

Answer 1:

Bibliographic Information

Enhanced therapeutic effects on the multi-drug resistant human leukemia cells in vitro and xenograft in mice using the stealthy liposomal vincristine plus quinacrine. Liang, Gong-Wen; Lu, Wan-Liang; Wu, Jin-Wei; Zhao, Ji-Hui; Hong, Hai-Yan; Long, Chuan; Li, Ting; Zhang, Yu-Teng; Zhang, Hua; Wang, Jian-Cheng; Zhang, Xuan; Zhang, Qiang. State Key Laboratory of Natural and Biomimetic Drugs and School of Pharmaceutical Sciences, Peking University, Beijing, Peop. Rep. China. *Fundamental & Clinical Pharmacology* (2008), 22(4), 429-437. Publisher: Wiley-Blackwell, CODEN: FCPHEZ ISSN: 0767-3981. Journal written in English. CAN 149:191353 AN 2008:932651 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The multi-drug resistance (MDR) could be caused by the over-expression of ATP binding cassette transporters such as p-glycoprotein, thereby resulting in the efflux of anti-cancer drugs from the cells. An anti-resistant stealthy liposomal vincristine plus quinacrine was defined in this study. Human chronic myelogenous leukemia K562 and MDR K562 cells were included for comparisons. Antitumor activity studies were performed on female BALB/c nude mice with MDR K562 cell xenografts. Results showed that quinacrine was effective in reversing the resistance in the MDR K562 cells, and enhanced the antitumor effect of vincristine in K562 cells. The caspase-9 and -3 activities in the MDR K562 and K562 cells were increased with the dose rise of quinacrine. In the MDR K562 cell xenografts in mice, the anti-resistant tumor effect of the stealthy liposomal vincristine plus quinacrine was evidently obsd. The enhanced antitumor effects of vincristine by quinacrine in the resistant/non-resistant K562 cells could be because of the direct injury and the potentiating apoptotic effect of vincristine via activating the initiator caspase-9 and subsequently the effector caspase-3, and the long circulatory effect of stealthy liposomes. The stealthy liposomal encapsulation of vincristine plus quinacrine could be a potential therapeutic approach for resistant human leukemia.

Answer 2:

Bibliographic Information

A role for altered microtubule polymer levels in vincristine resistance of childhood acute lymphoblastic leukemia xenografts. Ong, Vivien; Liem, Natalia L. M.; Schmid, Michael A.; Verrills, Nicole M.; Papa, Rachael A.; Marshall, Glenn M.; MacKenzie, Karen L.; Kavallaris, Maria; Lock, Richard B. Children's Cancer Institute Australia for Medical Research, Sydney, New South Wales, Australia. *Journal of Pharmacology and Experimental Therapeutics* (2008), 324(2), 434-442. Publisher: American Society for Pharmacology and Experimental Therapeutics, CODEN: JPETAB ISSN: 0022-3565. Journal written in English. CAN 148:253593 AN 2008:150243 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The microtubule-depolymerizing drug, vincristine, is effective in the treatment of acute lymphoblastic leukemia (ALL). Although vincristine resistance mechanisms have been extensively characterized in cell lines, their clin. relevance is poorly understood. The aim of the current study was to define clin. relevant mechanisms of vincristine resistance in a panel of childhood ALL xenografts established in immune-deficient (nonobese diabetic/severe combined immunodeficient) mice. We also studied two independent xenograft sublines that were selected by in vivo vincristine exposure. In vitro vincristine sensitivity detd. by a stromal coculture, murine bone marrow stromal cell line (MS-5), assay, but not methyl-thiazolyl-tetrazolium metabolic activity assay, significantly correlated ($P = 0.05$) with the length of the patients' first remission. Investigations into mechanisms of resistance revealed no assocn. with steady-state vincristine accumulation or increased activity and/or expression of ATP-binding cassette transporters, although increased intracellular levels of polymd. tubulin significantly correlated with resistance ($r = 0.85$; $P = 0.0019$). Two xenograft sublines selected by in vivo vincristine exposure exhibited a 2-fold increase in polymd. tubulin levels compared with the parental subline ($P < 0.05$), reflecting their in vivo vincristine resistance. In this study, a vincristine-resistant xenograft with high levels of polymd. tubulin was relatively sensitive to the microtubule-depolymerizing drug paclitaxel. These results indicate that the balance between polymd. and nonpolymd. tubulin may be an important determinant of response to Vinca alkaloid-based chemotherapy regimens in childhood ALL.

Answer 3:

Bibliographic Information

γ -secretase inhibitors enhance taxane-induced mitotic arrest and apoptosis in colon cancer cells. Akiyoshi, Takashi; Nakamura, Masafumi; Yanai, Kosuke; Nagai, Shuntaro; Wada, Junji; Koga, Kenichiro; Nakashima, Hiroshi; Sato, Norihiro; Tanaka, Masao; Katano, Mitsuo. Department of Cancer Therapy and Research, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan. *Gastroenterology* (2008), 134(1), 131-144. Publisher: Elsevier Inc., CODEN: GASTAB ISSN: 0016-5085. Journal written in English. CAN 148:346055 AN 2008:133246 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background & Aims: Colorectal cancers are resistant to conventional chemotherapeutic treatments, including taxanes. γ -Secretase is a multimeric membrane protein complex responsible for the intramembrane proteolysis of various type I transmembrane proteins, including amyloid β -precursor protein and Notch. γ -Secretase inhibitors have attracted increasing interest as anticancer drugs because of their ability to inhibit Notch signaling. However, the therapeutic usefulness of γ -secretase inhibitors against colorectal cancers remains unclear. **Methods:** The effects of γ -secretase inhibitors on growth and apoptosis induced by various chemotherapeutic agents in colon cancer cells were evaluated using Hoechst 33342 staining, colony formation assay, and cell cycle anal. The effect of γ -secretase inhibitors on taxane-induced mitotic arrest was evaluated using the cyclin B1-assocd. histone H1 kinase assay and MPM-2 reactivity. The involvement of Notch signaling was evaluated by the silencing of Notch/CBF1 signaling by RNA interference. **Results:** γ -Secretase inhibitors enhanced taxane-induced mitotic arrest and apoptosis of colon cancer cells both in vitro and in vivo, although γ -secretase inhibitors alone did not affect growth and apoptosis of colon cancer cells. We also showed that this effect by γ -secretase inhibitors was restricted to taxanes and colon cancer cells. Silencing of Notch/CBF1 signaling failed to affect paclitaxel-induced mitotic arrest and apoptosis. **Conclusions:** These data suggest that γ -secretase inhibitors could be a new therapeutic modality for overcoming resistance to taxanes in colorectal cancers.

Answer 4:

Bibliographic Information

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

Abstract

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

Answer 5:

Bibliographic Information

Vincristine Induces Dramatic Lysosomal Changes and Sensitizes Cancer Cells to Lysosome-Destabilizing Siramesine. Groth-Pedersen, Line; Ostefeld, Marie Stampe; Hoyer-Hansen, Maria; Nylandsted, Jesper; Jaaettelae, Marja. Apoptosis

Department and Centre for Genotoxic Stress Research, Institute of Cancer Biology, Danish Cancer Society, Copenhagen, Den. Cancer Research (2007), 67(5), 2217-2225. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 146:372114 AN 2007:230015 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Vincristine is a microtubule-destabilizing antimetabolic drug that has been used in cancer therapy for over 40 years. However, the knowledge on vincristine-induced cell death pathways is still sparse. Here, we show that vincristine induces dramatic changes in the lysosomal compartment and sensitizes cells to lysosomal membrane permeabilization. In HeLa cervix carcinoma cells, vincristine induced mitotic arrest and massive cell death assocd. with an early increase in the lysosomal vol. and lysosomal leakage followed by the activation of the intrinsic apoptosis program. In contrast, the majority of vincristine-treated MCF-7 breast carcinoma cells resisted apoptosis. Instead, they adapted to the spindle assembly checkpoint and escaped the mitotic arrest as micronucleated and senescent cells with an increase in the vol. and the activity of their lysosomal compartment. Consistent with its substantial effects on the lysosomes, vincristine greatly sensitized cultured cancer cells as well as orthotopic breast cancer xenografts in mice to the cytotoxicity induced by siramesine, a sigma-2 receptor ligand that kills cancer cells by destabilizing their lysosomes. Importantly, the combination of nontoxic concns. of vincristine and siramesine resulted in massive cell death even in MCF-7 cells that were capable of escaping vincristine-induced spindle assembly checkpoint and cell death. Similar synergism was obsd. when siramesine was combined with a semisynthetic vincristine analog, vinorelbine, or with microtubule-stabilizing paclitaxel. These data strongly suggest that combination therapies consisting of microtubule-disturbing and lysosome-destabilizing drugs may prove useful in the treatment of otherwise therapy-resistant human cancers.

Answer 6:

Bibliographic Information

The anti-hepatitis drug DDB chemosensitizes multidrug resistant cancer cells in vitro and in vivo by inhibiting P-gp and enhancing apoptosis. Jin, Jing; Sun, Hua; Wei, Huailing; Liu, Gengtao. Institute of Materia Medica, Peking Union Medical College & Chinese Academy of Medical Sciences, Beijing, Peop. Rep. China. Investigational New Drugs (2007), 25(2), 95-105. Publisher: Springer, CODEN: INNDDK ISSN: 0167-6997. Journal written in English. CAN 146:287830 AN 2006:1347361 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: DDB (dimethyl-4,4'-dimethoxy-5,6,5'6'-dimethylene dioxybiphenyl-2,2'-dicarboxylate) is a synthetic hepatoprotectant which has been widely used to treat chronic viral hepatitis B patients in China for more than 20 years. In this study, we evaluated DDB as a multidrug resistance (MDR) chemosensitizing agent. Methods: A panel of sensitive and resistant cancer cell lines were treated with various concn. of DDB, and the effect on chemosensitivity and accumulation of anticancer drugs; promotion of apoptosis and P-glycoprotein (P-gp) expression were detd. by MTT (Di-Me thiazolyl-2,5-diphenyltetrazolium bromide) assay, fluorospectrometry and flow cytometry resp. Drug resistance reversal activity of DDB was also examd. in BALB/c nude mice bearing both acquired MDR human nasopharyngeal carcinoma KBv200 and parental KB xenografts. The effect of DDB on the pharmacokinetics of Dox and hematol. toxicity induced by Dox was measured in ICR and C57/BL mice, resp. Results: DDB at nontoxic concns. of 12.5, 25 and 50 μ M partly reversed the resistance to vincristine, doxorubicin, paclitaxel in acquired MDR breast carcinoma MCF-7/Adr cells, KBv200 and intrinsic MDR human hepatocarcinoma Bel7402 cells, whereas no chemosensitizing effect of DDB was obsd. in sensitive KB and MCF-7 cells. DDB increased the intracellular accumulation of doxorubicin and inhibited surface P-gp expression in MCF-7/Adr cells. Furthermore, it was found that DDB promoted doxorubicin-induced apoptosis of Bel7402 cells through enhanced caspase-3 activation. Co-administration of DDB at 300 and 500 mg/kg orally to nude mice increased the antitumor activity of vincristine to KBv200 xenografts without a significant increase in toxicity. In contrast, Co-administration of DDB did not inhibit the growth of KB xenografts. DDB also markedly reduced the decrease of leukocytes in doxorubicin-treated C57/BL mice. Co-administration of DDB increased Dox concn. in ICR mice bearing S180 sarcoma, but no pharmacokinetical interaction with Dox was obsd.

Conclusion: These results indicate that DDB has MDR reversal activity by inhibiting P-gp and when used in combination with anti-cancer drugs, it could potentially be used as a clin. treatment for P-gp-mediated MDR cancers.

Answer 7:

Bibliographic Information

STI571 combined with vincristine greatly suppressed the tumor formation of multidrug-resistant K562 cells in a human-nude mice xenograft model. Gao, Lei; Chen, Li; Fei, Xin-hong; Qiu, Hui-ying; Zhou, Hong; Wang, Jian-min. Department of Hematology, Changhai Hospital, Second Military Medical University, Shanghai, Peop. Rep. China. Chinese Medical Journal (Beijing, China, English Edition) (2006), 119(11), 911-918. Publisher: Chinese Medical Association, CODEN: CMJODS ISSN: 0366-6999. Journal written in English. CAN 146:342 AN 2006:674791 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: The development of the targeted signal transduction inhibitor STI571 has prompted us to treat chronic myeloid leukemia in different ways. Since STI571 may reverse multidrug-resistance of K562/MDR cells in vitro, we studied the effect of STI571 on multidrug-resistant K562 cells in vivo. Methods: Multidrug-resistant human leukemia cell line K562-n/VCR expresses both bcr/abl fusion gene and multi-drug resistance (mdr1) gene. It is a vincristine resistant cell line subcloned from the vincristine (VCR) sensitive cell line K562-n induced by vincristine in vitro. K562-n and K562-n/VCR cells were inoculated s.c. into both sides of nude mice breast (5×10^6 cells/each) to establish a human leukemia xenograft model. The incidence and vol. of tumor were obsd. In the tumor-bearing nude mice, anti-tumor drugs vincristine, daunorubicin (DNR), STI571, and STI571 plus VCR for the treatment of mdr1 and bcr/abl double pos. leukemia were studied resp. Results: The tumor incidence was 100% in the nude mice inoculated with either K562-n or K562-n/VCR. The transcription of the mdr1 gene and expression of P-gp were neg. in K562-n cells but pos. in K562-n/VCR cells. The intracellular accumulation of DNR in K562-n cells was higher than that in K562-n/VCR cells ($P < 0.05$). The tumor incidence of K562-n/VCR cells in nude mice was much higher than that of K562-n cells in chemotherapy groups, and the mean vol. of the tumors was also larger ($P < 0.05$). STI571 combined with VCR significantly suppressed the proliferation of K562-n/VCR cells. Conclusions: The MDR characteristics of K562-n/VCR in vivo were the same as in vitro. STI571 had a significant tumor-suppressing effect on VCR-sensitive leukemia cells and a moderate effect on MDR leukemia cells. VCR combined with STI571 had an excellent tumor-suppressing effect on both K562-n/VCR and K562-n in the human-nude mice xenograft model.

Answer 8:

Bibliographic Information**Reversal of MDR1/P-glycoprotein-mediated multidrug resistance by vector-based RNA interference in vitro and in vivo.**

Shi, Zhi; Liang, Yong-ju; Chen, Zhe-sheng; Wang, Xiu-wen; Wang, Xiao-hong; Ding, Yan; Chen, Li-ming; Yang, Xiao-ping; Fu, Li-wu. State Key Laboratory for Oncology in South China; Cancer Center, Sun Yat-Sen University, Guangzhou, Peop. Rep. China. Cancer Biology & Therapy (2006), 5(1), 39-47. Publisher: Landes Bioscience, CODEN: CBTAO ISSN: 1538-4047. Journal written in English. CAN 145:513 AN 2006:480447 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Overexpression of P-glycoprotein (P-gp) encoded by MDR1 gene in cancer cells results in multidrug resistance (MDR) to structurally and mechanistically different chemotherapeutic drugs, which is a major cause for cancer chemotherapy failures to cancer patients. Recently, there were several reports showing that expression of siRNAs targeting MDR1 gene is able to reverse the P-gp mediated MDR, however, the in vivo reversal effects for MDR have still not been identified. We developed a novel MDR reversal system using RNA interference technique in human epidermoid carcinoma KBv200 cells. The stably expressing MDR1 shRNA cells (KBv200/MDR1 sh) were established with transfection of vector pEGFPC2-H1-MDR1 shDNA contg. MDR1-V siRNA expression cassette, and we found that more than 90% of MDR1 mRNA and P-gp were reduced. KBv200/MDR1 sh cells simultaneously showed stably expressing EGFP and kept low MDR1 expression beyond ten passages. Compared KBv200/MDR1 sh cells with KBv200 cells, resistance to vincristine and doxorubicin decreased from 62.4-fold to 10.5-fold and from 74.5-fold to 9.5-fold resp., and intracellular doxorubicin accumulation enhanced from 0.30 ± 0.08 nmoles/106 cells to 0.86 ± 0.16 nmoles/106 cells, and the fluorescence intensity of intracellular Rhodamine 123 accumulation increased from $3.58 \pm 1.63/106$ cells to $13.96 \pm 3.07/106$ cells. In the nude mice xenografts, vincristine (0.2 mg/kg of body wt.) inhibited the growth of KBv200/MDR1 sh solid tumors by 42.0%, but the same dose of vincristine did not inhibit the growth of KBv200 solid tumors significantly. These results suggest that administration of RNAi targeted MDR1 gene can effectively reverse MDR both in vitro and in vivo models.

Answer 9:

Bibliographic Information

Preferential extravasation and accumulation of liposomal vincristine in tumor comparing to normal tissue enhances antitumor activity. Shan, Siqing; Flowers, Clay; Peltz, Cathy D.; Sweet, Heather; Maurer, Norbert; Kwon, Eun-Joo Gina; Krol, Ave; Yuan, Fan; Dewhirst, Mark W. Department of Radiation Oncology, Duke University Medical Center, Durham, NC, USA. *Cancer Chemotherapy and Pharmacology* (2006), 58(2), 245-255. Publisher: Springer, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 145:369328 AN 2006:395157 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

To quant. evaluate the extravasation, accumulation and selectivity to tumor tissues of liposomal vincristine (LV), dorsal skin-fold window chambers on athymic mice with or without LX-1, a human small cell lung cancer, xenograft implants and fluorescent intravital microscopy imaging were used. In vitro studies show that minimal loss of fluorescence marker Dil from liposomes occurs after 4 days of inoculation in murine plasma, and the release profiles of Dil-LV and LV were essentially the same with approx. 40% of the encapsulated vincristine sulfate (VCR) released after 26 h. Significantly faster extravasation of Dil-LV from tumor vessels was shown compared to non-tumor tissue after single dose i.v. administration. The relative interstitial amts. at 60 min (RIA60) for tumor and non-tumor tissues were 0.837 ± 0.314 and 0.012 ± 0.091 , resp. ($P=0.01$). Dil-LV accumulation was significantly higher in tumor than in normal tissue, which continued beyond 48 h. Both Dil-LV and LV showed significant antitumor effects in window chambers and in flank tumors, compared with controls and VLS alone. The preferential extravasation of Dil-LV from tumor vasculature as well as its differential retention in tumor tissue provides the basis for the enhancement in antitumor activity of LV over VCR.

Answer 10:

Bibliographic Information

Anti-cancer effects of bortezomib against chemoresistant neuroblastoma cell lines in vitro and in vivo. Michaelis, Martin; Fichtner, Iduna; Behrens, Diana; Haider, Wolfram; Rothweiler, Florian; Mack, Andreas; Cinatl, Jaroslav; Doerr, Hans Wilhelm; Cinatl, Jindrich, Jr. Institut fuer Medizinische Virologie, Klinikum der Johann Wolfgang Goethe-Universitaet, Frankfurt am Main, Germany. *International Journal of Oncology* (2006), 28(2), 439-446. Publisher: International Journal of Oncology, CODEN: IJONES ISSN: 1019-6439. Journal written in English. CAN 145:95897 AN 2006:150396 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The proteasome inhibitor bortezomib (Velcade) was recently approved for the treatment of therapy-refractive multiple myeloma and is under investigation for numerous other types of cancer. A phase I clin. trial in pediatric patients resulted in tolerable toxicity. Since the emergence of chemoresistance represents one of the major drawbacks in cancer therapy, we investigated the influence of bortezomib on multi-drug resistant human neuroblastoma cell lines characterized by P-glycoprotein expression and p53 mutation. Nanomolar concns. of bortezomib inhibited the cell cycle and induced apoptosis in chemosensitive as well as in chemoresistant cell lines. In vivo growth of chemosensitive and chemoresistant neuroblastoma cell lines was inhibited to a similar extent. In addn., bortezomib inhibited vessel formation in neuroblastoma xenografts. These findings and the favorable toxicity profile of bortezomib in children make it reasonable to further pursue addnl. development of the drug for the treatment of neuroblastoma and other pediatric solid tumors.

Answer 11:

Bibliographic Information

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

ACS on SciFinder (R))

Abstract

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

Answer 12:

Bibliographic Information

Antitumor activity of the insulin-like growth factor-I receptor kinase inhibitor NVP-AEW541 in musculoskeletal tumors.

Scotlandi, Katia; Manara, Maria Cristina; Nicoletti, Giordano; Lollini, Pier-Luigi; Lukas, Stella; Benini, Stefania; Croci, Stefania; Perdichizzi, Stefania; Zambelli, Diana; Serra, Massimo; Garcia-Echeverria, Carlos; Hofmann, Francesco; Picci, Piero. Laboratory of Oncologic Research, Orthopaedic Rizzoli Institute, Department of Experimental Pathology, University of Bologna, Bologna, Italy. *Cancer Research* (2005), 65(9), 3868-3876. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 142:475589 AN 2005:375718 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Identification of new drugs is strongly needed for sarcomas. Insulin-like growth factor-I receptor (IGF-IR) was found to provide a major contribution to the malignant behavior of these tumors, therefore representing a very promising therapeutic target. In this study, we analyzed the therapeutic potential of a novel kinase inhibitor of IGF-IR, NVP-AEW541, in Ewing's sarcoma, osteosarcoma, and rhabdomyosarcoma, the three most frequent solid tumors in children and adolescents. NVP-AEW541 inhibits IGF-I-mediated receptor activation and downstream signaling. Ewing's sarcoma cells were generally found to be more sensitive to the effects of this drug compared with rhabdomyosarcoma and osteosarcoma, in agreement with the high dependency of this neoplasm to IGF-IR signaling. NVP-AEW541 induced a G1 cell cycle block in all cells tested, whereas apoptosis was obsd. only in those cells that show a high level of sensitivity. Concurrent exposure of cells to NVP-AEW541 and other chemotherapeutic agents resulted in pos. interactions with vincristine, actinomycin D, and ifosfamide and subadditive effects with doxorubicin and cisplatin. Accordingly, combined treatment with NVP-AEW541 and vincristine significantly inhibited tumor growth of Ewing's sarcoma xenografts in nude mice. Therefore, results encourage inclusion of this drug esp. in the treatment of patients with Ewing's sarcoma. For the broadest applicability and best efficacy in sarcomas, NVP-AEW541 may be combined with vincristine, actinomycin D, and ifosfamide, three major drugs in the treatment of sarcomas.

Answer 13:

Bibliographic Information

Betulinic acid augments the inhibitory effects of vincristine on growth and lung metastasis of B16F10 melanoma cells in mice.

Sawada, N.; Kataoka, K.; Kondo, K.; Arimochi, H.; Fujino, H.; Takahashi, Y.; Miyoshi, T.; Kuwahara, T.; Monden, Y.; Ohnishi, Y. School of Medicine, Department of Oncological and Regenerative Surgery, The University of Tokushima, Tokushima, Japan. *British Journal of Cancer* (2004), 90(8), 1672-1678. Publisher: Nature Publishing Group, CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 141:360267 AN 2004:301770 CAPI US (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We examd. the antitumor effect of a combination of betulinic acid (BA) and vincristine (VCR) on murine melanoma B16F10 cells in vitro and in vivo. Betulinic acid, a pentacyclic triterpene, showed a synergistic cytotoxic effect on melanoma cells by combinational use of VCR. Betulinic acid and VCR induced cell cycle arrest at different points (BA at G1 phase and VCR at G2/M phase) and caused apoptosis in B16F10 melanoma cells. In the in vivo study, VCR inhibited metastasis of tumor cells to the lung. The addn. of BA to VCR augmented suppression of the exptl. lung metastasis of melanoma cells in C57BL/6 mice. The no. of lung nodules of more than 1 mm in diam. in mice treated with BA and VCR was less than that in mice treated with VCR alone. These results suggest that BA is an effective supplement for enhancing the chemotherapeutic effect on malignant melanoma.

Answer 14:

Bibliographic Information

Characterization of tetrandrine, a potent inhibitor of P-glycoprotein-mediated multidrug resistance. Fu, Liwu; Liang, Yongju; Deng, Liwen; Ding, Yan; Chen, Liming; Ye, Yanli; Yang, Xiaoping; Pan, Qichao. Cancer Center, Sun Yat-Sen University, Guangzhou, Peop. Rep. China. *Cancer Chemotherapy and Pharmacology* (2004), 53(4), 349-356. Publisher: Springer-Verlag, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 141:325250 AN 2004:241298 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Multidrug resistance (MDR) is one of the main obstacles in tumor chemotherapy. A promising approach to solving this problem is to utilize a nontoxic and potent modulator able to reverse MDR, which in combination with anticancer drugs increases the anticancer effect. Expts. were carried out to examine the potential of tetrandrine (Tet) as a MDR-reversing agent. Survival of cells incubated with Tet at 2.5 $\mu\text{mol/l}$ for 72 h was over 90%. Tet at 2.5 $\mu\text{mol/l}$ almost completely reversed resistance to vincristine (VCR) in KBv200 cells. Tet at a concn. as low as 0.625 $\mu\text{mol/l}$ produced a 7.6-fold reversal of MDR, but showed no effect on the sensitivity of drug-sensitive KB cells in vitro. In the KBv200 cell xenograft model in nude mice, neither Tet nor VCR inhibited tumor growth. However, VCR and Tet combined inhibited tumor growth by 45.7%, 61.2% and 55.7% in three independent exptl. settings. In the KB cell xenograft model in nude mice, Tet did not inhibit tumor growth, but VCR and the combination of VCR and Tet inhibited tumor growth by 40.6% and 41.6%, resp. Mechanism studies showed that Tet inhibited [3H]azidopine photoaffinity labeling of P-gp and increased accumulation of VCR in MDR KBv200 cells in a concn.-dependent manner. The results suggest that Tet is a potent MDR-reversing agent in vitro and in vivo. Its mechanism of action is via directly binding to P-gp and increasing intracellular VCR accumulation.

Answer 15:

Bibliographic Information

In vivo antitumor activity of a novel sulfonamide, HMN-214, against human tumor xenografts in mice and the spectrum of cytotoxicity of its active metabolite, HMN-176. Takagi, Manabu; Honmura, Takuya; Watanabe, Shuuji; Yamaguchi, Reiko; Nogawa, Masaki; Nishimura, Ikumi; Katoh, Fumitaka; Matsuda, Masato; Hidaka, Hiroyoshi. Discovery Research Laboratories and Developmental Research Laboratories, Nippon Shinyaku Co., Kyoto, Japan. *Investigational New Drugs* (2003), 21(4), 387-399. Publisher: Kluwer Academic Publishers, CODEN: INNDDK ISSN: 0167-6997. Journal written in English. CAN 141:16960 AN 2003:833144 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The cytotoxic effects of HMN-176 ((E)-4-[[2-N-[4-methoxybenzenesulfonyl] amino] stilbazole} 1-oxide; Figure 1), a newly synthesized compd., were evaluated and compared with those of the clin. used antitumor agents cis-platinum, adriamycin, etoposide, taxol, and vincristine in 22 human tumor cell lines isolated from various organs. HMN-176 exhibited potent cytotoxicity with IC50 values in the nM range, and the variance of its cytotoxic efficacy was remarkably small. Drug-resistant cell lines also showed low cross-resistance to HMN-176 corresponding to overall resistance indexes of less than 14.3. HMN-214 was synthesized as an oral prodrug because of

the poor oral absorption of HMN-176 itself. Pharmacokinetic studies showed that HMN-214 was an acceptable oral prodrug of HMN-176. In the in vivo anal. of the schedule-dependency of HMN-214, the repeated administration for over 5 days elicited potent antitumor activity, as expected from the exposure-dependency of the cytotoxicity of HMN-176 and from the cytometric studies. The antitumor activity of HMN-214 against human tumor xenografts was equal or superior to that of clin. available agents, including cis-platinum, adriamycin, vincristine, and UFT without severe toxicity such as neurotoxicity. Because of its good activity in preclin. trials, HMN-214 has entered Phase I clin. trials in the USA.

Answer 16:

Bibliographic Information

Genome-wide cDNA microarray screening to correlate gene expression profiles with sensitivity of 85 human cancer xenografts to anticancer drugs. Zembutsu, Hitoshi; Ohnishi, Yasuyuki; Tsunoda, Tatsuhiko; Furukawa, Yoichi; Katagiri, Toyomasa; Ueyama, Yoshito; Tamaoki, Norikazu; Nomura, Tatsuji; Kitahara, Osamu; Yanagawa, Rempei; Hirata, Koichi; Nakamura, Yusuke. Laboratory of Molecular Medicine, Human Genome Center, Institute of Medical Science, The University of Tokyo, Tokyo, Japan. *Cancer Research* (2002), 62(2), 518-527. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 136:395496 AN 2002:108259 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

One of the most crit. issues to be solved in regard to cancer chemotherapy is the need to establish a method for predicting efficacy or toxicity of anticancer drugs for individual patients. To identify genes that might be assocd. with chemosensitivity, we used a cDNA microarray representing 23,040 genes to analyze expression profiles in a panel of 85 cancer xenografts derived from nine human organs. The xenografts, implanted into nude mice, were examd. for sensitivity to nine anticancer drugs (5-fluorouracil, 3-[4-amino-2-methyl-5-pyrimidinyl)methyl]-1-(2-chloroethyl)-1-nitrosourea hydrochloride, adriamycin, cyclophosphamide, cisplatin, mitomycin C, methotrexate, vincristine, and vinblastine). Comparison of the gene expression profiles of the tumors with sensitivities to each drug identified 1,578 genes whose expression levels correlated significantly with chemosensitivity; 333 of those genes showed significant correlation with two or more drugs, and 32 correlated with six or seven drugs. These data should contribute useful information for identifying predictive markers for drug sensitivity that may eventually provide "personalized chemotherapy" for individual patients, as well as for development of novel drugs to overcome acquired resistance of tumor cells to chem. agents.

Answer 17:

Bibliographic Information

Combining radioimmunotherapy and chemotherapy for treatment of medullary thyroid carcinoma: Effectiveness of dacarbazine. Stein, Rhona; Chen, Susan; Reed, Linda; Richel, Heidi; Goldenberg, David M. Garden State Cancer Center, Belleville, NJ, USA. *Cancer* (New York, NY, United States) (2002), 94(1), 51-61. Publisher: John Wiley & Sons, Inc., CODEN: CANSAR ISSN: 0008-543X. Journal written in English. CAN 136:259269 AN 2002:57632 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background. To enhance the efficacy of chemotherapy for medullary thyroid carcinoma (MTC), we evaluated the effect of combining radioimmunotherapy (RAIT) with 90Y-anticarcinoembryonic antigen (CEA) monoclonal antibody MN-14 and chemotherapy in nude mice bearing human MTC xenografts. A preliminary study evaluated doxorubicin, dacarbazine (DTIC), cyclophosphamide, and vincristine, singly and in combination, for their effect on the growth of MTC xenografts (TT) in nude mice. Given individually, DTIC yielded the most effective tumor growth inhibition, delaying the mean time to doubling from 1 wk for untreated tumor-bearing mice to 7.5 wk. Administering either the 4 drugs in combination or a 2-drug combination comprised of doxorubicin and DTIC significantly improved the efficacy compared with any single drug alone, increasing the mean doubling time to 10-12 wk. **Methods.** Drug doses were selected to conform to the doses of each drug given clin. For the combined modality therapy, administration of 90Y-labeled anti-CEA monoclonal

antibody MN-14 to nude mice bearing established TT tumors was followed by various chemotherapy regimens initiated 24 h after RAIT. Chemotherapy protocols combined with RAIT included doxorubicin or DTIC alone and in combination, and the doxorubicin, DTIC, cyclophosphamide, and vincristine 4-drug protocol. Tumor vols. were measured weekly, and toxicity was evaluated by measuring blood counts and body wt. Results. Combinations of RAIT and chemotherapy with DTIC or RAIT and chemotherapy with the drug combinations were found to augment the antitumor effects of RAIT or chemotherapy alone, without a significant increase in toxicity. The mean tumor vol. doubling times were increased up to 100% compared with the results of chemotherapy alone. No significant differences in tumor growth were obsd. between the RAIT plus DTIC protocol and the RAIT plus two- or four-drug protocols. Conclusions.

The superiority of the combined modality treatment argues for the integration of RAIT into chemotherapeutic regimens for MTC treatment. Clin. trials are needed to assess these principles in MTC patients.

Answer 18:

Bibliographic Information

Experimental chemotherapy against canine mammary cancer xenograft in SCID mice and prediction of its clinical effect.

Yamashita, Atsuko; Maruo, Kohji; Suzuki, Kaoru; Shiota, Kinji; Kobayashi, Kimio; Hioki, Kyoji. Department of Veterinary Surgery, Tokyo University of Agriculture and Technology, Tokyo, Japan. *Journal of Veterinary Medical Science* (2001), 63(8), 831-836. Publisher: Japanese Society of Veterinary Science, CODEN: JVMSEQ ISSN: 0916-7250. Journal written in English. CAN 136:379575 AN 2001:706827 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The effectiveness of 6 antitumor agents was evaluated for a canine mammary gland tumor (CMG-6) serially transplanted into mice with severe combined immunodeficiency. CMG-6, a solid carcinoma, was s.c. transplanted into immunodeficient mice, and 6 antitumor agents were given i.v. as a single injection. The min. EDs (MEDs; mg/kg) in mice were: cyclophosphamide (CPM) 65, doxorubicin (DXR) 6, cisplatin (CDDP) 5, vincristine (VCR) 1.6, vinblastine (VLB) >5.5, 5-fluorouracil (5-FU) 105. The clin. effects of the drugs were predicted based on the ratio of the area under the curve (AUC) in dogs given a clin. dose (AUC dog) to the AUC of mice given a MED (AUC mouse) from published refs. The AUC ratios were: CPM 2.24, DXR 0.19, CDDP 1.20, VCR 0.04, VLB <1.24 and 5-FU 1.15. The drugs having a value of >1.0 for the AUC dog/AUC mouse ratio were CPM, CDDP and 5-FU, suggesting that they might be effective in the original dogs with CMG-6. Combination chemotherapy using clin. equiv. doses of CDDP and CPM, which had the two highest values of the AUC dog/AUC mouse ratio in single-agent therapy, had addnl. effects as compared to the effectiveness of the single agents against CMG-6.

Answer 19:

Bibliographic Information

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

Abstract

The overexpression of P-glycoprotein (P-gp) on the surface of tumor cells causes multidrug resistance (MDR). This protein acts as an energy-dependent drug efflux pump reducing the intracellular concn. of structurally unrelated drugs. Modulators of P-gp function can restore the sensitivity of MDR cells to such drugs. XR9576 is a novel anthranilic acid deriv. developed as a potent and specific inhibitor of P-gp, and in this study we evaluate the in vitro and in vivo modulatory activity of this compd. The in vitro activity of XR9576 was evaluated using a panel of human (H69/LX4, 2780AD) and murine (EMT6 AR1.0, MC26) MDR cell lines. XR9576 potentiated the cytotoxicity of several drugs including doxorubicin, paclitaxel, etoposide, and vincristine; complete reversal of

resistance was achieved in the presence of 25-80 nM XR9576. Direct comparative studies with other modulators indicated that XR9576 was one of the most potent modulators described to date. Accumulation and efflux studies with the P-gp substrates, [3H]daunorubicin and rhodamine 123, demonstrated that XR9576 inhibited P-gp-mediated drug efflux. The inhibition of P-gp function was reversible, but the effects persisted for > 22 h after removal of the modulator from the incubation medium. This is in contrast to P-gp substrates such as cyclosporin A and verapamil, which lose their activity within 60 min, suggesting that XR9576 is not transported by P-gp. Also, XR9576 was a potent inhibitor of photoaffinity labeling of P-gp by [3H]azidopine implying a direct interaction with the protein. In mice bearing the intrinsically resistant MC26 colon tumors, coadministration of XR9576 potentiated the antitumor activity of doxorubicin without a significant increase in toxicity; max. potentiation was obsd. at 2.5-4.0 mg/kg dosed either i.v. or p.o.

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

Answer 20:

Bibliographic Information

Establishment of model of KBv200 nude mice xenograft tumor and study on its characterization of multidrug resistance.

Liang, Yongju; Fu, Liwu; Feng, Hailin; He, Lirong; Feng, Gongkan; Yang, Xiaoping; Pan, Qichao. Cancer Center, Sun Yat-Sen University of Medical Sciences, Canton, Peop. Rep. China. Zhongguo Yaolixue Tongbao (2000), 16(6), 705-707. Publisher: Anhui Yike Daxue Linchuan Yaoli Yanjiuso, CODEN: ZYTOE8 ISSN: 1001-1978. Journal written in Chinese. CAN 135:131653 AN 2001:108996 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Multidrug resistance (MDR) is a main obstacle for cancer chemotherapy. The modulators with potent MDR reversing activity and low toxicity were desired to be found. The MDR characterization was studied in KBv200 cells in vivo. HBv200 cells were grown as s.c. xenografts in athymic nude mice. The resistant difference between KBv200 (KBv200. MDR) and nude mice xenografts (KBv200/nude. MDR) was analyzed. Cytotoxicity was detd. with tetrazolium (MTT) assay. Glycoprotein P (Pgp) was examd. by flow cytometry. Tumor incidence was 100% at 5 days after implantation s.c. by 107 of cells. IC50 of vincristine (VCR) to KB (WT) and KBv200 (MDR), KB/nude, KBv200/nude (MDR) were 0.018, 1.479, 0.018, 1.472 $\mu\text{mol L}^{-1}$, resp. The expressions of Pgp in KBv200 (MDR) were similar to those in KBv200/nude (MDR). Like the MDR cells in culture, KBv200 nude xenografts were extremely resistant to VCR and retained the characteristics of MDR phenotype.

Answer 21:

Bibliographic Information

Mdr1 promoter-driven tumor necrosis factor- α expression for a chemotherapy-controllable combined in vivo gene therapy and chemotherapy of tumors.

Walther, Wolfgang; Stein, Ulrike; Fichtner, Iduna; Alexander, Mark; Shoemaker, Robert H.; Schlag, Peter M. Max-Delbrück-Center for Molecular Medicine, Berlin, Germany. Cancer Gene Therapy (2000), 7(6), 893-900. Publisher: Nature America Inc., CODEN: CGTHEG ISSN: 0929-1903. Journal written in English. CAN 133:175967 AN 2000:466621 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Cancer gene therapy approaches are often designed as single-agent treatments; however, greater therapeutic effect might be obtained if combined with an established conventional treatment regimen such as chemotherapy. In this context, conditional promoters are useful tools, because they may be induced by therapeutic modalities. The human multidrug resistance gene (mdr1) promoter is

inducible by cytostatic drugs and can be employed for the chemotherapy-regulated expression of therapeutic genes. In this in vivo study, the human *mdr1* promoter fragment (-207 to +158) was used for drug-inducible expression of human tumor necrosis factor- α (TNF- α) in the vector construct pM3*mdr-p-hTNF*. The single doxorubicin and vincristine treatment of nude mice xenografted with pM3*mdr-p-hTNF*-transduced MCF-7 mammary tumors resulted in drug-induced and time-dependent elevation of intratumoral TNF- α expression at the mRNA and protein level. The highest drug induction was achieved at 2 days after drug application, as reflected by a max. 25-fold increase in TNF- α secretion in the tumor. This drug-induced TNF- α expression is more effective in inhibiting tumor growth compared with the growth of tumors transduced with constitutively TNF- α -expressing vectors in combination with chemotherapy.

Answer 22:

Bibliographic Information

Antitumor effects of TZT-1027, a novel dolastatin 10 derivative, on human tumor xenografts in nude mice. Fujita, Fumiko; Koike, Masako; Fujita, Masahide; Sakamoto, Yasuo; Tsukagoshi, Shigeru. Experimental Cancer Chemotherapy Research Laboratory Co., Ltd., Japan. Gan to Kagaku Ryoho (2000), 27(3), 451-458. Publisher: Gan to Kagaku Ryohosha, CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 133:99219 AN 2000:263094 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

TZT-1027 was evaluated for its antitumor effects in sixteen human tumors xenografted in nude mice from gastric (H-81, H-106, H-30, H-154), breast (H-31, H-62), colon (H-110, H-143), lung (LC-376, H-74, Mqnu-1, LC-351), liver (H-181), renal cell (H-12) and ovarian (H-OC-3, COC-4) cancer lines. In the latter three and lung (Mqnu-1, LC-351) cancers the results were compared with those obtained with CPT-11, vincristine (VCR), CDDP, adriamycin (ADM). TZT-1027 showed effective antitumor activity (IR \geq 58%) against fifteen of the tumor lines, all but LC-351, and showed markedly effective activity (IR \geq 80%) against twelve tumor lines, including drug-resistant colon (H-110); lung (H-74) and ovarian (SOC-4) cancer lines. The complete regression was shown in five H-OC-3 tumor-bearing mice out of seven. Moreover, TZT-1027 was shown to be more potent in three cancer models (Mqnu-1, h-81, SOC-4) than CPT-11, and to have markedly effective antitumor activity in two cancers (H-12, H-OC-3) in which VCR was ineffective and in ovarian cancer (SOC-4) in which CPT-11, CDDP and ADM were ineffective. The administration of TZT-1027 induced fewer side effects; transient redn. of body wt. was obsd. in four lines out of sixteen tested. These results suggest that TZT-1027 is an excellent candidate for clin. trials for the treatment of cancer.

Answer 23:

Bibliographic Information

The influence of recombinant human insulin-like growth factor-I (rhIGF-I) on cell growth and cytotoxicity of drugs in childhood rhabdomyosarcoma cell lines and xenograft models. Gidding, Corrie E. M.; Germain, Glen S.; Dilling, Michael B.; Meeuwse-de Boer, Tiny G. J.; Ashmun, Richard A.; de Graaf, Siebold S. N.; Veverka, Karen A.; Kamps, Willem A.; Houghton, Peter J. Children's Cancer Center, Beatrix Children's Hospital, Groningen, Neth. Cancer Chemotherapy and Pharmacology (2000), 45(1), 21-30. Publisher: Springer-Verlag, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 132:343703 AN 2000:60862 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Recombinant human insulin-like growth factor I (rhIGF-I) has been reported to ameliorate vincristine-induced neuropathy, the dose-limiting side effect of this antimitotic anticancer drug. However, rhIGF-I also might have adverse effects, as has been shown in vitro, where it stimulates growth of cancer cells and protects them from cytotoxicity of anticancer drugs. The influence of rhIGF-I on the cytotoxicity of vincristine has not yet been studied. Furthermore, studies performed have been done under serum-free conditions, which are far from physiol. The authors studied the influence of rhIGF-I on the growth of two rhabdomyosarcoma cell lines (Rh30 and Rh1) and on the antitumor effects of vincristine, cisplatin, etoposide, doxorubicin, and topotecan under serum-free and serum-contg. conditions. To extend the in vitro data, the authors grew Rh30 cells as xenografts in mice and detd. the effects of vincristine, rhIGF-I or their combination on tumor growth. In vitro, both cell lines demonstrated a functional type I IGF receptor, as shown by the rapid

activation of ribosomal p70 S6 kinase after stimulation with rhIGF-I. Under serum-free conditions, rhIGF-I stimulated growth of both cell lines. Exposure to cytotoxic drugs with and without rhIGF-I resulted in higher cell nos. in cultures exposed to rhIGF-I. However, relative to the appropriate control, fractional growth inhibition and or cell kill of the cytotoxic drugs was identical with and without rhIGF-I. Under serum-contg. conditions, rhIGF-I had no effect on cell growth or drug cytotoxicity. In vivo the authors did not find a significant influence of rhIGF-I on HxRh30 cell growth, or on the antitumor activity of vincristine. These studies show that rhIGF-I has no adverse effects on human rhabdomyosarcoma growth or on the antitumor effect of cytotoxic drugs under serum-contg. conditions in vitro or in tumor-bearing mice.

Potentially, therefore, rhIGF-I may ameliorate vincristine-induced neuropathy without adversely influencing tumor growth or vincristine cytotoxicity in children.

Answer 24:

Bibliographic Information

Synergy of topotecan in combination with vincristine for treatment of pediatric solid tumor xenografts. Thompson, Joyce; George, E. Olusegun; Poquette, Catherine A.; Cheshire, Pamela J.; Richmond, Lois B.; De Graaf, Siebold S. N.; Ma, Margaret; Stewart, Clinton F.; Houghton, Peter J. Department of Hematology-Oncology, St. Jude Children's Research Hospital, Memphis, TN, USA. *Clinical Cancer Research* (1999), 5(11), 3617-3631. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 132:260198 AN 1999:809347 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Topotecan and vincristine were evaluated alone or in combination against 13 independent xenografts and 1 vincristine-resistant deriv., representing childhood neuroblastoma, rhabdomyosarcoma, or brain tumors, in immunosuppressed mice. Topotecan was given by i.v. bolus on a schedule found previously to be optimal. The drug was administered daily for 5 days on 2 consecutive weeks with cycles repeated every 21 days over a period of 8 wk. Doses of topotecan ranged 0.16-1.5 mg/kg to simulate clin. achievable plasma topotecan lactone systemic exposures. Vincristine was administered i.v. every 7 days at a fixed dose of 1 mg/kg. Given as a single agent, vincristine induced complete responses (CRs) in all mice bearing 2 rhabdomyosarcomas (Rh28 and Rh30) and some CRs in Rh12-bearing mice (57%) but relatively few CRs (<29%) in other tumors. As a single agent, topotecan induced CR in a low proportion of tumor lines. A dose-response model with a logit link function was used to investigate whether the combination of topotecan and vincristine resulted in greater than expected responses compared with the activity of the agents administered alone. Only CR was used to evaluate tumor responses. The combination resulted in greater than expected CRs than individual agents in nine tumor lines (four neuroblastoma, three brain tumors, and two rhabdomyosarcomas). Similar event-free (failure) distributions were shown in SJ-GBM2 glioblastoma xenografts, whether vincristine was administered on day 1 or day 5 of each topotecan course. To det. whether the increased antitumor activity with the combination was attributable to a change in drug disposition, extensive pharmacokinetic studies were performed. However, little or no interaction between these two agents was detd. Toxicity of the combination was marked by prolonged thrombocytopenia and decreased Hb. However, approx. 75 and 80%, resp., of the max.

tolerated dose of each single agent, topotecan (1.5 mg/kg) or vincristine (1 mg/kg), could be given in combination, resulting in a combination toxicity index of .apprx.1.5. These results show that the therapeutic effect of combining topotecan with vincristine was greater than additive in most tumor models of childhood solid tumors, and toxicity data suggest that this can be administered to mice with only moderate redn. in the dose levels for each agent.

Answer 25:

Bibliographic Information

Antitumor activity and novel DNA-self-strand-breaking mechanism of CNDAC (1-(2-C-cyano-2-deoxy- β -D-arabino-pentofuranosyl)cytosine) and its N4-palmitoyl derivative (CS-682). Hanaoka, Kenji; Suzuki, Masako; Kobayashi, Tomowo; Tanzawa, Fumie; Tanaka, Kazuo; Shibayama, Takahiro; Miura, Shinichi; Ikeda, Tomoko; Iwabuchi, Haruo; Nakagawa, Akihiko; Mitsunashi, Yoshihiro; Hisaoka, Masashi; Kaneko, Masakatsu; Tomida, Akihiro; Wataya, Yusuke; Nomura, Tatsuji; Sasaki, Takuma; Matsuda, Akira; Tsuruo, Takashi; Kurakata, Shinichi. Biological Research Laboratories, Sankyo Co., Ltd., Tokyo, Japan. *International Journal of Cancer* (1999), 82(2), 226-236. Publisher: Wiley-Liss, Inc., CODEN: IJCNW ISSN: 0020-7136.

Journal written in English. CAN 131:266648 AN 1999:438485 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We have studied the antitumor activity and the novel DNA-self-strand-breaking mechanism of CNDAC (1-(2-C-cyano-2-deoxy- β -D-arabino-pentofuranosyl)cytosine) and its N4-palmitoyl deriv. (CS-682). In vitro, CS-682 showed strong cytotoxicity against human tumor cells comparable with that of CNDAC; both compds. displayed a similar broad spectrum. In vivo, however, orally administered CS-682 showed a more potent activity against human tumor xenografts than CNDAC, 5'-deoxy-5-fluorouridine, 5-fluorouracil and 2',2'-difluorodeoxycytidine. Moreover, CS-682 was effective against various human organ tumor xenografts at a wide dose range and with low toxicity, and was effective against P388 leukemic cells resistant to mitomycin-C, vincristine, 5-fluorouracil or cisplatin in syngeneic mice. CNDAC, an active metabolite of CS-682, had a prolonged plasma half-life after repeated oral administrations of CS-682 but not after oral administrations of CNDAC itself. This difference may partially explain the higher antitumor activity of CS-682 relative to CNDAC. In both CNDAC- and CS-682-treated carcinoma cells, CNDAC 5'-triphosphate (CNDACTP) was generated and incorporated into a DNA strand. High performance liq. chromatog. (HPLC) and mass spectrometric anal. of the nucleosides prepd. by digestion of the DNA from the CNDAC-treated cells detected ddCNC (2'-C-cyano-2',3'-didehydro-2',3'-dideoxycytidine), which was shown to be generated only when the self-strand-breakage of CNDACTP-incorporated DNA occurred. The cytotoxicity of CNDAC was completely abrogated by the addn. of 2'-deoxycytidine and was low against cells with decreased deoxycytidine kinase. Our results suggest that CNDAC is converted to CNDACMP by deoxycytidine kinase and that the resulting CNDACTP incorporated into a DNA strand as CNDACMP may induce DNA-self-strand-breakage. This novel DNA-self-strand-breaking mechanism may contribute to the potent antitumor activity of CS-682.

Answer 26:

Bibliographic Information

Antitumor activity of SCH 66336, an orally bioavailable tricyclic inhibitor of farnesyl protein transferase, in human tumor xenograft models and wap-ras transgenic mice. Liu, Ming; Bryant, Matthew S.; Chen, Jianping; Lee, Suining; Yaremko, Bohdan; Lipari, Phil; Malkowski, Michael; Ferrari, Eric; Nielsen, Loretta; Prioli, Nicholas; Dell, Janet; Sinha, Dineshwar; Syed, Jameel; Korfmacher, Walter A.; Nomeir, Amin A.; Lin, C-C.; Wang, Lynn; Taveras, Arthur G.; Doll, Ronald J.; Njoroge, F. George; Mallams, Alan K.; Remiszewski, Stacy; Catino, Joseph J.; Girijavallabhan, Viyyoor M.; Kirschmeier, Paul; Bishop, W. Robert. Departments of Biological Research-Oncology, Schering-Plough Research Institute, Kenilworth, NJ, USA. Cancer Research (1998), 58(21), 4947-4956. Publisher: AACR Subscription Office, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 130:104933 AN 1998:728126 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We have been developing a series of nonpeptidic, small mol. farnesyl protein transferase inhibitors that share a common tricyclic nucleus and compete with peptide/protein substrates for binding to farnesyl protein transferase. Here, we report on pharmacol. and in vivo studies with SCH 66336, a lead compd. in this structural class. SCH 66336 potently inhibits Ha-Ras processing in whole cells and blocks the transformed growth properties of fibroblasts and human tumor cell lines expressing activated Ki-Ras proteins. The anchorage-independent growth of many human tumor lines that lack an activated ras oncogene is also blocked by treatment with SCH 66336. In mouse, rat, and monkey systems, SCH 66336 has excellent oral bioavailability and pharmacokinetic properties. In the nude mouse, SCH 66336 demonstrated potent oral activity in a wide array of human tumor xenograft models including tumors of colon, lung, pancreas, prostate, and urinary bladder origin. Enhanced in vivo efficacy was obsd. when SCH 66336 was combined with various cytotoxic agents (cyclophosphamide, 5-fluorouracil, and vincristine). In a Ha-Ras transgenic mouse model, prophylactic treatment with SCH 66336 delayed tumor onset, reduced the av. no. of tumors/mouse, and reduced the av. tumor wt./animal. In a therapeutic mode in which gavage treatment was initiated after the transgenic mice had developed palpable tumors, significant tumor regression was induced by SCH 66336 in a dose-dependent fashion. This was assocd. with increased apoptosis and decreased DNA synthesis in tumors of animals treated with SCH 66336. Enhanced efficacy was also obsd. in this model when SCH 66336 was combined with cyclophosphamide. SCH 66336 is presently being evaluated in Phase I clin. trials.

Answer 27:

Bibliographic Information

Sphingomyelin-cholesterol liposomes significantly enhance the pharmacokinetic and therapeutic properties of vincristine in murine and human tumor models. Webb, M S.; Harasym, T O.; Masin, D.; Bally, M B.; Mayer, L D. Division Medical Oncology, British Columbia Cancer Agency, Vancouver, BC, Can. British Journal of Cancer (1995), 72(4), 896-904. Publisher: Macmillan Scientific & Medical Division, CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 124:44967 AN 1995:936070 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

This study reports on the development of a liposomal formulation of vincristine with significantly enhanced stability and biol. properties. The in vitro and in vivo pharmacokinetic, tumor delivery and efficacy properties of liposomal vincristine formulations based on sphingomyelin (SM) and cholesterol were compared with liposomes composed of distearoylphosphatidylcholine (DSPC) and cholesterol. SM/cholesterol liposomes had significantly greater in vitro stability than did similar DSPC/cholesterol liposomes. SM/cholesterol liposomes also had significantly improved biol. properties compared with DSPC/cholesterol. Specifically, SM/cholesterol liposomes administered i.v. retained 25% of the entrapped vincristine after 72 h in the circulation, compared with 5% retention in DSPC/cholesterol liposomes. The improved retention properties of SM/cholesterol liposomes resulted in plasma vincristine levels 7-fold higher than in DSPC/cholesterol liposomes. The improved circulation lifetime of vincristine in SM/cholesterol liposomes correlated with increased vincristine accumulation in peritoneal ascitic murine P388 tumors and in s.c. solid A431 human xenograft tumors. Increased vincristine delivery to tumors was also accompanied by increased anti-tumor efficacy. Treatment with SM/cholesterol liposomal formulations of vincristine resulted in greater than 50% cures in mice bearing ascitic P388 tumors, an activity that could not be achieved with the DSPC/cholesterol formulation. Similarly, treatment of mice with severe combined immunodeficiency (SCID) bearing solid human A431 xenograft tumors with SM/cholesterol vincristine formulations delayed the time required for 100% increase in tumor mass to >40 days, compared with 5 days, 7 days and 14 days for mice receiving no treatment or treatment with free vincristine or DSPC/cholesterol formulations of vincristine resp.

Answer 28:

Bibliographic Information

Resistance of MGH-U1 bladder cancer spheroids to vincristine. Erlichman, C.; Wu, A. Ont. Cancer Inst., Univ. Toronto, Toronto, ON, Can. Anticancer Research (1992), 12(4), 1233-6. CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 121:26390 AN 1994:426390 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The authors compared the cytotoxicity of vincristine in MGH-U1 human bladder cancer cells growing as exponential monolayer culture, spheroids and xenografts. Cells treated as spheroids were resistant to vincristine as detd. by clonogenic survival and growth delay. The spheroid population had a smaller proportion of cells in G2+M than monolayer cells. Cell derived from increasing depths of the spheroid viable rim had similar cell cycle distribution characteristics and sensitivity to vincristine. Prolonged treatment of spheroid did not increase vincristine cytotoxicity significantly. When cells derived from spheroids were treated as monolayers, the cytotoxicity was the same as that of cells maintained as monolayer cultures. The vincristine resistance obsd. in spheroids was also obsd. in xenografted tumors treated in vivo. Vincristine decreased the clonogenic survival of xenografted cells at in vivo doses which were greater than the LD10 for the mice. The in vitro cytotoxicity of the xenografted tumors at these LDs was similar to that of cells treated as spheroids. The authors conclude that vincristine resistance in spheroids may be attributed in part to the small proportion of cells traversing mitosis but not to the development of intrinsic resistance by passage through spheroid growth. The authors' results are consistent with cell cycle kinetics and limited penetration contributing to vincristine resistance in spheroids. The spheroid system can serve as a model of in vivo cytotoxicity for antineoplastic agents with cell cycle phase specificity such as vincristine.

Answer 29:

Bibliographic Information

Modulation by verapamil of vincristine retention in an *mdr1* overexpressing xenograft and normal mouse tissues: comparison of bolus administration and continuous infusion vincristine. Horton, J. K.; Houghton, J. A.; Houghton, P. J. Dep. Biochem. Clin. Pharmacol., St Jude Child. Res. Hosp., Memphis, TN, USA. *Journal of Cellular Pharmacology* (1990), 1(1), 42-9. CODEN: JOCPEK ISSN: 0939-1096. Journal written in English. CAN 118:384 AN 1993:384 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Xenografts of a human cervical carcinoma cell line KB8-5 known to overexpress the *mdr1* gene were grown as xenografts in immune deprived mice. The modulating effect of verapamil (VRP) on vincristine (VCR) retention was detd. when VCR was administered by two different schedules. Plasma and tissue levels of $\approx 10 \mu\text{M}$ VRP could be achieved in the mice by infusion from osmotic pumps. When VCR was administered as a bolus 1.5 mg/kg injection, VRP modulated accumulation and retention of VCR in KB8-tumors, but the effect in mouse small intestine was even more marked (6- and 140-fold elevation). Verapamil modulating activity was shown previously to be related to the dose and therefore tissue level of VCR. Administration of VCR by const. infusion (1.5 mg/kg/8 days) resulted in lower tissue levels and lesser modulation by VRP in normal tissues although toxicity was still apparent. During the simultaneous infusion of VCR and VRP, there was no difference in tumor VCR levels between this group and saline treated controls.

Answer 30:

Bibliographic Information

Acquired drug resistance in human lung carcinoma xenografts. Volm, M.; Efferth, T.; Mattern, J. Inst. Exp. Pathol., Ger. Cancer Res. Cent., Heidelberg, Fed. Rep. Ger. *Arzneimittel-Forschung* (1989), 39(8), 828-31. CODEN: ARZNAD ISSN: 0004-4172. Journal written in English. CAN 111:166893 AN 1989:566893 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The development of resistance to vincristine and dactinomycin was studied in a human epidermoid lung xenograft in nude mice. Resistance was present at the 2nd transplant after exposure to vincristine at 1 mg/kg or dactinomycin at 0.5 mg/kg. The vincristine-resistant line was resistant to dactinomycin and doxorubicin and the dactinomycin-resistant line only to vincristine. The RNA levels were slightly elevated in both resistant lines, indicating increased multi-drug resistance gene expression.

Answer 31:

Bibliographic Information

Modulation by verapamil of vincristine pharmacokinetics and toxicity in mice bearing human tumor xenografts. Horton, Julie K.; Thimmaiah, Kuntebommanahalli N.; Houghton, Janet A.; Horowitz, Marc E.; Houghton, Peter J. Dep. Biochem. Clin. Pharmacol., St. Jude Child. Res. Hosp., Memphis, TN, USA. *Biochemical Pharmacology* (1989), 38(11), 1727-36. CODEN: BCPCA6 ISSN: 0006-2952. Journal written in English. CAN 111:33064 AN 1989:433064 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The effect of the calcium channel blocker verapamil (VRP) on the accumulation and retention of vincristine (VCR) has been examd. in mice bearing xenografts of human rhabdomyosarcomas. Administration of VRP by i.p. bolus at 75 mg/kg led to the maximal plasma concn. of $24 \mu\text{M}$, with rapid elimination such that plasma concns. reported to modulate tumor resistance in vitro (approx. 5-10 μM) were maintained for less than 60 min. To sustain a $10 \mu\text{M}$ plasma concn., mice were infused with VRP at 6.25 mg/kg/h for up to 7 days using osmotic pumps. Steady-state plasma levels were $\geq 10 \mu\text{M}$ for at least 96 h, and this schedule demonstrated minimal toxicity.

Administration of VCR 20 h after the start of VRP infusion produced lethality, requiring an 8-fold redn. in the VCR dose. Pharmacokinetic studies showed that VRP markedly increased the uptake and retention of VCR in the small intestine, liver and kidney. In the small intestine, 8-fold greater levels of VC were detd. 24 h after VCR administration, and this was assocd. with an increase in elimination $t_{1/2}$ from 350 to 913 min. HPLC anal. of exts. from the small intestine showed that >90% of the radiolabel eluted with VCR or 4-desacetyl-VCR. Modulation of VCR retention was also related to the dose of VCR administered. The VRP-sensitive efflux pathway appeared more effective in certain tissues only at higher concns. of VCR. In contrast, VRP did not alter the uptake and retention of VCR in either the parent or VCR-resistant human xenografts. Thus, in the mouse, VRP modulates the uptake and retention of VCR in several tissues, and this may indicate that drug efflux mediated by a VRP-sensitive mechanism has a protective function against xenobiotics in these tissues.

Answer 32:

Bibliographic Information

Relationships between tumor responsiveness, vincristine pharmacokinetics and arrest of mitosis in human tumor xenografts. Horton, Julie K.; Houghton, Peter J.; Houghton, Janet A. Dep. Biochem. Clin. Pharmacol., St. Jude Child. Res. Hosp., Memphis, TN, USA. *Biochemical Pharmacology* (1988), 37(20), 3995-4000. CODEN: BCPCA6 ISSN: 0006-2952. Journal written in English. CAN 110:450 AN 1989:450 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Tumor responsiveness to vincristine (VCR) was detd. in mice bearing xenografts of human rhabdomyosarcoma (RMS), in sublines of RMS selected in vivo for VCR resistance, in a KB line selected in vitro for colchicine resistance, and in a colon adenocarcinoma. Sensitivity to VCR was assocd. with prolonged retention of VCR by the tumors after a single i.p. injection, whereas in tumors with acquired or intrinsic VCR resistance the drug was eliminated more rapidly. The sensitive tumors with prolonged retention of drug also showed increased mitotic accumulation for ≤ 72 h following VCR administration. There were good correlations between VCR sensitivity, VCR retention and the proposed mechanism of VCR cytotoxicity-mitotic arrest. A model was developed, consistent with data, that can explain the responsiveness to VCR of a series of human tumor xenografts irresp. of their tissue of origin.

Answer 33:

Bibliographic Information

Development of drug resistance in a human epidermoid lung carcinoma xenograft line. Mattern, J.; Bak, M., Jr.; Hoever, K. H.; Volm, M. Inst. Exp. Pathol., Cancer Res. Cent., Heidelberg, Fed. Rep. Ger. *British Journal of Cancer* (1988), 58(1), 30-3. CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 109:183130 AN 1988:583130 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The development of resistance to vincristine, actinomycin D, and cisplatin has been examd. in a human epidermoid lung carcinoma xenograft line (HXL 55) growing in nude mice. Treatment of HXL 55 with 1 mg/kg vincristine or 0.5 mg/kg actinomycin D once in each in vivo passage resulted in a rapid redn. in tumor responsiveness to these drugs. A partial resistance was already acquired at the 2nd transplant generation. In contrast, a gradual decrease in therapeutic response was obsd. with 10 mg/kg cisplatin. Irradn. with a local dose of 10 Gy induced no resistance. The three induced drug-resistant sublines were characterized in terms of the time course of development of resistance, the degree of induced resistance cross-resistance, growth rate, and stability of the phenotype.

Answer 34:

Bibliographic Information

Therapeutic effect of 5-aza-2'-deoxycytidine in human head and neck tumor xenografts. Braakhuis, Boudewijn J. M.; Leyva, Albert; Pinedo, Herbert M.; Snow, Gordon B. Dep. Otolaryngol., Free Univ. Hosp., Amsterdam, Neth. Editor(s): Rygaard, Joergen. Immune-Defic. Anim. Biomed. Res., Int. Workshop Immune-Defic. Anim., 5th (1987), Meeting Date 1985, 380-3. Publisher: Karger, Basel, Switz CODEN: 55YNAL Conference written in English. CAN 107:108921 AN 1987:508921 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

In nude mice bearing xenografts of human head and neck tumors, 5-aza-5'-deoxycytidine retarded tumor growth, in some cases more effectively than vincristine, methotrexate, bleomycin, or 5-fluorouracil.

Answer 35:

Bibliographic Information

Stability of vincristine complexes in cytosols derived from xenografts of human rhabdomyosarcoma and normal tissues of the mouse. Houghton, Janet A.; Williams, Larry G.; Houghton, Peter J. Clin. Pharmacol., St. Jude Child. Res. Hosp., Memphis, TN, USA. Cancer Research (1985), 45(8), 3761-7. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 103:115647 AN 1985:515647 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The selective action of vincristine (VCR) [57-22-7] has been correlated with longer retention of the drug in neoplastic tissue compared with normal tissues of the mouse. In order to examine the basis for this differential, the stability of drug-protein complexes was examd. further. The stability of drug-protein complexes formed in cytosols derived from HxRh18 tumors, ileum, liver, kidney, skeletal muscle, blood, brain, spleen, lung, and bone marrow was examd. Protein-bound [3H]VCR was isolated by gel filtration of [3H]VCR-cytosol mixts. from each tissue except for ileum and blood. Complexes formed in brain and HxRh18 cytosols were stable at 37° for at least 2 h; all other complexes were unstable. For liver, kidney, and muscle, half-times of complexes were in a similar order to the initial rates of elimination of [3H]VCR from these tissues in vivo but were of shorter duration. The HxRh18-[3H]VCR complex was unstable at 37° in the presence of cytosols prep'd. from ileum, kidney, liver, and lung. Drug metab. by these tissues was not detected in vitro. In the presence of heat-treated exts. from ileum or kidney, [3H]VCR complex was stable, suggesting that the destabilizing factor may be enzymic. Degr'dn. of [125I]tubulin, analyzed by polyacrylamide-sodium dodecyl sulfate gel electrophoresis, occurred in the presence of ileum but not skeletal muscle or brain cytosols. This correlated with the stability of HxRh18-[3H]VCR complexes. In the presence of kidney cytosol, however, the mol. wt. of [125I]tubulin remained unchanged, suggesting a different mechanism. Based upon data obtained, cytosols from normal tissues may be categorized into 3 classes: (a) those that formed stable complexes (brain); (b) those that formed unstable complexes but also destabilized preformed complex (ileum, kidney, liver, lung); and (c) tissues that formed unstable complexes but did not destabilize preformed complex (skeletal muscle, spleen, bone marrow, blood). The degree of instability of complexes formed in cytosols prep'd.

from normal tissues appears to correlate with rapid loss of VCR from these tissues in vivo and hence may represent mechanism(s) for the selective action of this antineoplastic agent.

Answer 36:

Bibliographic Information

In situ selection of a human rhabdomyosarcoma resistant to vincristine with altered β -tubulins. Houghton, Janet A.; Houghton, Peter J.; Hazelton, Bonni J.; Douglass, Edwin C. Div. Biochem. Clin. Pharmacol., St. Jude Children's Res. Hosp., Memphis, TN, USA. Cancer Research (1985), 45(6), 2706-12. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 103:47895 AN 1985:447895 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

In order to simulate more closely conditions in which resistance to vincristine (VCR) [57-22-7] is selected in human solid tumors, a human rhabdomyosarcoma grown as a xenograft in immune-deprived mice has been selected for resistance in situ. Karyotype anal. showed the resistant line, HxRh18/VCR-3, to have a diploid modal no., with no apparent translocations, whereas the predominant population in the parental, sensitive HxRh18 xenograft demonstrated a modal no. near-tetraploid with many marker chromosomes. From the rapid rate at which resistance was selected and from karyotypic evidence, data strongly suggest that HxRh18/VCR-3 was a subpopulation within the parent tumor. When grown in the same host, HxRh18/VCR-3 tumors accumulated less drug, and the rate of [3H]VCR loss was 5-fold greater than in HxRh18 tumors. Thus, accumulation and retention of [3H]VCR in HxRh18/VCR-3 resistant tumors was identical to that of 3H-labeled vinblastine (VLB) [865-21-4] in HxRh18 xenografts. HxRh18 xenografts are intrinsically resistant to VLB. Anal. by HPLC of [3H]VCR:protein complexes in HxRh18 cytosols indicated 1 binding species (Mr 95,000 to 116,000), probably the tubulin heterodimer. Of interest was the observation that β -tubulin species, identified on Western blots by monoclonal antibody, differed in these tumors. In HxRh18/VCR-3, less acidic β -tubulins of HxRh18 were decreased or absent, with 3 addnl. more acidic isoforms present in the resistant line. As vincristine may bind to the β -subunit of tubulin, this may have importance to vincristine resistance in vivo.

Answer 37:

Bibliographic Information

Screening test of antitumor agents by human tumor cell lines in nude mice in ascitic form. Kitahara, Takeshi; Minato, Keisuke; Shimoyama, Masanori. Natl. Cancer Cent. Hosp., Japan. *Gan no Rinsho* (1984), 30(9), 1158-67. CODEN: GANRAE ISSN: 0021-4949. Journal written in Japanese. CAN 102:17008 AN 1985:17008 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Human breast cancer and leukemic cells implanted in nude mice appeared to be useful models for the screening of neoplasm inhibitors. The sensitivities of implanted tissues to drugs were similar to those found in patients. Studies on the suitable route of administration in these mice provide the best administration routes for humans.

Answer 38:

Bibliographic Information

Childhood rhabdomyosarcoma xenografts: responses to DNA-interacting agents and agents used in current clinical therapy. Houghton, Janet A.; Cook, Ruby L.; Lutz, Pamela J.; Houghton, Peter J. Div. Biochem. Clin. Pharmacol., St. Jude Child. Res. Hosp., Memphis, TN, USA. *European Journal of Cancer & Clinical Oncology* (1984), 20(7), 955-60. CODEN: EJCODS ISSN: 0277-5379. Journal written in English. CAN 101:163109 AN 1984:563109 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A lab. model of childhood rhabdomyosarcoma (RMS) has been used to evaluate cytotoxic agents used in current clin. protocols, and DNA-reacting agents that have had either limited or no evaluation in this histiotype. Seven lines of RMS each derived from a different patient were grown as xenografts in immune-deprived mice, six of these being from specimens derived from previously untreated patients. Of the conventional agents, vincristine [57-22-7] was the most effective. Of the other agents evaluated [L-phenylalanine mustard (L-PAM) [148-82-3], cis-dichlorodiammineplatinum (cis-DDP) [15663-27-1], mitomycin C [50-07-7] and 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide (DTIC) [4342-03-4]], L-PAM caused complete regressions in six of seven lines, including those resistant to cyclophosphamide [50-18-0]. DTIC had marked activity in five tumors, and mitomycin C in three lines. Cyclophosphamide was active in five tumors, although efficacy was less marked in two lines in comparison to DTIC and mitomycin C.

Answer 39:

Bibliographic Information

Effect of five antineoplastic agents on tumor xenografts with different growth rates. Mattern, Juergen; Wayss, Klaus; Volm, Manfred. Dep. Exp. Pathol., German Cancer Res. Cent., Heidelberg, Fed. Rep. Ger. JNCI, Journal of the National Cancer Institute (1984), 72(6), 1335-9. CODEN: JJIND8 ISSN: 0198-0157. Journal written in English. CAN 101:103754 AN 1984:503754 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The effects of cyclophosphamide (Cy) [50-18-0], doxorubicin (Dx) [23214-92-8], cisplatin (DDP) [15663-27-1], melphalan (L-PAM) [148-82-3], and vincristine (VCR) [57-22-7] on various human and animal tumor lines with different growth rates, growing as xenografts in NMRI (nu/nu) mice, were studied. Two types of response were obsd.: For Cy and Dx, the response of the xenografts was neg. correlated with tumor vol. doubling time (TD), indicating that rapidly growing tumors were more sensitive to these drugs than were slowly growing tumors. For DDP, L-PAM, and VCR, the effects were pos. correlated with the TD, indicating that slowly growing tumors were more sensitive to these drugs than rapidly growing tumors. The data are discussed in relation to the effects of the drugs on proliferating and nonproliferating cells obtained with other cell lines.

Answer 40:

Bibliographic Information

Determinants of intrinsic sensitivity to Vinca alkaloids in xenografts of pediatric rhabdomyosarcomas. Houghton, Janet A.; Williams, Larry G.; Torrance, Pamela M.; Houghton, Peter J. Dep. Biochem. Clin. Pharmacol., St. Jude Children's Res. Hosp., Memphis, TN, USA. Cancer Research (1984), 44(2), 582-90. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 100:96286 AN 1984:96286 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Three pediatric rhabdomyosarcoma xenografts maintained s.c. in immune-deprived mice differed in their sensitivity to vincristine (VCR) [57-22-7] and vinblastine (VBL) [865-21-4]; 2 lines (Rh12 and Rh28) were extremely sensitive to VCR, whereas Rh18 tumors were less sensitive. Rh28 tumors were also very responsive to VLB, which demonstrated only marginal activity in the other 2 lines. After administration of equimolar doses (3 mg/kg) of [3H]VCR and [3H]VLB to tumor-bearing mice, [3H]VCR reached concns. approaching 1.5 μ M in cell water of each tumor line within 4 h, at which time >93% of the drug was cell-assocd. The drug was subsequently retained at this level for at least 72 h. [3H]VLB accumulated to lower maximal concns. (approx. 1 μ M) within 8 h, but was not retained and, by 72 h, reached concns. that were 3- to 4-fold lower than those of [3H]VCR. The extent of drug retention correlated with the antitumor activity, except in Rh28 tumors, which were sensitive to VLB, but did not retain the drug. The threshold level for achieving cytotoxicity may, thus, be very low in this line. In normal tissues, maximal concns. of both [3H]VCR and [3H]VLB were achieved within 1 h of administration i.p. to tumor-bearing mice. In ileum, liver, and kidney, these were approx. 10-fold higher than the peak levels achieved within tumors or plasma, but declined rapidly to parallel the decrease in plasma, reaching concns. >5-fold lower than the concn. of [3H]VCR in tumors at 72 h after treatment. Drug concns. in skeletal muscle also declined rapidly, whereas neither [3H]VCR nor [3H]VLB accumulated to any great extent in brain. The blood vols. of ileum, kidney, and liver were greater than for tumor tissues. Hence, the extent of drug delivery did not necessarily influence therapeutic selectivity. In the case of [3H]VLB, concns. in tumors approached those of normal tissues at 72 h after injection.

By 24 h after treatment, 86-99% of [3H]VCR and 78-90% of [3H]VLB were present in tumors as the parent compd., which also predominated in normal tissues. Metabolites or in vivo degrdn. products were also identified. Hence, selective retention in tumors appears to be the mechanism by which therapeutic selectivity is achieved with VCR in rhabdomyosarcoma xenografts. The general lack of metab. by normal tissues suggests that metab. may not influence retention in these tissues. The importance of the interaction of these agents with tubulin in different tissues as well as factors influencing drug retention are discussed.

Answer 41:

Bibliographic Information

Chemotherapy of human yolk sac tumor heterotransplanted in nude mice. Sawada, Masumi; Matsui, Yoshiaki; Okudaira, Yoshio. Res. Inst. Microb. Dis., Osaka Univ., Suita, Japan. JNCI, Journal of the National Cancer Institute (1983), 71(6), 1221-5. CODEN: JJIND8 ISSN: 0198-0157. Journal written in English. CAN 100:96258 AN 1984:96258 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The chemotherapeutic effects of cis-diamminedichloroplatinum [15663-27-1] plus vinblastine [865-21-4] plus bleomycin [11056-06-7] (PVB) on 3 human yolk sac tumors (YST-1, YST-2, and YST-3) of the ovary, which were heterotransplanted into BALB/c nude mice, were compared with the effects of vincristine+actinomycin D+cyclophosphamide (VAC), the combination currently favored for treatment of yolk sac tumors. Both PVB and VAC significantly reduced the tumor vol. of all the treated tumors. The mean wts. of tumors in animals treated with PVB or VAC were, in percent of the mean tumor wt. in untreated animals: 1.3 and 1.6 for YST-1, 2.5 and 3.3 for YST-2, and 5.5 and 2.7 for YST-3, resp. A strong correlation was noted between tumor vol. and α -fetoprotein level in the sera of mice bearing YST-1 or TST-2 tumors.

Answer 42:

Bibliographic Information

Chromatographic analysis of vinca alkaloids in human neoplastic tissues and host (mouse) tissues after injection in vivo or after incubation in vitro. Houghton, Janet A.; Torrance, Pamela M.; Houghton, Peter J. Dep. Biochem. Clin. Pharmacol., St. Jude Child. Res. Hosp., Memphis, TN, USA. Analytical Biochemistry (1983), 134(2), 450-4. CODEN: ANBCA2 ISSN: 0003-2697. Journal written in English. CAN 99:205460 AN 1983:605460 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A method for extg. vinblastine [865-21-4], vincristine [57-22-7], and their metabolites from biol. samples, with subsequent anal. by high-performance liq. chromatog., has been developed. After excision, tissues are rapidly frozen in liq. nitrogen (<10 s) and powders are made under liq. N₂. Extn. of blood, plasma, or tissue powders was achieved using EtOH (95%) acidified to pH 4.9 with acetic acid. Exts. were analyzed using reverse-phase chromatog. capable of sepg. Vinca alkaloids with substitutions on the vindoline or catharanthine moiety. This technique was used to elucidate the metab. of vincristine and vinblastine in a human rhabdomyosarcoma growing as a xenograft in immune-deprived mice and in host tissue and fluid.

Answer 43:

Bibliographic Information

Chemotherapy and radiation therapy of human medulloblastoma in athymic nude mice. Friedman, Henry S.; Schold, S. Clifford, Jr.; Varia, Mahesh; Bigner, Darell D. Med. Cent., Duke Univ., Durham, NC, USA. Cancer Research (1983), 43(7), 3088-93. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 99:63962 AN 1983:463962 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The human medulloblastoma cell line TE-671 was grown s.c. and intracranially in athymic nude mice. Tumor-bearing animals treated with chemotherapeutic agents or radiation were compared to untreated tumor-bearing controls. Tumors growing s.c. were sensitive to cyclophosphamide [50-18-0] and vincristine [57-22-7] with growth delays in duplicate trials of 15.8/16.5 and 12.9/15.0 days, resp. These tumors were minimally responsive to the 2,5-bis(1-aziridiny)-3,6-dioxodiethyl ester of 1,4-cyclohexadiene-1,4-dicarbamic acid [57998-68-2] and cis-diamminedichloroplatinum II [15663-27-1] and unresponsive to methotrexate [59-05-2], NSC 351521

[72732-56-0], NSC 409962 [154-93-8], and procarbazine [671-16-9]. Radiation therapy with 2500 or 1500 rads as a single fraction produced a marked response, with growth delays of 39.5 and 21.1 days, resp. Cyclophosphamide produced a significant increase in the median survival of mice with intracranial tumors. Vincristine produced a minimal increase in the median survival while no response was seen to the 2,5-bis(1-aziridiny)-3,6-dioxodiethyl ester of 1,4-cyclohexadiene-1,4-dicarbamic acid at the dose level and schedule tested. This model system will allow further anal. of the therapeutic sensitivity of human medulloblastoma to other agents or combined-modality regimens.

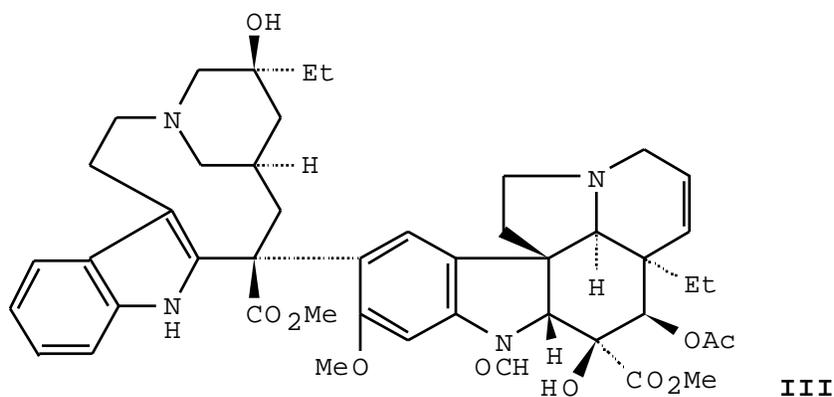
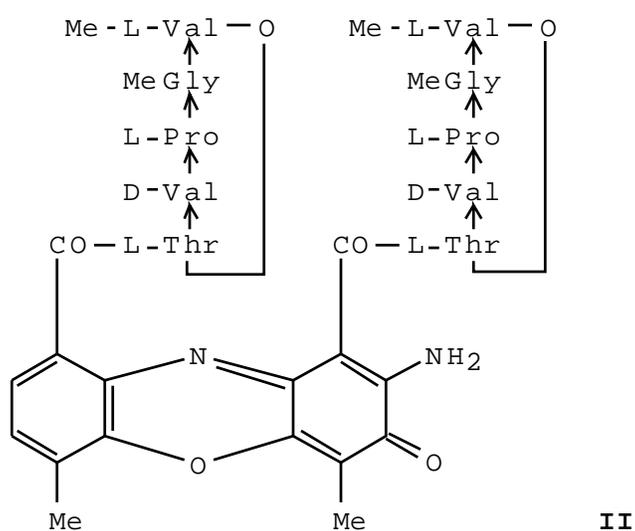
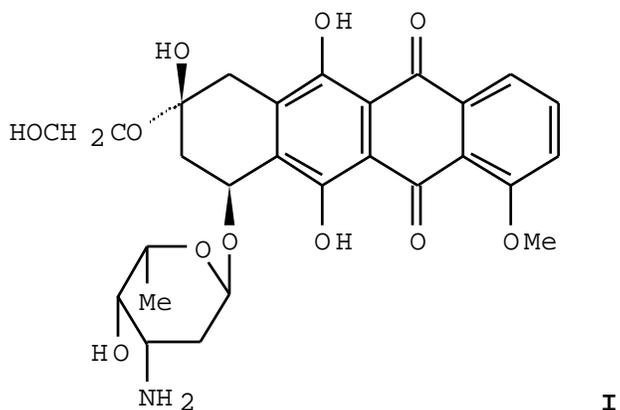
Answer 44:

Bibliographic Information

Chemotherapeutic response in xenografts: inter- and intra-tumor heterogeneity. Houghton, Peter J.; Houghton, Janet A. Dep. Biochem. Clin. Pharmacol., St. Jude Children's Res. Hosp., Memphis, TN, USA. UCLA Symposia on Molecular and Cellular Biology, New Series (1983), 4(Ration. Basis Chemother.), 61-9. CODEN: USMBD6 ISSN: 0735-9543. Journal written in English. CAN 98:209649 AN 1983:209649 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The sensitivity of 5 lines of rhabdomyosarcoma, each derived from a different child and grown as xenografts in mice, was examd. to doxorubicin (I) [23214-92-8] actinomycin D (II) [50-76-0] and vincristine (III) [57-22-7]. Resistance de novo to 1 agent was not assocd. necessarily with cross resistance. Development of resistance to vincristine in situ was examd. Resistant lines were derived only from 2 tumor lines which showed a slight sensitivity to vincristine initially. Apparently, the initial tumor response is detd. by subpopulations of cells having different intrinsic sensitivity to vincristine.



Answer 45:

Bibliographic Information

A comparison of the response of human lung carcinoma xenografts to vindesine and vincristine. Evans, B. D.; Smith, I. E.; Shorthouse, A. J.; Millar, J. L. *Inst. Cancer Res., Sutton/Surrey, UK. British Journal of Cancer* (1982), 45(3), 466-8. CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 97:16745 AN 1982:416745 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

vindesine [53643-48-4] (3.0 Mg/kg) was more effective than vincristine [57-22-7] (1.2 mg/kg) in delaying the growth of small-cell human lung carcinoma xenografts in mice, but the 2 were equally effective in inhibiting adenocarcinoma xenografts.

Answer 46:

Bibliographic Information

Chemotherapy of human breast-carcinoma xenografts. Bailey, M. J.; Gazet, J. C.; Smith, I. E.; Steel, G. G. Inst. Cancer Res., Sutton/Surrey, UK. British Journal of Cancer (1980), 42(4), 530-6. CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 94:95754 AN 1981:95754 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Sensitivities were varied for 5 lines of human breast carcinoma xenografts, grown and passaged in immune-suppressed mice, to cyclophosphamide [50-18-0], methotrexate [59-05-2], 5-fluorouracil [51-21-8], adriamycin [23214-92-8], vincristine [57-22-7], and melphalan [148-82-3], alone and in combination. The most effective single agent or combination differed for each tumor. This system may be useful for testing new cytotoxic agents and predicting clin. chemotherapy response.

Answer 47:

Bibliographic Information

Biochemical modulation of 'classical' multidrug resistance by BIBW22BS, a potent derivative of dipyridamole. Jansen W J; Pinedo H M; Kuiper C M; Lincke C; Bamberger U; Heckel A; Boven E Department of Medical Oncology, Free University Hospital, Amsterdam, The Netherlands Annals of oncology : official journal of the European Society for Medical Oncology / ESMO (1994), 5(8), 733-9. Journal code: 9007735. ISSN:0923-7534. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 7826906 AN 95127514 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

BACKGROUND: Modulators of the 'classical' multidrug resistance (mdr) phenotype have low efficacy in patients with solid tumors. We analyzed BIBW22BS, 4-[N-(2-hydroxy-2-methyl-propyl)-ethanolamino]-2,7-bis(cis-2,6-dimethyl-morpho- lino)-6-phenylpteridine, a derivative of dipyridamole, for its higher potential to modulate mdr. **MATERIALS AND METHODS:** Four human malignant cell lines: BRO, A2780, GLC4, SW1573, the Pgp-positive sublines: BRO/mdr1.1, 2780AD and the non-Pgp sublines: GLC4/ADR, SW1573/2R120 were used in vitro to investigate BIBW22BS as a modulator of the antiproliferative effects of vincristine and doxorubicin and to compare the potency of BIBW22BS with that of dipyridamole, verapamil, bepridil and flunarizine. BRO/mdr1.1 s.c. well-established xenografts in nude mice were used to study the modulating properties of BIBW22BS 50 mg/kg i.v. followed after one h by vincristine 1 mg/kg i.p. or doxorubicin 8 mg/kg i.p. weekly x 2. **RESULTS:** BIBW22BS was 20- to 100-fold more potent than dipyridamole in the reversal of resistance in the Pgp-positive sublines. Reversal of resistance was obtained in a dose-dependent manner and was complete at concentrations of 0.5-2.5 microM. At non-toxic, equimolar concentrations of 1.0 microM BIBW22BS showed higher modulating potency than the calcium-channel blockers. BIBW22BS did not affect resistance in the non-Pgp sublines. BRO/mdr1.1 s.c. xenografts have stable multidrug-resistance characteristics upon serial transplantation. BIBW22BS, vincristine, or doxorubicin as single agents were not effective in vivo, while the addition of BIBW22BS could significantly reduce the tumor growth expressed as the T/C% of vincristine from 109% to 48% and that of doxorubicin from 55% to 32%. However, reversal of vincristine resistance in BRO/mdr1.1 xenografts was not complete when compared to the efficacy of vincristine in BRO xenografts. **CONCLUSION:** The results encourage the further preclinical development of BIBW22BS as a modulator of 'classical' multidrug resistance in cancer patients.

Answer 48:

Bibliographic Information

Phase II study: treatment of non-Hodgkin's lymphoma with an oral antitumor derivative of bis(2,6-dioxopiperazine). Ohno R; Yamada K; Hirano M; Shirakawa S; Tanaka M; Oguri T; Koderu Y; Mitomo Y; Ikeda Y; Yokomaku S; + Department of Medicine, Nagoya University School of Medicine, Branch Hospital, Japan Journal of the National Cancer Institute (1992), 84(6), 435-8. Journal code: 7503089. ISSN:0027-8874. (CLINICAL TRIAL); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 1538420 AN 92167304 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

BACKGROUND: Although razoxane (ICRF-159), a derivative of bis(2,6-dioxopiperazine), has shown significant antitumor activity in several murine tumors, inadequate bioavailability has limited its clinical efficacy. Sobuzoxane (MST-16), another derivative of bis(2,6-dioxopiperazine), has shown activity against a broad spectrum of murine tumors and human tumor xenografts in nude mice and a lack of cross-resistance to vincristine, doxorubicin, cyclophosphamide, fluorouracil, etoposide, and mitomycin C. **These findings suggest that MST-16 has a mode of cytotoxic activity different from that of other antitumor agents.** **PURPOSE:** The present late phase II study was conducted to evaluate the clinical efficacy and toxicity of MST-16 in non-Hodgkin's lymphoma (NHL). **METHODS:** As part of a multi-institutional cooperative study, we conducted a study of MST-16 in 27 patients with NHL who were assessable for drug efficacy and toxicity. MST-16, a bis(2,6-dioxopiperazine) analogue and an inhibitor of topoisomerase II, was administered orally at a dose of 1600 mg/m² a day for 5-7 days at intervals of 2-3 weeks. **RESULTS:** Response consisted of one complete remission and seven partial remissions in 27 assessable patients. Response was achieved at a median of 13 days (range, 9-62 days) after initiation of therapy and lasted a median of 46 days (range, 29-155 days). Major toxic effects were leukopenia in 70% of the patients, thrombocytopenia in 44%, and gastrointestinal disorders in 37%. **CONCLUSIONS:** MST-16 was shown to be effective in NHL and deserves further clinical trial, since the drug shows little cross-resistance to available antitumor drugs. **IMPLICATIONS:** Phase II clinical studies of MST-16 in treatment of breast cancer, gastric cancer, and adult T-cell leukemia and lymphoma are also being conducted in Japan. Future trials of combination chemotherapy using MST-16 with other antitumor drugs are warranted in view of the additive effects observed in studies of MOLT-3 cells and studies of L1210 leukemia in mice.

Answer 49:

Bibliographic Information

Occurrence of drug resistance in human tumor implanted in nude mice. Inaba M; Nagashima K; Sakurai Y Gann = Gan (1982), 73(4), 633-6. Journal code: 8214471. ISSN:0016-450X. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 6818091 AN 83106270 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

A line of human breast tumor xenograft in nude mouse, MX-1, acquired resistance to vincristine or mitomycin C during multiple treatments; both drugs were effective against the parent line of this tumor. If the treatment was started when the tumor was smaller than 500 mm³ in size, MX-1 was responsive to the initial treatment with vincristine (0.8 mg/kg) or mitomycin C (3.4 mg/kg), and some animals survived with complete regression of the tumor. However, some of the recurrent tumors were able to tolerate multiple treatments with either of these agents, and finally acquired apparent resistance to the agent. On the other hand, when tumors larger than 5,000 mm³ were treated with vincristine, the occurrence of resistance was observed with much higher frequency than when small tumors were treated. Resistant tumors thus obtained exhibited significant refractoriness to each agent when they were reimplanted in new mice and treated in the same manner. This suggests that the occurrence of resistance can be ascribed to changes not in metabolic functions of the host animal but in the tumor cell populations.