

Answer 1:

### Bibliographic Information

**NCX 4040, an NO-donating acetylsalicylic acid derivative: Efficacy and mechanisms of action in cancer cells.** Tesei, Anna; Zoli, Wainer; Fabbri, Francesco; Leonetti, Carlo; Rosetti, Marco; Bolla, Manlio; Amadori, Dino; Silvestrini, Rosella. Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, Via Maroncelli 40, Meldola (FC), Italy. *Nitric Oxide* (2008), 19(2), 225-236. Publisher: Elsevier Inc., CODEN: NIOXF5 ISSN: 1089-8603. Journal written in English. AN 2008:871463 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) have repeatedly shown to be effective in tumor prevention, but important side-effects limit their wide clin. use. Nitric oxide-releasing derivs. (NO-NSAIDs) are a promising class of compds. synthesized by combining a classic NSAID mol. with an NO-releasing moiety to counteract side-effects. These new chem. entities exhibit a significantly higher activity and much lower toxicity with respect to the parental drug. In the present paper, we report the results obtained from in vitro exptl. systems aimed to evaluate the activity and mechanisms of action of the novel NO-releasing aspirin deriv., NCX 4040. The in vitro studies were carried out on a panel of human colon (LoVo, LoVo Dx, WiDr, LRWZ), bladder (HT1376, MCR), and pancreatic (Capan-2, MIA PaCa-2, T3M4) cancer cell lines. With regard to colon cancer, NCX 4040 activity was also investigated in vitro in combination with drugs currently used in clin. practice and was validated in vivo on tumor-bearing mice xenografted with the aforementioned colon cancer cell lines. The in vitro studies showed a high cytotoxic activity of NCX 4040 in all tumor histotypes and demonstrated the pivotal role of the NO component in drug activity. It was also obsd. that NCX 4040 exerts a pro-apoptotic activity via a mitochondria-dependent pathway. Moreover, the in vivo studies on xenografted mice further confirmed the antitumor efficacy and low toxicity of NCX 4040 in colon cancer and highlighted its role as sensitizing agent of oxaliplatin cytotoxicity.

Answer 2:

### Bibliographic Information

**Disruption of signaling through SEK1 and MKK7 yields differential responses in hypoxic colon cancer cells treated with oxaliplatin.** Vasilevskaya, Irina A.; Selvakumaran, Muthu; O'Dwyer, Peter J. Abramson Family Cancer Center, University of Pennsylvania, Philadelphia, PA, USA. *Molecular Pharmacology* (2008), 74(1), 246-254. Publisher: American Society for Pharmacology and Experimental Therapeutics, CODEN: MOPMA3 ISSN: 0026-895X. Journal written in English. AN 2008:822744 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Transcriptional changes in response to hypoxia are regulated in part through mitogen-activated protein (MAP) kinase signaling to activator protein 1 (AP-1), and thus contribute to resistance of cancer cells to therapy, including platinum compds. A key role for JNK in pro-apoptotic signaling in hypoxic cells has previously been established. Here we analyze hypoxic signaling through MAPK kinases to AP-1/c-Jun in the HT29 colon adenocarcinoma cell line, and observe activation of stress-activated pathways mediated predominantly by SEK1 and MKK7. In transient transfection assays, introduction of dominant-neg. constructs for both MKK7 and SEK1 abolished hypoxia-induced AP-1 activation. Functional studies of the pathway using HT29-derived cell lines stably expressing mutant SEK1 or MKK7 showed impaired activation of Jun NH2-terminal kinase (JNK) and AP-1 in response to hypoxia, more marked in MKK7-deficient than SEK1-deficient cells. Inhibition of SEK1 rendered hypoxic cells more sensitive to oxaliplatin in vitro, whereas the opposite effect was obsd. in MKK7-deficient cells. The mutant cell lines grown as mouse xenografts were treated with oxaliplatin, bevacizumab, or both. The SEK1-deficient tumors exhibited greater sensitivity to all treatments, whereas MKK7-deficient cells were resistant in vivo, consistent with in vitro observations. These data support a pos. contribution of MKK7/JNK to oxaliplatin cytotoxicity and identify SEK1 as a potential target for reversal of hypoxic resistance to oxaliplatin.

Answer 3:

**Bibliographic Information**

**Phase II trial of cetuximab in combination with fluorouracil, leucovorin, and oxaliplatin in the first-line treatment of metastatic colorectal cancer.** Taberero, Josep; Van Cutsem, Eric; Diaz-Rubio, Eduardo; Cervantes, Andres; Humblet, Yves; Andre, Thierry; Van Laethem, Jean-Luc; Soulie, Patrick; Casado, Esther; Verslype, Chris; Valera, Javier Sastre; Tortora, Giampaolo; Ciardiello, Fortunato; Kisker, Oliver; de Gramont, Aimery. Medical Oncology Service, Vall d'Hebron University Hospital, Barcelona, Spain. *Journal of Clinical Oncology* (2007), 25(33), 5225-5232. Publisher: American Society of Clinical Oncology, CODEN: JCONDN ISSN: 0732-183X. Journal written in English. CAN 148:253533 AN 2007:1464324 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

**Purpose:**This phase II study investigated the efficacy and safety of cetuximab combined with std. oxaliplatin-based chemotherapy (infusional fluorouracil, leucovorin, and oxaliplatin [FOLFOX-4]) in the first-line treatment of epidermal growth factor receptor-expressing metastatic colorectal cancer (mCRC). **Patients and Methods:** The activity of cetuximab plus oxaliplatin was investigated in colon cancer cell lines and xenograft models. In the clin. study, patients with mCRC received on day 1 of a 14 day cycle, cetuximab (initial dose 400 mg/m<sup>2</sup> during week 1, then 250 mg/m<sup>2</sup> weekly) followed by FOLFOX-4 (oxaliplatin 85 mg/m<sup>2</sup> on day 1; leucovorin 200 mg/m<sup>2</sup> on days 1 and 2, followed by fluorouracil 400 mg/m<sup>2</sup> bolus then 600 mg/m<sup>2</sup> i.v. infusion during 22 h on days 1 and 2). **Results:** The preclin. studies confirmed the supra-additive activity of cetuximab to oxaliplatin. In the clin. study, 43 patients were included, with a median age of 65 years (range, 43 to 78 years). Response rates (RRs) were 79% (unconfirmed) and 72% (confirmed), with 95% disease control. Median progression-free survival (mPFS) and median duration of response were 12.3 and 10.8 mo, resp. Ten patients (23%) underwent resection with curative intent of previously unresectable metastases. After a median follow-up of 30.5 mo, median overall survival (mOS) was 30.0 mo. Cetuximab did not increase the characteristic toxicity of FOLFOX-4 and was generally well tolerated. **Conclusion:** Cetuximab in combination with FOLFOX-4 is a highly active first-line treatment for mCRC, showing encouraging RR, mPFS, and mOS values. The treatment resulted in a high resectability rate, which could potentially result in an improved cure rate. This combination is under phase III development.

Answer 4:

**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 5:

**Bibliographic Information**

**Mechanistic analysis and comparison of viral fusogenic membrane proteins for their synergistic effects on chemotherapy.**

Hoffmann, Dennis; Grunwald, Thomas; Kuate, Seraphin; Wildner, Oliver. Department of Molecular and Medical Virology, Ruhr-University Bochum; Institute of Microbiology and Hygiene, Bochum, Germany. *Cancer Biology & Therapy* (2007), 6(4), 510-518. Publisher: Landes Bioscience, CODEN: CBTAAO ISSN: 1538-4047. Journal written in English. CAN 147:479955 AN 2007:1039368 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

Previously we demonstrated that the expression of fusogenic membrane proteins (FMG) of measles virus (MV-H/F) can synergistically enhance chemotherapy. In this study, we used median-effect anal. to evaluate whether the expression of respiratory syncytial virus (RSV-F), as well as vesicular stomatitis virus (VSV-G) can also synergistically enhance chemotherapy. Furthermore we elucidated by western blot anal. some mol. pathways that might be responsible for this effect. We showed in colorectal cancer cell lines that the expression of MV-H/F, but also of RSV-F, as well as VSV-G can synergistically enhance p53-independent clin. relevant chemotherapy (FOLFOX) over most of the cytotoxic dose range. In a s.c. HT-29 colorectal xenograft model, we demonstrated that the administration of replication-deficient adenovirus vectors encoding MV-H/F, RSV-G or VSV-G in combination with FOLFOX significantly enhanced treatment outcome when compared to the treatment with each compd. individually. The anti-neoplastic efficacy of RSV-F was somewhat better than that of MV-H/F and both were statistically significantly more efficacious than VSV-G alone or in combination with chemotherapy. Treatment efficacy was further significantly improved when the replication-deficient FMG encoding vectors were trans-complemented for replication with a replication-restricted oncolytic adenovirus to improve tumor transduction efficiency. The combination of FMG expression, chemotherapy and trans-complementing oncolytic vectors resulted in a significantly better treatment efficacy than treatment with its components as single- or double-agent therapy. Our data indicates that FMG expression (i.e., RSV-F and MV-H/F) in combination with chemotherapy and viral oncolysis warrants further investigations.

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; Roeie, 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 calculated and compared with tumor doubling growth delay. **Results:** No correlations between pretreatment ADC and changes in tumor volumes 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 positive 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**

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

#### Abstract

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

Answer 8:

#### Bibliographic Information

**Effects of recombinant human growth hormone on growth of human gastric carcinoma xenograft model in nude mice.**

Liang, Dao-Ming; Chen, Jia-Yong; Zhang, Yi; Gan, Ping; Lin, Jie; Chen, An-Bao. Department of Emergency Surgery of the Second Affiliated Hospital, Kunming Medical College, Kunming, Yunnan Province, Peop. Rep. China. World Journal of Gastroenterology (2006), 12(24), 3810-3813. Publisher: World Journal of Gastroenterology, CODEN: WJGAF2 ISSN: 1007-9327. Journal written in English. CAN 145:370044 AN 2006:826147 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

Aim: To study effects of recombinant human growth hormone (rhGH) on growth of a human gastric carcinoma cell in vivo. Methods: Exptl. mice were divided into control group, rhGH group, oxaliplatin (L-OHP) group and rhGH+L-OHP group. Cultured human gastric carcinoma cells BGC823 were inoculated into right axilla of nude mice and carcinoma xenograft model was established successfully. Inhibitory rate of xenograft tumor growth was estd. by measuring tumor vol.; expression of proliferating cell nuclear antigen (PCNA), Bax and Bcl-2 proteins of xenograft tumor was detected using immunohistochem. S-P method. Results: Tumor growth inhibitory rate, the pos. expression rate of PCNA, Bax and Bcl-2 were 49.3%, 58.2%, 65.2% and 59.2% in rhGH + L-OHP group resp.; 46.6%, 62.5%, 59.7% and 64.7% in L-OHP group; 5.0%, 82.7%, 23.2% and 82.2% in rhGH group and 0, 77.8%, 23.5% and 80.3% in control group. There was significant difference between rhGH+L-OHP group (or L-OHP group) and control group or rhGH group ( $P < 0.05$ ), whereas there were no significant differences ( $P > 0.05$ ) between L-OHP group and rhGH+L-OHP group and between rhGH group and control group. Conclusion: rhGH does not accelerate the proliferation of human gastric cancer cell in vivo.

Answer 9:

#### Bibliographic Information

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

Ciomei, Marina; Croci, Valter; Ciavolella, Antonella; Ballinari, Dario; Pesenti, Enrico. Department of Biology, Drug Discovery Oncology, Nerviano Medical Sciences, Milan, Italy. Clinical Cancer Research (2006), 12(9), 2856-2861. Publisher: American

Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 145:388833 AN 2006:532561 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

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

Answer 10:

### Bibliographic Information

**Efficacy of a nitric oxide-releasing nonsteroidal anti-inflammatory drug and cytotoxic drugs in human colon cancer cell lines in vitro and xenografts.** Leonetti, Carlo; Scarsella, Marco; Zupi, Gabriella; Zoli, Wainer; Amadori, Dino; Medri, Laura; Fabbri, Francesco; Rosetti, Marco; Ulivi, Paola; Ceconetto, Lorenzo; Bolla, Manlio; Tesei, Anna. Preclinical Experimental Laboratory, Regina Elena Institute for Cancer Research, Rome, Italy. Molecular Cancer Therapeutics (2006), 5(4), 919-926. Publisher: American Association for Cancer Research, CODEN: MCTOCF ISSN: 1535-7163. Journal written in English. CAN 145:39952 AN 2006:394746 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

We previously showed that NCX 4040 inhibits in vitro and in vivo tumor growth and induces apoptosis in human colon cancer cell lines. On the basis of these results, NCX 4040 antitumor activity in combination with 5-fluorouracil (5-FU) or oxaliplatin was evaluated in vitro and in vivo in human colon cancer models. The cytotoxicity of different NCX 4040 and 5-FU or oxaliplatin combination schemes was evaluated on a panel of colon cancer lines (LoVo, LoVo Dx, WiDr, and LRWZ) by the sulforhodamine B assay, and apoptosis was assessed by flow cytometry. NCX 4040 and 5-FU combination was always additive in vitro regardless of the scheme used. Sequential NCX 4040 oxaliplatin treatment produced a strong synergism in three cell lines, with a ratio index ranging from 3.7 to 4. The synergistic effect was accompanied by apoptosis induction (up to 40%). In the in vivo expts., xenografted mice were treated with the sequential combination of NCX 4040 and oxaliplatin, and apoptosis was evaluated immunohistochem. in excised tumors. Furthermore, in WiDr xenografts, this sequence caused a significantly higher redn. (.apprx.60%) in tumor growth compared with single-drug treatments and produced extensive apoptotic cell death (15.3%), significantly higher ( $P < 0.01$ ) than that obsd. in untreated tumors (2.7%) or in tumors treated with NCX 4040 (5.1%) or oxaliplatin (5.7%) alone. These data show that NCX 4040 sensitizes colon cancer cell lines to the effect of antitumor drugs and suggests that their combination could be useful for the clin. management of colon cancer.

Answer 11:

### Bibliographic Information

**In vivo and in vitro antitumor activity of oxaliplatin in combination with cetuximab in human colorectal tumor cell lines expressing different level of EGFR.** Balin-Gauthier, Diane; Delord, Jean-Pierre; Rochoix, Philippe; Mallard, Valerie; Thomas, Fabienne; Hennebelle, Isabelle; Bugat, Roland; Canal, Pierre; Allal, Cuider. EA 3035 Laboratoire de Pharmacologie Clinique et

Experimentale des Medicaments Anticancereux, Universite Paul Sabatier, Toulouse, Fr. Cancer Chemotherapy and Pharmacology (2006), 57(6), 709-718. Publisher: Springer, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 145:305843 AN 2006:331412 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

This study aimed to assess the effect of cetuximab (C225, Erbitux, a chimeric anti-epidermal growth factor receptor (EGFR) monoclonal antibody) in combination with oxaliplatin in vitro and in vivo on four colon cancer cell lines (HCT-8; HT-29, SW620, HCT-116) expressing different levels of EGFR. In vitro, cetuximab combined with oxaliplatin significantly decreased the IC50 values of oxaliplatin in HCT-8 (EGF-R moderate) and HT-29 (EGF-R weak) cell lines, while SW620 (EGF-R neg.) and HCT-116 (EGFR strong) cell lines remained unresponsive. This combination was synergistic in HCT-8 and HT-29 cell lines while cetuximab induced no major modification of the IC50 of oxaliplatin in HCT-116 or SW620 cell lines. We then detd. the effect of cetuximab on the EGF-induced EGFR phosphorylation and we highlight a correlation between the basal level of phospho-EGFR and the response to the combination. In vivo, the combination of cetuximab plus oxaliplatin significantly inhibited tumor growth of HCT-8 and HT-29 (tumor delay or Td = 21.6±2.9 and 18.0±2.9 days resp., synergistic effect) compared to either oxaliplatin (Td=12.6±2.3 and 14.4±3.2 days resp.) or cetuximab (Td=13.4±2.9 and 14.5±2.4 days, resp.) alone in xenograft models. The combination had no effect on HCT-116 and SW-620 cell lines. The obsd. responses are strictly dependent on the cell type, and are not correlated with the level of EGFR expression but related to the basal level of phospho-EGFR. This study provides promising preclin. results for a possible clin. investigation of the combination of oxaliplatin plus cetuximab in chemorefractory colorectal tumors.

Answer 12:

### Bibliographic Information

**Synergistic interaction between platinum-based antitumor agents and demethylcantharidin.** To, Kenneth K. W.; Ho, Yee-Ping; Au-Yeung, Steve C. F. School of Pharmacy, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, Peop. Rep. China. Cancer Letters (Amsterdam, Netherlands) (2005), 223(2), 227-237. Publisher: Elsevier B.V., CODEN: CALEDQ ISSN: 0304-3835. Journal written in English. CAN 143:125820 AN 2005:425268 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

A novel series of TCM-platinum complexes [Pt(C<sub>8</sub>H<sub>8</sub>O<sub>5</sub>)(NH<sub>2</sub>R)<sub>2</sub>], designed from incorporating demethylcantharidin, a modified component from a traditional Chinese medicine (TCM) with a platinum moiety was found to circumvent cisplatin resistance in mouse leukemia and human hepatocellular carcinoma. These properties are most likely due to the inclusion of the protein phosphatase 2A (PP2A)-inhibiting demethylcantharidin in the novel compds. We have investigated the potential synergistic effect of combining demethylcantharidin with a platinum-based antitumor agent, such as cisplatin, carboplatin, or oxaliplatin in vitro against L1210 mouse leukemia and SK-Hep-1 human hepatocellular carcinoma, and in vivo against a SK-Hep-1 s.c.-inoculated xenograft in nude mice, using median effect anal. Demethylcantharidin and the platinum antitumor agents were synergistic in all cell lines tested in vitro, and the most effective antiproliferative regimen was when demethylcantharidin was added 24 h before cisplatin. Synergistic antitumor activity was also demonstrated in vivo without undue toxicity; no excessive loss in mouse body wt. or overt pathol. were obsd. at the EDs. The results support a new approach for augmenting cytotoxic effect of established Pt-based drugs with demethylcantharidin in treating human hepatocellular carcinoma and other solid tumors.

Answer 13:

### Bibliographic Information

**Development of a chemoresistant orthotopic human nonsmall cell lung carcinoma model in nude mice: analyses of tumor heterogeneity in relation to the immunohistochemical levels of expression of cyclooxygenase-2, ornithine decarboxylase, lung-related resistance protein, prostaglandin E synthetase, and glutathione-S-transferase (GST)- $\alpha$ , GST- $\mu$ , and GST- $\pi$**  Mathieu, Anne; Rimmelink, Myriam; D'Haene, Nicky; Penant, Stanislas; Gaussin, Jean-Francois; van Ginckel, Rob; Darro, Francis;

Kiss, Robert; Salmon, Isabelle. Pathology Laboratory, Erasmus University Hospital, Universite Libre de Bruxelles, Brussels, Belg. Cancer (New York, NY, United States) (2004), 101(8), 1908-1918. Publisher: John Wiley & Sons, Inc., CODEN: CANCAR ISSN: 0008-543X. Journal written in English. CAN 142:169276 AN 2004:936957 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

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

Answer 14:

### Bibliographic Information

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

### Abstract

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

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

Answer 15:

### Bibliographic Information

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

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

### Abstract

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

Answer 16:

### Bibliographic Information

#### **Synergistic antitumoral activity of combined UFT, folinic acid and oxaliplatin against human colorectal HT29 cell xenografts in athymic nude mice.**

Louvet, Christophe; Coudray, Anne-Marie; Tournigand, Christophe; Prevost, Sophie; Raymond, Eric; De Gramont, Aimery; Chazard, Michel; Gespach, Christian. INSERM Unit 482, Department of Internal Medicine-Oncology, Hopital St-Antoine, Paris, Fr. *Anti-Cancer Drugs* (2000), 11(7), 579-582. Publisher: Lippincott Williams & Wilkins, CODEN: ANTDEV ISSN: 0959-4973. Journal written in English. CAN 134:13148 AN 2000:728300 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

This study was designed to assess the inhibition of tumor growth by oxaliplatin combined with UFT and folinic acid (FA). Growth inhibition was studied in nude mice transplanted with human colorectal HT29 tumor cell xenografts and treated for 28 days with oral UFT (20 mg/kg/day) and FA (4 mg/kg/day), i.p. oxaliplatin (10 mg/kg on day 1) or a combination of oxaliplatin, UFT and FA, or else not treated (controls). Tumor surface area and wt. were recorded twice a week, and mice were sacrificed at day 28. Two sep. expts. were performed for each group of 25 mice. At day 28, mean tumor wts. (g) were 2.89 $\pm$ 0.22 (controls), 2.03 $\pm$ 0.14 (oxaliplatin), 2.02 $\pm$ 0.21 (UFT/FA) and 1.23 $\pm$ 0.17 (oxaliplatin+UFT/FA). For the three treatment groups, tumor wt. decreases were 30.1% (p<0.05), 29.9% (p<0.05) and 57.5% (p<0.001), resp. Combined treatment (UFT/FA+oxaliplatin) reduced tumor wt. by 39% compared to oxaliplatin alone (p<0.05) or UFT/FA (p<0.05). These results demonstrate the synergistic effect of the combination of oxaliplatin, UFT and FA in this HT29 cell xenograft model, and warrant further investigations in patients with metastatic colorectal cancer.