

Answer 1:

Bibliographic Information

Gene expression predicts differential capecitabine metabolism, impacting on both pharmacokinetics and antitumor activity.

Guichard, Sylvie M.; Macpherson, Janet S.; Mayer, Iain; Reid, Eilidh; Muir, Morwenna; Dodds, Michael; Alexander, Susan; Jodrell, Duncan I. Cancer Research UK Pharmacology and Drug Development Group, Edinburgh Cancer Research Centre, University of Edinburgh, Edinburgh, UK. *European Journal of Cancer* (2008), 44(2), 310-317. Publisher: Elsevier Ltd., CODEN: EJCAEL ISSN: 0959-8049. Journal written in English. CAN 149:167255 AN 2008:82554 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Capecitabine is converted into 5'-deoxy-5-fluorocytidine (5'DFCR), 5'-deoxy-5-fluorouridine (5'DFUR) and 5-fluorouracil (5-FU) by CES1 and 2, CDD, and TP, in both liver and tumor. 5-FU is catabolized by DPD. Gene expression anal. of these enzymes was undertaken in fresh human hepatocytes, mouse liver, colorectal cancer cell lines and xenografts. Cell lines with low CDD expression (<1.5) had 5'DFCR/5'DFUR cytotoxicity ratios >2 and cell lines with TP/DPD < 0.6 had 5'DFUR IC₅₀ > 50 μM (SRB assay). A pharmacokinetic/pharmacodynamic study in nude mice bearing HCT 116 xenografts and treated with capecitabine by oral gavage assessed pharmacokinetic, gene expression and antitumor activity. Low liver CDD correlated with high 5'DFCR plasma concns. in mice. CDD expression was .apprx.100-fold higher in fresh human hepatocytes than mouse liver, explaining the higher plasma 5'DFUR concns. reported previously in humans. Tumor 5-FU concn. correlated with TP/DPD and with tumor response. These studies identify the potential utility of gene expression anal. and drug monitoring in tumor in patients.

Answer 2:

Bibliographic Information

Enhancement of capecitabine efficacy by oxaliplatin in human colorectal and gastric cancer xenografts. Sawada, Noriaki; Kondoh, Kumiko; Mori, Kazushige. Product Research Department, Kamakura Research Center, Chugai Pharmaceutical Co., Ltd., 200 Kajiwara, Kamakura, Kanagawa, Japan. *Oncology Reports* (2007), 18(4), 775-778. Publisher: Oncology Reports, CODEN: OCRPEW ISSN: 1021-335X. Journal written in English. CAN 148:112444 AN 2007:1183957 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We have evaluated the antitumor activity of XELOX (a combination therapy of capecitabine (Xeloda) and oxaliplatin) in human colorectal and gastric cancer xenograft models. In human colorectal cancer model CXF280, antitumor activity of the combination at two-thirds of the max. tolerated dose (MTD) was superior to that of each monotherapy at MTD. Furthermore, in human colorectal cancer model COL-05-JCK and human gastric cancer xenograft model GXF 97, the combination also showed at least additive antitumor activity. In addn., toxicity was not augmented with the combination therapy in these three models. As demonstrated using ELISA or immunohistochem., oxaliplatin in xenograft model tumors up-regulated the level of thymidine phosphorylate (dThdPase), a key enzyme for the metab. of capecitabine to 5-fluorouracil. These results suggest that oxaliplatin might potentiate the antitumor activity of capecitabine by up-regulating the tumor level of dThdPase. Based on these results, clin. trials of XELOX against colorectal and gastric cancers are warranted.

Answer 3:

Bibliographic Information

The effects of various chemotherapy regimens on the expression of PCNA and Bcl-2 in human breast cancer xenograft (MCF-7) transplanted in nude mice.

Wang, Yu-dong; Liu, Wei; Ji, Zhi-min; Zhang, Zhi-gang; Lv, Ya-lei; Wang, Shu-qin. Department of Medical Oncology, The 4th Hospital of Hebei Medical University, Shijiazhuang, Peop. Rep. China. Linchuang

Zhongliuxue Zazhi (2007), 12(3), 173-176. Publisher: Institution of Chinese Clinical Oncology Journal, CODEN: LZZIA5 ISSN: 1009-0460. Journal written in Chinese. CAN 148:205626 AN 2007:1152600 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

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

Answer 4:

Bibliographic Information

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

Abstract

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

Answer 5:

Bibliographic Information

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

Abstract

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

Answer 6:

Bibliographic Information

Early changes in apparent diffusion coefficient predict the quantitative antitumoral activity of capecitabine, oxaliplatin, and irradiation in HT29 xenografts in athymic nude mice. Seierstad, Therese; Folkvord, Sigurd; Roe, Kathrine; Flatmark, Kjersti; Skretting, Arne; Olsen, Dag Rune. Department of Medical Physics, Rikshospitalet-Radiumhospitalet Medical Center, Oslo, Norway. *Neoplasia* (Ann Arbor, MI, United States) (2007), 9(5), 392-400. Publisher: Neoplasia Press Inc., CODEN: NEOPFL ISSN: 1522-8002. <http://www.neoplasia.com/pdf/manuscript/neo07154.pdf> Journal; Online Computer File written in English. CAN 147:203373 AN 2007:666838 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: The purpose of this study was to evaluate the possible use of changes in apparent diffusion coeff. (ADC) measured by magnetic resonance imaging for pretreatment prediction and early detection of tumor response in a mouse model during fractionated chemoradiotherapy. **Materials and Methods:** Athymic mice with bilateral HT29 xenografts on rear flanks were allocated into three groups: control, capecitabine, and capecitabine and oxaliplatin. The left flanks of the mice received daily irradiation. T2 and diffusion images were acquired before therapy and weekly for the following 9 wk. Pretreatment and changes in ADC were calcd. and compared with tumor doubling growth delay. **Results:** No correlations between pretreatment ADC and changes in tumor vols. after therapy were seen. All treated tumors, except those receiving capecitabine ($P = .06$), showed increased mean tumor ADC values 11 days after initialization of therapy ($P < .05$) before returning to pretreatment values within 5 days posttherapy (day 18 after onset of therapy). This increase in mean tumor ADC showed a strong pos. correlation ($r = 0.92$, $P < .01$) with mean tumor doubling growth delay. **Conclusions:** Pretreatment ADC values did not predict the effectiveness of therapy, whereas early changes in mean ADC quant. correlated with treatment outcome.

Answer 7:

Bibliographic Information

Inhibition of peginterferon- α combined with capecitabine on tumor growth in nude mice bearing human hepatocellular carcinoma xenografts with high metastatic potential. Shen, Zaozhao; Zhou, Jian; Xiao, Yongsheng; Fan, Jia; Xue, Qiong; Gao, Dongmei; Tang, Zhaoyou. Zhongshan Hospital, Fudan University, Shanghai, Peop. Rep. China. *Zhonghua Shiyan Waike Zazhi* (2006), 23(3), 274-275. Publisher: Hubei Sheng Yixuehui, Bianji Chubanbu, CODEN: ZSWZAA ISSN: 1001-9030. Journal written in Chinese. CAN 147:109403 AN 2007:651736 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The therapeutic and side effects of peginterferon- α combined with capecitabine on tumor growth in nude mice bearing human hepatocellular carcinoma xenografts with high metastatic potential were investigated. Thirty nude mice were randomly divided into 4 groups and were administered resp. with water, Peginterferon- α , capecitabine, combination of Peginterferon- α and capecitabine, resp. The wt. of nude mice was measured once a week. The tumor size was calcd. after the mice were killed. The blood was collected for the routine anal. of liver and renal functions. In the control, peginterferon- α , capecitabine and combination groups, tumor vol. was (2275 \pm 1337), (336 \pm 220), (889 \pm 614) and (26 \pm 56) mm³, resp. After the intervention, the tumor vol. was significantly smaller than that in the control. The tumor shrinkage was most significantly obsd. in the group of peginterferon- α combined with capecitabine (P<0.01). The combination of peginterferon- α and capecitabine showed no synergistic toxicity in terms of wt. loss or damage of liver and renal functions. Peginterferon- α combined with capecitabine may significantly inhibit the liver tumor growth in LCI-D20 nude mice with no significant toxicity and side effects.

Answer 8:

Bibliographic Information

Effects of various chemotherapy regimens on the expression of PCNA and growth of human breast cancer xenograft (MCF-7) in nude mice. Wang, Yu-dong; Liu, Wei; Ji, Zhi-min; Zhang, Zhi-gang; Wang, Jun-ling; Yan, Xia; Zhang, Xiang-hong. Department of Medical Oncology, 4th Hospital, Hebei Medical University, Shijiazhuang Hebei, Peop. Rep. China. Zhongguo Aizheng Zazhi (2007), 17(2), 139-143. Publisher: Fudan Daxue Fushu Zhongliu Yiyuan, CODEN: ZAZHAF ISSN: 1007-3639. Journal written in Chinese. CAN 147:86596 AN 2007:395164 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Although standardized therapy has been widely adapted in clin. practice and results are being improved, effective protocols for truly individualized chemotherapy is still lacking. The anti-tumor activity of different combination regimens on human breast cancer xenograft (MCF-7) transplanted in nude mice and their impacts on the expression of PCNA were investigated, and to evaluate the value of PCNA as predictive factors for the res. 88 Nude mice with human breast cancer xenograft (MCF-7) were randomly divided into control and 10 chemotherapy groups, and 8 mice were assigned into each group. Among 5 chemotherapy groups, they were treated either i.p. or orally by 5 different combinations of chemotherapy regimens (CMF, CAF, NP, TP, Xeloda) at one-third of LD10 dosage, and another 5 chemotherapy groups were treated at two-third. Control animals were given normal saline i.p. The body wt. of nude mice and transplanted tumor growth were recorded on a regular basis, and tumor growth inhibition was calcd. The pathol. features of the transplanted tumor were studied under the microscope before and after treatment. The expression of PCNA was evaluated by SP immunohistochem. method and flow cytometry. The results show that body wt. and tumor wt. of nude mice treated by two-third LD10 dosage of various chemotherapy combinations were significantly lower than that in the control (P<0.05), and the inhibition rate of tumor growth for the groups we. The results showed that the two-third LD10 dosage of chemotherapy could reflect the anti-tumor effect of various combinations chemotherapy better and more accurately, so this dosage was used for the next study. The expression at PCNA by immunohistochem. studies shows that the expression of PCNA in every chemotherapy group was significantly lower than that of the control (P<0.05).

Moreover, the expressions of PCNA in NP group was significantly lower than that of CMF, CAF, TP and Xeloda group (P<0.05), while TP and Xeloda group was significantly lower than that of CMF and CAF group (P<0.05). FCM anal. shows that FI value of PCNA in every chemotherapy group was significantly lower than that of the control (P<0.05). FI value of PCNA in TP and Xeloda group was significantly lower than that of CMF and CAF group (P<0.05), while NP group a significantly lower than that of CMF group (P<0.05). Relationship between PCNA expression and pathol. response shows that the expression of PCNA was pos. correlated with pathol. therapeutic response of transplanted breast carcinoma (r=0.540, P<0.05). It was concluded that in vivo chemosensitivity testing with two third LD10 dosage of various combinations of chemotherapy cancer could somewhat predict the clin. situations. All of various chemotherapy regimens can decrease the expression of PCNA in breast cancer. The expression of PCNA could perhaps serve as the factor to judge the response to chemotherapy, and play a role in the selection of the kind of chemotherapy to be used in the clinic.

Answer 9:

Bibliographic Information

Changes to the dihydropyrimidine dehydrogenase gene copy number influence the susceptibility of cancers to 5-FU-based drugs: Data mining of the NCI-DTP data sets and validation with human tumour xenografts. Kobunai, Takashi; Ooyama, Akio; Sasaki, Shin; Wierzba, Konstanty; Takechi, Teiji; Fukushima, Masakazu; Watanabe, Toshiaki; Nagawa, Hirokazu. Department of Systematic Clinical Oncology, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, Japan. *European Journal of Cancer* (2007), 43(4), 791-798. Publisher: Elsevier Ltd., CODEN: EJCAEL ISSN: 0959-8049. Journal written in English. CAN 147:1058 AN 2007:213726 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Patient response to the anti-tumor drug 5-fluorouracil (5-FU) is variable, but predicting the response rate is important for the selection of effective chemotherapy. Our aim was to identify alterations in DNA copy no. that influence susceptibility of cancer cells to 5-FU-based drugs. The NCI public database was used to identify chromosome loci assocd. with drug sensitivity and DNA copy no. One of the 11 candidates, the cytogenetic band 1p21.3, harbors the dihydropyrimidine dehydrogenase (DPD) gene. To validate this finding, the DPD copy no. and in vivo sensitivity to 5-FU-based drugs were detd. in 31 human tumor xenografts. Those xenografts demonstrating low sensitivity had significantly higher DPD copy nos. than highly sensitive tumors ($P < 0.002$). Moreover, DPD mRNA expression levels were significantly correlated with DPD copy nos. ($P < 0.046$). An assessment of copy no. may be a more precise method of predicting the sensitivity of cancer patients to 5-FU related drugs.

Answer 10:

Bibliographic Information

Interferon- α and capecitabine inhibited recurrence and metastasis of hepatocellular carcinoma after curative resection in nude mice. Pan, Ye; Zheng, Qi; Ai, Kaixing; Yan, Jun; Xue, Qiong. Shanghai Sixth People's Hospital, Shanghai Jiaotong University, Shanghai, Peop. Rep. China. *Zhongliu* (2005), 25(5), 439-441. Publisher: Shanghai Zhongliu Yanjiusuo, CODEN: ZHONEV ISSN: 1000-7431. Journal written in Chinese. CAN 145:499685 AN 2006:638649 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Nude mice bearing orthotopic xenograft highly metastatic human hepatocellular carcinoma (HCC, LCI-D20) were randomly divided into 4 groups, control group (saline soln.), capecitabine group (Xeloda), interferon group (Intefen), combined treatment group (both Xeloda and Intefen). Curative resection was performed at 10th day after implantation in 40 nude mice. Drugs were given at the next day after resection. Interferon- α was administered s.c. at a dose of 3×10^5 U/d. Capecitabine was administered p.o. at a dose of 2.10 mmol/kg every day. The mice were sacrificed at 36th day after treatment. The size of recurrence tumor was measured, the presence of intrahepatic dissemination and lung metastasis was recorded, and at the same time, intratumoral microvessel d. (MVD), vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) were measured. The size of main recurrence lesion was (3981.54 ± 262.59) mm³, (1012.05 ± 70.61) mm³, (714.34 ± 60.37) mm³ and (35.60 ± 5.25) mm³ in the control, interferon group, capecitabine group and combination group, resp. The recurrence tumor vol. significantly decreased in treatment groups compared with the control ($P < 0.05$). Compared with capecitabine group and interferon group, the recurrence lesion decreased in combination group ($P < 0.05$). Compared to the control, the no. of intrahepatic dissemination and the lung metastatic ratio were reduced (6.30 ± 1.02 vs. 1.70 ± 1.37 , 2.40 ± 1.61 , 0.20 ± 0.91 and 90% vs. 40%, 60%, 0). A decrease of MVD and VEGF was obsd. in administration of interferon- α groups compared with that in unuse of interferon- α groups, and at the same time, no difference was found in the pos. rate of bFGF between each group. Both interferon- α and capecitabine are capable of inhibiting recurrence and metastasis of HCC after curative resection in nude mice. Interferon- α exerts its effect by inhibiting tumor angiogenesis. There was a synergistic action between interferon- α and capecitabine in inhibiting the recurrence and metastasis of HCC in nude mice.

Answer 11:

Bibliographic Information

Antitumor activity of erlotinib in combination with capecitabine in human tumor xenograft models. Ouchi, Kaori F.; Yanagisawa, Mieko; Sekiguchi, Fumiko; Tanaka, Yutaka. Product Research Department, Chugai Pharmaceutical Company, Ltd., 200 Kajiwara Kamakura, Kanagawa, Japan. *Cancer Chemotherapy and Pharmacology* (2006), 57(5), 693-702. Publisher: Springer, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 145:180374 AN 2006:366769 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: To examine the antitumor activity and tolerability of a combination comprising erlotinib and capecitabine in human colorectal, breast and epidermal cancer xenograft models. Further aims of the study were to examine the effects of single-agent erlotinib therapy on tumor growth, and on thymidine phosphorylase (TP) and dihydropyrimidine dehydrogenase (DPD) levels, (enzymes which activate and deactivate capecitabine, resp.) in tumor tissue. **Methods:** BALB/c nu/nu mice bearing LoVo and HT-29 (colon cancer), A-431 (vulval cancer), and KPL-4 and MAXF401 (breast cancer) human tumors were treated with erlotinib 100 mg/kg/day and/or capecitabine 359 or 90 mg/kg/day, by oral administration once daily for 14 days. **Results:** The max. tolerated dose (MTD) of erlotinib, formulated in carboxymethylcellulose/Tween 80, was identified as 125 mg/kg/day. Erlotinib at a dose of 100 mg/kg/day achieved significant tumor-growth inhibition in the, LoVo, KPL-4, and A-431 models. Some inhibition of MAXF401 tumor growth was obsd., but was not significant. In the HT-29 model, erlotinib showed less marked but statistically significant antitumor activity. On day 15, mean tumor-growth inhibition in HT-29, LoVo, KPL-4, MAXF401, and A-431 models was 46, 74, 71, 20, and 85%, resp. Evaluation of erlotinib/capecitabine combination therapy, at sub-optimal doses, in the three erlotinib-sensitive tumor models LoVo, KPL-4 and A-431, demonstrated at least additive activity with the combination compared with the single agents. In the A-431 and LoVo models, the combination of agents had greater antitumor activity than the single agent capecitabine alone at the MTD. Erlotinib in combination with capecitabine was not assocd. with significantly increased toxicity compared with single-agent therapy. Erlotinib 100 mg/kg/day induced significant upregulation of TP and DPD in the LoVo model, a significant upregulation of TP in the HT-29, MAXF401 and A-431 models, but had no obvious effect on TP and DPD levels in the KPL-4 model.

In the A-431 model, selective upregulation of TP by erlotinib 100 mg/kg resulted in an increased TP:DPD ratio. In the LoVo model, immunohistochem. revealed marked upregulation of TP (but not DPD by erlotinib). **Conclusions:** Erlotinib inhibits tumor growth in a range of human tumor xenograft models, including breast and colorectal cancer (CRC). Erlotinib and capecitabine demonstrated at least additive activity in LoVo, KPL-4 and A-431 tumor models. The antitumor activity of the combination was greater than that of capecitabine alone at the MTD. Erlotinib treatment did affect the TP in the CRC tumor models as confirmed immunohistochem. The findings of this study support clin. evaluation of erlotinib, both as a single agent and in combination with capecitabine, for the treatment of CRC and breast cancer.

Answer 12:

Bibliographic Information

Antitumor Efficacy of Capecitabine and Celecoxib in Irradiated and Lead-Shielded, Contralateral Human BxPC-3 Pancreatic Cancer Xenografts: Clinical Implications of Abscopal Effects. Blanquicett, Carmelo; Saif, M. Wasif; Buchsbaum, Donald J.; Eloubeidi, Mohamad; Vickers, Selwyn M.; Chhieng, David C.; Carpenter, Mark D.; Sellers, Jeffrey C.; Russo, Suzanne; Diasio, Robert B.; Johnson, Martin R. Division of Clinical Pharmacology, Departments of Pharmacology and Toxicology, University of Alabama at Birmingham, Birmingham, AL, USA. *Clinical Cancer Research* (2005), 11(24, Pt. 1), 8773-8781. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 144:460402 AN 2005:1318363 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: X-ray therapy (XRT) remains one of the major modalities used to treat patients diagnosed with locally advanced pancreatic adenocarcinoma. However, the effect of XRT on metastatic tumors outside the field of irradiation (abscopal effect) remains largely unknown. In the current study, we examined the effect of XRT alone and in combination with capecitabine and/or celecoxib in both irradiated and lead-shielded contralateral BxPC-3 pancreatic cancer xenografts. This chemoradiation regimen was chosen based on our molecular analysis of pancreatic adenocarcinoma. **Exptl. Design:** Athymic mice were injected bilaterally with BxPC-3 cells and treatment was initiated 28 days postimplant. During XRT (2 Gy for 5 consecutive days, administered on days 0 and 24), one flank was irradiated whereas the rest of the body (including the contralateral tumor) was lead shielded. Capecitabine (350 mg/kg) was administered on days

0 to 13 and 24 to 37. Celecoxib was initiated in the diet at 100 ppm (equiv. to 20 mg/kg/d p.o.) and administered throughout the study. Results: In irradiated xenografts, capecitabine and XRT showed synergistic antitumor efficacy ($P = 0.008$), which was further improved with the addn. of celecoxib ($P < 0.001$). In contralateral shielded xenografts, abscopal effects were obsd. Whereas monotherapy with XRT showed significant redn. in tumor area in irradiated xenografts, growth was promoted by 23% ($P < 0.001$) in contralateral lead-shielded tumors in the same animals relative to untreated tumors. Interestingly, synergistic antiproliferative efficacy occurred in these contralateral tumors when capecitabine was administered ($P < 0.001$), despite being outside the irradiated field. The addn. of celecoxib further inhibited tumor growth ($P < 0.001$). This trimodal combination most effectively stabilized disease in both shielded and irradiated tumors; however, tumor eradication was not obsd.

There were no significant changes in thymidine phosphorylase, dihydropyrimidine dehydrogenase, or cyclooxygenase-2 mRNA levels in irradiated or lead-shielded tumors, suggesting that efficacy cannot be predicted solely from these previously identified indicators of response. Immunohistochem. examg. the proliferation marker Ki-67 showed concordance with tumor response in both irradiated and contralateral shielded xenografts. Conclusions: These results have implications in the rational design of treatment paradigms for pancreatic cancer where metastatic disease remains the primary cause of patient morbidity and abscopal effects in tumors outside the field of irradiation may affect tumor response.

Answer 13:

Bibliographic Information

Simultaneous determination of capecitabine and its metabolites by HPLC and mass spectrometry for preclinical and clinical studies. Guichard, Sylvie M.; Mayer, Iain; Jodrell, Duncan I. Pharmacology and Drug Development Team, Cancer Research UK Centre, University of Edinburgh, Edinburgh, UK. *Journal of Chromatography, B: Analytical Technologies in the Biomedical and Life Sciences* (2005), 826(1-2), 232-237. Publisher: Elsevier B.V., CODEN: JCBAAL ISSN: 1570-0232. Journal written in English. CAN 143:378962 AN 2005:1105446 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A reverse-phase high-performance liq. chromatog. method with electrospray ionization and detection by mass spectrometry is described for the simultaneous detn. of capecitabine, its intermediate metabolites (DFCR, DFUR) and the active metabolite 5-fluorouracil in mouse plasma, liver and human xenograft tumors. The method was also cross-validated in human plasma and human tumor for clin. application. The method has greater sensitivity than previously published methods with an equiv. accuracy and precision. It uses less biol. material (plasma, tissue) and should therefore be applicable to biopsies in patients treated with capecitabine.

Answer 14:

Bibliographic Information

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

Abstract

Background: The synergistic antitumor effect of a combination of docetaxel and capecitabine is reported to be attributable to docetaxel-mediated up-regulation of thymidine phosphorylase (dThdPase). Materials and Methods: I.v. docetaxel (15 mg/kg) was given to nude mice bearing xenografts of the gastric cancer cell lines MKN45 and MKN28. Mice were sacrificed on days 7, 10 and 22 and tumor samples were taken to measure the activities of thymidylate synthase, dihydropyrimidine dehydrogenase, dThdPase and orotate phosphoribosyltransferase. The efficacy of capecitabine or S-1, alone and in combination with docetaxel, was then evaluated

in vivo. Docetaxel was administered i.v. on days 8 and 22 at 15 mg/kg, while capecitabine (269 mg/kg) or S-1 (7.5 mg/kg) were administered orally 5 times a week for 4 wk. Results: Tumor regression was obsd. only for a combination of capecitabine and docetaxel against MKN28, while additive growth inhibition was obtained by the combination of docetaxel and both S-1 and capecitabine on MKN45 tumor xenografts. Induction of dThdPase activity was obsd. only for MKN45. The activity of no other enzyme was significantly affected following administration of docetaxel. Conclusion: The combination of oral fluoropyrimidine and docetaxel showed augmented antitumor activity, but this may be attributed to mechanisms other than changes in 5-fluorouracil-metabolizing enzymes.

Answer 15:

Bibliographic Information

Correlations between antitumor activities of fluoropyrimidines and DPD activity in lung tumor xenografts. Takechi, Teiji; Okabe, Hiroyuki; Ikeda, Kazumasa; Fujioka, Akio; Nakagawa, Fumio; Ohshimo, Hideyuki; Kitazato, Kenji; Fukushima, Masakazu. Cancer Research Laboratory, Taiho Pharmaceutical Co., Ltd., Hanno-city, Saitama, Japan. *Oncology Reports* (2005), 14(1), 33-39. Publisher: Oncology Reports, CODEN: OCRPEW ISSN: 1021-335X. Journal written in English. CAN 143:146057 AN 2005:624267 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The purposes of this study were to evaluate the antitumor activity of S-1 (1 M tegafur, 0.4 M 5-chloro-2,4-dihydroxypyridine and 1 M potassium oxonate) on human lung tumor xenografts, as compared with other fluoropyrimidines, and to investigate the relationships between fluoropyrimidine antitumor activities and four distinct enzymic activities involved in the phosphorylation and degradn. pathways of 5-fluorouracil (5-FU) metab. S-1, UFT (1 M tegafur - 4 M uracil), 5'-deoxy-5-fluorouridine (5'-DFUR), capecitabine and 5-FU were administered for 14 consecutive days to nude mice bearing lung tumor xenografts. S-1 showed stronger tumor growth inhibition in four of the seven tumors than the other drugs. Cluster anal., on the basis of antitumor activity, indicated that S-1/UFT and 5'-DFUR/capecitabine/5-FU could be classified into another group. We investigated tumor thymidylate synthase content, dihydropyrimidine dehydrogenase (DPD) activity, thymidine phosphorylase (TP) activity and orotate phosphoribosyl transferase activity in seven human lung tumor xenografts and performed regression analyses for the antitumor activities of fluoropyrimidines. There were inverse correlations between antitumor and DPD activities for 5'-DFUR ($r=-0.79$, $P=0.034$), capecitabine ($r=-0.56$, $P=0.19$) and 5-FU ($r=-0.86$, $P=0.013$). However, no such correlations were obsd. for S-1 and UFT. These findings suggest that S-1 contg. a potent DPD inhibitor may have an antitumor effect on lung tumors, with high basal DPD activity, superior to those of other fluoropyrimidines.

Answer 16:

Bibliographic Information

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

Abstract

5-Fluorouracil (5-FU) and capecitabine alone and in combination with irinotecan/oxaliplatin are clin. active in the treatment of colorectal and other solid tumors. Studies of the antitumor activity and toxicity of capecitabine or irinotecan alone and in combination with each other, were compared with 5-FU and raltitrexed in human tumor xenografts of colorectal and squamous cell carcinoma of the head and neck using clin. relevant schedules. Antitumor activity and toxicity were evaluated in nude mice bearing human colon carcinomas of HCT-8 and HT-29 and in head and neck squamous cell carcinomas of A253 and FaDu xenografts using the max. tolerable dose of single-agent capecitabine, 5-FU, or raltitrexed, or each of the drugs in combination with irinotecan. Mice were treated with capecitabine and irinotecan alone or in combination using 2 different schedules: (1) capecitabine orally once a day for 7 days and a single dose of

irinotecan (50 mg/kg i.v.), with each drug alone or in combination, and (2) capecitabine orally 5 days a week for 3 wk and irinotecan 50 mg/kg (I.V. injection) once a week for 3 wk, with each drug alone or in combination. For comparative purposes, the antitumor activity of single-agent capecitabine, 5-FU, or raltitrexed, or each drug in combination with irinotecan was carried out at its max. tolerated dose (MTD) using a 3-wk schedule. Results indicated that HT-29 and A253 xenografts were de novo resistant (no cure) to capecitabine and irinotecan alone at the MTD, whereas HCT-8 and FaDu xenografts were relatively more sensitive, yielding 10-20% cures. The combination of irinotecan/capecitabine was much more active than either drug alone against all 4 tumor models. The cure rates were increased from 0 to 20% in A253 and HT-29 xenografts and from 10-20% to 80-100% in HCT-8 and FaDu tumor xenografts, resp. Irinotecan/capecitabine had clear advantage over irinotecan/5-FU and irinotecan/raltitrexed in efficacy and selectivity in that they were more active and less toxic.

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

Answer 17:

Bibliographic Information

Anti-metastatic effect of capecitabine on human colon cancer xenografts in nude mouse rectum. Ninomiya, Itasu; Terada, Itsuro; Yoshizumi, Tetsuya; Takino, Takahisa; Nagai, Noboru; Morita, Akihiko; Fushida, Sachio; Nishimura, Genichi; Fujimura, Takashi; Ohta, Tetsuo; Miwa, Koichi. Gastroenterologic Surgery, Department of Oncology, Division of Cancer Medicine, Graduate School of Medical Science, Kanazawa University, Kanazawa, Japan. International Journal of Cancer (2004), 112(1), 135-142. Publisher: Wiley-Liss, Inc., CODEN: IJCNAW ISSN: 0020-7136. Journal written in English. CAN 142:106753 AN 2004:781648 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Capecitabine (N 4-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine) is a new fluoropyrimidine carbamate, which is converted to 5-fluorouracil (5-FU) by 3 sequential steps of enzyme reactions. We investigated the possibility of using capecitabine to prevent metastasis with a metastasis model of gastrointestinal cancer developed by the intrarectal injection of green fluorescent protein (GFP)-expressing colon cancer HT-29 cells (HT-29-GFP) into nude mice. Lung and lymph node metastasis in the HT-29-GFP rectal xenograft was assessed through both observation of GFP fluorescence and quantification of metastasis by amplification of a cancer-related human DNA by TaqMan PCR. Furthermore, for each organ, we examd. mRNA levels of cancer-specific thymidine phosphorylase (dThdPase), which is an essential enzyme for capecitabine activation, by the quant. RT-PCR method. Capecitabine inhibited the HT-29-GFP xenograft growth by 60.8% and 43.8% in the s.c. and rectal xenograft models, resp. Furthermore, it inhibited both lung and lymph node metastasis by 99.9%. DThdPase expression in the tumor cells of both the rectal xenograft and metastatic lung tumor cells was upregulated by 10.0- and 24.3-fold that in the HT-29-GFP cells in vitro, resp. These results indicated that capecitabine might effectively inhibit or suppress metastasis via upregulation of dThdPase expression. Capecitabine administration might be highly expected to reduce metastasis and improve survival of patients with gastrointestinal cancers.

Answer 18:

Bibliographic Information

Interferon-alpha 2a up-regulated thymidine phosphorylase and enhanced antitumor effect of capecitabine on hepatocellular carcinoma in nude mice. Xiao, Yong-Sheng; Tang, Zhao-You; Fan, Jia; Zhou, Jian; Wu, Zhi-Quan; Sun, Qi-Man; Xue, Qiong; Zhao, Yan; Liu, Yin-Kun; Ye, Sheng-Long. Liver Cancer Institute and Zhongshan Hospital, Fudan University, Shanghai, Peop. Rep. China. Journal of Cancer Research and Clinical Oncology (2004), 130(9), 546-550. Publisher: Springer GmbH, CODEN: JCROD7 ISSN: 0171-5216. Journal written in English. CAN 141:378610 AN 2004:626870 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose was to investigate the antitumor effect of interferon-alpha 2a (IFN- α 2a) combined with capecitabine on hepatocellular carcinoma (HCC) in nude mice in relation to thymidine phosphorylase (TP) expression. Thirty nude mice bearing orthotopic xenografts of a human HCC tumor (LCI-D20) were divided into control, capecitabine, IFN- α 2a, and combination (capecitabine plus IFN- α 2a) groups. Tumor growth was detd. by measuring the tumor vol. An ELISA was used to study the TP expression in the cancer tissues of the liver. IFN- α 2a enhanced the sensitivity of the LCI-D20 tumor response to capecitabine treatment. The tumor vol. was reduced in the capecitabine (455 mm³), IFN- α 2a (248 mm³), or combination (46 mm³) treatment groups as compared to the control (1033 mm³). A difference was also found between the single treatment (capecitabine or interferon) and combination treatment groups. IFN- α 2a up-regulated TP expression in the LCI-D20 tumor. An approx. 1.5-fold increase in TP expression was obsd. in mice which received IFN- α 2a treatment compared to the controls. Thus, IFN- α 2a enhanced the antitumor effect of capecitabine on HCC in nude mice, which might be ascribed to up-regulation of TP expression in liver cancer tissues by IFN- α 2a.

Answer 19:

Bibliographic Information

Noninvasive measurements of capecitabine metabolism in bladder tumors overexpressing thymidine phosphorylase by fluorine-19 magnetic resonance spectroscopy. Chung, Yuen-Li; Troy, Helen; Judson, Ian R.; Leek, Russell; Leach, Martin O.; Stubbs, Marion; Harris, Adrian L.; Griffiths, John R. Department of Basic Medical Sciences, Cancer Research United Kingdom Biomedical Magnetic Resonance Group, St. George's Hospital Medical School, London, UK. *Clinical Cancer Research* (2004), 10(11), 3863-3870. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 141:420011 AN 2004:446458 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Previous studies have shown that tumor response to capecitabine strongly correlates with tumor thymidine phosphorylase (TP). The aims of our study were to (a) investigate the pharmacol. role of TP by measuring the pharmacokinetics (PK) of capecitabine in a human bladder tumor model that was characterized by the overexpression of TP and (b) develop the use of PK measurements for capecitabine by fluorine-19 magnetic resonance spectroscopy as a noninvasive surrogate marker for detg. TP levels in tumors and for predicting tumor response to capecitabine in patients. TP overexpressing (2T10) and control tumors were grown s.c. in nude mice. Mice were given a dose of capecitabine or 5'-deoxy-5-fluorouridine (5'DFUR). 19F tumor spectra were acquired for detn. of rate consts. of capecitabine breakdown and buildup and subsequent breakdown of intermediates, 5'-deoxy-5-fluorocytidine (5'DFCR) and 5'DFUR. The rate const. of 5'DFUR breakdown was also evaluated. The rate const. of breakdown of intermediates was significantly faster in 2T10 tumors than controls ($P < 0.003$). No significant differences in the rate of capecitabine breakdown or intermediate buildup were obsd. The rate const. of 5'DFUR breakdown in the 2T10 tumors was doubled compared with controls ($P < 0.001$). This study confirmed the expected pathway of capecitabine metab. and showed that the level of TP was related to the rate of 5'DFUR conversion. Using in vivo fluorine-19 magnetic resonance spectroscopy to measure the PK of capecitabine and its intermediate metabolites in tumors may provide a noninvasive surrogate method for detg. TP levels in tumors and for predicting tumor response to capecitabine in patients.

Answer 20:

Bibliographic Information

Schedule dependency of antitumor activity in combination therapy with capecitabine/5'-deoxy-5-fluorouridine, and docetaxel in breast cancer models. Fujimoto-Ouchi, Kaori; Tanaka, Yutaka; Tominaga, Takeshi. *Oncology*, Nippon Roche Research Center, Kanagawa, Japan. *Clinical Cancer Research* (2001), 7(4), 1079-1086. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 136:48073 AN 2001:363667 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Docetaxel and capecitabine are being prescribed for the treatment of breast cancer. In this study, the authors tried to identify the

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