tumors, the MXT tumor and CD8F1 adenocarcinoma, as well as on human mammary carcinoma MX-1 xenograft. Mol. modeling techniques were adopted to predict a possible location and interaction mode of the mol. into LBD. Lactandrate induced significantly high antitumor effect against all tested in vitro and in vivo models. The cell lines with pos. ER expression found to be significantly more sensitive to lactandrate. Moreover, lactandrate found to be positioned inside the binding cavity with its steroidal moiety, while the alkylating moiety protrudes out of receptor's pocket. Lactandrate produced important anticancer activity on breast cancer in vitro and in vivo. Some correlation between ER and lactandrate effect was demonstrated. Docking studies provide the basis for the structure-based design of improved steroidal alkylating esters for the treatment of estrogen-related cancers.

Answer 40:

Bibliographic Information

Evaluation of Combined 177Lu-DOTA-8-AOC-BBN (7-14)NH₂ GRP Receptor-Targeted Radiotherapy and Chemotherapy in PC-3 Human Prostate Tumor Cell Xenografted SCID Mice. Johnson, Christopher V.; Shelton, Tiffani; Smith, Charles J.; Ma, Lixin; Perry, Michael C.; Volkert, Wynn A.; Hoffman, Timothy J. Department of Veterinary Pathobiology, University of Missouri-Columbia, Columbia, MO, USA. Cancer Biotherapy & Radiopharmaceuticals (2006), 21(2), 155-166. Publisher: Mary Ann Liebert, Inc., CODEN: CBRAFJ ISSN: 1084-9785. Journal written in English. CAN 146:179504 AN 2006:462042 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The focus of this study was to evaluate the therapeutic benefit of combined gastrin-releasing peptide (GRP) receptor-targeted radiotherapy (TRT) with chemotherapy, using the PC-3 xenograft severe combined immunodeficiency (SCID) mouse model. 177Lu-DOTA-8-AOC-BBN(7-14)NH₂ is a radiotherapeutic peptide that specifically targets the gastrin-releasing peptide receptor overexpressed on primary and metastatic prostate cancer. The chemotherapeutic agents, docetaxel and estramustine, were administered as single agents or in combination with the receptor-targeted radiotherapeutic agent. Combination receptor TRT/chemotherapy studies were begun 21 days postxenografting and were conducted as multiple-dose trials. The GRP receptor TRT agent was administered every 14 days, and single and combination chemotherapy dose regimens were given weekly. Tumor size, body wt., and body condition score were evaluated twice-weekly and a hematol. profile once-weekly. Therapy study tumor vols. were

evaluated by way of a repeated measures anal. of variance (ANOVA). Tumor vol. measurements at 12 days postdose administration demonstrated a statistically significant (two-tailed P-value <0.05) tumor growth suppression in all exptl. groups receiving GRP receptor-targeted radiotherapy, when compared to the control group. The two combined GRP receptor TRT/chemotherapy treatment groups demonstrated the greatest tumor growth suppression of all treatment groups. In comparing the two combined GRP receptor TRT/chemotherapy groups to the GRP receptor TRT alone group, a statistically significant difference was demonstrated for the combined groups by day 30, postdose administration. These data demonstrate that GRP receptor-targeted radiation therapy, using ^{177}Lu -DOTA-8-AOC-BBN(7-14)NH₂, used either alone or in combination with conventional chemotherapy, can suppress the growth of androgen-independent prostate cancer (AIPC).

Answer 41:

Bibliographic Information

Expression and significance of vascular endothelial growth factor receptor 2 in bladder cancer. Xia, Guangbin; Kumar, S. Ram; Hawes, Debra; Cai, Jie; Hassanieh, Loubna; Groshen, Susan; Zhu, Suta; Masood, Rizwan; Quinn, David I.; Broek, Daniel; Stein, John P.; Gill, Parkash S. Departments of Medicine, Keck School of Medicine, Vasgene Therapeutics, Inc., University of Southern California, Los Angeles, CA, USA. *Journal of Urology* (New York, NY, United States) (2006), 175(4), 1245-1252. Publisher: Elsevier, CODEN: JOURAA ISSN: 0022-5347. Journal written in English. CAN 145:246018 AN 2006:331779 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: Vascular endothelial growth factor has a crit. role in maintaining tumor microvasculature and, as such, is an attractive target for anti-angiogenic therapy. Aberrant expression of VEGF receptors, esp. VEGFR2, on epithelial tumor cells allows VEGF to stimulate growth and migration of tumor cells in an autocrine and/or paracrine manner. Therefore, we studied the expression of VEGF and VEGFR2 in bladder cancer, and the relationship to disease characteristics. Materials and Methods: Expression of VEGF and VEGFR2 was studied in a cohort of 72 patients with transitional cell cancer of the bladder. Tumor tissues from all patients were analyzed by immunohistochem. and examd. by a pathologist blinded to patient outcome. Patient demographics and disease outcome were correlated with expression of these markers. Bladder cancer cell lines that express VEGFR2 were studied in vitro and in vivo to establish the significance of VEGF/VEGFR2 signaling. Results: Expression of VEGF and VEGFR2 was obsd. in 58% and 50% of urothelial tumor cells, resp. VEGF expression failed to correlate with clin. variables. However, VEGFR2 expression correlated with disease stage (coeff. 0.23, $p = 0.05$). In addn., VEGFR2 expression increased with tumor invasion into the muscle ($p < 0.01$). Expts. with VEGFR2 pos. bladder cancer cell lines in vitro demonstrated increased invasion in response to VEGF. In addn., VEGF inhibition augmented the effect of docetaxel in a murine xenograft model of bladder cancer with a significant inhibition in proliferative index and microvascular d., and induction of apoptosis. Conclusions: Increased VEGFR2 expression correlates with several features that predict progression of urothelial cancer, including disease stage and invasive phenotype. VEGF targeted therapy may enhance the efficacy of std. therapy for bladder cancer.

Answer 42:

Bibliographic Information

Antitumor effect of docetaxel against human esophagus tumor cell lines and tumor xenografts in nude mice. Shakuto, Shuji; Fujita, Fumiko; Fujita, Masahide. Drug Safety Evaluation, Preclinical Development, Scientific Affairs, sanofi-aventis K.K., Japan. *Gan to Kagaku Ryoho* (2006), 33(3), 337-343. Publisher: Gan to Kagaku Ryohosha, CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 145:20633 AN 2006:311739 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The antitumor effect of docetaxel against cultured human esophagus tumor cell lines and tumor xenografts in nude mice was investigated. In the in vitro study, docetaxel showed concn.-dependent inhibition of the growth of 4 tumor cell lines having different degrees of differentiation (T. T, TE-5, TE-9 and TE-15) with IC₅₀ values ranging from 0.84 to 1.68 ng/mL when exposed for 72 h.

These values represent ca. 1/2,700.apprx.1/1,400 of the mean max. plasma concn. of 2.27 µg/mL attained in the clin. setting. In addn., the activity was found to be ca. two-fold stronger than that of paclitaxel, and much more potent than fluorouracil and cisplatin. The in vivo antitumor effect of docetaxel was also investigated against xenografts of human esophagus squamous cell carcinoma H-190 (highly differentiated) and H-204 (moderately differentiated) in nude mice. Docetaxel at its Maximum Tolerated Dose (MTD) and the lower dose (4.5, 6.7 mg/kg/dose, q 4 d × 3, iv) showed a significant growth inhibition of ca. 100% against H-190 tumor, resulting in the tumor shrinkage. Paclitaxel (6.7, 10 mg/kg/dose, q 4 d × 3, iv) showed a tumor-shrinking effect similar to that seen with docetaxel. In the H-204 xenograft model, docetaxel (4.5, 6.7, 10 mg/kg/dose) exhibited a dose-dependent effect in delaying the tumor growth, while paclitaxel failed to suppress the tumor growth even at its MTD. Those results demonstrated that docetaxel has potent antitumor efficacy against human esophagus tumor cells, leading to the expectation that it will be useful as a therapeutic agent for esophagus cancer.

Answer 43:

Bibliographic Information

Administration of zoledronic acid enhances the effects of docetaxel on growth of prostate cancer in the bone environment.

Brubaker, Kristen D.; Brown, Lisha G.; Vessella, Robert L.; Corey, Eva. Department of Biological and Allied Health Sciences, Bloomsburg University, Bloomsburg, PA, USA. BMC Cancer (2006), 6 No pp. given. Publisher: BioMed Central Ltd., CODEN: BCMACL ISSN: 1471-2407. <http://www.biomedcentral.com/content/pdf/1471-2407-6-15.pdf> Journal; Online Computer File written in English. CAN 145:39912 AN 2006:120688 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

After development of hormone-refractory metastatic disease, prostate cancer is incurable. The recent history of chemotherapy has shown that with difficult disease targets, combinatorial therapy frequently offers the best chance of a cure. In this study we have examd. the effects of a combination of zoledronic acid (ZOL), a new-generation bisphosphonate, and docetaxel on LuCaP 23.1, a prostate cancer xenograft that stimulates the osteoblastic reaction when grown in the bone environment. Intra-tibial injections of LuCaP 23.1 cells were used to generate tumors in the bone environment, and animals were treated with ZOL, docetaxel, or a combination of these. Effects on bone and tumor were evaluated by measurements of bone mineral d. and histomorphometrical anal. ZOL decreased proliferation of LuCaP 23.1 in the bone environment, while docetaxel at a dose that effectively inhibited growth of s.c. tumors did not show any effects in the bone environment. The combination of the drugs significantly inhibited the growth of LuCaP 23.1 tumors in the bone. In conclusion, the use of the osteolysis-inhibitory agent ZOL in combination with docetaxel inhibits growth of prostate tumors in bone and represents a potential treatment option.

Answer 44:

Bibliographic Information

Enhancement of antitumor activity of docetaxel by celecoxib in lung tumors. Shaik, Madhu Sudhan; Chatterjee, Abhijit; Jackson, Tanise; Singh, Mandip. College of Pharmacy, Florida A and M University, Tallahassee, FL, USA. International Journal of Cancer (2005), Volume Date 2006, 118(2), 396-404. Publisher: Wiley-Liss, Inc., CODEN: IJCNW ISSN: 0020-7136. Journal written in English. CAN 144:163725 AN 2005:1319207 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Our study investigates the effect of a highly selective cyclooxygenase-2 (COX-2) inhibitor, celecoxib, on the cytotoxicity of docetaxel in nude mice bearing A549 tumor xenografts and elucidates the mol. mechanisms of the antitumor effect of this combination. Female nu/nu mice, xenografted with s.c. A549 tumors were treated with either celecoxib (150 mg/kg/day), docetaxel (10 mg/kg) or a combination of both. The tumor tissues were quantified for the induction of apoptosis, intratumor levels/expressions of prostaglandin E2 (PGE2), 15 deoxy prostaglandin J2 (15-d PGJ2), microsomal prostaglandin E synthase (mPGES) and cytoplasmic phospholipase A2 (cPLA2). The combination of celecoxib with docetaxel significantly inhibited the tumor growth ($p < 0.03$) as compared to celecoxib or docetaxel alone, decreased the levels of PGE2 by 10-fold and increased the 15-d PGJ2 levels by 4-fold as compared to control. The

combination also enhanced the peroxisome proliferator-activated receptor (PPAR)- γ expression, decreased the expression of cPLA2, mPGES and vascular endothelial growth factor (VEGF), but had no effect on the expression of COX-1 or COX-2 in tumor tissues. TUNEL staining of the tumor tissues showed a marked increase in the apoptosis in the combination group as compared to the celecoxib- or docetaxel-treated groups and this was assocd. with an increase in the intratumor p53 expression. In conclusion, the combination of celecoxib with docetaxel produces a greater antitumor effect in s.c. A549 tumors as compared to celecoxib or docetaxel alone and this effect is assocd. with concomitant alterations in the intratumor levels of PGE2 and 15-d PGJ2.

Answer 45:

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 46:

Bibliographic Information

Antitumor effect of docetaxel against human endometrial tumor cell lines. Shakuto, Shuji; Noguchi, Keiko; Bissery, Marie-Christine. Sanofi-Aventis Group, Drug Safety Evaluation, Preclinical De., Scientefic Affaors, Aventis Pharma Ltd., Kawagoe-shi, Saitama, Japan. *Gan to Kagaku Ryoho* (2005), 32(10), 1437-1442. Publisher: Gan to Kagaku Ryohosha, CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 144:163701 AN 2005:1209975 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The antitumor effect of docetaxel against human endometrial tumor cell lines was investigated in vitro and in vivo. In the in vitro study, docetaxel showed concn.-dependent inhibition of the growth of 4 tumor cell lines having different degrees of differentiation (AN3 CA, KLE, HEC-1-A and HEC-1-B), with IC50 values ranging from 2.48 to 82.40 ng/mL. These values represent 1/900.apprx.1/30 of the mean max. plasma concn. of 2.27 μ g/mL attained when the recommended dose of 70 mg/m² for patients with endometrial cancer was administered to patients with various types of cancer in phase I trial. In addn., the activity was nearly equal to paclitaxel, and much

more potent than fluorouracil, cisplatin and doxorubicin. Docetaxel also showed strong antitumor activity against xenografts of the AN3 CA human endometrial adenocarcinoma cell line in nude mice. In the docetaxel-treated group at its MTD (33 mg/kg/dose, q 6 d × 3, iv), all of the animals were tumor-free survivors on Day 62 after xenografting. The antitumor effect in the MTD-administered group was the strongest of all of the tested anticancer drug groups (cyclophosphamide, mitomycin C, fluorouracil, cisplatin, doxorubicin). Even at two docetaxel dosages below its MTD (20.5 and 12.5 mg/kg/day), the drug showed a marked cytotoxic activity. These results demonstrated that docetaxel shows potent antitumor efficacy against human endometrial tumor cell lines, leading to the expectation that it will be useful as a therapeutic agent for endometrial cancer.

Answer 47:

Bibliographic Information

The angiogenesis inhibitor NM-3 is active against human NSCLC xenografts alone and in combination with docetaxel.

Agata, Naoki; Nogi, Hiroko; Bamberg, Michael; Milhollen, Michael; Pu, Minying; Weitman, Steven; Kharbanda, Surender; Kufe, Donald. ILEX Products, Inc., Boston, MA, USA. *Cancer Chemotherapy and Pharmacology* (2005), 56(6), 610-614. Publisher: Springer, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 144:163637 AN 2005:1069981 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The novel isocoumarin 2-(8-hydroxy-6-methoxy-1-oxo-1H-2-benzopyran-3-yl) propionic acid (NM-3) has completed phase I clin. evaluation as an orally bioavailable angiogenesis inhibitor. NM-3 directly kills both endothelial and tumor cells in vitro at low mM concns. and is effective in the treatment of diverse human tumor xenografts in mice. The present work has assessed the activity of NM-3 against human non-small-cell lung cancer (NSCLC) cells when used alone and in combination with docetaxel. The results demonstrate that NM-3 decreases clonogenic survival of NSCLC cells at clin. achievable concns. The results also demonstrate that NM-3 is effective in the treatment of NSCLC (A549, NCI-H460) tumor xenografts in mice. Moreover, NM-3 potentiated the antitumor activity of docetaxel against NSCLC xenografts without increasing toxicity. Our findings indicate that NM-3 may be effective alone or in combination with docetaxel in the treatment of patients with NSCLC.

Answer 48:

Bibliographic Information

Combination of oral fluoropyrimidine and docetaxel: Reappraisal of synergistic effect against gastric carcinoma xenografts.

Kodera, Yasuhiro; Fujiwara, Michitaka; Yokoyama, Hiroyuki; Ohashi, Norifumi; Miura, Shinichi; Ito, Yuichi; Koike, Masahiko; Ito, Katsuki; Nakao, Akimasa. Department of Surgery II, Nagoya University Graduate School of Medicine, Aichi, Japan. *In Vivo* (2005), 19(5), 861-866. Publisher: International Institute of Anticancer Research, CODEN: IVIVE4 ISSN: 0258-851X. Journal written in English. CAN 143:432165 AN 2005:943890 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: The synergistic antitumor effect of a combination of docetaxel and capecitabine is reported to be attributable to docetaxel-mediated up-regulation of thymidine phosphorylase (dThdPase). Materials and Methods: I.v. docetaxel (15 mg/kg) was given to nude mice bearing xenografts of the gastric cancer cell lines MKN45 and MKN28. Mice were sacrificed on days 7, 10 and 22 and tumor samples were taken to measure the activities of thymidylate synthase, dihydropyrimidine dehydrogenase, dThdPase and orotate phosphoribosyltransferase. The efficacy of capecitabine or S-1, alone and in combination with docetaxel, was then evaluated in vivo. Docetaxel was administered i.v. on days 8 and 22 at 15 mg/kg, while capecitabine (269 mg/kg) or S-1 (7.5 mg/kg) were administered orally 5 times a week for 4 wk. Results: Tumor regression was obsd. only for a combination of capecitabine and docetaxel against MKN28, while additive growth inhibition was obtained by the combination of docetaxel and both S-1 and capecitabine on MKN45 tumor xenografts. Induction of dThdPase activity was obsd. only for MKN45. The activity of no other enzyme was significantly affected following administration of docetaxel. Conclusion: The combination of oral fluoropyrimidine and docetaxel showed augmented antitumor activity, but this may be attributed to mechanisms other than changes in 5-fluorouracil-metabolizing

enzymes.

Answer 49:

Bibliographic Information

Nontoxic Suramin Treatments Enhance Docetaxel Activity in Chemotherapy-Pretreated Non-Small Cell Lung Xenograft Tumors. Lu, Ze; Wientjes, Trini S.-S.; Au, Jessie L.-S. College of Pharmacy, The Ohio State University, Columbus, OH, USA. *Pharmaceutical Research* (2005), 22(7), 1069-1078. Publisher: Springer, CODEN: PHREEB ISSN: 0724-8741. Journal written in English. CAN 143:259713 AN 2005:628482 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose. We reported that nontoxic suramin treatments enhance the activity of chemotherapy in preclin. models, a finding supported by the results of subsequent phase I/II trials in chemotherapy-naive non-small cell lung cancer (NSCLC) patients who received/carboplatin (P/C) combination therapy. The present study evaluated whether suramin enhances the activity of docetaxel in human NSCLC xenografts. **Methods.** The in vitro effect of suramin on docetaxel activity was evaluated using 3-D histocultures of chemotherapy-naive A549 tumors. For in vivo activity evaluation, we first established the P/C pretreatment schedule that produced tumor growth inhibition, but not tumor eradication, and established the maximally tolerated docetaxel/suramin regimens. In the second study, P/C-treated animals received physiol. saline, single-agent suramin (10 mg/kg), docetaxel (10 mg/kg), or the combination twice weekly for 3 wk. **Results.** The in vitro results showed that 20 μ M suramin, which had no activity as single agent, enhanced the docetaxel activity (measured as 50% inhibition of DNA synthesis) by more than 10-fold. The in vivo studies showed reduced tumor growth by P/C (30% growth in 14 days vs. 75% in control). In contrast, docetaxel produced tumor regression (15% redn.) in P/C-treated animals, significantly reduced, on a cellular level, the viable cell d. and the proliferating fraction (40% redn. for both measurements), and enhanced the apoptotic fraction 4-fold ($p < 0.05$ for all effects). Suramin had no activity or toxicity (measured as body wt. loss) but significantly enhanced the docetaxel activity. Compared to docetaxel alone, the combination showed earlier onset of tumor size redn., greater extent of tumor regression (31 vs. 15%), greater redn. of viable cell d. and proliferating fraction (addnl. 15-25% redn.), and greater apoptotic fraction (addnl. 2.5-fold increase) ($p < 0.05$ for all parameters). **Conclusions.**

Results of the present study indicate that nontoxic suramin treatments enhanced the activity of docetaxel in P/C-pretreated A549 xenograft tumors in mice without enhancing host toxicity. These encouraging results provided the basis for phase I/II trials of docetaxel plus low-dose suramin in patients with NSCLC in second-/third-line settings.

Answer 50:

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 51:

Bibliographic Information

Inhibition of cyclooxygenase (COX)-2 expression by tet-Inducible COX-2 antisense cDNA in hormone-refractory prostate cancer significantly slows tumor growth and improves efficacy of chemotherapeutic drugs. Dandekar, Devendra S.; Lokeshwar, Bal L. Department of Urology and Sylvester Comprehensive Cancer Center, University of Miami School of Medicine, Miami, FL, USA. *Clinical Cancer Research* (2004), 10(23), 8037-8047. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 142:253964 AN 2004:1048149 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Overexpression of the proinflammatory enzyme cyclooxygenase (COX)-2 is assocd. with the progression of various malignancies; the role of COX-2 in prostate cancer is less clear. The significance of COX-2 in prostate cancer growth and response to chemotherapy was investigated in an androgen-refractory prostate cancer cell line using a Tet-inducible antisense COX-2 expression system. An antisense COX-2 cDNA construct under the control of a doxycycline-inducible promoter was transfected into a prostate cancer cell line, PC-3ML. Modulations of cell growth, apoptosis, and chemosensitivity in the presence or absence of doxycycline were analyzed. Tumor incidence, growth rate, and response to two cytotoxic drugs, COL-3 [chem. modified tetracycline-3-(6-demethyl-6-deoxy-4-dedimethylamino-tetracycline)] and Taxotere (docetaxel), were investigated in tumor xenografts. Apoptotic incidences and tumor microvessel d. in tumors were detd. by immunohistochem. Conditional suppression of COX-2 in PC-3ML caused reduced cell proliferation, decreased levels of phosphorylated AKT, G0-G1 arrest, and increased apoptosis and caspase-3 activity. Suppression of COX-2 increased Bax protein and decreased Bcl-xL protein in vitro. COX-2 antisense-expressing PC-3ML tumors showed a 57% growth delay compared with nontransfected or vector controls. Oral administration of COL-3 (40 mg/kg, oral gavage) or Taxotere (2.3 mg/kg, i.p.; 3x per wk) in tumor-bearing mice further slowed tumor growth (65% and .apprx.94%, resp.). Compared with the control group, the occurrence of apoptosis in antisense COX-2 tumors was eight times higher, and the tumor microvessel d. was three times lower. These results provide direct evidence that constitutive expression of COX-2 in prostate cancer has both angiogenic and cytoprotective functions. Suppression of tumor cell COX-2 is sufficient to enhance chemotherapy response in prostate cancer.

Answer 52:

Bibliographic Information

Low dose fractionated radiation potentiates the effects of taxotere in nude mice xenografts of squamous cell carcinoma of head and neck. Spring, Paul M.; Arnold, Susanne M.; Shajahan, Shahin; Brown, Brandee; Dey, Swatee; Lele, Subodh M.; Valentino, Joseph; Jones, Raleigh; Mohiuddin, Mohammed; Ahmed, Mansoor M. Division of Otolaryngology, Department of Surgery, University of Kentucky, Lexington, KY, USA. *Cell Cycle* (2004), 3(4), 479-485. Publisher: Landes Bioscience, CODEN: CCEYAS ISSN: 1538-4101. Journal written in English. CAN 142:193444 AN 2004:1001110 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

This study evaluated the combined effect of Low Dose Fractionated Radiation (LDFRT) and Taxotere (TXT) therapy on the growth of SCCHN (squamous cell carcinoma of head and neck; SQ-20B, a p53 mutant SCCHN cell line) tumors in a nude mouse model to exploit the increased hyper radiation sensitivity (HRS) phenomenon present in G2/M cell cycle phase when induced by low doses of radiation that was demonstrated in in vitro settings. Seventy-eight animals were randomized into one control group and 5 treatment groups (treatments were administered weekly for six weeks). Tumor regression was obsd. in all the groups, however, tumor regression was not significant in 2 Gy or TXT or 2 Gy plus TXT treated groups when compared to control group. The tumor regression was significant in both the LDFRT group ($p < 0.0043$) and LDFRT + TXT group ($p < 0.0006$) when compared to the other groups. A significantly prolonged tumor growth delay was obsd. in LDFRT group ($p < 0.0081$). Importantly, in combination of TXT and LDFRT, no tumor regrowth was obsd. in 12 out of 13 mice since LDFRT + TXT treatment caused a sustained regression of tumors for 9 wk. Mol. anal. of resected tumor specimens demonstrated that Bax levels were elevated with a concomitant increase in cytochrome c release

into the cytosol in treatment Group VI. These findings strongly suggest that LDFRT can be used in combination with TXT to potentiate the effects of drug on tumor regression through an apoptotic mode of death. Furthermore, the G2/M cell cycle arrest by TXT appears to be an important component of the enhanced apoptotic effect of TXT + LDFRT combined treatment.

Answer 53:

Bibliographic Information

HIV-1 Protease Inhibitor, Ritonavir: A Potent Inhibitor of CYP3A4, Enhanced the Anticancer Effects of Docetaxel in Androgen-Independent Prostate Cancer Cells In vitro and In vivo. Ikezoe, Takayuki; Hisatake, Yasuko; Takeuchi, Tamotsu; Ohtsuki, Yuji; Yang, Yang; Said, Jonathan W.; Taguchi, Hirokuni; Koeffler, H. Phillip. Cedars-Sinai Medical Center, Division of Hematology/Oncology, UCLA School of Medicine, Los Angeles, CA, USA. *Cancer Research* (2004), 64(20), 7426-7431. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 141:360326 AN 2004:858477 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We previously showed that HIV-1 protease inhibitors (PIs) slowed the proliferation of human myeloid leukemia cells and enhanced their differentiation in the presence of all-trans-retinoic acid. In this study, we found that PIs, including ritonavir, saquinavir, and indinavir, inhibited the growth of DU145 and PC-3 androgen-independent prostate cancer cells as measured by a clonal proliferation assay. Recent studies showed that ritonavir inhibited cytochrome P 450 3A4 enzyme (CYP3A4) in liver microsomes. The CYP3A4 is involved in drug metab. and acquisition of drug resistance. To clarify the drug interaction between ritonavir and other anticancer drugs, we cultured DU145 cells with docetaxel either alone or in combination with ritonavir. Ritonavir enhanced the antiproliferative and proapoptotic effects of docetaxel in the hormonally independent DU145 prostate cancer cells in vitro as measured by the clonogenic soft agar assay and detection of the activated form of caspase-3 and cleavage of poly(ADP-ribose) polymerase using Western blot anal. Real-time PCR showed that docetaxel induced the expression of CYP3A4 at the transcriptional level, and ritonavir (10⁻⁵ mol/L) completely blocked this induction. An ELISA-based assay also showed that ritonavir inhibited DNA binding activity of nuclear factor κ B (NF κ B) in DU145 cells, which is a contributor to drug resistance in cancer cells. Furthermore, combination treatment of docetaxel and ritonavir dramatically inhibited the growth of DU145 cells present as tumor xenografts in BNX nude mice compared with either drug alone. Importantly, docetaxel induced expression of CYP3A4 in DU145 xenografts, and ritonavir completely blocked this induction. Ritonavir also inhibited NF κ B DNA binding activity in DU145 xenografts. Extensive histol. analyses of the liver, spleen, kidneys, bone marrow, skin, and s.c. fat pads from these mice showed no abnormalities.

In summary, combination therapy of ritonavir and anticancer drugs holds promise for the treatment of individuals with advanced, drug resistant cancers.

Answer 54:

Bibliographic Information

Targeting vascular and avascular compartments of tumors with C. novyi-NT and anti-microtubule agents. Dang, Long H.; Bettegowda, Chetan; Agrawal, Nishant; Cheong, Ian; Huso, David; Frost, Philip; Loganzo, Frank; Greenberger, Lee; Barkoczy, Jozsef; Pettit, George R.; Smith, Amos B., III; Gurulingappa, Hallur; Khan, Saeed; Kinzler, Kenneth W.; Zhou, Shibin; Vogelstein, Bert. Howard Hughes Medical Institute and Sidney Kimmel Cancer Center, USA. *Cancer Biology & Therapy* (2004), 3(3), 326-337. Publisher: Landes Bioscience, CODEN: CBTAO ISSN: 1538-4047. Journal written in English. CAN 142:106673 AN 2004:624546 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Current approaches for treating cancer are limited, in part, by the inability of drugs to affect the poorly vascularized regions of tumors. We have found that C. novyi-NT in combination with anti-microtubule agents can cause the destruction of both the vascular and avascular compartments of tumors. The two classes of microtubule inhibitors were found to exert markedly different effects. Some agents that inhibited microtubule synthesis, such as HTI-286 and vinorelbine, caused rapid, massive hemorrhagic necrosis when used

in combination with *C. novyi*-NT. In contrast, agents that stabilized microtubules, such as the taxanes docetaxel and MAC-321, resulted in slow tumor regressions that killed most neoplastic cells. Remaining cells in the poorly perfused regions of tumors could be eradicated by *C. novyi*-NT. Mechanistic studies showed that the microtubule destabilizers, but not the microtubule stabilizers, radically reduced blood flow to tumors, thereby enlarging the hypoxic niche in which *C. novyi*-NT spores could germinate. A single i.v. injection of *C. novyi*-NT plus selected anti-microtubule agents was able to cause regressions of several human tumor xenografts in nude mice in the absence of excessive toxicity.

Answer 55:

Bibliographic Information

Antitumor activity of irifolven monotherapy and in combination with mitoxantrone or docetaxel against human prostate cancer models. van Laar, Emily S.; Weitman, Steven; MacDonald, John R.; Waters, Stephen J. Research and Development Department, MGI Pharma, Inc., Bloomington, MN, USA. *Prostate (New York, NY, United States)* (2004), 59(1), 22-32. Publisher: Wiley-Liss, Inc., CODEN: PRSTDS ISSN: 0270-4137. Journal written in English. CAN 141:325309 AN 2004:341654 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

BACKGROUND: Irifolven (6-hydroxymethylacylfulvene, HMAF, MGI 114) is a novel antitumor agent currently undergoing clin. trials in hormone-refractory prostate cancer. This report examines the efficacy of irifolven alone or in combination with mitoxantrone or docetaxel against androgen-independent prostate cancer cell lines. **METHODS:** To elucidate the activity of irifolven monotherapy and in combination, PC-3 and DU-145 cell lines were utilized in cellular viability assessments and tumor growth inhibition studies. **RESULTS:** Viability assays with irifolven and mitoxantrone show additive to synergistic activity. Furthermore, irifolven and mitoxantrone in combination exhibit enhanced antitumor activity against PC-3 and DU-145 xenografts. Additive combination effects are also obsd. when irifolven and docetaxel were tested against PC-3 xenografts and curative activity (8/10 CR) is obsd. in DU-145 xenografts. **CONCLUSIONS:** These studies demonstrate that irifolven displays strong activity as monotherapy and in combination with mitoxantrone or docetaxel against androgen-independent prostate cancer in vitro and in vivo; thus, supporting the clin. investigation of irifolven against hormone-refractory prostate cancer.

Answer 56:

Bibliographic Information

Potentiation of tumor response to radiation or chemoradiation by selective cyclooxygenase-2 enzyme inhibitors. Nakata, Eiko; Mason, Kathryn A.; Hunter, Nancy; Husain, Amir; Raju, Uma; Liao, Zhongxing; Ang, Kian K.; Milas, Luka. Department of Experimental Radiation Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA. *International Journal of Radiation Oncology, Biology, Physics* (2004), 58(2), 369-375. Publisher: Elsevier Science Inc., CODEN: IOBPD3 ISSN: 0360-3016. Journal written in English. CAN 141:291330 AN 2004:78653 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Cyclooxygenase-2 (COX-2) is an enzyme expressed primarily in pathol. states, such as inflammatory disorders and cancer, where it mediates prostaglandin prodn. Its overexpression is assocd. with more aggressive biol. tumor behavior and adverse patient outcome. Increasing evidence shows that agents that selectively inhibit COX-2 enhance tumor response to radiation or chemotherapeutic agents. This article gives an overview of some of this evidence. In addn., we describe new results showing that celecoxib, a selective COX-2 inhibitor, enhanced response of A431 human tumor xenografts in nude mice to radiation by an enhancement factor (EF) of 1.43 and to the chemotherapeutic agent docetaxel by an EF of 2.07. Celecoxib also enhanced tumor response when added to the combined docetaxel plus radiation treatment (EF = 2.13). Further expts. showed that selective COX-2 inhibitors enhanced tumor cell sensitivity to ionizing radiation, involving inhibition of cellular repair from radiation damage and cell cycle redistribution as mechanisms for some cell types. The results show that selective COX-2 inhibitors have the potential to improve tumor radiotherapy or radiochemotherapy, and this therapeutic strategy is currently under clin. testing.

Answer 57:

Bibliographic Information

Preclinical evaluation of the tyrosine kinase inhibitor SU11248 as a single agent and in combination with "standard of care" therapeutic agents for the treatment of breast cancer. Abrams, Tinya J.; Murray, Lesley J.; Pesenti, Enrico; Walker Holway, Vicky; Colombo, Tina; Lee, Leslie B.; Cherrington, Julie M.; Pryer, Nancy K. Preclinical Research and Experimental Development, SUGEN, Inc., South San Francisco, CA, USA. *Molecular Cancer Therapeutics* (2003), 2(10), 1011-1021. Publisher: American Association for Cancer Research, CODEN: MCTOCF ISSN: 1535-7163. Journal written in English. CAN 140:192417 AN 2003:844931 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

SU11248 is an oral multitargeted tyrosine kinase inhibitor with antitumor and antiangiogenic activities through targeting platelet-derived growth factor receptor, vascular endothelial growth factor receptor, KIT, and FLT3, the first three of which are expressed in human breast cancer and/or its supporting tissues. The purpose of the present studies was to demonstrate the potent anticancer activity of SU11248 alone or in combination with conventional cytotoxic agents against several distinct preclin. models of breast cancer. SU11248 was administered as a monotherapy to (1) mouse mammary tumor virus-v-Ha-ras mice and 7,12-dimethylbenz(a)anthracene-treated rats bearing mammary tumors and (2) mice bearing human breast cancer xenografts of s.c. MX-1 tumors and osseous metastasis of a MDA-MB-435-derived cell line (435/HAL-Luc). SU11248 was also administered in combination with docetaxel both in xenograft models and in combination with 5-fluorouracil and doxorubicin in the MX-1 model. SU11248 treatment potently regressed growth of mammary cancers in mouse mammary tumor virus-v-Ha-ras transgenic mice (82% regression) and 7,12-dimethylbenz(a)anthracene-induced mammary tumors in rats (99% regression at the highest dose; $P < 0.05$ for both). This agent also inhibited MX-1 tumor growth by 52%, with markedly enhanced anticancer effects when administered in combination with docetaxel, 5-fluorouracil, or doxorubicin compared with either agent alone ($P < 0.05$). SU11248 treatment in combination with docetaxel effectively prolonged survival of mice, with 435/HAL-Luc cancer xenografts established in bone compared with either agent alone ($P < 0.05$). These results demonstrate that SU11248 is effective in preclin. breast cancer models and suggest that it may be useful in the treatment of breast cancer in the clinic.

Answer 58:

Bibliographic Information

Antitumor activity of doxorubicin in combination with docetaxel against human breast cancer xenografts. Egawa, Tomohisa; Kubota, Tetsuro; Suto, Akihiko; Otani, Yoshihide; Furukawa, Toshiharu; Saikawa, Yoshiro; Watanabe, Masahiko; Kumai, Koichiro; Kitajima, Masaki. Department of Surgery, School of Medicine, Keio University, Shinjuku-ku, Tokyo, Japan. *In Vivo* (2003), 17(1), 23-28. Publisher: International Institute of Anticancer Research, CODEN: IVIVE4 ISSN: 0258-851X. Journal written in English. CAN 139:285841 AN 2003:271051 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

In this study we assessed the in vivo antitumor activity of combined docetaxel (DOCE) and doxorubicin (DXR) treatment using 2 human breast carcinoma cell xenografts (R-27 and MX-1) in the nude mouse model. The transplanted tumors were allowed to reach exponential growth, whereupon 10 or 40 mg DOCE per kg alone (i.p.), 8 mg DXR per kg alone (iv), or 10 mg/kg DOCE (i.p.) and 8 mg/kg of DXR (iv), in the sequence of DOCE followed by DXR, were administered. The in vivo antitumor activity of combined DOCE and DXR was synergistic against R-27 and additive against MX-1. P-glycoprotein (P-gp) was detected immunohistochem., and was highly expressed in R-27, but not in MX-1. In conclusion, DOCE may increase the antitumor activity of DXR against P-gp-pos. breast cancer xenografts, such that the DOCE and DXR combination may be a useful treatment in clin. breast cancer.

Answer 59:

Bibliographic Information

Early response of prostate carcinoma xenografts to docetaxel chemotherapy monitored with diffusion MRI. Jennings, Dominique; Hatton, B. Nicholas; Guo, Jingyu; Galons, Jean-Philippe; Trouard, Theodore P.; Raghunand, Natarajan; Marshall, James; Gillies, Robert J. Department of Biochemistry, University of Arizona Health Sciences Center, Tucson, AZ, USA. *Neoplasia* (New York, NY, United States) (2002), 4(3), 255-262. Publisher: Nature Publishing Group, CODEN: NEOPFL ISSN: 1522-8002. Journal written in English. CAN 138:52014 AN 2002:455497 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

For many anticancer therapies, it would be desirable to accurately monitor and quantify tumor response early in the treatment regimen. This would allow oncologists to continue effective therapies or discontinue ineffective therapies early in the course of treatment, and hence, reduce morbidity. This is esp. true for second-line therapies, which have reduced response rates and increased toxicities. Previous works by others and ourselves have shown that water mobility, measured by diffusion-weighted magnetic resonance imaging (DW-MRI), increases early in tumors destined to respond to therapies. In the current communication, we further characterize the utility of DW-MRI to predict response of prostate cancer xenografts to docetaxel in SCID mice in a preclin. setting. The current data illustrate that tumor vols. and secreted prostate-specific antigen both respond strongly to docetaxel in a dose-responsive manner, and the apparent diffusion coeff. of water (ADC_w) increases significantly by 2 days even at the lowest doses (10 mg/kg). The ADC_w data were parsed by histogram analyses. Our results indicate that DW-MRI can be used for early detection of prostate carcinoma xenograft response to docetaxel chemotherapy.

Answer 60:

Bibliographic Information

Combined modality radioimmunotherapy for human prostate cancer xenografts with taxanes and 90yttrium-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 90yttrium-(90Y)-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 90Y-DOTA-peptide-ChL6. Nude mice bearing human prostate cancer PC3 xenografts were treated with 90Y-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 61:

Bibliographic Information

Schedule dependency of antitumor activity in combination therapy with capecitabine/5'-deoxy-5-fluorouridine, and docetaxel in breast cancer models. Fujimoto-Ouchi, Kaori; Tanaka, Yutaka; Tominaga, Takeshi. Oncology, Nippon Roche Research Center, Kanagawa, Japan. *Clinical Cancer Research* (2001), 7(4), 1079-1086. Publisher: American Association for Cancer Research, CODEN: CCREFA ISSN: 1078-0432. Journal written in English. CAN 136:48073 AN 2001:363667 CAPLUS

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Abstract

Docetaxel and capecitabine are being prescribed for the treatment of breast cancer. In this study, the authors tried to identify the optimal administration schedule in combination therapy with these anticancer drugs in human cancer xenograft models. Capecitabine was given p.o. daily for 2 wk (days 1-14), whereas docetaxel was given i.v. on day 1, day 8, or day 15 in a 3-wk regimen to the mice bearing MX-1 human breast cancer xenograft. The combination showed better antitumor efficacy than the monotherapy of either agent in either dosing regimen. However, the most potent and synergistic activity was obsd. when docetaxel was given on day 8. This potent effect appears to be characteristic of the combination of docetaxel with capecitabine or its intermediate metabolite 5'-deoxy-5-fluorouridine (doxifluridine: 5'-dFUrd). Docetaxel given on day 8 showed a potent effect in combination with 5'-dFUrd, but a much weaker effect was obsd. in combination with 5-fluorouracil or UFT, a fixed combination of tegafur and uracil. Better efficacy was also obsd. in the MAXF401 human breast cancer xenograft and in the mouse A755 mammary tumor when docetaxel was given at the middle of the capecitabine or 5'-dFUrd treatment rather than other dosing regimens. In contrast, the efficacy in WiDr human colon cancer xenograft was somewhat better when docetaxel was given on day 1. One possible explanation for the synergy is that docetaxel up-regulates tumor levels of thymidine phosphorylase, the enzyme essential for the activation of capecitabine and 5'-dFUrd to 5-fluorouracil. In fact, docetaxel up-regulated the thymidine phosphorylase levels 4.8- and 1.9-fold in the WiDr and MX-1 models, resp. However, it did not up-regulate in the MAXF401 and A755 models in which a potent combination effect was obsd. as well. Other mechanisms, particularly those for the synergy with docetaxel given at the middle during capecitabine/5'-dFUrd administration, would also exist. Based on these observations, clin.

studies on the day 8 combination regimen with docetaxel and capecitabine/5'-dFUrd are warranted.

Answer 62:

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 63:

Bibliographic Information

Response of human tumor xenografts in athymic nude mice to docetaxel (RP 56976, Taxotere). Dykes, Donald J.; Bissery, Marie Christine; Harrison, Steadman D. Jr.; Waud, William R. Southern Research Institute, Birmingham, AL, USA. *Investigational New Drugs* (1995), 13(1), 1-11. Publisher: Kluwer, CODEN: INNDDK ISSN: 0167-6997. Journal written in English.

CAN 123:306136 AN 1995:870275 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Docetaxel (Taxotere, RP 56976, NSC 628503), a new taxoid, was evaluated for preclin. evidence of anticancer activity in athymic nude (NCR-nu) mice bearing established, s.c. implanted human tumor xenografts CX-1 or KM20L2 (colon carcinomas), LX-1 (lung carcinoma), MX-1 (mammary carcinoma), and SK-MEL-2 (melanoma). Other evaluations used OVCAR-3 (ovarian carcinoma) xenografts implanted i.p. Docetaxel was administered i.v. every 4 days for 3 injections (q4d × 3) except for one OVCAR-3 expt. in which the drug was given i.p. every 7 days for 3 injections. Tumor measurements, animal body wts., and mortality were detd. The highest dosage used (50 mg/kg/dose) was toxic in all expts. in which the 4-day treatment interval was used. The maximally tolerated dosage (MTD) ranged from 15 to 33 mg/kg/dose. Therapeutic responses among these xenografts ranged from clin. important long-term tumor-free survivors (MX-1, SK-MEL-2, and OVCAR-3) to tumor growth delays of various durations (CX-1, LX-1, and KM20L2). The response of SK-MEL-2, a xenograft highly refractory to available drugs, was particularly noteworthy. These results are indicative of a broad spectrum of antitumor activity for docetaxel.

Answer 64:

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 65:

Bibliographic Information

Effectiveness of taxanes-based chemotherapy against hormone-refractory prostate carcinoma. Shiroki Ryoichi; Kuwahara Yoshitaka; Sakurai Takahiko; Maruyama Takahiro; Hoshinaga Kiyotaka The Department of Urology, Fujita Health University School of Medicine Hinyokika kyo. Acta urologica Japonica (2006), 52(6), 481-5. Journal code: 0421145. ISSN:0018-1994. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 16848362 AN 2006426323 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

We performed an investigative and clinical study of docetaxel, and evaluated its efficacy against hormone-refractory prostate carcinoma (HRPC). In an in vitro experiment, docetaxel suppressed the human prostate cell line proliferation not

only in an androgen-dependent cell line, LNCaP, but also in androgen-independent cell line, PC-3, in a dose-dependent manner. In an in vivo experiment applying an SCID mouse xenograft model with PC-3, docetaxel administration suppressed the tumor growth more than 95%. In a clinical study, eight cases were enrolled to low-dose (20 mg/m²/wk) weekly regimen and an other eight to high-dose (60 mg/m²/wk) administration of docetaxel every three weeks. A prostate specific antigen (PSA) decline of more than 50% were observed in 4 (50%) in the low-dose group and 5 (63%) in the high-dose group. The median time to progression and overall survival were 8.5 and 13.2 months in the low-dose group and more than 5.5 and 8.5 months in the high-dose one, respectively. This regimen was well tolerated, and the incidence of adverse effect was relatively low and light. Grade 3 neutropenia or leukocytopenia without fever was seen in three patients (18.8%). Only one patient required administration of granulocyte-colony stimulating factor because of neutropenia. No other grade 3 or 4 toxicity was observed. In conclusion, docetaxel-based chemotherapy was well tolerated and an active treatment for HRPC cases.

Answer 66:

Bibliographic Information

Enhancement of antitumor activity of docetaxel by celecoxib in lung tumors. Shaik Madhu Sudhan; Chatterjee Abhijit; Jackson Tanise; Singh Mandip College of Pharmacy, Florida A&M University, Tallahassee, FL 32307, USA International journal of cancer. Journal international du cancer (2006), 118(2), 396-404. Journal code: 0042124. ISSN:0020-7136. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, N.I.H., EXTRAMURAL) written in English. PubMed ID 16052515 AN 2005606687 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Our study investigates the effect of a highly selective cyclooxygenase-2 (COX-2) inhibitor, celecoxib, on the cytotoxicity of docetaxel in nude mice bearing A549 tumor xenografts and elucidates the molecular mechanisms of the antitumor effect of this combination. Female nu/nu mice, xenografted with s.c. A549 tumors were treated with either celecoxib (150 mg/kg/day), docetaxel (10 mg/kg) or a combination of both. The tumor tissues were quantified for the induction of apoptosis, intratumor levels/expressions of prostaglandin E2 (PGE2), 15 deoxy prostaglandin J2 (15-d PGJ2), microsomal prostaglandin E synthase (mPGES) and cytoplasmic phospholipase A2 (cPLA2). The combination of celecoxib with docetaxel significantly inhibited the tumor growth ($p < 0.03$) as compared to celecoxib or docetaxel alone, decreased the levels of PGE2 by 10-fold and increased the 15-d PGJ2 levels by 4-fold as compared to control. The combination also enhanced the peroxisome proliferator-activated receptor (PPAR)-gamma expression, decreased the expression of cPLA2, mPGES and vascular endothelial growth factor (VEGF), but had no effect on the expression of COX-1 or COX-2 in tumor tissues. TUNEL staining of the tumor tissues showed a marked increase in the apoptosis in the combination group as compared to the celecoxib- or docetaxel-treated groups and this was associated with an increase in the intratumor p53 expression. In conclusion, the combination of celecoxib with docetaxel produces a greater antitumor effect in s.c. A549 tumors as compared to celecoxib or docetaxel alone and this effect is associated with concomitant alterations in the intratumor levels of PGE2 and 15-d PGJ2. Copyright 2005 Wiley-Liss, Inc.

Answer 67:

Bibliographic Information

Experimental chemotherapy of xenotransplanted oral squamous epithelial carcinoma: effectiveness of docetaxel (taxotere) in the nude mouse model. Huttmann C; Eckardt A; Fokas K; Haindl J Klinik und Poliklinik für Mund-, Kiefer- und Gesichtschirurgie, Medizinische Hochschule Hannover. Huttmann.Chr@t-online.de Mund-, Kiefer- und Gesichtschirurgie : MKG (1999), 3(5), 257-62. Journal code: 9716576. ISSN:1432-9417. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in German. PubMed ID 10540826 AN 2000008340 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Originating from plants, the taxoids, in particular docetaxel (Taxotere), represent progress in antitumoral chemotherapy. In addition to their use as palliative treatment they have also proved to be increasingly important for adjuvant and neoadjuvant treatment of oral squamous cell carcinoma (SCC). In the present nude mouse model the efficacy of chemotherapeutic agents against exemplary oral SCC were examined using cell line HNSCC 001. Typical biological properties such as expression of serum tumor markers and treatment-related alteration were reviewed. Intraperitoneal administration of 30 mg docetaxel per kilogram body weight at a time resulted in significant growth inhibition ($P < 0.001$), however without complete remission. Mean values of relative tumor volume ranged from 95% to 131% in the treated groups as compared to 311% in animals without treatment. Application more frequently than weekly did not result in a significant increase in antitumor activity. From the present experimental study no final conclusion can be drawn regarding weekly docetaxel administration mostly used in clinical phase II trials. Except for SCC, for which values correlated well with tumor volume ($r = 0.85$ without treatment and $r = 0.87$ with treatment), on the one hand, and a distinct treatment-related decrease, on the other, the tested tumor markers TPA and TPS proved to be less valuable for screening of treatment and follow-up in this murine model.

Answer 68:

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.