

Answer 1:

Bibliographic Information

Pharmacological targeting of NF- κ B potentiates the effect of the topoisomerase inhibitor CPT-11 on colon cancer cells.

Lagadec, P.; Griessinger, E.; Nawrot, M. P.; Fenouille, N.; Colosetti, P.; Imbert, V.; Mari, M.; Hofman, P.; Czerucka, D.; Rousseau, D.; Berard, E.; Dreano, M.; Peyron, J. F. INSERM U526, Nice, Fr. *British Journal of Cancer* (2008), 98(2), 335-344. Publisher: Nature Publishing Group, CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 149:191165 AN 2008:106023 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

NF- κ B interferes with the effect of most anti-cancer drugs through induction of anti-apoptotic genes. Targeting NF- κ B is therefore expected to potentiate conventional treatments in adjuvant strategies. Here we used a pharmacol. inhibitor of the IKK2 kinase (AS602868) to block NF- κ B activation. In human colon cancer cells, inhibition of NF- κ B using 10 μ AS602868 induced a 30-50% growth inhibitory effect and strongly enhanced the action of SN-38, the topoisomerase I inhibitor and CPT-11 active metabolite. AS602868 also potentiated the cytotoxic effect of two other antineoplastic drugs: 5-fluorouracil and etoposide. In xenografts expts., inhibition of NF- κ B potentiated the antitumoral effect of CPT-11 in a dose-dependent manner. Eighty-five and 75% decreases in tumor size were obsd. when mice were treated with, resp., 20 or 5 mg kg⁻¹ AS602868 assocd. with 30 mg kg⁻¹ CPT-11 compared to 47% with CPT-11 alone. Ex vivo tumor analyses as well as in vitro studies showed that AS602868 impaired CPT-11-induced NF- κ B activation, and enhanced tumor cell cycle arrest and apoptosis. AS602868 also enhanced the apoptotic potential of TNF α on HT-29 cells. This study is the first demonstration that a pharmacol. inhibitor of the IKK2 kinase can potentiate the therapeutic efficiency of antineoplastic drugs on solid tumors.

Answer 2:

Bibliographic Information

Investigation of Two Dosing Schedules of Vandetanib (ZD6474), an Inhibitor of Vascular Endothelial Growth Factor Receptor and Epidermal Growth Factor Receptor Signaling, in Combination with Irinotecan in a Human Colon Cancer Xenograft Model.

Troiani, Teresa; Serkova, Natalie J.; Gustafson, Daniel L.; Henthorn, Thomas K.; Lockerbie, Owen; Merz, Andrea; Long, Michael; Morrow, Mark; Ciardiello, Fortunato; Eckhardt, S. Gail. Division of Medical Oncology, University of Colorado at Denver and Health Sciences Center, Aurora, CO, USA. *Clinical Cancer Research* (2007), 13(21), 6450-6458. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 148:417358 AN 2007:1243727 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: This in vivo study was designed to det. the optimal doses and schedules of vandetanib, a dual epidermal growth factor receptor (EGFR)-vascular endothelial growth factor receptor tyrosine kinase inhibitor, in combination with irinotecan in a murine xenograft model of human colon cancer. Exptl. Design: HT-29 tumor-bearing nude mice were treated with two doses of vandetanib (12.5 and 25 mg/kg/d) with or without irinotecan (100 mg/kg) using either sequential or concurrent schedules for 30 days. Tumor size was measured using std. variables, whereas the antiangiogenic response was evaluated using dynamic contrast-enhanced magnetic resonance imaging. Addnl., effects on EGFR-dependent signal transduction pathways and proliferation were assessed using immunohistochem. These pharmacodynamic end points were then evaluated for assocns. with antitumor efficacy and/or to plasma/tumor concns. of vandetanib. Results: The greatest antitumor efficacy was obsd. in the groups receiving the highest dose of vandetanib given continuously (concurrent schedule), alone or in combination with irinotecan. These dosing schedules resulted in significant effects on tumor vasculature, with decreased vol. transfer consts., area under the curve, and permeability surface factor as well as increased gadolinium clearance after 30 days of treatment. In addn., these groups showed the greatest inhibition of EGFR signaling. Interestingly, tumor concns. of vandetanib were increased by irinotecan in the concurrent schedule, possibly due to decreased tumor perfusion in this group. Conclusions: These data suggest that higher, sustained concns. of vandetanib (vs. intermittent), alone and in combination with irinotecan, result in optimal antitumor efficacy in this model and may have implications for the design of future clin. studies with this drug.

Answer 3:

Bibliographic Information

Efficacy of increasing the therapeutic index of irinotecan, plasma and tissue selenium concentrations is methylselenocysteine dose dependent. Azrak, Rami G.; Cao, Shousong; Pendyala, Lakshmi; Durrani, Farukh A.; Fakhri, Marwan; Combs, Gerald F.; Prey, Joshua; Smith, Patrick F.; Rustum, Youcef M. Department of Cancer Biology, Roswell Park Cancer Institute, Buffalo, NY, USA. *Biochemical Pharmacology* (2007), 73(9), 1280-1287. Publisher: Elsevier B.V., CODEN: BCPCA6 ISSN: 0006-2952. Journal written in English. CAN 147:1079 AN 2007:345159 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

This study was designed to understand the basis for the efficacy of methylselenocysteine (MSC) in increasing the therapeutic index of irinotecan against human tumor xenografts. Nude mice bearing human head and neck squamous cells carcinoma xenografts (FaDu and A253) were treated orally with different doses of MSC and irinotecan. Plasma, tumor and normal tissue samples were collected at different times after MSC treatments and were analyzed for selenium (Se) concn. using electrothermal at. absorption spectrophotometry. MSC is highly effective in modulating the therapeutic index of irinotecan. Enhanced irinotecan efficacy was greater in FaDu tumors (100% CR) than in A253 tumors (60% CR), and depended on MSC dose with a min. ED of 0.01 mg/d × 28. The highest plasma Se concn. was achieved 1 h after a single dose and 28 d after daily treatments of MSC. The ability of FaDu tumors to retain Se was significantly better than A253 tumors, and the highest Se concn. in normal tissue was achieved in the liver. Peak plasma and tissue Se concns. were functions of the dose and duration of MSC treatment. The MSC-dependent increase in Se level in normal tissues may contribute to the protective effect against irinotecan toxicity obsd. in those tissues. Intratumoral total Se concn. was not found to be predictive of the combination therapy response rates. There is a crit. need to develop a method to measure the active metabolite of MSC, rather than total Se.

Answer 4:

Bibliographic Information

Chimmitecan, a Novel 9-Substituted Camptothecin, with Improved Anticancer Pharmacologic Profiles In vitro and In vivo. Huang, Min; Gao, Heyong; Chen, Yi; Zhu, Hong; Cai, Yujun; Zhang, Xiongwen; Miao, Zehong; Jiang, Hualiang; Zhang, Jian; Shen, Hongwu; Lin, Liping; Lu, Wei; Ding, Jian. Divisions of Anti-Tumor Pharmacology and Chemistry, Drug Discovery and Design Center, and Center for Drug Metabolism and Pharmacokinetics Research, State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, Peop. Rep. China. *Clinical Cancer Research* (2007), 13(4), 1298-1307. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 147:45433 AN 2007:199246 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

PURPOSE: This study aimed to evaluate antitumor activities and pharmacol. profiles of chimmitecan, a novel 9-small-alkyl-substituted lipophilic camptothecin, in comparison with irinotecan (CPT-11) and topotecan. **Exptl. Design:** The in vitro cytotoxicities of chimmitecan in human tumor cell lines and multidrug resistance (MDR) cells were evaluated by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide and sulforhodamin B assays. DNA relaxation, cleavage assays, and cellular band depletion assay were combined to delineate its effects on topoisomerase I. DNA damage, cell cycle arrest, and apoptosis were assessed using comet assay, flow cytometry, and DNA ladder anal., resp. The in vivo antitumor activities were measured in nude mice bearing human tumor xenografts. **RESULTS:** Chimmitecan displayed more potent cytotoxicity than SN38 and topotecan. Neither a cross-resistance to chimmitecan in MDR cells nor an influence of human serum albumin in its cytotoxicity was obsd. Chimmitecan exhibited comparable effects on topoisomerase I compared with the ref. drugs, including inhibiting topoisomerase I catalytic activity and trapping and stabilizing covalent topoisomerase I-DNA complexes. Furthermore, nanomolar levels of chimmitecan caused impressive DNA damage, G2-M phase arrest, and apoptosis in human leukemia HL60 cells. I.v. administration of chimmitecan inhibited the growth of HCT-116, MDA-MB-435, BEL-7402, and A549 human carcinoma xenografts in nude mice, with greater potency than CPT-11 against the latter two tumors models. Chimmitecan presented potent efficacy in A549 tumor model when given orally. **CONCLUSIONS:** Chimmitecan is a potent inhibitor of

topoisomerase I and displays outstanding activity in vitro and in vivo. The substitution at the 9-position benefits chimmitecan a salient anti-MDR activity, stability in human serum albumin, improved soly., and oral availability, which might favorably promise its therapeutic potential in clin. settings.

Answer 5:

Bibliographic Information

Antitumor efficacy of edotecarin as a single agent and in combination with chemotherapy agents in a xenograft model.

Ciomei, Marina; Croci, Valter; Ciavolella, Antonella; Ballinari, Dario; Pesenti, Enrico. Department of Biology, Drug Discovery Oncology, Nerviano Medical Sciences, Milan, Italy. *Clinical Cancer Research* (2006), 12(9), 2856-2861. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 145:388833 AN 2006:532561 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The novel indolocarbazole edotecarin (J-107088, formerly ED-749) differs from other topoisomerase I inhibitors both pharmacokinetically and pharmacodynamically. In vitro, it is more potent than camptothecins and has a variable cytotoxic activity in 31 different human cancer cell lines. Edotecarin also possesses greater than additive inhibitory effects on cell proliferation when used in combination with other agents tested in vitro against various cancer cell lines. The present in vivo studies were done to extend the in vitro findings to characterize the antitumor effects of edotecarin when used either alone or in combination with other agents (i.e., 5-fluorouracil, irinotecan, cisplatin, oxaliplatin, and SU11248) in the HCT-116 human colon cancer xenograft model. Treatment effects were based on the delay in onset of an exponential growth of tumors in drug-treated vs. vehicle control-treated groups. In all studies, edotecarin was active both as a single agent and in combination with other agents. Combination therapy resulted in greater than additive effects, the extent of which depended on the specific dosage regimen. Toxicity in these expts. was minimal. Of all 359 treated mice, the six that died of toxicity were in the high-dose edotecarin/oxaliplatin group. The results suggest that edotecarin may serve as effective chemotherapy of colon cancer when used as a single agent, in combination with std. regimens and other topoisomerase inhibitors or with novel agents, such as the multitargeted tyrosine kinase inhibitor SU11248.

Answer 6:

Bibliographic Information

Activity of irinotecan and the tyrosine kinase inhibitor CEP-751 in medullary thyroid cancer.

Strock, Christopher J.; Park, Jong-In; Rosen, D. Marc; Ruggeri, Bruce; Denmeade, Samuel R.; Ball, Douglas W.; Nelkin, Barry D. Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA. *Journal of Clinical Endocrinology and Metabolism* (2006), 91(1), 79-84. Publisher: Endocrine Society, CODEN: JCEMAZ ISSN: 0021-972X. Journal written in English. CAN 144:121179 AN 2006:66228 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Context: Medullary thyroid cancer (MTC) is a cancer of the parafollicular C cells that commonly presents with an inherited or acquired RET gene mutation. There is currently no effective systemic treatment for MTC. Objective: The objective of this study was to investigate a systemic therapeutic approach to treat MTC. We studied the sensitivity of an MTC cell line and xenograft to irinotecan, alone and in combination with the tyrosine kinase inhibitor, CEP-751. Results: In TT cell culture and xenografts, irinotecan treatment was highly effective. This effect was augmented by treatment with CEP-751. Treatment of TT cell xenografts resulted in durable complete remission in 100% of the mice, with median time to recurrence of 70 d for irinotecan alone and more than 130 d for irinotecan plus CEP-751. Although irinotecan induced an S phase checkpoint arrest in TT cells, CEP-751 in combination with irinotecan resulted in a loss of this arrest. CEP-751 induced a loss in the induction of the DNA repair program marked by phospho-H2AX and the checkpoint pathway marked by the activated Chk1 pathway. Conclusions: Irinotecan treatment was highly effective in a preclin. model of human MTC, resulting in complete remission in 100% of the xenografts treated. The duration of remission was further enhanced by combination with the kinase inhibitor, CEP-751. These results suggest that irinotecan, alone or in combination, may be useful for the

treatment of MTC.

Answer 7:

Bibliographic Information

Cetuximab and Irinotecan Interact Synergistically to Inhibit the Growth of Orthotopic Anaplastic Thyroid Carcinoma Xenografts in Nude Mice. Kim, Seungwon; Prichard, Christopher N.; Younes, Maher N.; Yazici, Yasemin D.; Jasser, Samar A.; Bekele, B. Nebiyou; Myers, Jeffrey N. Departments of Head and Neck Surgery, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA. *Clinical Cancer Research* (2006), 12(2), 600-607. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 145:55478 AN 2006:63632 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: Anaplastic thyroid carcinoma (ATC) remains one of the most lethal known human cancers. Targeted mol. therapy with cetuximab, a monoclonal antibody against epidermal growth factor receptor, offers new treatment potentials for patient with ATC. Cetuximab has also been reported to have synergistic effects when combined with irinotecan, a topoisomerase inhibitor. Therefore, we hypothesized that cetuximab and irinotecan would be effective in inhibiting the growth and progression of ATC in a murine orthotopic model. **Exptl. Design:** The in vitro antiproliferative effects of cetuximab and irinotecan on ATC cell line ARO were examd. We also studied the in vivo effects of cetuximab and irinotecan on the growth, invasion, and metastasis of orthotopic ATC tumors in nude mice. The in vivo antitumor efficacy of cetuximab/irinotecan combination was also compared with that of doxorubicin. **Results:** Cetuximab alone did not show any antiproliferative or proapoptotic effect on this cell line. However, when combined with irinotecan, cetuximab potentiated the in vitro antiproliferative and proapoptotic effect of irinotecan. Cetuximab, irinotecan, and cetuximab/irinotecan combination resulted in 77%, 79%, and 93% in vivo inhibition of tumor growth, resp. Incidences of lymph node metastasis, laryngeal invasion, and tumor microvessel d. were also significantly decreased in these treatment groups. Furthermore, the cetuximab/irinotecan combination was significantly more effective than doxorubicin in inhibiting the growth of orthotopic ATC xenografts. **Conclusions:** Combination therapy with cetuximab/irinotecan inhibits the growth and progression of orthotopic ATC xenografts in nude mice. Given the lack of curative options for patients with ATC, combination therapy with cetuximab and irinotecan treatment warrants further study.

Answer 8:

Bibliographic Information

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

Abstract

Purpose: Immunostimulating Toll-like receptor 9 (TLR9) agonists cause antitumor activity interfering also with cancer proliferation and angiogenesis by mechanisms still incompletely understood. We hypothesized that modified TLR9 agonists could impair epidermal growth factor receptor (EGFR) signaling and, by this means, greatly enhance EGFR inhibitors effect, acting on both the receptor targeting and the immunol. arm. **Exptl. Design:** We used a novel second-generation, modified, immunomodulatory TLR9 agonist (IMO), alone and in combination with the anti-EGFR monoclonal antibody cetuximab or tyrosine kinase inhibitor gefitinib, on the growth of GEO and cetuximab-resistant derivs. GEO-CR colon cancer xenografts. We have also evaluated the expression of several proteins crit. for cell proliferation, apoptosis, and angiogenesis, including EGFR, mitogen-activated protein kinase, Akt, bcl-2, cyclooxygenase-2, vascular endothelial growth factor, and nuclear factor- κ B. **Results:** IMO inhibited GEO growth and signaling by EGFR and the other

proteins crit. for cell proliferation and angiogenesis. IMO plus the anti-EGFR antibody cetuximab synergistically inhibited tumor growth, signaling proteins, and microvessel formation. EGFR signaling inhibition by IMO is relevant because IMO cooperated also with EGFR tyrosine kinase inhibitor gefitinib in GEO tumors, while it was inactive against GEO-CR xenografts. On the other hand, IMO boosted the non-EGFR-dependent cetuximab activity, causing a cooperative antitumor effect in GEO-CR cells. Finally, combination of IMO, cetuximab and chemotherapeutic irinotecan eradicated the tumors in 90% of mice. Conclusion: IMO interferes with EGFR-related signaling and angiogenesis and has a synergistic antitumor effect with EGFR inhibitors, esp. with cetuximab, boosting both the EGFR dependent and independent activity of this agent. Moreover, this therapeutic strategy could be translated in patients affected by colorectal cancer.

Answer 9:

Bibliographic Information

Delta-24 Increases the Expression and Activity of Topoisomerase I and Enhances the Antiglioma Effect of Irinotecan.

Gomez-Manzano, Candelaria; Alonso, Marta M.; Yung, W. K. Alfred; McCormick, Frank; Curiel, David T.; Lang, Frederick F.; Jiang, Hong; Bekele, B. Nebiyu; Zhou, Xian; Alemany, Ramon; Fueyo, Juan. Departments of Neuro-Oncology, Neurosurgery, and Biostatistics, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA. *Clinical Cancer Research* (2006), 12(2), 556-562. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 145:55473 AN 2006:63626 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: In this study, we sought to det. whether Delta-24 could sensitize glioma cells to the topoisomerase I inhibitor irinotecan (CPT-11) and to identify the mechanisms underlying this enhanced anticancer effect. **Exptl. Design:** We used human glioblastoma cell lines for the in vitro studies. The expression of topoisomerase I was detd. in Western blot analyses, and topoisomerase I activity was detd. by measuring the relaxation of a supercoiled DNA. The cell cycle distribution of cells was detd. by flow cytometry anal. of the cellular DNA content. Cell viability was quantified by a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay. Tissue culture infection dose assays were used to quantitate adenovirus replication. For the in vivo studies, athymic mice received intracranial/intratumoral injections of Delta-24 in combination with CPT-11, after which animal survival was monitored. **Results:** Delta-24 infection caused human glioma cells to accumulate in the S phase and induced the expression and activity of topoisomerase I as shown by Western blot and in vitro enzymic activity assays. Further, we showed that the sequential administration of Delta-24 and CPT-11 to human glioma cell cultures potentiated the CPT-11-mediated anticancer effect in vitro without modifying the replicative phenotype of the oncolytic adenovirus. In vivo expts. showed that the single intratumoral administration of Delta-24 to intracranially implanted human glioma xenografts followed by the systemic administration of CPT-11 resulted in significantly prolonged animal survival. **Conclusions:** The combination of Delta-24 treatment with CPT-11 showed an enhanced anticancer effect, which suggests that the interaction between adenoviral and human proteins can be exploited in rational anticancer therapies comprising replication-competent adenoviruses and conventional chemotherapeutic agents.

Answer 10:

Bibliographic Information

Activation and antitumor activity of CPT-11 in plasma esterase-deficient mice. Morton, Christopher L.; Iacono, Lisa; Hyatt, Janice L.; Taylor, Kody R.; Cheshire, Pamela J.; Houghton, Peter J.; Danks, Mary K.; Stewart, Clinton F.; Potter, Philip M. Department of Molecular Pharmacology, St. Jude Children's Research Hospital, Memphis, TN, USA. *Cancer Chemotherapy and Pharmacology* (2005), 56(6), 629-636. Publisher: Springer, CODEN: CCPhDZ ISSN: 0344-5704. Journal written in English. CAN 144:163635 AN 2005:1069979 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: To examine the antitumor activity and the pharmacokinetics of CPT-11 (irinotecan, 7-ethyl-10-[4-(1-piperidino)-1-piperidino] carbonyloxycamptothecin) in a plasma esterase-deficient scid mouse model, bearing human tumor xenografts. **Exptl. design:** Plasma

carboxylesterase (CE)-deficient mice were bred with scid animals to develop a strain that would allow growth of human tumor xenografts. Following xenotransplantation, the effect of the plasma esterase on antitumor activity following CPT-11 administration was assessed. In addn., detailed pharmacokinetic studies examg. plasma and biliary disposition of CPT-11 and its metabolites were performed. Results: In mice lacking plasma carboxylesterase, the mean SN-38 systemic exposures were approx. fourfold less than that obsd. in control animals. Consistent with the pharmacokinetic data, four to fivefold more CPT-11 was required to induce regressions in human Rh30 xenografts grown in esterase-deficient scid mice, as opposed to those grown in scid animals. Addnl., the route of elimination of CPT-11, SN-38, and SN-38 glucuronide (SN-38G) was principally in the bile. Conclusions: The pharmacokinetic profile for CPT-11 and its metabolites in the esterase-deficient mice more closely reflects that seen in humans. Hence, these mice may represent a more accurate model for antitumor studies with this drug and other agents metabolized by CEs.

Answer 11:

Bibliographic Information

In vivo efficacy of HSV-TK transcriptionally targeted to the tumour vasculature is augmented by combination with cytotoxic chemotherapy. Mavria, Georgia; Harrington, Kevin J.; Marshall, Christopher J.; Porter, Colin D. Section of Cell and Molecular Biology, Institute of Cancer Research, London, UK. *Journal of Gene Medicine* (2005), 7(3), 263-275. Publisher: John Wiley & Sons Ltd., CODEN: JGMEFG ISSN: 1099-498X. Journal written in English. CAN 142:475556 AN 2005:332581 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: Retroviral vectors are suitable for targeting endothelial cells in the tumor neovasculature because of their intrinsic selectivity for proliferating cells. Previously, we inserted regulatory elements of the endothelial-specific prepro-endothelin-1 (ppET1) promoter in retroviral vectors to generate high-titer, replication-defective recombinant retroviruses that restricted gene expression to the vascular compartment of tumors. Methods: A retroviral vector was generated in which expression of herpes simplex virus thymidine kinase (HSV-TK) was transcriptionally restricted to endothelial cells, under the control of a hybrid ppET-1 LTR. Xenograft tumor models were used to det. the efficacy of targeting HSV-TK to the tumor vasculature. Subsequently, vascular-targeted gene therapy was combined with chemotherapeutic agents. Results: Breast or colorectal xenograft tumor growth was reduced and survival was increased in response to ganciclovir treatment. Treatment resulted in widespread vascular disruption and tumor cell apoptosis. In colorectal tumors, combination with irinotecan, a cytotoxic drug used to treat colorectal cancer, significantly increased survival compared to drug alone. No beneficial effect on survival was obsd. when combined with cisplatin, a cytotoxic drug not in clin. use for this tumor type. On the basis of their relative efficacies in vitro against tumor and endothelial cells, co-operativity with irinotecan likely derives from addnl. targeting the peripheral tumor cells that survive the anti-vascular treatment. Conclusions: We show that the ppET1-targeted vector is efficacious for therapeutic gene expression in vivo, validating a strategy targeted to tumor vasculature, and demonstrate that vascular targeting combined with appropriate chemotherapy is more effective than either therapy alone.

Answer 12:

Bibliographic Information

Enhanced antitumor activity of irifolven in combination with irinotecan in pediatric solid tumor xenograft models. Woo, Michael H.; Peterson, Jennifer K.; Billups, Catherine; Liang, Hua; Bjornsti, Mary-Ann; Houghton, Peter J. *Clinical Discovery, Bristol Myers Squibb, Princeton, NJ, USA. Cancer Chemotherapy and Pharmacology* (2005), 55(5), 411-419. Publisher: Springer GmbH, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 143:125988 AN 2005:301539 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: Irofulven, a novel chemotherapeutic agent with a broad spectrum of activity, is effective against preclin. models of pediatric tumors. The cytotoxic activity of irofulven is augmented when combined with agents that interact with DNA topoisomerase I; however, none of the reported studies have used the protracted dosing schedule found to be active clin. in treatment of childhood cancers. The

objective of this study was to evaluate the antitumor activity of irifolven in combination with irinotecan administered on a protracted schedule in a panel of pediatric solid tumor xenografts. Methods: Irifolven and irinotecan were evaluated alone or in combination against eight independent xenografts, which included childhood brain tumors (n=5), neuroblastoma (n=1), and rhabdomyosarcoma (n=2). Irifolven was administered i.v. daily for 5 days with courses repeated every 21 days for a total of three cycles. Doses of irifolven ranged from 1.33 to 4.6 mg/kg. Irinotecan was given i.v. daily for 5 days each week for 2 wk repeated every 21 days for three cycles at doses between 0.28 and 1.25 mg/kg. Results: Irifolven and irinotecan, given as single agents, induced few responses in pediatric solid tumor xenografts at the selected doses. At the same doses, irifolven in combination with irinotecan demonstrated superior antitumor activity, inducing complete responses in seven of the eight xenograft lines. Conclusions: These studies show that the cytotoxic activity of irifolven is greater when combined with protracted administration of irinotecan. Although the systemic exposure of irifolven required to induce objective responses in this panel of pediatric solid tumors was in excess of that achievable in patients receiving maximally tolerated doses using this schedule of drug administration, the enhanced activity of irifolven in combination with irinotecan supports the pursuit of alternative administration strategies and combinations.

Answer 13:

Bibliographic Information

Synergistic antitumor activity of capecitabine in combination with irinotecan. Cao, Shousong; Durrani, Farukh A.; Rustum, Youcef M. Grace Cancer Drug Center, Roswell Park Cancer Institute, Buffalo, NY, USA. *Clinical Colorectal Cancer* (2005), 4(5), 336-343. Publisher: Cancer Information Group, CODEN: CCCLCF ISSN: 1533-0028. Journal written in English. CAN 142:385338 AN 2005:198981 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

5-Fluorouracil (5-FU) and capecitabine alone and in combination with irinotecan/oxaliplatin are clin. active in the treatment of colorectal and other solid tumors. Studies of the antitumor activity and toxicity of capecitabine or irinotecan alone and in combination with each other, were compared with 5-FU and raltitrexed in human tumor xenografts of colorectal and squamous cell carcinoma of the head and neck using clin. relevant schedules. Antitumor activity and toxicity were evaluated in nude mice bearing human colon carcinomas of HCT-8 and HT-29 and in head and neck squamous cell carcinomas of A253 and FaDu xenografts using the max. tolerable dose of single-agent capecitabine, 5-FU, or raltitrexed, or each of the drugs in combination with irinotecan. Mice were treated with capecitabine and irinotecan alone or in combination using 2 different schedules: (1) capecitabine orally once a day for 7 days and a single dose of irinotecan (50 mg/kg i.v.), with each drug alone or in combination, and (2) capecitabine orally 5 days a week for 3 wk and irinotecan 50 mg/kg (I.V. injection) once a week for 3 wk, with each drug alone or in combination. For comparative purposes, the antitumor activity of single-agent capecitabine, 5-FU, or raltitrexed, or each drug in combination with irinotecan was carried out at its max. tolerated dose (MTD) using a 3-wk schedule. Results indicated that HT-29 and A253 xenografts were de novo resistant (no cure) to capecitabine and irinotecan alone at the MTD, whereas HCT-8 and FaDu xenografts were relatively more sensitive, yielding 10-20% cures. The combination of irinotecan/capecitabine was much more active than either drug alone against all 4 tumor models. The cure rates were increased from 0 to 20% in A253 and HT-29 xenografts and from 10-20% to 80-100% in HCT-8 and FaDu tumor xenografts, resp. Irinotecan/capecitabine had clear advantage over irinotecan/5-FU and irinotecan/raltitrexed in efficacy and selectivity in that they were more active and less toxic.

The extent of synergy with irinotecan/capecitabine appears to be tumor-dependent and independent of the status of p53 expression. The potential impact of the preclin. results on clin. practice for the use of these drugs in combination needs clin. validation.

Answer 14:

Bibliographic Information

MEN4901/T-0128, a new camptothecin derivative-carboxymethyl-dextran conjugate, has potent antitumor activities in a panel of human tumor xenografts in nude mice. Fujita, Fumiko; Koike, Masako; Fujita, Masahide; Sakamoto, Yasuo; Okuno, Satoshi; Kawaguchi, Takayuki; Yano, Shigeru; Yano, Toshiro; Kiuchi, Satoko; Fujiwara, Toshihisa; Kudoh, Shinzoh; Kakushima, Masatoshi. *Experimental Cancer Chemotherapy Research Laboratories Co., USA. Clinical Cancer Research* (2005), 11(4), 1650-1657. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN

143:19385 AN 2005:180853 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The purpose of the present study was to evaluate the antitumor activity and pharmacokinetic profile of MEN4901/T-0128 in nude mice bearing human tumor xenografts in comparison with irinotecan (CPT-11) and T-2513. We have detd. the antitumor activity of MEN4901/T-0128, CPT-11, and T-2513 in BALB/cA Jcl nude mice bearing human gastric (H-81), colon (H-110), lung (Mqnu-1, H-74), esophageal (H-204), liver (H-181), and pancreatic (H-48) cancer lines, which had been serially transplanted s.c. and maintained in nude mice, and characterized the pharmacokinetic profile of MEN4901/T-0128 in nude mice bearing human gastric carcinoma St-4. MEN4901/T-0128 administered i.v. showed a marked antitumor activity in each of these tumor models, producing tumor shrinkage in the models of H-204 and H-181 carcinomas at its max. tolerated dose of 80 mg/kg (expressed as T-2513) weekly for 4 wk (q7d x 4) and tumor-shrinking or marked growth-inhibitory effects in the models of H-81, H-110, Mqnu-1, H-74, and H-48 carcinomas at 1/3 of its max. tolerated dose (q7d x 4). Pharmacokinetic anal. showed that MEN4901/T-0128 had an extended plasma half-life with sustained tumor levels of T-2513, which may explain the superior activity of MEN4901/T-0128 in vivo. Because the efficacies of some drugs in this human cancer-nude mouse panel correlated well with their clin. outcomes in patients with the same type of cancers, the findings provide direct support that MEN4901/T-0128 is more efficacious than CPT-11 and is an excellent candidate for clin. trials for the treatment of solid tumors.

Answer 15:

Bibliographic Information

Antitumour activity of XR5944 in vitro and in vivo in combination with 5-fluorouracil and irinotecan in colon cancer cell lines. Harris, S. M.; Mistry, P.; Freathy, C.; Brown, J. L.; Charlton, P. A. Xenova Ltd, Berkshire, UK. British Journal of Cancer (2005), 92(4), 722-728. Publisher: Nature Publishing Group, CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 142:456397 AN 2005:151667 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

XR5944 (MLN944), a novel bis-phenazine, has demonstrated potent cytotoxic activity against a variety of murine and human tumor models. In the present study, the antitumor activity of XR5944 was investigated in combination with 5-fluorouracil (5-FU) or irinotecan in human colon carcinoma cell lines and xenografts. In vitro cytotoxicity of the combinations following exposure to the drugs sequentially or simultaneously was evaluated by the sulforhodamine-B assay and interactions were detd. using median-effect anal. Antagonism was obsd. (CI>1) following exposure of HT29 cells simultaneously to XR5944 and 5-FU or SN38 (active metabolite of irinotecan). In contrast, sequential exposure of either combination in either order demonstrated at least an additive response (CI ≤ 1). At least an additive response was also obsd. with these combinations in HCT116 cells regardless of schedule. Antitumor activity in HT29 xenografts in nude mice was enhanced by sequential administration of 5-FU (65 mg kg⁻¹) or irinotecan (CPT-11) (35 mg kg⁻¹) 48 h before XR5944 (5, 10, or 15 mg kg⁻¹) compared to single agent treatment at the same or higher doses. Administration of irinotecan (35 mg kg⁻¹) and XR5944 (15 mg kg⁻¹) just 30 min apart yielded similar efficacy to sequential administration 48 h apart. All combinations were well tolerated. These data suggest that combinations of XR5944 with irinotecan or 5-FU are of significant interest in the treatment of colon cancer.

Answer 16:

Bibliographic Information

Effect of carboxylesterase inhibition on the anti-tumour effects of irinotecan. Morishita, Y.; Fujii, M.; Kasakura, Y.; Takayama, T. Department of Digestive Surgery, Nihon University School of Medicine, Itabashi-Ku, Tokyo, Japan. Journal of International Medical Research (2005), 33(1), 84-89. Publisher: Cambridge Medical Publications Ltd., CODEN: JIMRBV ISSN: 0300-0605. Journal written in English. CAN 142:423184 AN 2005:68070 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Irinotecan (CPT-11) is an important anticancer agent activated by carboxylesterase (CE). Treatment with CPT-11 may be assocd. with severe adverse effects, however, so detg. the optimal dose would greatly benefit patients. We investigated the relationship between the anti-tumor effects of CPT-11 and CE concn. using bis-p-nitrophenylphosphate (BNPP), a specific inhibitor of CE, in nude mice with xenograft tumors. Initial expts. showed that the optimal dose of CPT-11 was 100 mg/kg. This dose was then used to study the anti-tumor effects of CPT-11 with and without BNPP. A direct correlation was found between the dose of administered BNPP and the growth rate of the tumor, demonstrating that the antitumor effects of CPT-11 were related to the CE concn. Measuring the concn. of CE may allow the optimum dose of CPT-11 to be detd., opening up the possibility of individualized chemotherapy programs.

Answer 17:

Bibliographic Information

Lack of microvessels in well-differentiated regions of human head and neck squamous cell carcinoma A253 associated with functional magnetic resonance imaging detectable hypoxia, limited drug delivery, and resistance to irinotecan therapy.

Bhattacharya, Arup; Toth, Karoly; Mazurchuk, Richard; Spemyak, Joseph A.; Slocum, Harry K.; Pendyala, Lakshmi; Azrak, Rami; Cao, Shousong; Durrani, Farukh A.; Rustum, Youcef M. Department of Cancer Biology, Roswell Park Cancer Institute, Buffalo, NY, USA. *Clinical Cancer Research* (2004), 10(23), 8005-8017. Publisher: American Association for Cancer Research, CODEN: CCREFA ISSN: 1078-0432. Journal written in English. CAN 142:273563 AN 2004:1048146 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Combination chemotherapy with irinotecan (CPT-11; 50 mg/kg/wk x 4 i.v.), followed 24 h later by 5-fluorouracil (50 mg/kg/wk x 4 i.v.), results in 10 and 100% cure rates of animals bearing human head and neck squamous cell carcinoma xenografts A253 and FaDu, resp. A253 consists of 30% well-differentiated and avascular and 70% poorly differentiated regions with low microvessel d. (10/x400), whereas FaDu is uniformly poorly differentiated with higher microvessel d. (19/x400). Studies were carried out for detg. the role of well-differentiated and avascular regions in drug resistance in A253 and detection of such regions with noninvasive functional magnetic resonance (fMR) imaging. Tumors were harvested for histopathol. evaluation and immunohistochem. (CD31, CD34; differentiation marker: involucrin; hypoxia markers: carbonic anhydrase IX, pimonidazole; vascular endothelial factor (VEGF) and Ki67) immediately after fMR imaging following the 3rd dose of chemotherapy. High-performance liq. chromatog. detn. of intratumoral drug concn. of 7-ethyl-10-hydroxyl-camptothecin and autoradiog. with ¹⁴C-labeled CPT-11 was done 2 h after CPT-11 administration. Although A253 xenografts showed three times higher concn. of 7-ethyl-10-hydroxyl-camptothecin, FaDu was more responsive to therapy. After therapy, A253 tumor consisted mostly (.apprx.80%) of well-differentiated regions (pos. for involucrin) lacking microvessels with a hypoxic rim (pos. for carbonic anhydrase IX and pimonidazole) contg. few proliferating (Ki67 pos.) poorly differentiated cells. Autoradiog. revealed that well-differentiated A253 tumor regions showed 5-fold lower ¹⁴C-labeled CPT-11 concns. compared with poorly differentiated areas (P < 0.001). Blood oxygen level dependant fMR imaging was able to noninvasively distinguish the hypoxic and well-vascularized regions within the tumors.

Avascular-differentiated regions in squamous cell carcinoma offer sanctuary to some hypoxic but viable tumor cells (carbonic anhydrase IX and Ki67 pos.) that escape therapy because of limited drug delivery. This study provides direct evidence that because of a specific histol. structure, avascular, well-differentiated hypoxic regions in tumors exhibit low drug uptake and represent a unique form of drug resistance.

Answer 18:

Bibliographic Information

Development of a chemoresistant orthotopic human nonsmall cell lung carcinoma model in nude mice: analyses of tumor heterogeneity in relation to the immunohistochemical levels of expression of cyclooxygenase-2, ornithine decarboxylase, lung-related resistance protein, prostaglandin E synthetase, and glutathione-S-transferase (GST)- α , GST- μ , and GST- π

Mathieu, Anne; Remmelink, Myriam; D'Haene, Nicky; Penant, Stanislas; Gaussin, Jean-Francois; van Ginckel, Rob; Darro, Francis; Kiss, Robert; Salmon, Isabelle. Pathology Laboratory, Erasmus University Hospital, Universite Libre de Bruxelles, Brussels, Belg. *Cancer* (New York, NY, United States) (2004), 101(8), 1908-1918. Publisher: John Wiley & Sons, Inc., CODEN: CANCAR ISSN: 0008-543X. Journal written in English. CAN 142:169276 AN 2004:936957 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

BACKGROUND: Nonsmall cell lung carcinomas (NSCLCs) are assocd. with very dismal prognoses, and adjuvant chemotherapy, including irinotecan, taxanes, platin, and vinca alkaloid derivs., offer patients only slight clin. benefits. Part of the chemoresistance of NSCLC results from the expression in NSCLC cells of a very large set of endogenous proteins, which antagonize chemotherapy-mediated attacks on these tumor cells. **METHODS:** The authors set up an orthotopic model of a human NSCLC by grafting A549 cells into the lungs of nude mice. They tried treating these A549 NSCLC orthotopic xenograft-bearing nude mice on the basis of various chemotherapeutic protocols, including chronic administrations of taxol, oxaliplatin, and irinotecan. A cyclooxygenase-2 (COX-2) inhibitor (NS-398) also was assayed in combination with taxol. The immunohistochem. expression levels of COX-2, prostaglandin E synthetase (PGES), ornithine decarboxylase (ODC), the lung-related resistance protein (LRP), and glutathione-S-transferase- α (GST- α), GST-P μ , and GST- π were quant. detd. by means of computer-assisted microscopy in control and drug-treated NSCLC orthotopic xenografts. **RESULTS:** The orthotopic A549 xenograft model developed in 100% of the grafted mice, leading to brain metastases in approx. 61% mice and to liver metastases in approx. 40% of mice. The model was resistant to taxol and oxaliplatin and was only weakly sensitive to irinotecan. High levels of chemoresistant markers (i.e., COX-2, PGES, ODC, LRP, GST- α , GST- μ , and GST- π) were obsd. in the nontreated A549 xenografts, although with dramatic variations in individual expression. Taxol and oxaliplatin significantly increased the levels of expression of COX-2, PGES, GST- μ , and GST- π in a no. of different exptl. protocols. **CONCLUSIONS:** The A549 orthotopic xenograft model could be used to evaluate investigational chemotherapeutic agents to identify drugs rapidly that are more active than the drugs currently in use in hospitals.

Answer 19:

Bibliographic Information

Liposomal irinotecan: formulation development and therapeutic assessment in murine xenograft models of colorectal cancer. Messerer, Corrie Lynn; Ramsay, Euan C.; Waterhouse, Dawn; Ng, Rebecca; Simms, Eva-Maria; Harasym, Natashia; Tardi, Paul; Mayer, Lawrence D.; Bally, Marcel B. Department of Advanced Therapeutics, British Columbia Cancer Agency, Vancouver, Can. Clinical Cancer Research (2004), 10(19), 6638-6649. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 142:190382 AN 2004:827196 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The purpose is to demonstrate whether an appropriately designed liposomal formulation of irinotecan is effective in treating mice with liver-localized colorectal carcinomas. Irinotecan was encapsulated in 1,2-distearoyl-sn-glycero-3-phosphocholine/cholesterol (55:45 molar ratio) liposomes using an ionophore (A23187)-generated transmembrane proton gradient. This formulation was evaluated in vivo by measuring plasma elimination of liposomal lipid and drug after i.v. administration. Therapeutic activity was detd. in SCID/Rag-2M mice bearing s.c. LS180 tumors or orthotopic LS174T colorectal metastases. Drug elimination from the plasma was significantly reduced when irinotecan was administered in the liposomal formulation. At 1 h after i.v. administration, circulating levels of the liposomal drug were 100-fold greater than that of irinotecan given at the same dose. High-performance liq. chromatog. anal. of plasma samples indicated that liposomal irinotecan was protected from inactivating hydrolysis to the carboxylate form. This formulation exhibited substantially improved therapeutic effects. For the LS180 solid tumor model, it was shown that after a single injection of liposomal irinotecan at 50 mg/kg, the time to progress to a 400-mg tumor was 34 days (as compared with 22 days for animals treated with free drug at an equiv. dose). In the model of colorectal liver metastases (LS174T), a median survival time of 79 days was obsd. after treatment with liposomal irinotecan (50 mg/kg, given every 4 days for a total of three doses). Saline and free drug treated mice survived for 34 and 53 days, resp. These results illustrate that liposomal encapsulation can substantially enhance the therapeutic activity of irinotecan and emphasize the potential for using liposomal irinotecan to treat liver metastases.

Answer 20:

Bibliographic Information

No topoisomerase I alteration in a neuroblastoma model with in vivo acquired resistance to irinotecan. Calvet, L.; Santos, A.; Valent, A.; Terrier-Lacombe, M-J.; Opolon, P.; Merlin, J-L.; Aubert, G.; Morizet, J.; Schellens, J. H. M.; Benard, J.; Vassal, G.

Pharmacology and New Treatments in Cancer (UPRES EA 3535), Institut Gustave-Roussy, Villejuif, Fr. British Journal of Cancer (2004), 91(6), 1205-1212. Publisher: Nature Publishing Group, CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 142:169216 AN 2004:824732 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

CPT-11 (irinotecan) is a DNA-topoisomerase I inhibitor with preclin. activity against neuroblastoma (NB) xenografts. The aim was to establish in vivo an NB xenograft resistant to CPT-11 in order to study the resistance mechanisms acquired in a therapeutic setting. IGR-NB8 is an immature NB xenograft with MYCN amplification and 1p deletion, which is sensitive to CPT-11. Athymic mice bearing advanced-stage s.c. tumors were treated with CPT-11 (27 mg kg⁻¹ day⁻¹ × 5) every 21 days (1 cycle) for a max. of four cycles. After tumor regrowth, a new in vivo passage was performed and the CPT-11 treatment was repeated. After the third passage, a resistant xenograft was obtained (IGRNB8-R). The tumor growth delay (TGD) was reduced from 115 at passage 1 to 40 at passage 4 and no complete or partial regression was obsd. After further exposure to the drug, up to 28 passages, the resistant xenograft was definitively established with a TGD from 17 at passage 28. Resistant tumors reverted to sensitive tumors after 15 passages without treatment. IGR-NB8-R remained sensitive to cyclophosphamide and cisplatin and cross-resistance was obsd. with the topoisomerase I inhibitor topotecan. No quant. or qual. topoisomerase I modifications were obsd. The level of expression of multidrug resistance 1 (MDR1), MDR-assocd. protein 1 (MRP1) and, breast cancer resistance protein, three members of the ATP-binding cassette transporter family was not modified over passages. Our results suggest a novel resistance mechanism, probably not involving the mechanisms usually obsd. in vitro.

Answer 21:

Bibliographic Information

Selective modulation of the therapeutic efficacy of anticancer drugs by selenium containing compounds against human tumor xenografts. Cao, Shousong; Durrani, Farukh A.; Rustum, Youcef M. Department of Pharmacology and Therapeutics, Roswell Park Cancer Institute, Buffalo, NY, USA. Clinical Cancer Research (2004), 10(7), 2561-2569. Publisher: American Association for Cancer Research, CODEN: CCREFA ISSN: 1078-0432. Journal written in English. CAN 141:360262 AN 2004:290939 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

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

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

Answer 22:

Bibliographic Information

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

Abstract

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

Answer 23:

Bibliographic Information

Camptothecin analogues and vinblastine in the treatment of renal cell carcinoma: an in vivo study using a human orthotopic renal cancer xenograft. El-Galley, Rizk; Keane, Thomas E.; Sun, Carrie. Department of Urology, Emory University, Atlanta, GA, USA. *Urologic Oncology: Seminars and Original Investigations* (2003), 21(1), 49-57. Publisher: Elsevier, CODEN: UOSOAA Journal written in English. CAN 141:184720 AN 2004:147742 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

To perform a series of in vivo cytotoxicity studies using a variety of doses of the camptothecin analogs 9-Aminocamptothecin (9-AC) and Irinotecan (CPT-11) with a human RCC xenograft tumor line (DU11983m). Using the subrenal capsule assay (80 nude mice) (NM-SRCA), 9-AC was evaluated at both low and high dosage levels (0.75 mg/kg and 1.25 mg/kg oral $\times 10$ doses over 12 days). Following an initial assessment of acute tumor inhibition, the study was extended to a survival assay with some cohorts receiving retreatment boluses on a once or twice weekly basis. CPT-11 was assessed at a dose of 100 mg/kg $\times 3$ over 9 days with weekly retreatment and two cohorts received 9-AC combined with Vinblastine (2.7 mg/kg) and Vinblastine alone, resp. Tumor inhibition: tumor growth inhibition was significant (over 80%) with all cohorts receiving any camptothecin analog and was virtually complete (>99% tumor inhibition) at the high dose 9-AC (1.25 mg/kg). Vinblastine alone achieved only moderate cytotoxic effect (46%) and induced the largest recorded cohort wt. loss (toxicity). Survival anal.: the low and high dose 9-AC single agent cohorts were not significantly different; however, the CPT-11 cohort experienced maximal survival benefit. ($P = 0.003$) and the addn. of Vinblastine did not enhance this survival advantage among the 9-AC cohorts. Control and single agent Vinblastine cohorts had the poorest survival with the treated group still surviving longer ($P = 0.02$). At 35 days after final assessment of acute tumor inhibition, all animals in both the control and Vinblastine alone cohorts were dead. None of the animals in any of the other cohorts (all of which had experienced a greater than 80% tumor inhibition) had died. No deaths occurred due to surgery or treatment toxicity and all deaths were deemed tumor

related. CPT-11 and 9-AC produced a marked survival advantage in an orthotopic model of human advanced renal carcinoma and are identified as agents for further clin. assessment.

Answer 24:

Bibliographic Information

Therapeutic synergy between irinotecan and 5-fluorouracil against human tumor xenografts. Azrak, Rami G.; Cao, Shousong; Slocum, Harry K.; Toth, Karoly; Durrani, Farukh A.; Yin, Ming-biao; Pendyala, Lakshmi; Zhang, Wanghai; McLeod, Howard L.; Rustum, Youcef M. Department of Pharmacology and Therapeutics and Medicine, Roswell Park Cancer Institute, Buffalo, NY, USA. *Clinical Cancer Research* (2004), 10(3), 1121-1129. Publisher: American Association for Cancer Research, CODEN: CCRE4 ISSN: 1078-0432. Journal written in English. CAN 141:218407 AN 2004:114400 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Although the combination of irinotecan and 5-fluorouracil is clin. active, it is assocd. with significant toxicity and resistance. Studies were carried out to define the optimal dosage, sequence, and timing for the combination in mice bearing xenografted human tumors. The max. tolerated dose of irinotecan and 5-fluorouracil in combination was detd. in nude mice. Therapeutic efficacy against established human colon carcinoma xenografts, HCT-8 and HT-29, and human head and neck squamous cell carcinoma xenografts, FaDu and A253, was detd. using the rugs individually, simultaneously, and in sequence with various intervals in between. Treatments were i.v. weekly x 4. Immunohistochem. and reverse transcription-PCR measurements of relevant drug-metabolizing enzymes, apoptosis-related proteins, cell cycle distribution, cyclin A, and S phase fraction expression were carried out and compared with the therapeutic outcome. The max. tolerated dose of irinotecan resulted in cure rates of 30% or less in all xenografts. No cures were achieved with FUra alone. Concurrent administration of irinotecan and FUra, or of FUra 24 h before irinotecan, resulted in cure rates of <20%, except for FaDu (60%). Administration of irinotecan 24 h before FUra resulted in the highest cure rates, 80% in HCT-8, 0% in HT-29, 100% in FaDu, and 10% in A253. The optimal therapeutic synergy was achieved when irinotecan was administered 24 h before 5-Fluorouracil. Sensitivity to this combination was assocd. with poor differentiation status, higher cyclin A index, recruitment of cells into S phase, and induction of Bax expression and apoptosis.

Answer 25:

Bibliographic Information

Thrombospondin-1 plus irinotecan: a novel antiangiogenic-chemotherapeutic combination that inhibits the growth of advanced human colon tumor xenografts in mice. Allegrini, Giacomo; Goulette, Frederick A.; Darnowski, James W.; Calabresi, Paul. Division of Clinical Pharmacology, Department of Medicine, Rhode Island Hospital (Brown University), Providence, RI, USA. *Cancer Chemotherapy and Pharmacology* (2004), 53(3), 261-266. Publisher: Springer-Verlag, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 141:199578 AN 2004:86399 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Chemotherapy for the treatment of advanced or metastatic colon cancer, utilizing agents such as 5-fluorouracil (5-FU) and irinotecan (CPT-11), produce a 5-yr survival of about 10%. Thus, the identification of new, effective, therapeutic regimens to treat this disease remains critically important. To this end, selected antiangiogenic agents, compds. that inhibit neovascularization, have been shown to produce a modest tumor growth-inhibitory effect with little systemic toxicity. Thus these agents are attractive candidates for use with conventional chemotherapeutic agents to treat this disease. To evaluate this approach, expts. were undertaken to assess the cytotoxic and antineoplastic activity of CPT-11 and the antiangiogenic agent thrombospondin-1 (TSP-1) in the HT-29 model of human colon cancer. These agents were chosen since CPT-11 is a camptothecin analog efficacious in the treatment of colon cancer and TSP-1 is a human glycoprotein that possess antiangiogenic activity. As expected, in vitro studies revealed that a 5-day exposure to TSP-1 at concns. up to 130 µg/mL was not cytotoxic alone and did not affect the cytotoxicity of CPT-11, or of its active metabolite SN38, in HT-29 cells. Similarly, in human umbilical vein endothelial cells, TSP-1 alone induced only a slight cell growth-inhibitory effect

and did not significantly increase the cytotoxicity of either CPT-11 or SN38. The antineoplastic activities of TSP-1 and CPT-11 were assessed in athymic (nude) female mice bearing advanced s.c. xenografts of HT-29 cells. Mice received TSP-1 alone (5-40 mg/kg per day) i.p., CPT-11 alone (100-300 mg/kg, i.p.), TSP-1 (10 mg/kg per day) plus CPT-11 (125 mg/kg), or TSP-1 (20 mg/kg per day) plus CPT-11 (150 mg/kg). TSP-1 was injected daily (Monday through Friday) for 4 wk (20 injections in total) whereas CPT-11 was administered once weekly on days 0, 7, 14 and 21. By day 28, treatment with TSP-1 alone (5, 10 or 20 mg/kg per day) induced a dose-dependent inhibition of xenograft growth.

Further, treatment with 10 or 20 mg/kg per day resulted in an av. treated tumor size/control tumor size (T/C) on day 28 of 0.68 (range 0.64-0.71) or 0.58 (range 0.54-0.60), resp. CPT-11 at all doses significantly inhibited tumor growth with an av. T/C value of 0.21 (range 0.15-0.27). However, the 250 and 300 mg/kg regimens induced significant toxicity and mortality. When TSP-1 was combined with CPT-11, a significant ($P \leq 0.05$) inhibition of tumor growth also was obsd. ($T/C \leq 0.17$, range 0.11-0.20). Importantly, this enhanced tumor growth inhibition was obtained without significant toxicity. The therapeutic implications of these findings are discussed.

Answer 26:

Bibliographic Information

Anticancer drug response and expression of molecular markers in early-passage xenotransplanted colon carcinomas.

Fichtner, I.; Slisow, W.; Gill, J.; Becker, M.; Elbe, B.; Hillebrand, T.; Bibby, M. Max-Delbrueck-Center for Molecular Medicine, Berlin, Germany. *European Journal of Cancer* (2004), 40(2), 298-307. Publisher: Elsevier Science Ltd., CODEN: EJCAEL ISSN: 0959-8049. Journal written in English. CAN 141:150528 AN 2004:34767 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Despite some success in the treatment of colorectal carcinomas, novel rational therapies targeting specific cancer-related mols. are under development and urgently needed. These approaches need careful preclin. evaluation in models that closely mirror the clin. situation. Therefore, we established a panel of 15 xenotransplantable tumors directly from fresh surgical material. We showed that both the histol. and expression of tumor-assocd. markers (Epithelial Cell Adhesion mol. (EpCAM), E-cadherin, carcinoembryonic antigen (CEA)) could be maintained during passaging in nude mice. Xenotransplanted tumors were characterized for chemosensitivity and revealed a response rate of 5/15 (33%) for 5-fluorouracil (5-FU), 15/15 (100%) for irinotecan and 8/14 (57%) for oxaliplatin. 5 Patients out of 15 were treated with cytostatics because of synchronous metastases. The response to chemotherapy in these patients coincided very closely with the response of the individual xenografts. All of the xenografts expressed the proliferation marker Ki67 and the nuclear enzyme, Topoisomerase II α (Topo II α) at the protein level. Most of the xenografts also expressed the tumor suppressor, p53 (9/14) and the nuclear enzyme Topoisomerase I α (Topo I α) (13/14) at the protein level. Interestingly, the presence of a K-ras mutation in codon 12 (5/15 xenografts) coincided with a low response rate towards oxaliplatin. This observation needs further confirmation using a larger no. of tumors. In conclusion, we were able to establish transplantable xenografts suitable to mimic the clin. situation. These well characterized models are useful tools for the preclin. development of novel therapeutic approaches and for investigating translational research aspects.

Answer 27:

Bibliographic Information

Anticancer Chemosensitization and Radiosensitization by the Novel Poly(ADP-ribose) Polymerase-1 Inhibitor AG14361.

Calabrese, Christopher R.; Almasy, Robert; Barton, Stephanie; Batey, Michael A.; Calvert, A. Hilary; Canan-Koch, Stacie; Durkacz, Barbara W.; Hostomsky, Zdenek; Kumpf, Robert A.; Kyle, Suzanne; Li, Jianke; Maegley, Karen; Newell, David R.; Notarianni, Elena; Stratford, Ian J.; Skalizky, Donald; Thomas, Huw D.; Wang, Lan-Zhen; Webber, Stephen E.; Williams, Kaye J.; Curtin, Nicola J. Northern Institute for Cancer Research, Medical School, University of Newcastle upon Tyne, New Castle upon Tyne, UK. *Journal of the National Cancer Institute* (2004), 96(1), 56-67. Publisher: Oxford University Press, CODEN: JNCIEQ ISSN: 0027-8874. Journal written in English. CAN 141:220937 AN 2004:27281 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: Poly(ADP-ribose) polymerase-1 (PARP-1) facilitates the repair of DNA strand breaks. Inhibiting PARP-1 increases the cytotoxicity of DNA-damaging chemotherapy and radiation therapy in vitro. Because classical PARP-1 inhibitors have limited clinical utility, we investigated whether AG14361, a novel potent PARP-1 inhibitor (inhibition const. <5 nM), enhances the effects of chemotherapy and radiation therapy in human cancer cell cultures and xenografts. **Methods:** The effect of AG14361 on the antitumor activity of the DNA alkylating agent temozolomide, topoisomerase I poisons topotecan or irinotecan, or x-irradn. or γ -radiation was investigated in human cancer cell lines A549, LoVo, and SW620 by proliferation and survival assays and in xenografts in mice by tumor vol. detn. The specificity of AG14361 for PARP-1 was investigated by microarray anal. and by antiproliferation and acute toxicity assays in PARP-1^{-/-} and PARP-1^{+/+} cells and mice. After i.p. administration, the concn. of AG14361 was detd. in mouse plasma and tissues, and its effect on PARP-1 activity was detd. in tumor homogenates. All statistical tests were two-sided. **Results:** AG14361 at 0.4 μ M did not affect cancer cell gene expression or growth, but it did increase the antiproliferative activity of temozolomide (e.g., in LoVo cells by 5.5-fold, 95% confidence interval [CI] = 4.9-fold to 5.9-fold; P = .004) and topotecan (e.g., in LoVo cells by 1.6-fold, 95% CI = 1.3-fold to 1.9-fold; P = .002) and inhibited recovery from potentially lethal γ -radiation damage in LoVo cells by 73% (95% CI = 48% to 98%). In vivo, nontoxic doses of AG14361 increased the delay of LoVo xenograft growth induced by irinotecan, x-irradn., or temozolomide by two- to threefold. The combination of AG14361 and temozolomide caused complete regression of SW620 xenograft tumors. AG14361 was retained in xenografts in which PARP-1 activity was inhibited by more than 75% for at least 4 h.

Conclusion: AG14361 is, to our knowledge, the first high-potency PARP-1 inhibitor with the specificity and in vivo activity to enhance chemotherapy and radiation therapy of human cancer.

Answer 28:

Bibliographic Information

The emerging role of irinotecan (CPT-11) in the treatment of malignant glioma in brain tumors. Friedman, Henry S.; Keir, Stephen T.; Houghton, Peter J. Department of Surgery, Duke University Medical Center, Durham, NC, USA. *Cancer* (New York, NY, United States) (2003), 97(9, Suppl.), 2359-2362. Publisher: John Wiley & Sons, Inc., CODEN: CANCAR ISSN: 0008-543X. Journal written in English. CAN 139:94999 AN 2003:380307 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Irinotecan is a water-sol. deriv. of camptothecin, an alkylator originally extd. from the Chinese tree *Camptotheca acuminata*. Lab. studies have demonstrated the activity of irinotecan in a broad panel of pediatric and adult central nervous system tumor xenografts in athymic nude mice. These studies led to a Phase II trial confirmed the activity of this agent in the treatment of recurrent malignant glioma. Subsequent lab. studies have demonstrated that a combination of irinotecan (CPT-11) and alkylating agents, particularly 1, 3-bis(2-chloroethyl)-1-nitrosourea (BCNU), increases antitumor effects to a level well above the additive effects of the individual agents. These lab. studies generated a recently completed Phase I trial of CPT-11 + BCNU, which now is being evaluated in a formal Phase II trial for adults with newly diagnosed or recurrent malignant glioma. More recent studies have demonstrated similar interaction between CPT-11 and temozolomide and have led to a Phase I trial of these agents in the treatment of adults with malignant glioma. Studies currently are addressing the role of O6-alkylguanine-DNA alkyltransferase (AGT) in reducing the benefits of combining CPT-11 with temozolomide and the potential therapeutic gain from utilizing an inhibitor of AGT.

Answer 29:

Bibliographic Information

The importance of tumor glucuronidase in the activation of irinotecan in a mouse xenograft model. Dodds, Helen M.; Tobin, Peter J.; Stewart, Clinton F.; Cheshire, Pam; Hanna, Suzan; Houghton, Peter; Rivory, Laurent P. Department of Pharmacology, University of Sydney, New South Wales, Australia. *Journal of Pharmacology and Experimental Therapeutics* (2002), 303(2), 649-655. Publisher: American Society for Pharmacology and Experimental Therapeutics, CODEN: JPETAB ISSN: 0022-3565. Journal written in English. CAN 138:331157 AN 2002:834402 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The anticancer drug irinotecan (CPT-11) is activated to the potent topoisomerase I inhibitor, SN-38 (7-ethyl-10-hydroxycamptothecin), by esterases. SN-38 is in turn conjugated to the inactive SN-38 glucuronide (SN-38G). The reverse reaction is mediated by β -glucuronidases. Hence, prodn. of SN-38 may occur through either pathway. In this study we conducted in vitro studies to examine these two reactions in neuroblastoma xenograft tumors (NB1691) and compared the rates of SN-38 prodn. with those obsd. in the liver and plasma of the host SCID (severe-combined immunodeficient) mice. The rate of formation of SN-38 from CPT-11 by esterases slowed considerably during a 60-min incubation, consistent with the known deacylation-limited nature of this reaction. For xenograft tumor tissue, Km and Vmax values of 1.6 μ M and 4.4 pmol/min/mg of protein, resp., were obsd. By comparison, these parameters were estd. to be 6.9 μ M and 9.4 pmol/min/mg for mouse liver and 2.1 μ M and 40.0 pmol/min/mg for mouse plasma, resp. The formation of SN-38 from SN-38G was very pronounced in both liver and xenograft tumor tissue, in which it was nonsaturable (0.125-50 μ M) and time-independent (0-60 min). The derived values of Vmax/Km were 0.65 μ l/min/mg for the tumor and 2.12 μ l/min/mg for the liver preps. Microdialyate expts. revealed the concns. of SN-38G and CPT-11 in tumor to be comparable. At equal substrate concns., prodn. of SN-38 from SN-38G in tumor exts. was comparable with that from CPT-11. Therefore, reactivation of SN-38 in the tumor by β -glucuronidases may represent an important route of tumor drug activation for CPT-11.

Answer 30:

Bibliographic Information

Irinotecan in patients with relapsed or cisplatin-refractory germ cell cancer: a phase II study of the German Testicular Cancer Study Group. Kollmannsberger, C.; Rick, O.; Klapproth, H.; Kubin, T.; Sayer, H. G.; Hentrich, M.; Welslau, M.; Mayer, F.; Kuczyk, M.; Spott, C.; Kanz, L.; Bokemeyer, C. Department of hematology/Oncology, University of Tuebingen Medical Center, Germany. *British Journal of Cancer* (2002), 87(7), 729-732. Publisher: Nature Publishing Group, CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 139:398 AN 2002:699708 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Despite generally high cure rates in patients with metastatic germ cell cancer, patients with progressive disease on first-line cisplatin-based chemotherapy or with relapsed disease following high-dose salvage therapy exhibit a very poor prognosis. Irinotecan has shown antitumor activity in human testicular tumor xenografts in nude mice. We have performed a phase II study examng. the single agent activity of irinotecan in patients with metastatic relapsed or cisplatin-refractory germ cell cancer. Refractory disease was defined as progression or relapse within 4 wk after cisplatin-based chemotherapy or relapse after salvage high-dose chemotherapy with autologous stem cell support. Irinotecan was administered at a dose of 300 (-350) mg m⁻² every 3 wk. Response was evaluated every 4 wk. Fifteen patients have been enrolled. Median age was 35 (19-53) years. Primary tumor localization was gonadal/mediastinal in 12/3 patients. Patients had been pretreated with a median of six (4-12) cisplatin-contg. cycles and 13 out of 15 patients had previously failed high-dose chemotherapy with blood stem cell support. Median no. of irinotecan applications was two (1-3). Fourteen patients are assessable for response and all for toxicity. In one patient, no adequate response evaluation was performed. Toxicity was generally acceptable and consisted mainly of hematomol. side effects with common toxicity criteria 3° anemia (two patients), common toxicity criteria 3° leukocytopenia (one patient) and common toxicity criteria 3° thrombocytopenia (three patients). Common toxicity criteria 3/4° non-hematomol. toxicity occurred in five patients (33%): 1×diarrhoea, 2×alopecia, 1×fever and in one patient worsening of pre-existing peripheral polyneuropathy from 1° to 4°. No response was obsd. to irinotecan therapy. Currently, 13 patients have died of the disease and two patients are alive with the disease.

The patients included in our study exhibit similar prognostic characteristics as patients treated in previous trials evaluating new drugs in this setting. Irinotecan at a dose of 300-350 mg m⁻² every 3 wk appears to have no antitumor activity in patients with cisplatin-refractory germ cell cancer and, thus, further investigation in this disease is not justified.

Answer 31:

Bibliographic Information

Antisense oligonucleotide targeted to RI α subunit of cAMP-dependent protein kinase (GEM231) enhances therapeutic effectiveness of cancer chemotherapeutic agent irinotecan in nude mice bearing human cancer xenografts: In vivo synergistic activity, pharmacokinetics and host toxicity. Wang, Hui; Hang, Jie; Shi, Zhenqi; Li, Mao; Yu, Dong; Kandimalla, Ekambar R.; Agrawal, Sudhir; Zhang, Ruiwen. Department of Pharmacology and Toxicology, Division of Clinical Pharmacology,

University of Alabama at Birmingham, Birmingham, AL, USA. International Journal of Oncology (2002), 21(1), 73-80. Publisher: International Journal of Oncology, CODEN: IJONES ISSN: 1019-6439. Journal written in English. CAN 138:83048 AN 2002:526265 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The R1 α -subunit of cAMP-dependent protein kinase (PKA) is overexpressed in various human cancers and PKA has been suggested to be a potential target for cancer therapy. We have shown an antisense oligonucleotide with advanced chem. (mixed-backbone oligonucleotide) targeted to PKA R1 α -subunit (GEM231) to have anti-tumor activity in vitro and in vivo. In the present study, we demonstrated synergistic effects between the anti-PKA antisense oligonucleotide and the clin. used anticancer agent irinotecan, using nude mouse models of human cancers of colon (LS174T and DLD-1), breast (MCF-7), prostate (DU-145 and PC-3) and lung (H1299). To elucidate the underlying mechanisms, in vivo pharmacokinetics of irinotecan was detd. following pre-treatment of oligo GEM 231 in CD-1 mice and nude mice bearing LS174T xenografts GEM 231 increased tissue uptake of irinotecan. However, no significant change in host toxicity was obsd. following combination treatment of irinotecan and GEM231 compared with irinotecan alone. These results suggest that GEM231 have a role in irinotecan metab. and its antitumor activity, providing a basis for future development of this oligonucleotide as a chemosensitizer for irinotecan-based therapy.

Answer 32:

Bibliographic Information

GEM 231, a second-generation antisense agent complementary to protein kinase A R1 α subunit, potentiates antitumor activity of irinotecan in human colon, pancreas, prostate and lung cancer xenografts. Agrawal, Sudhir; Kandimalla, Ekambar R.; Yu, Dong; Ball, Robin; Lombardi, Gina; Lucas, Terri; Dexter, Daniel L.; Hollister, Beth A.; Chen, Shih-Fong. Hybridon, Inc., Cambridge, MA, USA. International Journal of Oncology (2002), 21(1), 65-72. Publisher: International Journal of Oncology, CODEN: IJONES ISSN: 1019-6439. Journal written in English. CAN 138:83047 AN 2002:526264 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

GEM 231, a second-generation antisense oligonucleotide targeted against the R1 α subunit of protein kinase A (PKA) was co-administered with the chemotherapeutic agent irinotecan, a topoisomerase-I inhibitor, to study the antitumor efficacy of the combination in nude mice bearing various human tumor xenografts. The combination treatment of GEM 231 and irinotecan produced enhanced and prolonged tumor-growth inhibition, compared with irinotecan monotherapy, against human colon (HCT-116), pancreas (Panc-1), prostate (PC3) and lung (SKMES) tumors in mice. The extent of tumor-growth inhibition, however, varied among the different tumor models studied. The tumor-growth inhibition depended on the dose of GEM 231 co-administered with irinotecan. The combination of GEM 231 (20 mg/kg, i.p., 5 days on 2 days off \times 7) and irinotecan (50 mg/kg, i.v., qwk \times 3) produced significantly longer tumor-growth delay than did irinotecan administered alone. Importantly, the coadministration of irinotecan and GEM 231 did not result in higher toxicity compared with monotherapies in the several tumor models tested. These results suggest that the use of irinotecan in combination with GEM 231 may increase the therapeutic index of irinotecan in cancer patients.

Answer 33:

Bibliographic Information

Antisense anti-MDM2 mixed-backbone oligonucleotides enhance therapeutic efficacy of topoisomerase I inhibitor irinotecan in nude mice bearing human cancer xenografts: In vivo activity and mechanisms. Wang, Hui; Wang, Shuyi; Nan, Li; Yu, Dong; Agrawal, Sudhir; Zhang, Ruiwen. Department of Pharmacology and Toxicology, University of Alabama at Birmingham, Birmingham, AL, USA. International Journal of Oncology (2002), 20(4), 745-752. Publisher: International Journal of Oncology, CODEN: IJONES ISSN: 1019-6439. Journal written in English. CAN 137:257324 AN 2002:277896 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Antisense oligonucleotides were investigated as anticancer agents administered alone or in combination with conventional chemotherapeutics. In the present study, the authors demonstrated synergistic effects between anti-MDM2 antisense oligonucleotides and the clin. used anticancer agent irinotecan, using nude mouse models of human colon cancers (LS174T and DLD-1). Surprisingly, a 5-base mismatch oligonucleotide also showed similar effects. To elucidate the underlying mechanisms, in vitro and in vivo pharmacokinetic and pharmacodynamic studies were performed. In LS174T cells, the antisense oligonucleotide, but not the mismatch oligonucleotide, specifically inhibited MDM2 expression, resulting in a significant increase in irinotecan-assocd. p53 activation and p21 induction. In DLD-1 cells, the antisense oligonucleotide specifically inhibited MDM2 expression, resulting in a significant increase in irinotecan-assocd. p21 induction although mutant p53 levels remained unchanged. Both oligonucleotides increased tissue uptake of irinotecan and the conversion of irinotecan to its active metabolite SN-38. These results suggest that oligonucleotides have a role in irinotecan metab. and action, providing a basis for future development of antisense oligonucleotides as a sensitizer for irinotecan-based therapy.

Answer 34:

Bibliographic Information

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

Abstract

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

Answer 35:

Bibliographic Information

Schedule-dependent activity of irinotecan plus BCNU against malignant glioma xenografts. Friedman, Henry S.; Castellino, Robert C.; Elion, Gertrude B.; Keir, Stephen T.; Houghton, Peter J.; Johnson, Stewart P.; Bigner, Darell D. Department of Surgery, Duke University Medical Center, South Hospital, Durham, NC, USA. *Cancer Chemotherapy and Pharmacology* (2000), 45(4), 345-349. Publisher: Springer-Verlag, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 133:171873 AN 2000:134874 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: To further evaluate the activity of irinotecan (CPT-11) plus 1,3-bis-(chloroethyl)-1-nitrosourea (BCNU) in the treatment of central nervous system tumor-derived xenografts in athymic nude mice. Methods: We report studies evaluating the schedule-dependence of this regimen in the treatment of the malignant glioma xenograft D-54 MG. Results: The combination of BCNU and CPT-11 showed the highest enhancement index (2.0-3.3) when BCNU was given on day 1 and CPT-11 was given on days 1-5 and 8-12. Delay of CPT-11 administration to day 3 or day 5 substantially decreased activity with enhancement indexes of 1.6-1.8 and

0.6-1.0, resp. Delay of BCNU administration to day 8 also reduced the CPT-11 activity with enhancement indexes of 1.2-1.4. Conclusions: These results suggest that the presence of a BCNU-induced adduct or possibly crosslink prior to administration of CPT-11 is crit. for enhanced activity. Although the mechanism of this enhancement is not currently known, a phase I trial of CPT-11 plus BCNU for adults with recurrent malignant glioma based on these results is in progress.

Answer 36:

Bibliographic Information

Efficacy of treatment of colon, lung and breast human carcinoma xenografts with: doxorubicin, cisplatin, irinotecan or topotecan. Hardman, W. Elaine; Moyer, Mary Pat; Cameron, Ivan L. Department of Cellular and Structural Biology, The University of Texas Health Science Center at San Antonio, San Antonio, TX, USA. *Anticancer Research* (1999), 19(3B), 2269-2274. Publisher: International Institute of Anticancer Research, CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 132:117206 AN 1999:654636 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Given that human cancer xenografts tend to retain chemosensitivities similar to the cancerous tissue of origin, human carcinoma xenografts grown in nude mice were tested for sensitivity to 4 drug protocols: doxorubicin at 5 mg/kg, i.v., every 5 days; irinotecan at 60 mg/kg, i.v., every 4 days; cisplatin at 5 mg/kg, i.p., every 7 days; and topotecan at 1.5 mg/kg, orally, on 5 of 7 days. The irinotecan and doxorubicin protocols either halted or caused significant regression of the breast cancer cell lines (MCF7, MDA-MB 231 and T47D). None of the protocols tested resulted in significant regression of the lung cancer xenografts (H460, A549 and H226) although both irinotecan and doxorubicin did halt growth of the H226 xenograft. The ability of the irinotecan treatment to cause regression of xenograft size in all 3 colon cancer cell lines (SW620, COLO205 and HT29) justifies further clin. trials of irinotecan as an esp. promising drug for the treatment of colon cancer.

Answer 37:

Bibliographic Information

Altered irinotecan and SN-38 disposition after intravenous and oral administration of irinotecan in mice bearing human neuroblastoma xenografts. Zamboni, William C.; Houghton, Peter J.; Thompson, Joyce; Cheshire, Pamela J.; Hanna, Suzan K.; Richmond, Lois B.; Lou, Xiaolong; Stewart, Clinton F. Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, TN, USA. *Clinical Cancer Research* (1998), 4(2), 455-462. Publisher: American Association for Cancer Research, CODEN: CCRE4 ISSN: 1078-0432. Journal written in English. CAN 128:239083 AN 1998:130544 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The antitumor activity of irinotecan in vitro primarily results from its hydrolysis by carboxylesterase to the active metabolite SN-38. The present study was conducted to evaluate the effect of human neuroblastoma xenografts on irinotecan and SN-38 disposition after i.v. and oral irinotecan administration. Non-tumor-bearing mice and mice bearing three different human neuroblastoma xenograft lines (NB1691, NB1643, and NBEB) were given irinotecan (10 mg/kg) by short i.v. injection into the tail vein or by oral gavage. Serial plasma samples were obtained, processed to isolate irinotecan and SN-38 lactone, and assayed with a sensitive and specific high-performance liq. chromatog. assay. Non-compartmental and compartmental pharmacokinetic analyses were performed. A four-compartment model was used for anal. of irinotecan and SN-38 concn.-time data after i.v. administration. The presence of tumor increased irinotecan systemic exposure (1.2-3.8-fold) after i.v. and oral administration in mice bearing neuroblastoma xenografts compared to non-tumor-bearing mice. Moreover, SN-38 systemic exposures were higher (1.3-3.8-fold) in mice bearing human neuroblastoma xenografts as compared to non-tumor-bearing mice, with the greatest effect obsd. after oral administration of irinotecan. A schematic model is presented to provide a mechanistic basis for these observations. These results emphasize the need to perform preclin. pharmacokinetic studies to evaluate the influence of tumor on drug disposition.

Answer 38:

Bibliographic Information

DNA-topoisomerase I, a new target for the treatment of neuroblastoma. Vassal, G.; Pondarre, C.; Cappelli, C.; Terrier-Lacombe, M. J.; Boland, I.; Morizet, J.; Benard, J.; Venuat, A. M.; Ardouin, P.; Hartmann, O.; Gouyette, A. Lab. Pharmacotoxicology and Pharmacogenetics, Inst. Gustave-Roussy, Villejuif, Fr. *European Journal of Cancer* (1997), 33(12), 2011-2015. Publisher: Elsevier Science Ltd., CODEN: EJCAEL ISSN: 0959-8049. Journal written in English. CAN 128:136221 AN 1998:32175 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

DNA-topoisomerase I is the nuclear target of new anticancer drugs, namely camptothecin and its derivs. In order to establish the rational basis for their clin. development in pediatric oncol., the antitumor activity of irinotecan (CPT-11) and topotecan, two camptothecin water-sol. derivs., was studied in nude mice bearing neuroblastoma xenografts. The panel was composed of 4 previously established s.c. xenograft lines (IGR-N835, IGR-N91, IGR-NB3, IGR-NB8) that exhibited the common biol. markers of poor prognosis in children (MYCN amplification, 1p deletion, paradiplody and/or MDR1 overexpression). Irinotecan and topotecan were administered i.v. or i.p. over 5 consecutive days in animals bearing tumors. Irinotecan (40 mg/kg/day) induced 20-100% complete regressions with tumor growth delays ranging from 20 to 46 days. Two out of 10 IGR-N91 bearing animals were tumor free more than 120 days after treatment with the top dose (50 mg/kg/day). Topotecan (2.7 mg/kg/day) induced 0-67% complete regressions with tumor growth delays ranging from 23 to 50 days. One out of 8 IGR-NB3 bearing mice was tumor free at the end of the expt. The antitumor activity of both drugs was clearly sustained at a lower dose level. Topoisomerase I activity was assayed in 15 neuroblastomas, 3 ganglioneuroblastomas and 2 normal adrenal glands, using a DNA relaxation assay. Topoisomerase I activity ranged from 69 to 1304 arbitrary units/mg of protein, and was significantly higher in immature neuroblastomas than in ganglioneuroblastomas and adrenal glands. In conclusion, irinotecan and topotecan are active against neuroblastoma xenografts. Their target is expressed in patient's tumor samples. Clin. development of topoisomerase I inhibitors in children with neuroblastoma is warranted.

Answer 39:

Bibliographic Information

Sequence-dependent activity of the irinotecan-5FU combination in human colon-cancer model HT-29 in vitro and in vivo. Guichard, Sylvie; Cussac, Daniel; Hennebelle, Isabelle; Bugat, Roland; Canal, Pierre. Groupe de Pharmacologie Clinique et Experimentale, Institut Claudius Regaud, Universite Paul Sabatier, Toulouse, Fr. *International Journal of Cancer* (1997), 73(5), 729-734. Publisher: Wiley-Liss, Inc., CODEN: IJCNAA ISSN: 0020-7136. Journal written in English. CAN 128:97405 AN 1997:766784 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Irinotecan, a DNA-topoisomerase-I inhibitor, is active against metastatic colon carcinoma. We investigated the effects of irinotecan and 5FU combinations in human colon-carcinoma cell line HT-29, both in vitro and in vivo. Cytotoxicity of 24-h exposure was evaluated by SRB technique and the nature of interactions were detd. by median-effect anal. Strong synergism between irinotecan and 5FU was obsd. after sequential exposure, and only additivity after simultaneous exposure. At 50% level of kill, the mean sums of fractional effects were 0.13 and 0.18 resp. for the 2 sequential schedules, indicating that the combined amt. of the 2 drugs necessary to kill 50% cells was only 0.18 and 0.13 times resp., as much as would be required if they demonstrated purely additive behavior. In nude-mice xenografts, schedule-dependent toxicity was obsd.: the schedule in which irinotecan was administered i.v. 6 h before 5FU was the most toxic. Higher antitumor activity was noted when 20 mg/kg/day of each drug was administered sequentially (a delay of 6 h between the 2 drugs) to mice over 5 days, in comparison with simultaneous administration. In vivo data confirmed those obtained in vitro in the same human colon-cancer model. These results suggest that irinotecan and 5FU combinations are of clin. interest and that the schedule of administration is a crit. parameter for chemotherapeutic efficacy.

Answer 40:

Bibliographic Information

Potent therapeutic activity of irinotecan (CPT-11) and its schedule dependency in medulloblastoma xenografts in nude mice.

Vassal, Gilles; Boland, Isabelle; Santos, Alexandre; Bissery, Marie-Christine; Terrier-Lacombe, Marie-Jose; Morizet, Jackie; Sainte-Rose, Christian; Lellouch-Tubiana, Arielle; Kalifa, Chantal; Gouyette, Alain. Laboratory of Pharmacotoxicology and Pharmacogenetics (CNRS URA147), Institut Gustave-Roussy, Villejuif, Fr. *International Journal of Cancer* (1997), 73(1), 156-163. Publisher: Wiley-Liss, CODEN: IJCNW ISSN: 0020-7136. Journal written in English. CAN 128:18460 AN 1997:693561 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The anti-tumor activity of irinotecan (CPT-11), a DNA-topoisomerase I inhibitor, was evaluated in 5 advanced stage s.c. medulloblastoma xenografts in nude mice, using different schedules of administration. With a 5-day schedule, the highest i.v. dose tested (40 mg kg⁻¹ day⁻¹) induced complete regressions in all xenografts but 1, and delays in tumor growth always exceeded 30 days. Two xenografts, IGRM11 and IGRM33, were highly sensitive, and animals survived tumor-free beyond 120 days after treatment. CPT-11 clearly retained its anti-tumor activity at a lower dosage (27 mg kg⁻¹ day⁻¹). CPT-11 was significantly more active than cyclophosphamide, thiotepa and etoposide against the 3 xenografts evaluated. To study the schedule dependency of its anti-tumor activity, CPT-11 was given i.v. at the same total doses over the same period (33 days) using either a protracted or a sequential schedule in IGRM34-bearing mice. With a dose of 10 mg kg⁻¹ day⁻¹ given on days 0-4, days 7-11, days 21-25 and days 28-32 (total dose, 200 mg kg⁻¹), 3 of 6 animals were tumor free on day 378. The same total dose given with a sequential schedule, i.e., 20 mg kg⁻¹ day⁻¹ on days 0-4 and days 28-32, failed to induce complete regression. The plasma pharmacokinetics of CPT-11 and SN-38 (active metabolite of CPT-11) were studied in IGRM34-bearing animals after a single i.v. dose of 10 and 40 mg kg⁻¹. The plasma clearance rate of CPT-11 was dose dependent. The ratio between the SN-38 and CPT-11 area under the curve in plasma was 0.4-0.65, i.e., significantly higher than that obsd. in humans at the max. tolerated dose (0.01-0.05). Conversely, this ratio was 10-fold lower in tumor than in plasma. Clin. development of irinotecan is warranted in pediatric malignancies.

Answer 41:

Bibliographic Information

Disposition of irinotecan and SN-38 following oral and intravenous irinotecan dosing in mice. Stewart, Clinton F.; Zamboni, William C.; Crom, William R.; Houghton, Peter J. Department Pharmaceutical Sciences, St Jude Children Research Hospital, Memphis, TN, USA. *Cancer Chemotherapy and Pharmacology* (1997), 40(3), 259-265. Publisher: Springer, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 127:144742 AN 1997:399788 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The disposition of irinotecan (IRT) lactone and its active metabolite SN-38 (SN) lactone was evaluated in mice following oral and i.v. administration, and the systemic exposure of IRT and SN assocd. with antitumor doses of IRT in mice bearing human tumor xenografts. Nontumor-bearing mice were given a single oral or i.v. IRT dose (5, 10, 40, or 75 mg/kg). The disposition of i.v. IRT was modeled using a 2-compartment pharmacokinetic model, and those of oral IRT and SN was modeled with noncompartmental methods. IRT showed biphasic blood plasma disposition following i.v. dosing with a terminal half-life between 1.1 to 3 h. IRT disposition was linear at lower doses (5 and 10 mg/kg). At 40 mg/kg IRT clearance decreased and a nonlinear increase in IRT area under the curve (AUC) was obsd. The steady-state vol. of distribution ranged from 19.1-48.1 L/m². After oral dosing, peak IRT and SN concn. occurred within 1 h, and the IRT bioavailability was 0.12 and 0.21 at 10 and 40 mg/kg, resp. The % unbound SN in murine plasma at 1000 and 100 ng/mL was 3.4 and 1.18%, resp. IRT and SN AUCs in mice-bearing human neuroblastoma xenografts were greater than in nontumor-bearing animals. Systemic exposure to unbound SN in nontumor-bearing animals after a single oral IRT dose of 40, 10, and 5 mg/kg was 28.3, 8.6, and 2.9 ng h/mL, resp.

Answer 42:

Bibliographic Information

Topoisomerase I interactive drugs in children with cancer. Stewart, Clinton F.; Zamboni, William C.; Crom, William R.; Gajjar, Amar; Heideman, Richard L.; Furman, Wayne L.; Meyer, William H.; Houghton, Peter J.; Pratt, Charles B. Department Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, TN, USA. *Investigational New Drugs* (1996), 14(1), 37-47. Publisher: Kluwer, CODEN: INNDDK ISSN: 0167-6997. Journal; General Review written in English. CAN 125:264746 AN 1996:620013 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A review with 45 refs. Topotecan, irinotecan, and 9-aminocamptothecin (9-AC) are analogs of the plant alkaloid 20(S)-camptothecin (CMT), the prototypical DNA topoisomerase I interactive agent. These agents interact with the topoisomerase I-DNA complex and prevent resealing topoisomerase I-mediated DNA single-strand breaks. This eventually leads to double-strand DNA breaks and apoptosis or cell death. Topotecan, irinotecan, and 9-AC have shown significant activity in mice bearing pediatric solid tumor xenografts; the greatest antitumor responses were found with protracted continuous schedules. Preclin. data also suggest that maintenance of an exposure-duration threshold (EDT) may be required to achieve optimal cytotoxicity. Pediatric Phase I trials have evaluated the toxicity and safety of camptothecin analogs in children with relapsed solid tumors and relapsed acute leukemia. The primary dose-limiting toxicity (DLT) for the CMT analogs in children has been myelosuppression, except for mucositis obsd. with the 120-h continuous topotecan infusion schedule. Pharmacodynamic relationships with these analogs have been reported between systemic exposure, and myelosuppression and mucositis. Although not a primary objective of the early Phase I studies, antitumor responses have been reported. In this review, the pharmacokinetics and pharmacodynamics of the CMT analogs studied in children are summarized, and future studies of these agents are discussed.

Answer 43:

Bibliographic Information

Efficacy of topoisomerase I inhibitors, topotecan and irinotecan, administered at low dose levels in protracted schedules to mice bearing xenografts of human tumors. Houghton, Peter J.; Cheshire, Pamela J.; Hallman, James D.; Lutz, Lois; Friedman, Henry S.; Danks, Mary K.; Houghton, Janet A. Department Molecular Pharmacology, St. Jude Children's Research Hospital, Memphis, TN, USA. *Cancer Chemotherapy and Pharmacology* (1995), 36(5), 393-403. Publisher: Springer, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 123:329466 AN 1995:872801 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The efficacy of protracted schedules of therapy with the topoisomerase I inhibitors topotecan and irinotecan was evaluated against a panel of 21 human tumor xenografts derived from adult and pediatric malignancies. The tumors included 8 colon adenocarcinomas, representing an intrinsically chemorefractory malignancy, 6 lines derived from childhood rhabdomyosarcoma (3 embryonal, 3 alveolar), representing a chemoresponsive histiotype, sublines of rhabdomyosarcomas selected in vivo for resistance to vincristine and melphalan, and 3 pediatric brain tumors. All the tumors were grown s.c. in mice. Topotecan was administered by oral gavage 5 days/wk for 12 consecutive weeks. The max. tolerated dose (MTD) was 1.5 mg/kg per dose. Irinotecan was given by i.v. administration daily for 5 days each week for 2 wk, repeated every 21 days. The MTD for 3 such cycles was 10 mg/kg per dose. Treatment was started against advanced tumors. Topotecan caused a high frequency of objective regressions in one of 8 colon tumor lines, whereas irinotecan caused complete regressions (CR) of all tumors in 3 colon lines and a high frequency of CR in 3 addnl. lines. Both drugs demonstrated similar activity against rhabdomyosarcoma xenografts. Topotecan caused CR of all tumors in four of 6 lines, and irinotecan in five of 6 lines evaluated. Both agents retained full activity against tumors selected for primary resistance to vincristine, but only irinotecan retained activity against a tumor selected for primary resistance to melphalan. Both agents demonstrated good activity against brain tumor xenografts, with irinotecan causing CR in two of 3 lines and topotecan inducing CR in one of 3 lines. The results indicate that low-dose protracted schedules of daily administration of these topoisomerase I inhibitors is either equieffective or more effective than the more intense shorter schedules of administration reported previously.

Answer 44:

Bibliographic Information

Rational design of irinotecan administration based on preclinical models. Minderman H; Cao S; Rustman Y M Department of Pharmacology and Therapeutics, Roswell Park Cancer Institute, Buffalo, New York, USA Oncology (Williston Park, N.Y.) (1998), 12(8 Suppl 6), 22-30. Journal code: 8712059. ISSN:0890-9091. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 9726087 AN 1998394150 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Most clinical drug regimens for irinotecan (CPT-11 [Camptosar]) have been empirically based on classic in vivo pharmacokinetic and pharmacodynamic considerations. We propose an alternative approach that attempts to provide a rationally designed schedule of irinotecan administration based on preclinical data. HL60 cells grown in suspension or as subcutaneously implanted solid xenografts in nude mice served as in vitro and in vivo models to test the activity of irinotecan or its active metabolite, SN-38. For SN-38, within an effective drug concentration range, scheduling drug administration based on duration of DNA synthesis inhibition significantly potentiated cell kill in vitro, and increasing drug concentrations at suboptimal scheduling did not result in additive cell kill. These data suggested that even though high drug doses may be attainable in vivo, they may not be required to achieve maximum antitumor activity. To test this hypothesis, a sensitive in vivo model to test the toxicity and antitumor activity of CPT-11 is required, which is provided in the human myeloid HL60 xenograft model grown in nude mice. In this model, CPT-11 at a dose 50 mg/kg, daily x5 (MTD) achieved 100% complete tumor regression. This model should be useful to test the hypothesis that for irinotecan, administration of a minimum effective dose (MED) at an optimal schedule can achieve maximum antitumor activity and should therefore prevail over the classic approach of administering the MTD.

Answer 45:

Bibliographic Information

Antitumor effect of irinotecan hydrochloride (CPT-11) on human renal tumors heterotransplanted in nude mice. Miki T; Nonomura N; Takaha N; Nishimura K; Kojima Y; Sawada M; Okuyama A Department of Urology, Osaka University Medical School, Suita, Japan International journal of urology : official journal of the Japanese Urological Association (1998), 5(4), 370-3. Journal code: 9440237. ISSN:0919-8172. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 9712447 AN 1998376292 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

BACKGROUND: There has been a paucity of antitumor drugs that are active against renal tumors. Irinotecan hydrochloride (CPT-11), a DNA topoisomerase type 1 inhibitor, has demonstrated antitumor activity against human tumors, however, no antitumor effect of CPT-11 on renal tumors has been reported. The antitumor effect of CPT-11 was investigated on 2 human renal tumors (OUR-10 and OUR-20) heterotransplanted into nude mice. **METHODS:** Tumor-bearing nude mice were given daily intraperitoneal injections of multiple anticancer drugs suspended in 0.2 mL of phosphate-buffered saline (PBS) 3 times at 3-day intervals. Control mice were injected with 0.2 mL of PBS. The antitumor effects were evaluated by calculating the T/C ratio (treated tumors/controls) of the tumor volume. **RESULTS:** Among the 10 anticancer drugs tested, 50 mg/kg of CPT-11 showed an active antitumor effect on OUR-20 (T/C ratio 34). However, all drugs tested on OUR-10 failed to show antitumor activity. **CONCLUSION:** Since CPT-11 was effective in 1 of 2 renal tumors examined without severe toxicity, this drug could be a candidate for chemotherapy of renal cell carcinoma.