

Answer 1:

### Bibliographic Information

**Diagnostic and therapeutic evaluation of 111In-vinorelbine-liposomes in a human colorectal carcinoma HT-29/luc-bearing animal model.** Chow, Tong-Hsien; Lin, Yi-Yu; Hwang, Jeng-Jong; Wang, Hsin-ElI; Tseng, Yun-Long; Pang, Victor Fei; Wang, Shyh-Jen; Whang-Peng, Jacqueline; Ting, Gann. Department of Biomedical Imaging and Radiological Sciences, National Yang-Ming University, Taipei, Taiwan. Nuclear Medicine and Biology (2008), 35(5), 623-634. Publisher: Elsevier Inc., CODEN: NMBIEO ISSN: 0969-8051. Journal written in English. AN 2008:786435 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Colorectal carcinoma is a highly prevalent and common cause of cancer in Taiwan. There is still no available cure for this malignant disease. To address this issue, we applied the multimodality of mol. imaging to explore the efficacy of diagnostic and therapeutic nanoradiopharmaceuticals in an animal model of human colorectal adenocarcinoma [colorectal cancer (CRC)] that stably expresses luciferase (luc) as a reporter. In this study, an in vivo therapeutic efficacy evaluation of dual-nanoliposome (100 nm in diam.) encaged vinorelbine (VNB) and 111In-oxine on HT-29/luc mouse xenografts was carried out. HT-29/luc tumor cells were transplanted s.c. into male SCID mice. Multimodality of mol. imaging approaches including bioluminescence imaging (BLI), gamma scintigraphy, whole-body autoradiog. (WBAR) and in vivo tumor growth tracing, histopathol. and biochem./hematol. analyses were applied on xenografted SCID mice to study the treatments with 6% polyethylene glycol (PEG) of 111In-NanoX/VNB-liposomes. In vivo tumor growth tracing and BLI showed that tumor vol. could be completely inhibited by the combination therapy with 111In-VNB-liposomes and by chemotherapy with NanoX/VNB-liposomes (i.e., without Indium-111) ( $P < .01$ ). The nuclear medicine images of gamma scintigraphy and WBAR also revealed the conspicuous inhibition of tumor growth by the combination therapy with 111In-VNB-liposomes. Animal body wts., histopathol. and biochem./hematol. analyses were used to confirm the safety and feasibility of radiopharmaceuticals. A synergistic therapeutic effect on CRC xenografted SCID mice was proven by combining an Auger electron-emitting radioisotope (Indium-111) with an anticancer drug (VNB). This study further demonstrates the beneficial potential applications of multimodality mol. imaging as part of the diagnostic and therapeutic approaches available for the evaluation of new drugs and other strategic approaches to disease treatment.

Answer 2:

### 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 3:

### 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 4:

### Bibliographic Information

**In vitro and in vivo characterization of a combination chemotherapy formulation consisting of vinorelbine and phosphatidylserine.** Webb, Murray S.; Johnstone, Sharon; Morris, Tara J.; Kennedy, Allison; Gallagher, Ryan; Harasym, Natashia; Harasym, Troy; Shew, Clifford R.; Tardi, Paul; Dragowska, Wieslawa H.; Mayer, Lawrence D.; Bally, Marcel B. Celator Pharmaceuticals Inc., Vancouver, BC, Can. *European Journal of Pharmaceutics and Biopharmaceutics* (2007), 65(3), 289-299. Publisher: Elsevier B.V., CODEN: EJPBEL ISSN: 0939-6411. Journal written in English. CAN 147:16167 AN 2007:244319 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

The purpose of these studies was to design an i.v. drug formulation consisting of two active agents having synergistic in vitro activity. Specifically, we describe a novel drug combination consisting of a cytotoxic agent (vinorelbine) with an apoptosis-inducing lipid (phosphatidylserine, PS). In vitro cytotoxicity screening of PS and vinorelbine, alone and in combination, against human MDA435/LCC6 breast cancer and H460 lung cancer cells was used to identify the molar ratio of these two agents required for synergistic activity. PS and vinorelbine were co-formulated in a lipid-based system at the synergistic molar ratio and the pharmacokinetic and antitumor characteristics of the combination assessed in mice bearing H460 tumors. The cytotoxicity of the lipid, and the synergy between the lipid and vinorelbine, were specific to PS; these effects were not obsd. using control lipids. A novel formulation of PS, incorporated as a membrane component in liposomes, and encapsulating vinorelbine using a pH gradient based loading method was developed. The PS to vinorelbine ratio in this formulation was 1/1, a ratio that produced synergistic in vitro cytotoxicity over a broad concn. range. The vinorelbine and PS dual-agent treatment significantly delayed the growth of s.c. human H460 xenograft tumors in Rag2M mice compared to the same dose of free vinorelbine given alone or given as a cocktail of the free vinorelbine simultaneously with empty PS-contg. liposomes. These studies demonstrate the potential to develop clin. relevant drug combinations identified using in vitro drug-drug interactions combined with lipid-based delivery systems to co-formulate drugs at their synergistic ratios.

Answer 5:

**Bibliographic Information****Therapeutic efficacy evaluation of <sup>111</sup>In-VNB-liposome on human colorectal adenocarcinoma HT-29/luc mouse xenografts.**

Lee, Wan-Chi; Hwang, Jeng-Jong; Tseng, Yun-Long; Wang, Hsin-Ell; Chang, Ya-Fang; Lu, Yi-Ching; Ting, Gann; Whang-Peng, Jaqueline; Wang, Shyh-Jen. Institute of Radiological Sciences, National Yang-Ming University, Taipei, Taiwan. Nuclear Instruments & Methods in Physics Research, Section A: Accelerators, Spectrometers, Detectors, and Associated Equipment (2006), 569(2), 497-504. Publisher: Elsevier B.V., CODEN: NIMAER ISSN: 0168-9002. Journal written in English. CAN 146:117001 AN 2006:1263596 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

The purpose of this study is to evaluate the therapeutic efficacy of the liposome encaged with vinorelbine (VNB) and <sup>111</sup>In-oxine on human colorectal adenocarcinoma (HT-29) using HT-29/luc mouse xenografts. HT-29 cells stably transfected with plasmid vectors contg. luciferase gene (luc) were transplanted s.c. into the male NOD/SCID mice. Biodistribution of the drug was performed when tumor size reached 500-600 mm<sup>3</sup>. The uptakes of <sup>111</sup>In-VNB-liposome in tumor and normal tissues/organs at various time points postinjection were assayed. Multimodalities, including gamma scintigraphy, bioluminescence imaging (BLI) and whole-body autoradiog. (WBAR), were applied for evaluating the therapeutic efficacy when tumor size was about 100 mm<sup>3</sup>. The tumor/blood ratios of <sup>111</sup>In-VNB-liposome were 0.044, 0.058, 2.690, 20.628 and 24.327, resp., at 1, 4, 24, 48 and 72 h postinjection. Gamma scintigraphy showed that the tumor/muscle ratios were 2.04, 2.25 and 4.39, resp., at 0, 5 and 10 mg/kg VNB. BLI showed that significant tumor control was achieved in the group of 10 mg/kg VNB (<sup>111</sup>In-VNB-liposome). WBAR also confirmed this result. In this study, we have demonstrated a non-invasive imaging technique with a luciferase reporter gene and BLI for evaluation of tumor treatment efficacy in vivo. The SCID mice bearing HT-29/luc xenografts treated with <sup>111</sup>In-VNB-liposome were shown with tumor redn. by this technique.

Answer 6:

**Bibliographic Information****Effects of cryotherapy or chemotherapy on apoptosis in a non-small-cell lung cancer xenografted into SCID mice.**

Forest, Valerie; Peoc'h, Michel; Campos, Lydia; Guyotat, Denis; Vergnon, Jean-Michel. Faculte de Medecine Jacques Lisfranc, UPRES-EA3063, Saint-Etienne, Fr. Cryobiology (2005), 50(1), 29-37. Publisher: Elsevier, CODEN: CRYBAS ISSN: 0011-2240. Journal written in English. CAN 142:461089 AN 2005:135039 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

Lung cancers are among the most frequent and the most lethal tumors. They are mainly treated by surgery or by chemotherapy, but in the most advanced stages a local cryotherapy can be proposed as a palliative option for bronchial clearance. This therapy, based on the cytotoxic effects of low temps., acts by mechanisms which are not yet totally understood. The aim of this work was to investigate in vivo the biol. effects of cryotherapy in a model of human non-small-cell lung cancer. We used a xenograft system: cells from the A549 cell line (adenocarcinoma) were injected s.c. into SCID mice. Cryotherapy was performed (three cycles, nitrous oxide cryoprobe). Chemotherapy (i.v. injection of Vinorelbine (Navelbine), 4.8 mg/kg) was used as a control treatment. Tumor nodes were excised at variable time points and studied morphol. The induction of apoptosis was analyzed by immunohistochem. staining of cleaved caspase-3 and by TUNEL. Results showed that cryotherapy was an efficient technique to induce cell death either by necrosis or by apoptosis. Necrosis was found near the cryoprobe impact site and was maximal 2 h after treatment (65%); a second peak was obsd. after 4 days (77%). Around this central necrotic area, apoptotic cells were found. Apoptosis was maximal after 8 h (47%). Chemotherapy induced apoptosis in a fewer no. of cells and this effect was not time-dependent. Taken together, these results demonstrate the differential effects of cryotherapy and chemotherapy in vivo, suggesting different modes of action and the potential benefit to combine them.

Answer 7:

### Bibliographic Information

#### **Synergism between the anticancer actions of 2-methoxyestradiol and microtubule-disrupting agents in human breast cancer.**

Han, Gui-Zhen; Liu, Zhi-Jian; Shimoi, Kayoko; Zhu, Bao Ting. Department of Basic Pharmaceutical Sciences, College of Pharmacy, University of South Carolina, Columbia, SC, USA. *Cancer Research* (2005), 65(2), 387-393. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 142:170236 AN 2005:76681 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

2-Methoxyestradiol (2-MeO-E2), a well-known nonpolar endogenous metabolite of 17 $\beta$ -estradiol, has strong antiproliferative, apoptotic, and antiangiogenic actions in vitro and in vivo at pharmacol. concns. We detd. in the present study whether 2-MeO-E2 can enhance the anticancer actions of paclitaxel or vinorelbine (two commonly used microtubule-disrupting agents) in several human breast cancer cell lines, including the estrogen receptor-pos. MCF-7 and T-47D cells and the receptor-neg. MDA-MB-435s and MDA-MB-231 cells. 2-MeO-E2 in combination with paclitaxel or vinorelbine exhibited a synergistic anticancer effect in these human breast cancer cells in vitro, and this synergistic effect was more pronounced when each of the drugs was used at relatively low concns. Addnl. expts. using female athymic BALB/c nu/nu mice showed that p.o. administration of 2-MeO-E2 at 30 mg/kg body wt., once a week for 6 wk, markedly enhanced the activity of paclitaxel or vinorelbine against the growth of the estrogen receptor-neg. MDA-MB-231 human breast cancer xenografts in these animals. By contrast, combination of 2-MeO-E2 with 5-fluorouracil only had a partial additive effect against the growth of these cell lines in culture, and no synergistic effect was obsd. Interestingly, when doxorubicin was used in combination with 2-MeO-E2, the antiproliferative effect of 2-MeO-E2 was somewhat antagonized by doxorubicin when it was present at high concns. Our results showed that 2-MeO-E2 at nontoxic or subtoxic doses selectively enhanced the effects of certain microtubule-disrupting agents (such as paclitaxel and vinorelbine) against the growth of the receptor-neg. human breast cancer cells in culture and also in athymic nude mice.

Answer 8:

### Bibliographic Information

#### **Schedule-dependent synergism of vinorelbine and 5-fluorouracil/UFT against non-small cell lung cancer.**

Matsumoto, Shingo; Igishi, Tadashi; Hashimoto, Kiyoshi; Kodani, Masahiro; Shigeoka, Yasushi; Nakanishi, Hirofumi; Touge, Hirokazu; Kurai, Jun; Makino, Haruhiko; Takeda, Kenichi; Yasuda, Kazuhito; Hitsuda, Yutaka; Shimizu, Eiji. Division of Medical Oncology and Molecular Respiriology, Faculty of Medicine, Tottori University, Yonago, Japan. *International Journal of Oncology* (2004), 25(5), 1311-1318. Publisher: International Journal of Oncology, CODEN: IJONES ISSN: 1019-6439. Journal written in English. CAN 142:190514 AN 2004:1007765 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Elderly patients with advanced non-small cell lung cancer (NSCLC) require chemotherapy that is effective and minimally toxic. We evaluated the activity of a combination of vinorelbine and 5-fluorouracil (5-FU)/UFT (a fixed combination of tegafur and uracil) in vitro and in vivo to establish a rationale for clin. use. The cytotoxic activities of various combinations of vinorelbine and 5-FU, the active metabolite of tegafur, were analyzed by a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay and isobologram technique in vitro, using 3 NSCLC cell lines (A549, PC14, and Ma10). Sequential exposure to vinorelbine followed by 5-FU showed additive or synergistic activity against all 3 NSCLC cell lines tested. The reverse sequence showed no synergism. Antitumor activity and survival prolongation after treatment with different combinations of vinorelbine and UFT were evaluated in nude mice bearing PC14 xenografts. Treatment with vinorelbine before UFT was assocd. with higher antitumor activity, less toxicity, and longer survival than the reverse sequence. To clarify the underlying mechanism by which the combination exerts the synergistic effects, the expression of thymidylate synthase (TS) was assessed by Western blot anal. in vitro and by immunohistochem. anal. in an animal model. Vinorelbine suppressed the 5-FU-induced increase in TS protein in A549 cells. In PC14 tumor tissues of animal models, TS expression in cancer cells was suppressed by vinorelbine. Our data suggest that treatment with vinorelbine injection before oral UFT may have synergistic activity against NSCLC. This synergistic activity may be attributed to increased chemosensitivity to UFT caused by vinorelbine-induced suppression of TS.

Answer 9:

### Bibliographic Information

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

### Abstract

Current approaches for treating cancer are limited, in part, by the inability of drugs to affect the poorly vascularized regions of tumors. We have found that C. novyi-NT in combination with anti-microtubule agents can cause the destruction of both the vascular and avascular compartments of tumors. The two classes of microtubule inhibitors were found to exert markedly different effects. Some agents that inhibited microtubule synthesis, such as HTI-286 and vinorelbine, caused rapid, massive hemorrhagic necrosis when used in combination with C. novyi-NT. In contrast, agents that stabilized microtubules, such as the taxanes docetaxel and MAC-321, resulted in slow tumor regressions that killed most neoplastic cells. Remaining cells in the poorly perfused regions of tumors could be eradicated by C. novyi-NT. Mechanistic studies showed that the microtubule destabilizers, but not the microtubule stabilizers, radically reduced blood flow to tumors, thereby enlarging the hypoxic niche in which C. novyi-NT spores could germinate. A single i.v. injection of C. novyi-NT plus selected anti-microtubule agents was able to cause regressions of several human tumor xenografts in nude mice in the absence of excessive toxicity.

Answer 10:

### Bibliographic Information

**Definite antitumour activity of vinflunine, a novel fluorinated vinca alkaloid, against human tumour xenografts.** Kruczynski, A.; Astruc, J.; Ricome, C.; Colpaert, F.; Hill, B. T. Division of Experimental Cancer Research, Centre de Recherche Pierre Fabre, Castres, Fr. *Contributions to Oncology* (1999), 54(Relevance of Tumor Models for Anticancer Drug Development), 369-378. Publisher: S. Karger AG, CODEN: COONEV ISSN: 0250-3220. Journal written in English. CAN 133:12438 AN 2000:242569 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

The antitumor effects of vinflunine were evaluated relative to vinorelbine, against a panel of transplantable s.c. implanted human

tumor xenografts with different chemosensitivities, namely the LX-1 (small-cell lung carcinoma), MX-1 (breast carcinoma), and DLD-1 (colon adenocarcinoma) xenografts in athymic nude mice. Vinflunine (20 and 40 mg/kg/injection 4 weekly treatments) demonstrated definite in vivo activity against s.c. implanted LX-1 human lung xenografts as judged by its effects on tumor growth of LX-1 tumor bearing mice. Relative areas under the tumor growth curves (rAUC) values of 53 and 36% resp. corresponded to an overall tumor growth inhibition of 47 and 64%. Optimal tumor growth inhibition of 60 and 77% (median tumor vol. of the drug-treated group/median tumor vol. of the vehicle treated group  $\times 100 = T/C$  of 40 and 23%) were reached on days 16 and 26, resp. T/C values representative of a min. level of activity ( $T/C \leq 42\%$ ) were recorded from days 9-33 at the optimal dose of 40 mg/kg/injection. Values of  $T/C \leq 42\%$  were obsd. with vinorelbine, at the equitoxic dose of 5 mg/kg, only from days 12-23. The rAUC value recorded with vinorelbine was 56 vs. 36% with vinflunine. Weekly i.p. administration of 20 and 40 mg/kg/injection of vinflunine for 4 wk resulted in definite in vivo activity against MX-1 xenografts with optimal T/C ratios of 42 and 30%, resp., and a rAUC value of 39% at 40 mg/kg/injection. T/C values  $\leq 42\%$  were recorded from days 16-19 and 26-37, at 40 mg/kg/injection. Vinflunine did not demonstrate any in vivo activity against the human DLD-1 colon cancer xenografts.

Answer 11:

### Bibliographic Information

**Human ovarian cancer xenografts in nude mice: chemotherapy trials with paclitaxel, cisplatin, vinorelbine and titanocene dichloride.** Vellena-Heinsen, C.; Friedrich, M.; Ertan, A. K.; Farnhammer, C.; Schmidt, W. Department Obstetrics Gynecology, University Saarland, Homburg/Saar, Germany. *Anti-Cancer Drugs* (1998), 9(6), 557-563. Publisher: Lippincott-Raven Publishers, CODEN: ANTDEV ISSN: 0959-4973. Journal written in English. CAN 129:225378 AN 1998:496740 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

The new cytostatics titanocene dichloride and vinorelbine were compared to cisplatin and paclitaxel using a human ovarian cancer xenografts model. Biopsy material from a native human ovarian carcinoma was expanded and transplanted into 96 nude mice. The animals were divided into six treatment groups: cisplatin  $3 \times 4$  mg/kg, paclitaxel  $5 \times 26$  mg/kg, vinorelbine  $1 \times 20$  mg/kg, titanocene dichloride  $3 \times 30$  mg/kg, titanocene dichloride  $3 \times 40$  mg/kg and a control group treated with 0.9% saline. Each expt. was repeated with eight mice in each treatment group. Treatment groups were evaluated in terms of av. daily increase in tumor vol. and av. daily body wt. increase of nude mice based on slopes of least-square regressions performed on individual animals. The slope factors  $\alpha$  and  $\beta$  of the body wt. ( $\alpha$ ) and tumor vol. changes ( $\beta$ ) within each group during the course of an expt. were calcd. Both a statistically significant decrease ( $p < 0.05$ ) in the body wt. of the exptl. animals (cisplatin:  $\alpha = -0.5163$ , vinorelbine:  $\alpha = -0.6598$ , paclitaxel:  $\alpha = -0.6746$ , titanocene dichloride  $3 \times 30$  mg/kg:  $\alpha = -0.6259$ , titanocene dichloride  $3 \times 40$  mg/kg:  $\alpha = -0.7758$ ) and a significant redn. ( $p < 0.05$ ) of the increase in tumor vol. (cisplatin:  $\beta = 12.049$ , vinorelbine:  $\beta = 0.504$ , paclitaxel:  $\beta = -1.636$ , titanocene dichloride  $3 \times 30$  mg/kg:  $\beta = -6.212$ , titanocene dichloride  $3 \times 40$  mg/kg:  $\beta = -0.685$ ) was shown in all treated groups compared to the control group ( $\alpha = -0.1398$ ;  $\beta = 23.056$ ). No significant wt. changes were obsd. between the individually treated groups. A statistically significant redn. of the tumor growth occurred under paclitaxel ( $\beta = -1.636$ ), vinorelbine ( $\beta = -0.504$ ) and titanocene dichloride medication  $3 \times 40$  mg/kg ( $\beta = -0.685$ ), as compared to the group treated with cisplatin ( $\beta = 12.049$ ). We found titanocene dichloride to be as effective as paclitaxel and more effective than cisplatin. Vinorelbine seems to be a very effective antineoplastic agent exhibiting a significant higher cytostatic effect than cisplatin.

Both titanocene dichloride and vinorelbine provide new therapeutic options in women with ovarian carcinoma not responding to std. chemotherapy.

Answer 12:

### Bibliographic Information

**Evaluation of antitumor activity of navelbine (vinorelbine ditartrate) against human breast carcinoma xenografts based on its pharmacokinetics in nude mice.** Tsuruo, Takashi; Inaba, Makoto; Tashiro, Tazuko; Yamori, Takao; Ohnishi, Yasuyuki; Ashizawa, Tadashi; Sakai, Toki; Kobayashi, Satoshi; Gomi, Katsushige. Cancer Chemotherapy Center, Japanese Foundation Cancer Res., Tokyo, Japan. *Anti-Cancer Drugs* (1994), 5(6), 634-40. Publisher: Rapid Science Publishers, CODEN: ANTDEV ISSN: 0959-4973. Journal written in English. CAN 122:71523 AN 1995:301729 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

The in vitro antitumor activity of navelbine (NVB, KW-2307), a newly synthesized vinca alkaloid, was compared with that of adriamycin (ADM) against human breast carcinomas inoculated into nude mice at the max. tolerated dose (MTD) and clin. equiv. dose (CED). The plasma levels of NVB after i.v. injection into nude mice at doses of 1.2 and 4.8 mg/kg mg/kg diminished rapidly during the early phase (0-1 h), followed by a very long shallow one. NVB was still detected 96 h after administration at a dose of 4.8 mg/kg. The pharmacokinetic parameters of NVB in plasma indicated that NVB extensively distributes to tissues. The CED of NVB was provisionally decided to be 4.8 mg/kg based on the comparison of AUC values at 24-∞ h between human patients and nude mice. When compared by a single injection of MTD (NVB, 16 mg/kg; ADM 12 mg/kg), NVB was effective against all four tumor lines MC-2, MC-8, MMKY and H-31, while ADM was effective only against H-31. The body wt. loss by NVB was mild as compared with that by ADM, indicating that the antitumor activity of NVB is superior to that of ADM at their MTDs. A single injection of NVB at its CED (4.8 mg/kg) produced a poor antitumor effect and no or little toxicity in terms of body wt. loss, as compared with those at MTD. However, when NVB was administered intermittently at CED, it exhibited significant antitumor activity against three tumor lines. The body wt. loss was still mild even on this intermittent schedule. These results indicate that NVB can offer antitumor activity against human breast carcinoma xenografts at its CED.

Answer 13:

**Bibliographic Information**

**Combination effect of navelbine (vinorelbine ditartrate) with cisplatin against murine P388 leukemia and human lung carcinoma xenografts in mice.** Ashizawa, Tadashi; Asada, Masao; Kobayashi, Eiji; Okabe, Masami; Gomi, Katsushige; Hirata, Tadashi. Pharm. Res. Lab., Kyowa Hakko Kogyo Co. Ltd, Nagaizumi, Japan. Anti-Cancer Drugs (1993), 4(5), 577-83. CODEN: ANTDEV ISSN: 0959-4973. Journal written in English. CAN 120:182566 AN 1994:182566 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

The in vivo combination effect of navelbine (NVB, KW-2307) plus cisplatin was compared with that of vindesine (VDS) plus cisplatin in terms of antitumor activity and side effects. The antitumor activity of NVB or cisplatin against i.p. inoculated P388 leukemia was augmented by their combination on various schedules when the interval of administrations was within 24 h. Against i.v. inoculated P388 leukemia, the most significant combination effect was obsd. when cisplatin was administered 4 h after NVB injection (ILS(%) > 451) and three long-term survivors were obsd. On this schedule, the combination of LD10 of each drug was achieved, indicating the lack of addn. of toxicity. This was further proved by examn. of body wt. change, white blood cell count and platelet count. Interestingly, significant elevation of blood urea nitrogen concn. by cisplatin was prevented by the combination with NVB. The combination of max. tolerated dose of NVB and cisplatin was also tolerable in nude mice, and their combination effect was obsd. against human lung large cell carcinoma Lu-65 and adenocarcinoma PC-12. The no. of toxic death mice was more in VDS plus cisplatin-treated groups than in NVB plus cisplatin-treated groups, indicating that the combination chemotherapy of NVB plus cisplatin is a better regimen than that of VDS plus cisplatin in exptl. tumor systems.

Answer 14:

**Bibliographic Information**

**Relationship between chemotherapy with paclitaxel, cisplatin, vinorelbine and titanocene dichloride and expression of proliferation markers and tumour suppressor gene p53 in human ovarian cancer xenografts in nude mice.** Kolberg H C; Villena-Heinsen C; Deml M M; Kraemer S; Diedrich K; Friedrich M Department of Gynecology and Obstetrics, University Clinic of Schleswig-Holstein, Campus Lubeck, Germany European journal of gynaecological oncology (2005), 26(4), 398-402. Journal code: 8100357. ISSN:0392-2936. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 16122187 AN 2005455203 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

**Abstract**

**PURPOSE:** In this study the relationship between therapy with paclitaxel, cisplatin, vinorelbine and titanocene dichloride and of the expression of proliferation markers (ki67 and S-phase fraction) and tumour suppressor gene p53 was analyzed using a human ovarian cancer xenograft model. **METHODS:** Biopsy material from one human ovarian cancer was expanded and transplanted into 102 nude mice. The mice were divided into six groups with different intraperitoneal treatments with paclitaxel, cisplatin, vinorelbine, titanocene dichloride and a control group treated with 0.9% saline solution. After the observation period the tumours were extracted and immunohistochemically stained with monoclonal antibodies against ki67 and p53. The S-phase-fraction was identified by flow cytometry. **RESULTS:** There were no statistically significant differences. Regarding the treatment groups, the vinorelbine-group showed the highest percentage (53.3%) and the titanocene dichloride-3x40 mg/kg-group the lowest percentage (7.1%) of ki67-positive specimens, whereas in the control group 35.7% of the specimens were positively stained for ki67. The results for the expression of p53 were similar. The vinorelbine-group had the highest percentage of p53-positive specimens (60%), in both titanocene-groups no specimen showed a positive staining for p53 and in the control group 7.1% of the specimens were positively stained for p53. The mean S-phase-fraction was 14.48% (SD +/- 3.98), no statistically significant relation between S-phase-fraction and expression of p53 ( $p = 0.883$ ) or of ki67 ( $p = 0.351$ ) could be shown. The change of tumour volume was independent of the results for ki67, p53 and the S-phase-fraction. **CONCLUSION:** Although, as previously published, a significant difference of tumour volume change occurred between the treatment groups, in this study we could not find a relation between this change of tumour volume and the expression of p53 or ki67.

The absolute number of p53- and ki67-positive staining specimens was too small for statistical analysis, therefore the relevance of the differences between the different treatment groups and the control remains unclear. The results for the S-phase-fraction showed no correlation between the change of tumour volume, different treatment protocols or the expression of p53- and ki67. Our findings contribute to the controversy of the influence of chemotherapy on the expression of proliferation markers and p53.

Answer 15:

### Bibliographic Information

**Effects of vinorelbine and titanocene dichloride on human tumour xenografts in nude mice.** Friedrich M; Villena-Heinsen C; Farnhammer C; Schmidt W Department of Obstetrics and Gynecology, University of the Saarland, Homburg/Saar, Germany European journal of gynaecological oncology (1998), 19(4), 333-7. Journal code: 8100357. ISSN:0392-2936. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 9744720 AN 1998415969 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

### Abstract

**PURPOSE:** In this study, the new antineoplastic agents titanocene dichloride and vinorelbine are compared to cisplatin and paclitaxel using a human ovarian cancer xenograft model. **METHODS:** Biopsy material from one native human ovarian carcinoma was expanded and transplanted into 48 nude mice. The animals were divided into six treatment groups: cisplatin 3x4 mg/kg, paclitaxel 5x26 mg/kg, vinorelbine 1x20 mg/kg, titanocene dichloride 3x30 mg/kg, titanocene dichloride 3x40 mg/kg and a control group treated with 0.9% saline. Treatment groups were evaluated in terms of average daily increase in tumour volume and average daily body weight increase of the nude mice based on slopes of least square regressions performed on individual animals. The slope factors alpha and beta of the body weight (alpha) and tumour volume changes (beta) within each group were calculated. **RESULTS:** A statistically significant decrease ( $p < 0.05$ ) in body weight of the experimental animals was shown in groups treated with paclitaxel (alpha = -0.6878) and titanocene dichloride 3x40 mg/kg (alpha = -0.7194) compared to the control group which was treated with 0.9% saline (alpha = -0.2643). Significant body weight changes were not observed in the comparison of the remaining treated groups (cisplatin: alpha = -0.4552, vinorelbine: alpha = -0.5606, titanocene dichloride 3x30 mg/kg: alpha = -0.6173 to the control group. A significant reduction ( $p < 0.05$ ) of the increase tumour volume (vinorelbine: beta = 5.260, paclitaxel: beta = 0.478, titanocene dichloride 3x30 mg/kg: beta = 10.283, titanocene dichloride 3x40 mg/kg: beta = 5.768) was shown in treated groups except for cisplatin (beta = 18.722) compared to the tumour bearing control group (beta = 30.136). A statistically significant reduction of the increase in tumour volume occurred under paclitaxel medication compared to the group treated with cisplatin. **CONCLUSION:** We found titanocene dichloride to be effective as vinorelbine and more effective than cisplatin.

Vinorelbine seems to be a very effective antineoplastic agent with a significantly higher cytostatic effect than cisplatin.

Both titanocene dichloride and vinorelbine provide new therapeutic options in women with ovarian carcinoma not responding to standard chemotherapies.

Answer 16:

#### **Bibliographic Information**

**Vinorelbine: a new promising drug in Hodgkin's disease.** Devizzi L; Santoro A; Bonfante V; Viviani S; Bonadonna G Division of Medical Oncology, Istituto Nazionale Tumori, Milan, Italy *Leukemia & lymphoma* (1996), 22(5-6), 409-14. Journal code: 9007422. ISSN:1042-8194. Journal; Article; (JOURNAL ARTICLE); General Review; (REVIEW) written in English. PubMed ID 8882953 AN 97037306 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

#### **Abstract**

Vinorelbine is a new semisynthetic vinca alkaloid that differs chemically from vinblastine by a substitution of the catharanthine moiety. The powerful cytostatic activity of vinorelbine against murine tumors, human malignant cell lines and human tumor xenografts in nude mice has been demonstrated. Phase I-II studies of intravenous vinorelbine, administered weekly as single agent or in combination chemotherapy have been conducted since 1986. Results suggest that vinorelbine has high activity in non-small cell lung cancer, breast cancer and cisplatin-resistant ovarian cancer with mild toxicity, being neutropenia the major treatment related complication. In this paper we critically review the activity of vinorelbine in pretreated Hodgkin's patients. Available results strongly suggest the inclusion of this drug in first or second line chemotherapy regimens in Hodgkin's disease.

Answer 17:

#### **Bibliographic Information**

**The current and future place of vinorelbine in cancer therapy.** Cvitkovic E; Izzo J Hopital Paul Brousse, Villejuif, France *Drugs* (1992), 44 Suppl 4 36-45; discussion 66-9. Journal code: 7600076. ISSN:0012-6667. (CLINICAL TRIAL); Journal; Article; (JOURNAL ARTICLE); General Review; (REVIEW) written in English. PubMed ID 1283849 AN 93170193 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

#### **Abstract**

Vinorelbine is a new semisynthetic vinca alkaloid that differs chemically from vinblastine by a substitution of the catharanthine moiety. The antitumour activity of vinorelbine against murine tumours, human malignant cell lines and human tumour xenografts in nude mice is evidence of its powerful cytostatic activity against all tumour types. Phase I and phase II studies of intravenous vinorelbine, administered weekly as a single agent or in combination chemotherapy, have been conducted since 1985. Results suggest that vinorelbine has high activity in non-small cell lung cancer (with an overall response rate of 33 to 65%), breast cancer (overall response rate of 46 to 78%) and cisplatin-resistant ovarian carcinoma (over-all response rate of 16% and 35% with single-agent and combination therapy, respectively). In Hodgkin's disease, vinorelbine as a single agent demonstrates high activity, with overall responses ranging from 34 to 90%. Recent phase II studies assessing vinorelbine administered by continuous infusion or orally show promising response rates; however, further trials are needed to validate these preliminary results.