

Answer 1:

### Bibliographic Information

**The investigation on molecular level in radiosensitizing effect of topotecan of nude mouse with nasopharyngeal carcinoma in vivo.** Wen, Qinglian; Wu, Jingbo; He, Fen; Lang, Jinyi; Fan, Juan. Department of Oncology, The Affiliated Hospital of Luzhou Medical College, Luzhou, Sichuan, Peop. Rep. China. *Zhongguo Zhongliu Linchuang* (2006), 33(23), 1367-1370. Publisher: Zhongguo Zhongliu Linchang Bianji Weiyuanhui, CODEN: ZZLIEP ISSN: 1000-8179. Journal written in Chinese. CAN 148:372874 AN 2007:1126247 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

The objective is to detect the mol. mechanism of radiosensitizing effect of Topotecan on Nasopharyngeal carcinoma nude mice xenografts. The real-time fluorescence quant. RT-PCR was used to detect the active mRNA gene level of topoisomerase I in tumor specimens received from radiosensitizing study. The results show that the linear coeff. of correlation of the quant. std. curve was -0.99. The results in the groups were as follows: the mRNA gene level of Topo-I was  $45 \pm 2.128$  copies/ $\mu\text{l}$  in the RT+ TPT group (the radiosensitizing group),  $2112 \pm 1.208$  copies/ $\mu\text{l}$  in the TPT group,  $1699 \pm 1.317$  copies/ $\mu\text{l}$  in the RT 20Gy group and  $3\ 559\ 295 \pm 1.154$  copies/ $\mu\text{l}$  in the control group, resp. The level of Topo-I in RT+ TPT group was the lowest in all the four groups. The statistical significance was shown as compared to the level of TPT group or of RT 20Gy group ( $P < 0.05$ ). The statistical significance had also been shown as compared with that in each groups with the controls ( $P < 0.05$ ). It was concluded that administration of topotecan with concurrent radiotherapy can affect and decrease the level of gene activity of topoisomerase in the nasopharyngeal-carcinoma cells and this might be an important mechanism of sensitizing effect in the mol. level.

Answer 2:

### Bibliographic Information

**Phenoxodiol-topotecan co-administration exhibit significant anti-tumor activity without major adverse side effects.** Alvero, Ayesha B.; Brown, David; Montagna, Michele; Matthews, Marissa; Mor, Gil. Department of Obstetrics & Gynecology, Yale University School of Medicine, New Haven, CT, USA. *Cancer Biology & Therapy* (2007), 6(4), 612-617. Publisher: Landes Bioscience, CODEN: CBTAAO ISSN: 1538-4047. Journal written in English. CAN 147:479958 AN 2007:1039381 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Objective: We previously showed that Phenoxodiol is able to sensitize epithelial ovarian cancer cells to Paclitaxel, Carboplatin, Gemcitabine, and Docetaxel. The aim of this study was to det. the value of Phenoxodiol-Topotecan coadministration. Methods: Nine epithelial ovarian cancer cell lines isolated from ascites or ovarian tissue were treated with increasing concns. of Topotecan (5-500 ng/mL) with or without Phenoxodiol pretreatment (10  $\mu\text{g/mL}$ ) for 24 h and cell viability was measured using CellTiter 96 Aq. One Soln. Cell Proliferation Assay. The effect of Phenoxodiol-Topotecan combination therapy in vivo was detd. using the topotecan resistant A2780 mouse xenograft model. Results: In vitro, pretreatment with Phenoxodiol lowers the topotecan IC<sub>50</sub> from  $>500$  ng/mL to 2.5-100 ng/mL in five out of nine cell lines tested. Results from animal expts. confirmed the advantage of Phenoxodiol-Topotecan combination therapy over monotherapy controls. Median tumor kinetics from animals receiving Phenoxodiol-Topotecan in combination was significantly slower compared to those animals receiving the resp. monotherapies. In addn., co-administration with Phenoxodiol reversed Topotecan-induced myelosuppression. Conclusion: Phenoxodiol-Topotecan combination therapy allows the administration of both agents at lower doses while retaining significant anti-tumor activity compared to monotherapy. These findings suggest that the Phenoxodiol-Topotecan combination may represent an alternative treatment modality for the management of ovarian cancer and justifies further investigation in the clin. setting.

Answer 3:

### Bibliographic Information

**STEALTH liposomal CKD-602, a topoisomerase I inhibitor, improves the therapeutic index in human tumor xenograft models.** Yu, Ning Y.; Conway, Colleen; Pena, Rhoneil L. S.; Chen, Joy Y. ALZA Corporation, Mountain View, CA, USA. *Anticancer Research* (2007), 27(4B), 2541-2545. Publisher: International Institute of Anticancer Research, CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 147:439718 AN 2007:994224 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

Background: CKD-602, a topoisomerase I inhibitor, has antitumor activity in a broad spectrum of tumor types. STEALTH liposomal CKD-602 (S-CKD602) prolongs circulation of CKD-602 in plasma, increases drug exposure in tumors and improves efficacy compared with free drug. Materials and Methods: Different dosing regimens of S-CKD602, free CKD-602 and topotecan were compared for antitumor activity in female athymic nude mice bearing human A375 melanoma, ES-2 ovarian, H82 SCLC or HT-29 colon tumor xenografts. Results: S-CKD602 was more efficacious than free drug in all tumor types studied. The therapeutic index (TI) of S-CKD602 was estd. to be .apprx.6-fold greater than that of free CKD-602 in ES-2 and .apprx.3-fold greater in H82 tumors. TI of S-CKD602 was .apprx.2-fold greater than that of free CKD-602 and .apprx.5-fold greater than that of topotecan in A375, and  $\geq 3$ -fold greater in HT-29 tumors. In A375 tumors, once-weekly dosing of S-CKD602 was superior to once every 2 wk or twice weekly schedules. Conclusion: The therapeutic index of S-CKD602 was greater than that of free CKD-602 and topotecan in several human tumor types.

Answer 4:

#### 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 5:

#### Bibliographic Information

**Preclinical selection of a novel poly(ADP-ribose) polymerase inhibitor for clinical trial.** Thomas, Huw D.; Calabrese, Christopher R.; Batey, Michael A.; Canan, Stacie; Hostomsky, Zdenek; Kyle, Suzanne; Maegley, Karen A.; Newell, David R.; Skalitzy, Donald; Wang, Lan-Zhen; Webber, Stephen E.; Curtin, Nicola J. Northern Institute for Cancer Research, Medical School,

Newcastle University, Newcastle upon Tyne, UK. *Molecular Cancer Therapeutics* (2007), 6(3), 945-956. Publisher: American Association for Cancer Research, CODEN: MCTOCF ISSN: 1535-7163. Journal written in English. CAN 146:513969 AN 2007:289482 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Poly(ADP-ribose) polymerase (PARP)-1 (EC 2.4.2.30) is a nuclear enzyme that promotes the base excision repair of DNA breaks. Inhibition of PARP-1 enhances the efficacy of DNA alkylating agents, topoisomerase I poisons, and ionizing radiation. Our aim was to identify a PARP inhibitor for clin. trial from a panel of 42 potent PARP inhibitors (Ki, 1.4-15.1 nmol/L) based on the quinazolinone, benzimidazole, tricyclic benzimidazole, tricyclic indole, and tricyclic indole-1-one core structures. We evaluated chemosensitization of temozolomide and topotecan using LoVo and SW620 human colorectal cells; in vitro radiosensitization was measured using LoVo cells, and the enhancement of antitumor activity of temozolomide was evaluated in mice bearing SW620 xenografts. Excellent chemopotential and radiopotential were obsd. in vitro, with 17 of the compds. causing a greater temozolomide and topotecan sensitization than the benchmark inhibitor AG14361 and 10 compds. were more potent radiosensitizers than AG14361. In tumor-bearing mice, none of the compds. were toxic when given alone, and the antitumor activity of the PARP inhibitor-temozolomide combinations was unrelated to toxicity. Compds. that were more potent chemosensitizers in vivo than AG14361 were also more potent in vitro, validating in vitro assays as a prescreen. These studies have identified a compd., AG14447, as a PARP inhibitor with outstanding in vivo chemosensitization potency at tolerable doses, which is at least 10 times more potent than the initial lead, AG14361. The phosphate salt of AG14447 (AG014699), which has improved aq. soly., has been selected for clin. trial.

Answer 6:

### Bibliographic Information

#### **Chimmitecan, a Novel 9-Substituted Camptothecin, with Improved Anticancer Pharmacologic Profiles In vitro and In vivo.**

Huang, Min; Gao, Heyong; Chen, Yi; Zhu, Hong; Cai, Yujun; Zhang, Xiongwen; Miao, Zehong; Jiang, Hualiang; Zhang, Jian; Shen, Hongwu; Lin, Liping; Lu, Wei; Ding, Jian. Divisions of Anti-Tumor Pharmacology and Chemistry, Drug Discovery and Design Center, and Center for Drug Metabolism and Pharmacokinetics Research, State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, Peop. Rep. China. *Clinical Cancer Research* (2007), 13(4), 1298-1307. Publisher: American Association for Cancer Research, CODEN: CCRE4 ISSN: 1078-0432. Journal written in English. CAN 147:45433 AN 2007:199246 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

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

Answer 7:

**Bibliographic Information**

**Effect of stealthy liposomal topotecan plus amlodipine on the multidrug-resistant leukemia cells in vitro and xenograft in mice.** Li, X.; Lu, W. L.; Liang, G. W.; Ruan, G. R.; Hong, H. Y.; Long, C.; Zhang, Y. T.; Liu, Y.; Wang, J. C.; Zhang, X.; Zhang, Q. School of Pharmaceutical Sciences and State Key Laboratory of Natural and Biometric Drugs, Peking University, Beijing, Peop. Rep. China. *European Journal of Clinical Investigation* (2006), 36(6), 409-418. Publisher: Blackwell Publishing Ltd., CODEN: EJCIB8 ISSN: 0014-2972. Journal written in English. CAN 145:465296 AN 2006:639260 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

Background: Multidrug resistance (MDR) is a major obstacle to successful cancer chemotherapy as the over-expressed MDR protein acts as an efflux pump, which leads to a redn. in the uptake of the anticancer agent by tumor cells. We combined topotecan and amlodipine together into the stealthy liposomes, in which amlodipine was applied as a MDR reversing agent to overcome the resistance. Materials and methods: Cytotoxicity, apoptosis and the signalling pathway assays were performed on human chronic myelogenous leukemia K562, promyelocytic leukemia HL-60 and MDR HL-60 cells, resp. Pharmacokinetics and antitumor activity studies were performed on normal Kunming mice and female BALB/c nude mice with MDR HL-60 xenografts, resp. Results: Topotecan alone was effective in inhibiting the growth of non-resistant leukemia cells, K562 and HL-60 cells but not the growth of MDR HL-60 cells. The resistance of topotecan in MDR HL-60 cells was potently reversed by the addn. of amlodipine. Moreover, amlodipine enhanced the apoptosis-inducing effect of topotecan synergistically. Apoptosis was through activating caspases in a cascade: first, the initiator caspase 8 and then effectors caspase 3/7 (total activity of caspases 3 and 7) were activated. Being encapsulated into the stealthy liposomes with an acidic internal medium, topotecan existed dominantly in an active lactone species, which was reversibly changed from an inactive carboxylate form via a pH-dependent reaction. After administration of stealthy liposomes to mice, the blood exposure of the lactone form was evidently increased and extended. The antitumor effects in the MDR HL-60 xenografted tumor were stealthy liposomal topotecan (SLT) plus amlodipine > SLT > un-encapsulated topotecan > blank control.

Conclusions: The enhanced antitumor activity in the MDR HL-60 cells by the SLT plus amlodipine could be owing to multiple reasons: (a) synergistic apoptosis inducing effect, (b) reversing MDR by amlodipine and (c) increasing the availability of active lactone of topotecan by the stealthy liposomes. The apoptosis induced by amlodipine is through caspase 8 and then the 3/7 signalling pathway.

Answer 8:

**Bibliographic Information**

**A novel stealth liposomal topotecan with amlodipine: Apoptotic effect is associated with deletion of intracellular Ca<sup>2+</sup> by amlodipine thus leading to an enhanced antitumor activity in leukemia.** Li, Xing; Ruan, Guo-Rui; Lu, Wan-Liang; Hong, Hai-Yan; Liang, Gong-Wen; Zhang, Yu-Teng; Liu, Yang; Long, Chuan; Ma, Xi; Yuan, Lan; Wang, Jian-Cheng; Zhang, Xuan; Zhang, Qiang. Department of Pharmaceutics, School of Pharmaceutical Sciences, Peking University, Beijing, Peop. Rep. China. *Journal of Controlled Release* (2006), 112(2), 186-198. Publisher: Elsevier B.V., CODEN: JCREEC ISSN: 0168-3659. Journal written in English. CAN 145:217561 AN 2006:401420 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

The objectives of the present study were to define whether amlodipine induces apoptosis and what mechanism is involved in the process in human resistant and non-resistant leukemia cells following co-administration of stealth liposomal topotecan with amlodipine, a novel antiresistant liposomes developed by our institution. In three leukemias, K562, HL-60, and multidrug resistant (MDR) HL-60, cytotoxicity of topotecan was potentiated by amlodipine, while topotecan alone was resistant to MDR HL-60 cells. In two selected K562 or MDR HL-60 cells, the apoptotic effects were increased by addn. of amlodipine, showing a dose-dependent manner. The activities of caspase 3 and 7 (marked as caspase 3/7), and caspase 8 were significantly activated by topotecan with amlodipine co-treated as the stealth liposomes. The deletions of intracellular Ca<sup>2+</sup> stores induced by amlodipine correlated with the activated activities of caspase 3/7, or 8, resp. In xenograft model with MDR HL-60 in nude mice, antitumor activity of stealth liposomal topotecan with amlodipine was significantly enhanced as compared to that of stealth liposomal topotecan or topotecan alone. In conclusion, apoptotic effect is assocd. with deletion of intracellular Ca<sup>2+</sup> by amlodipine through activation of caspase 8 and then 3/7

activities. The enhanced antitumor activities by stealth liposomal topotecan with amlodipine are mainly due to the potentiating apoptotic effect and reversing the resistance by amlodipine. Stealth liposomal encapsulation of anticancer agent with a modulator may provide a novel strategy for improving the chemotherapeutic effects.

Answer 9:

#### **Bibliographic Information**

**Topotecan can compensate for protracted radiation treatment time effects in high grade glioma xenografts.** Pinel, Sophie; Chastagner, Pascal; Merlin, Jean-Louis; Marchal, Christian; Taghian, Alphonse; Barberi-Heyob, Muriel. Laboratoire de Recherche en Oncologie, Centre A. Vautrin, Vandœuvre-les-Nancy, Fr. *Journal of Neuro-Oncology* (2006), 76(1), 31-38. Publisher: Springer, CODEN: JNODD2 ISSN: 0167-594X. Journal written in English. CAN 145:180359 AN 2006:229160 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### **Abstract**

**Purpose:** Several studies reported that prolongation of overall treatment time of fractionated radiotherapy reduces the chance of tumor control. In the present study, we hypothesize that combining topotecan with irradiation could compensate for this detrimental time effect on the radioresponse. Therefore, we investigated the efficiency of different schedules of topotecan (TPT), radiotherapy (RT) or concomitant combination TPT + RT. **Methods and Materials:** Expts. were performed in two human high-grade glioma xenograft models (U87 and GBM Nan1). TPT and RT were delivered at a total dose of 3 mg/kg and 40 Gy, resp. For the TPT + RT groups, TPT was injected 5 min before radiation. Total radiation doses were delivered in 5, 10, 20, or 30 fractions over 1, 2, 4, or 6 wk, resp. The efficiency of TPT, RT, and TPT + RT was evaluated by tumor growth delay (TGD). **Results:** At this low total dose, and independent of the schedule, no efficacy was found in TPT-treated glioma xenografts. Conversely, radiotherapy-induced antitumor effect decreased with prolongation of treatment time. For TPT + RT combination, antitumor activity was not influenced by schedule, and tumor response was always comparable to those measured for the shortest and the most efficient irradiation schedule (i.e. 1 wk). When treatment was delivered over 4 or 6 wk in U87 glioma xenografts, therapeutic enhancement ratios reached 2.6 and 3.7, resp. This indicated that the interaction between ionizing radiation and topotecan was synergistic. **Conclusion:** The present study demonstrated that concomitant topotecan can compensate for the detrimental effect of treatment time protraction on radiotherapy efficacy in two malignant glioma xenografts.

Answer 10:

#### **Bibliographic Information**

**Anti-tumor activity of TRA-8 anti-death receptor 5 (DR5) monoclonal antibody in combination with chemotherapy and radiation therapy in a cervical cancer model.** Straughn, J. Michael, Jr.; Oliver, Patsy G.; Zhou, Tong; Wang, Wenquan; Alvarez, Ronald D.; Grizzle, William E.; Buchsbaum, Donald J. Division of Gynecologic Oncology, University of Alabama at Birmingham, Birmingham, AL, USA. *Gynecologic Oncology* (2006), 101(1), 46-54. Publisher: Elsevier, CODEN: GYNOA3 ISSN: 0090-8258. Journal written in English. CAN 145:202098 AN 2006:178025 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### **Abstract**

**Objectives:** There is substantial evidence that tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) causes apoptosis via activation of death receptors 4 and 5 (DR4 and DR5). We sought to determine the therapeutic potential of TRA-8 (anti-DR5 monoclonal antibody) in combination with chemotherapy and radiation therapy in a cervical cancer model. **Methods:** DR5 expression in 7 human cervical cancer cell lines was analyzed by indirect immunofluorescence using murine TRA-8 in combination with flow cytometry. Cell lines were treated with TRA-8 alone or in combination with cisplatin, topotecan, or radiation, and cytotoxicity assays were performed. Mice were inoculated with ME-180 cancer cells and treated with different combinations of therapy. Animals receiving antibody were injected i.p. with 200 µg of TRA-8. Animals received 9 Gy 60Co radiation divided into 3 fractions and 3 i.p. doses of cisplatin (6 mg/kg) 1 h before radiation. A similar expt. was performed using topotecan (2 mg/kg) as the chemotherapeutic agent. **Results:** DR5 was expressed to a varying degree on the cervical cancer cell lines. Combination treatment with TRA-8 and chemotherapy or radiation

resulted in synergistic cytotoxicity in vitro. In vivo, combination therapy with TRA-8, cisplatin, and radiation produced tumor growth inhibition that was significantly greater than the other groups. Similar results were seen in combination studies with topotecan. Conclusions: These data suggest that DR5 is a good target for activation of the apoptotic pathway. Monoclonal antibodies such as TRA-8 may play an important role in the development of an effective treatment strategy for patients with advanced cervical cancer.

Answer 11:

### Bibliographic Information

**Augmenting tumor sensitivity to topotecan by transient hypoxia.** Lund, Eva L.; Hansen, Lasse T.; Kristjansen, Paul E. G. Laboratory of Experimental Oncology, Department of Molecular Pathology, University of Copenhagen, Copenhagen, Den. Cancer Chemotherapy and Pharmacology (2005), 56(5), 473-480. Publisher: Springer, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 144:184163 AN 2005:1156563 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

We examd. how the effect of topotecan is modulated by transient hypoxia in three different tumor lines, Lewis lung carcinoma (LLC), U87 human glioblastoma and DMS273 human small cell lung cancer. Four groups of tumor bearing mice were treated with saline or a single dose of topotecan, immediately followed by 6-h or 72-h exposure to a hypoxic environment (10% O<sub>2</sub>) or normal air. Topotecan + hypoxia resulted in significantly greater suppression of tumor growth than normoxic topotecan or hypoxia alone. Correspondingly, the sensitivity of LLC cells to topotecan in a clonogenic survival assay was significantly higher under hypoxia. This effect of hypoxia was not a general phenomenon, since the tumor growth inhibitory effect of the alkylating agent cisplatin was not changed by hypoxic environment. In a parallel series of in vitro expts., cell cultures were exposed to hypoxia (0.1% or 0.7% O<sub>2</sub>) in a hypoxic chamber or normoxia for 24 h. We found a dose-dependent downregulation of HIF-1 $\alpha$  by topotecan (30-270 nM). The hypoxic upregulation of Glucose transporter-1 and VEGF secretion to the culture medium was inhibited by the addn. of topotecan, while doses up to 270 nM had no effect on VEGF under normoxia. VEGF protein levels in tumors were also reduced by topotecan. These data show that the effect of topotecan is increased by transient hypoxia, and this may be a direct effect on the ability of cells to survive under hypoxia as well as an antiangiogenic effect, mediated through the HIF-1 inhibitory effect of topotecan.

Answer 12:

### Bibliographic Information

**Expression of Bcl-xL in ovarian carcinoma is associated with chemoresistance and recurrent disease.** Williams, Jennifer; Lucas, Peter C.; Griffith, Kent A.; Choi, Milheon; Fogoros, Sarah; Hu, Yuan Yuan; Liu, J. Rebecca. Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA. Gynecologic Oncology (2005), 96(2), 287-295. Publisher: Elsevier, CODEN: GYNOA3 ISSN: 0090-8258. Journal written in English. CAN 143:37973 AN 2005:66520 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Objective: The long-term survival of patients with epithelial ovarian cancer is limited by the emergence of tumor cells that are resistant to chemotherapy. We hypothesized that expression of Bcl-xL, a homolog of Bcl-2 that confers protection from chemotherapy-induced apoptosis, may be predictive of patients' clin. response to treatment, and that treatment with chemotherapy may result in the selection of tumor cells that overexpress this protein. Methods: We detd. the expression of Bcl-xL in epithelial ovarian cancers from 28 patients at the time of initial staging laparotomy and in recurrent tumors in the same patients following treatment with platinum-based chemotherapy. The data were analyzed to det. whether Bcl-xL expression was predictive of clin. outcome. A2780 ovarian cancer cells were stably transfected with Bcl-xL or control plasmid. Chemotherapy-induced apoptosis in these cell lines was detd. in vitro and in a xenograft model. Results: Bcl-xL expression in primary tumors was assocd. with a significantly shorter disease-free interval as compared to patients whose tumors did not express Bcl-xL (1.6 mo as compared to 7.7 mo). We found that Bcl-xL expression conferred resistance to chemotherapy-induced apoptosis resulting from treatment with cisplatin, paclitaxel, topotecan, and gemcitabine in vitro. In a xenograft model, Bcl-xL expressing tumors continued to grow following treatment with cisplatin, paclitaxel, topotecan, and

gemcitabine, in contrast to control tumors, which disappeared. Conclusions: These results portray an important role for Bcl-xL as a key factor assocd. with chemotherapy failure in the treatment of ovarian cancer.

Answer 13:

#### Bibliographic Information

**No topoisomerase I alteration in a neuroblastoma model with in vivo acquired resistance to irinotecan.** Calvet, L.; Santos, A.; Valent, A.; Terrier-Lacombe, M.-J.; Opolon, P.; Merlin, J.-L.; Aubert, G.; Morizet, J.; Schellens, J. H. M.; Benard, J.; Vassal, G. *Pharmacology and New Treatments in Cancer (UPRES EA 3535), Institut Gustave-Roussy, Villejuif, Fr.* *British Journal of Cancer* (2004), 91(6), 1205-1212. Publisher: Nature Publishing Group, CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 142:169216 AN 2004:824732 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

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

Answer 14:

#### Bibliographic Information

**Ribozyme-mediated down-regulation of survivin expression sensitizes human melanoma cells to topotecan in vitro and in vivo.** Pennati, Marzia; Binda, Mara; De Cesare, Michelandrea; Pratesi, Graziella; Folini, Marco; Citti, Lorenzo; Daidone, Maria Grazia; Zunino, Franco; Zaffaroni, Nadia. *Department of Experimental Oncology, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy.* *Carcinogenesis* (2004), 25(7), 1129-1136. Publisher: Oxford University Press, CODEN: CRNGDP ISSN: 0143-3334. Journal written in English. CAN 141:81876 AN 2004:501508 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

The ability of melanoma cells to evade engagement of apoptosis plays a significant role in their resistance to chemotherapy. To lower the apoptotic threshold of melanoma cells as a possible strategy to increase their drug sensitivity, we generated a hammerhead ribozyme to down-regulate the expression of the anti-apoptotic protein survivin. The JR8 human melanoma cell line was stably transfected with the active ribozyme RZsurv (targeting the 3' end of the GUC294 triplet in the exon 3 of the survivin mRNA) or the catalytically inactive ribozyme mutRZsurv (carrying a mutation in the catalytic core of RZsurv). Two polyclonal cell populations expressing the active (JR8/RZsurv) or the mutant (JR8/mutRZsurv) ribozyme were selected for the study. JR8/RZsurv cells were characterized by a markedly lower survivin protein level than JR8 parental cells, whereas a negligible redn. in survivin expression was obsd. in JR8/mutRZsurv cells. JR8/RZsurv cells showed a significantly increased sensitivity to the topoisomerase-I inhibitor topotecan (as detected by clonogenic cell survival) compared with JR8/mutRZsurv cells. Moreover, the extent of drug-induced apoptosis (in terms of percentage of apoptotic nuclei and level of caspase-9 and caspase-3 catalytic activity) was significantly greater in JR8/RZsurv than in JR8/mutRZsurv cells. Finally, an increased antitumor activity of oral topotecan was obsd. in JR8/RZsurv cells

grown as xenograft tumors in athymic nude mice compared with JR8/mutRZsurv cells. These results demonstrate that attenuation of survivin expression renders human melanoma cells more susceptible to topotecan-induced apoptosis and more responsive to in vivo treatment, and support the concept that survivin is an attractive target for new therapeutic interventions in melanoma.

Answer 15:

#### **Bibliographic Information**

##### **Combination of a CpG-oligodeoxynucleotide and a topoisomerase I inhibitor in the therapy of human tumour xenografts.**

Balsari, A.; Tortoreto, M.; Besusso, D.; Petrangolini, G.; Sfondrini, L.; Maggi, R.; Menard, S.; Pratesi, G. Institute of Pathology, University of Milan, Milan, Italy. *European Journal of Cancer* (2004), 40(8), 1275-1281. Publisher: Elsevier Science Ltd., CODEN: EJCAEL ISSN: 0959-8049. Journal written in English. CAN 141:374495 AN 2004:339460 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### **Abstract**

The study was conducted to investigate the effects of a novel therapeutic approach, i.e. the combination of chemotherapy and immunotherapy, against a human prostate carcinoma xenograft. A topoisomerase I inhibitor, topotecan, and CpG-contg. oligodeoxynucleotides (CpG-ODN) were combined. Athymic mice bearing the PC-3 human prostate carcinoma were treated with the max. tolerated dose (MTD) of topotecan (3 weekly treatments) and with repeated treatments of CpG-ODN (40 and 20 µg/mouse); tumor growth and lethal toxicity were monitored. Topotecan effect on CpG-ODN-induced prodn. of interleukin (IL) 12, interferon (IFN)-γ and tumor necrosis factor-α was also assessed. Since topotecan pretreatment differentially influenced CpG-ODN-induced prodn. of IL-12 and IFN-γ, the antitumor effects of the two therapies were investigated in a sequential (full topotecan regimen followed by CpG-ODN) or in an alternating sequence (starting with CpG-ODN). Topotecan inhibited PC-3 tumor growth, inducing 95% tumor vol. inhibition. All combined treatments resulted in a significant delay in tumor growth, compared to the effects in topotecan-treated mice (P<0.01, by anal. of tumor growth curves). The combination regimens were well tolerated, except for the alternating sequence of 40 µg CpG-ODN and topotecan, which resulted in three out of eight toxic deaths. This alternating sequence was highly toxic even when another cytotoxic drug (doxorubicin) was used in healthy mice. In conclusion, the combination of topotecan and CpG-ODN increased antitumor effects over chemotherapy alone in the growth of a human prostate carcinoma xenograft. Administration sequence was crit. to the combination toxicity: the complete regimen of the cytotoxic drug followed by repeated administrations of the immunomodulator seemed the most promising for further investigations.

Answer 16:

#### **Bibliographic Information**

##### **Therapeutic synergy between irinotecan and 5-fluorouracil against human tumor xenografts.**

Azrak, Rami G.; Cao, Shousong; Slocum, Harry K.; Toth, Karoly; Durrani, Farukh A.; Yin, Ming-biao; Pendyala, Lakshmi; Zhang, Wanghai; McLeod, Howard L.; Rustum, Youcef M. Department of Pharmacology and Therapeutics and Medicine, Roswell Park Cancer Institute, Buffalo, NY, USA. *Clinical Cancer Research* (2004), 10(3), 1121-1129. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 141:218407 AN 2004:114400 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### **Abstract**

Although the combination of irinotecan and 5-fluorouracil is clin. active, it is assocd. with significant toxicity and resistance. Studies were carried out to define the optimal dosage, sequence, and timing for the combination in mice bearing xenografted human tumors. The max. tolerated dose of irinotecan and 5-fluorouracil in combination was detd. in nude mice. Therapeutic efficacy against established human colon carcinoma xenografts, HCT-8 and HT-29, and human head and neck squamous cell carcinoma xenografts, FaDu and A253, was detd. using the rugs individually, simultaneously, and in sequence with various intervals in between. Treatments were i.v. weekly x 4. Immunohistochem. and reverse transcription-PCR measurements of relevant drug-metabolizing enzymes, apoptosis-related proteins, cell cycle distribution, cyclin A, and S phase fraction expression were carried out and compared with the

therapeutic outcome. The max. tolerated dose of irinotecan resulted in cure rates of 30% or less in all xenografts. No cures were achieved with FUra alone. Concurrent administration of irinotecan and FUra, or of FUra 24 h before irinotecan, resulted in cure rates of <20%, except for FaDu (60%). Administration of irinotecan 24 h before FUra resulted in the highest cure rates, 80% in HCT-8, 0% in HT-29, 100% in FaDu, and 10% in A253. The optimal therapeutic synergy was achieved when irinotecan was administered 24 h before 5-Fluorouracil. Sensitivity to this combination was assocd. with poor differentiation status, higher cyclin A index, recruitment of cells into S phase, and induction of Bax expression and apoptosis.

Answer 17:

### Bibliographic Information

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

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

### Abstract

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

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

Answer 18:

### Bibliographic Information

#### **Topotecan selectively enhances the radioresponse of human small-cell lung carcinoma and glioblastoma multiforme xenografts in nude mice.**

Chastagner, P.; Kozin, S. V.; Taghian, A. Department of Radiation Oncology, Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA. *International Journal of Radiation Oncology, Biology, Physics* (2001), 50(3), 777-782. Publisher: Elsevier Science Inc., CODEN: IOBPD3 ISSN: 0360-3016. Journal written in English. CAN 136:66263 AN 2001:407175 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

**Purpose:** To evaluate the therapeutic efficacy of different combinations of the DNA topoisomerase I-targeting drug, topotecan (TPT), with radiation for treatment of two human tumor xenografts. **Methods and Materials:** The small cell lung carcinoma 54A and glioblastoma multiforme U87 were transplanted into nude mice. Equal i.p. injections of TPT and/or equal fractions of tumor irradiation were administered daily, for 5 consecutive days. When combined, TPT was injected at different constant time intervals prior to or after each radiation fraction. The tumor growth delay and changes in skin radiation reaction by TPT were evaluated. Tumor oxygenation was measured using the Eppendorf pO<sub>2</sub> histog. **Results:** The tumor growth delay induced by such chemoradiotherapy was independent of interval and sequencing of the agents for either tumor model. The efficacy of TPT alone or in combination with radiation was always dose-dependent, although of different magnitude in the two xenografts. In 54A xenografts, TPT alone induced longer growth delay, but its combined effect with radiation was not more than additive. In contrast, U87 responded less to TPT alone, however the drug and radiation interacted synergistically in this tumor model. Using both a radiobiological approach (tumor irradiation under normoxia vs. clamp hypoxia conditions) and the polarographic electrode measurements, it was shown that TPT did not modify tumor oxygenation and, thus, unlikely modulated oxygen-related tumor radiosensitivity. In contrast to tumors, TPT virtually unchanged skin radiation reaction. **Conclusions:** Our data suggest that TPT, when combined with radiation treatment of tumors, provides a therapeutic gain without substantial local and systemic adverse effects.

Answer 19:

### Bibliographic Information

**Radiosensitization of tumor-targeted radioimmunotherapy with prolonged topotecan infusion in human breast cancer xenografts.** Ng, Bruce; Kramer, Elissa; Liebes, Leonard; Wasserheit, Caroline; Hochster, Howard; Blank, Edward; Ceriani, Roberto; Furmanski, Philip. Laboratory of Cell Biology, Biology Department, New York University, New York, NY, USA. *Cancer Research* (2001), 61(7), 2996-3001. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 135:42817 AN 2001:295912 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Clin. radioimmunotherapy (RIT) of solid tumors holds great promise, but as yet has been unable to deliver tumoricidal radiation doses without unacceptable toxicity. Our experimental approach aims to potentiate the therapeutic action of radioimmunoconjugates at the tumor site and thus improve the efficacy of RIT by combination with other treatment modalities. The topoisomerase I inhibitors are a unique class of chemotherapeutic agents that interfere with DNA breakage-reunion by inhibiting the action of topoisomerase I. Preclinical studies suggest that prolonged infusion of topoisomerase I inhibitors enhances cell toxicity due to ionizing radiation. We evaluated the efficacy of combined treatment with continuous administration of topotecan and 90Y-MX-DPTA BrE3 monoclonal antibody (which recognizes an epitope of breast epithelial mucin expressed in most breast cancers) on human mammary carcinoma xenografts in nude mice. Topotecan or 90Y-BrE3 treatment alone delayed overall tumor growth rate transiently but did not affect survival. The combination of RIT with topotecan substantially reduced growth of relatively large established tumors and caused complete tumor regressions and prolonged tumor-free survival in a substantial proportion of treated animals. In vitro studies demonstrated an increase in apoptotic rate and a decrease in cell proliferation of tumor cell lines treated with this combination. We combined the radiosensitization property of topotecan and the specificity of systemic RIT to establish a novel therapy for solid tumors in an experimental tumor xenograft model.

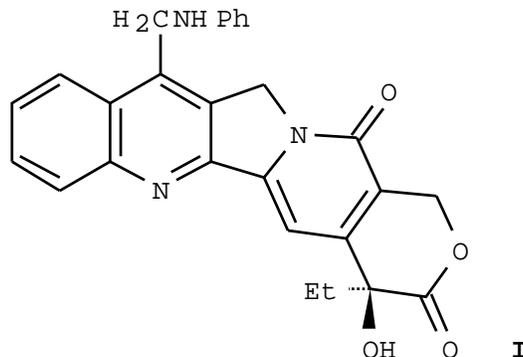
Answer 20:

### Bibliographic Information

**Novel cytotoxic 7-iminomethyl and 7-aminomethyl derivatives of camptothecin.** Dallavalle, S.; Ferrari, A.; Merlini, L.; Penco, S.; Carenini, N.; De Cesare, M.; Perego, P.; Pratesi, G.; Zunino, F. Dipartimento di Scienze Molecolari Agroalimentari, Sezione di Chimica, Università di Milano, Milan, Italy. *Bioorganic & Medicinal Chemistry Letters* (2001), 11(3), 291-294. Publisher: Elsevier Science Ltd., CODEN: BMCLE8 ISSN: 0960-894X. Journal written in English. CAN 134:295980 AN 2001:118604 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

A series of new 7-iminomethyl derivs. of camptothecin were obtained from camptothecin-7-aldehyde and arom., alicyclic and aliph. amines. Their hydrogenation led to the corresponding amines, e.g. I. All the imines and the less polar amines showed a marked increase of the cytotoxic activity against H460 non-small lung carcinoma cell line, with respect to topotecan. The lipophilicity of the substituent in position 7 of camptothecin seems to play an important role for cytotoxic potency. The 7-phenyliminomethyl deriv. showed efficacy comparable to topotecan in vivo against NSCLC H460 xenografted in athymic nude mice.



Answer 21:

#### Bibliographic Information

**Improvement of therapeutic index of low-dose topotecan delivered per os.** Pratesi, Graziella; De Cesare, Michelandrea; Zunino, Franco. Istituto Nazionale Tumori, Milan, Italy. *Annals of the New York Academy of Sciences* (2000), 922(Camptothecins), 330-333. Publisher: New York Academy of Sciences, CODEN: ANYAA9 ISSN: 0077-8923. Journal written in English. CAN 135:131854 AN 2001:70502 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

The aim of this study was to compare the antitumor potential of topotecan, administered orally, on a panel of human tumors xenografted s.c. (s.c.) in athymic nude mice. The tumors were representative of several histotypes and responded differently to i.v. topotecan. The comparison was carried out under various treatment conditions. Tumor lines were established and maintained in our lab. according to previously described tech. procedures, topotecan was dissolved in sterile, distd. water and delivered in a vol. of 10 ml/kg of body wt. The drug was administered by gavage or i.v. using the same schedule, i.e., every fourth day for four times. Many dose levels were investigated, and the max. tolerated dose (MTD) was considered the one that induced one death in the group of treated mice, or a body wt. loss >15%. A daily schedule using very low doses of topotecan was also investigated for the oral route. The antitumor efficacy of topotecan delivered i.v. or per os q4dx4 against a panel of human tumor xenografts is reported. Oral topotecan was significantly more effective than i.v. drug against four tumor lines, NCI-H460, JCA-1, POVD, and U87. The study in a panel of human tumor xenograft indicated that using an intermittent schedule (q4dx4) oral topotecan was at least as active as i.v. topotecan. Moreover, a therapeutic advantage could be achieved in the highly responsive tumors. The comparable activity achieved by i.v. and oral topotecan in a clin. study may reflect the low sensitivity of advanced pretreated tumors; the MTD of topotecan was the same with the oral or i.v. route despite low drug availability. Finally, the results indicated that daily oral treatment with low doses of topotecan allowed a higher cumulative drug dose without toxicity and achieved greater antitumor efficacy, thus resulting in an improved therapeutic index.

Answer 22:

#### Bibliographic Information

**In vivo potentiation of radiation response by topotecan in human rhabdomyosarcoma xenografted into nude mice.**

Chastagner, P.; Merlin, J. L.; Marchal, C.; Hoffstetter, S.; Barberi-Heyob, M.; Vassal, G.; Duprez, A. *Pediatric Oncology*

Department, CHU Nancy, Nancy, Fr. Clinical Cancer Research (2000), 6(8), 3327-3333. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 134:248894 AN 2000:647565 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

The lack of new highly efficacious drugs for cancer treatment promotes the search for innovative therapeutic modalities. The authors reported the results leading to the definition of parameters needed to demonstrate a possible radiopotentiality by topotecan (TPT) on two representative human rhabdomyosarcomas (RMSs) xenografted into nude mice. Exptl. studies of radiopotentiality with different doses of topotecan showed that concomitant assocn. of topotecan and RT for 5 consecutive days provided a synergistic therapeutic effect. Response rates were statistically higher with the radiochemotherapeutic combination ( $P < 0.001$ ). Efficacy enhancement factors of this combination compared with the sum of the antitumoral activity of these treatments sep. administrated were 1.54 and 1.60, resp., on both rhabdomyosarcomas. Moreover, the efficiency of the combination of radiotherapy at the dose of 20 Gy with topotecan (12.5 mg/kg) was not statistically different from that of radiotherapy at the dose of 40 Gy. According to microscopy results, the analyses performed at different periods after topotecan treatment alone, radiotherapy alone, and their combination seemed to show that tumoral repopulation by malignant cells is as fast as the dose of radiotherapy and/or topotecan is low. Furthermore, lesions obsd. with the dose of 40 Gy were similar to those obtained with the assocn. of topotecan at the dose of 12.5 mg/kg and radiotherapy at the dose of 20 Gy. In conclusion, all clin. and pathol. results are consistent with a radiopotentiality effect of topotecan on the two xenografted human rhabdomyosarcomas and are currently leading to the design of clin. studies.

Answer 23:

### Bibliographic Information

**Efficacy and toxicity profile of oral topotecan in a panel of human tumour xenografts.** De Cesare, M.; Zunino, F.; Pace, S.; Pisano, C.; Pratesi, G. Istituto Nazionale Tumori, Milan, Italy. European Journal of Cancer (2000), 36(12), 1558-1564. Publisher: Elsevier Science Ltd., CODEN: EJCAEL ISSN: 0959-8049. Journal written in English. CAN 134:141413 AN 2000:526051 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

On the basis of their mechanism of action (cell killing during DNA replication) and the potential reversibility of the drug effects, protracted therapy with camptothecins is reported to provide optimal antitumor effects. Furthermore, oral administration may be a useful modality for optimization of treatment. The aim of this study was to compare the therapeutic profile of topotecan given orally or i.v. in human tumors xenografted into athymic nude mice. The drug topotecan was given according to an intermittent (every 4th day, 4 times) or daily (qd  $\times$  5/weekly  $\times$  5-10 wk; only orally) schedule. Tumor growth inhibition and persistence of drug effects were assessed and compared with untreated mice. In a panel of 7 tumor xenografts, oral topotecan was at least as effective on 3 and significantly more effective on 4 tumors. Using the intermittent schedule, the max. tolerated dose (MTD) was comparable for the 2 routes (15 mg/kg), but the toxicity profile suggested a better tolerability in terms of lethal effects after oral administration. The daily oral treatment of low drug doses allowed a higher cumulative dose to be delivered with improved antitumor efficacy (2/10 cured in a large cell lung cancer) and no evidence of toxicity. In spite of the low bioavailability of oral topotecan (23.5%), the persistent blood plasma levels of the drug suggest that the time of exposure to the drug is more crit. than the plasma concns. for antitumor efficacy. This interpretation is consistent with the increased efficacy of prolonged daily treatment with low-dose levels. The results may have implications for the future design of clin. studies.

Answer 24:

### Bibliographic Information

**Complete regression of xenografted human carcinomas by camptothecin analogue-carboxymethyl dextran conjugate (T-0128).** Okuno, Satoshi; Harada, Mitsunori; Yano, Toshiro; Yano, Shigeru; Kiuchi, Satoko; Tsuda, Naoki; Sakamura, Yumi; Imai, Jun; Kawaguchi, Takayuki; Tsujihara, Kenji. Discovery Research Laboratory, Tanabe Seiyaku Co., Ltd., Saitama, Japan. Cancer

Research (2000), 60(11), 2988-2995. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 133:171937 AN 2000:397653 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Clin. available camptothecins (CPTs), such as irinotecan (CPT-11) and topotecan, represent one of the most promising classes of antitumor agents, despite their toxicity. To improve their pharmacol. profiles, a new macromol. prodrug, denoted T-0128, was synthesized. This prodrug is a novel CPT analog (T-2513)-carboxymethyl (CM) dextran conjugate via a triglycine spacer, with a mol. wt. of Mr 130,000. This study was designed to test the concept that the rational design of a CPT-polymer conjugate would increase the efficacy of the parent drug. The in vivo antitumor study against Walker-256 carcinoma demonstrated that T-0128 was 10 times as active as T-2513, supporting this concept. Addnl., comparative efficacy studies of T-0128, T-2513, CPT-11, and topotecan were performed using a panel of human tumor xenografts in nude mice, showing the advantage of T-0128 over these CPTs. The maximal tolerated doses (MTDs) of T-0128, T-2513, and CPT-11 were comparable. Even a single i.v. injection of T-0128 at 6 mg/kg (based on the amt. of T-2513 bound to CM dextran) induced complete regression of MX-1 mammary carcinoma. T-0128 at 10 mg/kg weekly for 3 wk (one-tenth of its MTD) cured LX-1 lung carcinoma. Also, T-0128 below its MTD consistently cured or regressed St-4 gastric and HT-29 colorectal tumor xenografts that are highly refractory to CPTs. These demonstrate the broad range of therapeutic doses achieved with T-0128. Pharmacokinetic studies were performed to correlate the efficacy results obtained for T-0128 with plasma and tissue drug concns. using Walker-256 tumor-bearing rats. Results showed that after i.v. administration of T-0128, the conjugate continued to circulate at a high concn. for an extended period, resulting in tumor accumulation. In the tumor, the sustained release of T-2513 occurred. In contrast, T-2513 disappeared rapidly from the body. The significant increases in the amt. and exposure time of released T-2513 in the tumor explain well the enhanced efficacy of T-0128.

In conclusion, this study indicated that T-0128 improved the potency of T-2513, demonstrating the proof of the above concept.

Answer 25:

### Bibliographic Information

**Synergy of topotecan in combination with vincristine for treatment of pediatric solid tumor xenografts.** Thompson, Joyce; George, E. Olusegun; Poquette, Catherine A.; Cheshire, Pamela J.; Richmond, Lois B.; De Graaf, Siebold S. N.; Ma, Margaret; Stewart, Clinton F.; Houghton, Peter J. Department of Hematology-Oncology, St. Jude Children's Research Hospital, Memphis, TN, USA. Clinical Cancer Research (1999), 5(11), 3617-3631. Publisher: American Association for Cancer Research, CODEN: CCRE44 ISSN: 1078-0432. Journal written in English. CAN 132:260198 AN 1999:809347 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

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

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

Answer 26:

### Bibliographic Information

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

### Abstract

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

Answer 27:

### Bibliographic Information

**Antitumor activity of sequential treatment with topotecan and anti-epidermal growth factor receptor monoclonal antibody C225.** Ciardiello, Fortunato; Bianco, Roberto; Damiano, Vincenzo; De Lorenzo, Sonya; Pepe, Stefano; De Placido, Sabino; Fan, Zhen; Mendelsohn, John; Bianco, A. Raffaele; Tortora, Giampaolo. Cattedra di Oncologia Medica, Dipartimento di Endocrinologia e Oncologia, Universita degli Studi di Napoli Federico II, Naples, Italy. *Clinical Cancer Research* (1999), 5(4), 909-916. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 131:97097 AN 1999:277437 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Epidermal growth factor (EGF)-related proteins such as transforming growth factor  $\alpha$  (TGF- $\alpha$ ) control cancer cell growth through autocrine and paracrine pathways. Overexpression of TGF- $\alpha$  and/or its receptor (EGFR) has been assocd. with a more aggressive disease and a poor prognosis. The blockade of EGFR activation has been proposed as a target for anticancer therapy. Monoclonal antibody (MAb) C225 is an anti-EGFR humanized chimeric mouse MAb that is presently in Phase II clin. trials in cancer patients. Previous studies have suggested the potentiation of the antitumor activity of certain cytotoxic drugs, such as cisplatin and doxorubicin, in human cancer cell lines by treatment with anti-EGFR antibodies. We have evaluated in human ovarian, breast, and colon cancer cell lines, which express functional EGFR, the antiproliferative activity of MAb C225 in combination with topotecan, a cytotoxic drug that specifically inhibits topoisomerase I and that has shown antitumor activity in these malignancies. A dose-dependent supraadditive increase of growth inhibition in vitro was obsd. when cancer cells were treated with topotecan and MAb C225 in a sequential schedule. In this respect, the cooperativity quotient, defined as the ratio between the actual growth inhibition obtained by treatment with topotecan followed by MAb C225 and the sum of the growth inhibition achieved by each agent, ranged from 1.2 to 3, depending on drug concn. and cancer cell line. Treatment with MAb C225 also markedly enhanced apoptotic cell death induced by topotecan. For example, in GEO colon cancer cells, 5 nM topotecan, followed by 0.5  $\mu$ g/mL MAb C225, induced apoptosis in 45% cells as compared with untreated cells (6%) or to 5 nM topotecan-treated cells (22%). Treatment of mice bearing established

human GEO colon cancer xenografts with topotecan or with MAb C225 detd. a transient inhibition of tumor growth because GEO tumors resumed the growth rate of untreated tumors at the end of the treatment period.

In contrast, an almost complete tumor regression was obsd. in all mice treated with the two agents in combination. This detd. a prolonged life span of the mice that was significantly different as compared with controls ( $P < 0.001$ ), to MAb C225-treated group ( $P < 0.001$ ), or to the topotecan-treated group ( $P < 0.001$ ). All mice of the topotecan plus MAb C225 group were the only animals alive 14 wk after tumor cell injection. Furthermore, 20% of mice in this group were still alive after 19 wk. The combined treatment with MAb C225 and topotecan was well tolerated by mice with no signs of acute or delayed toxicity. These results provide a rationale for the evaluation of the anticancer activity of the combination of topoisomerase I inhibitors and anti-EGFR blocking MAbs in clin. trials.

Answer 28:

### Bibliographic Information

**Detection of poly(ADP-ribose) polymerase cleavage in response to treatment with topoisomerase I inhibitors: a potential surrogate end point to assess treatment effectiveness.** Whitacre, Cecilia M.; Zborowska, Elizabeth; Willson, James K. V.; Berger, Nathan A. Departments of Medicine and Cancer Center, School of Medicine, Case Western Reserve University, Cleveland, OH, USA. *Clinical Cancer Research* (1999), 5(3), 665-672. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 131:53654 AN 1999:208137 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Cleavage of poly(ADP-ribose) polymerase (PARP) by caspases is a prominent characteristic of apoptosis or programmed cell death shown to be induced by topoisomerase (Topo) inhibitors. Because Topo I inhibitors have been shown to be effective in the treatment of some patients with colon cancer, we considered the possibility of using PARP cleavage as an early predictor of responsiveness to this class of agents. We show cleavage of PARP in response to treatment with Topo I inhibitors in colon cancer both in vitro and in vivo: (a) in vitro in SW480, HCT116, VACO5, VACO6, VACO8, VACO411, VACO425, and VACO451 human colon cancer cell lines treated with topotecan (TPT) or CPT-11; (b) in vivo in SW480, VACO451, and VRC5 colon cancer xenografts grown in athymic mice treated with TPT or CPT-11; and (c) in vivo in colon cancer samples from patients undergoing a Phase II clin. trial with CPT-11. Our results show a strong correlation between percentage of PARP cleavage and percentage of acridine orange-pos. cells in colon cancer cell lines treated with 0.1  $\mu\text{M}$  TPT for 24 and 48 h, confirming that PARP cleavage is a useful marker for programmed cell death in colon cancer cell lines. Results from expts. performed on colon cancer xenografts also show an assocn. between PARP cleavage and response to treatment with TPT or CPT-11. The increase of PARP cleavage in xenografts and in clin. samples corresponding to treatment with Topo I inhibitors suggests that this procedure may have early predictive value to assess effectiveness of treatment. These results provide the basis for detg. the validity of using PARP cleavage as an early marker of chemotherapeutic effectiveness in human samples.

Answer 29:

### Bibliographic Information

**Therapy of colon cancer with oncolytic adenovirus is enhanced by the addition of herpes simplex virus-thymidine kinase.** Wildner, Oliver; Blaese, R. Michael; Morris, John C. Clinical Gene Therapy Branch, National Human Genome Research Institute, NIH, Bethesda, MD, USA. *Cancer Research* (1999), 59(2), 410-413. Publisher: AACR Subscription Office, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 130:246466 AN 1999:71704 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

A major obstacle to the successful application of suicide gene therapy strategies that rely on in situ transduction of tumor cells is the poor distribution of the vector throughout the tumor mass. To address this problem, we evaluated the use of Ad.TKRC, an E1b Mr

55,000 deleted replicating adenoviral vector engineered to express the herpes simplex virus type 1 thymidine kinase gene (HSV-tk) in combination with ganciclovir (GCV) as a treatment for human colon cancer xenografts in nude mice. We compared the efficacy of this system with that of a std. replication-deficient adenovirus expressing HSV-tk (Ad.TK) in mice bearing LS180 tumors. In this system, Ad.TKRC alone was as effective as a traditional Ad.TK vector in combination with GCV. The addn. of GCV significantly enhanced the antitumor effect of Ad.TKRC. Furthermore, we demonstrated that the survival of HT-29 human colon cancer xenografted mice treated with Ad.TKRC and GCV was prolonged compared with Ad.TKRC alone or with administration of a single cycle of topotecan. These data demonstrate that the addn. of direct viral oncolysis to the HSV-tk/GCV suicide gene system resulted in a striking improvement in treatment efficacy and that it may offer advantages over the use of chemotherapeutic agents for treatment of localized disease.

Answer 30:

### Bibliographic Information

**Effective schedules of exposure of medulloblastoma and rhabdomyosarcoma xenografts to topotecan correlate with in vitro assays.** Pawlik, Cynthia A.; Houghton, Peter J.; Stewart, Clinton F.; Cheshire, Pamela J.; Richmond, Lois B.; Danks, Mary K. Department of Molecular Pharmacology, St. Jude Children's Research Hospital, Memphis, TN, USA. *Clinical Cancer Research* (1998), 4(8), 1995-2002. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 129:270192 AN 1998:565301 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

The camptothecin deriv. topotecan has been postulated to mediate its antitumor effect through a drug-induced increase in covalent topoisomerase I-DNA complexes. If this hypothesis is correct, then schedules of exposure to topotecan that maximize the no. of topoisomerase I-DNA complexes should produce the greatest cytotoxicity. The authors identified schedules of exposure to topotecan that maximize levels of complexes in vitro and used these schedules to postulate effective schedules of exposure in vivo in a mouse xenograft model. Unexpectedly, K+-SDS pptn. assays quantitating covalent topoisomerase I-DNA complexes showed that Daoy medulloblastoma and Rh30 rhabdomyosarcoma cells became refractory to drug-induced increases in complexes after an 8-h exposure to 2.5  $\mu$ M topotecan. In contrast, assays using 10-50 nM topotecan showed that the cells did not become refractory, and more importantly, intermittent exposure to drug increased the level of complexes .apprx.2-fold above the max. level obsd. after a single drug exposure. The data indicate that continuous exposure to topotecan does not maximize topoisomerase I-DNA complexes and suggest that effective intermittent schedules of exposures to topotecan might be identified. Growth inhibition assays confirmed this hypothesis and showed that growth inhibition by topotecan was extremely schedule dependent in Rh30 cells but not in Daoy cells. Xenograft studies showed that schedules modeled after the in vitro expts. produced complete tumor regressions in mice. Topotecan given daily (0.6-2.2 mg/kg) or every other day (1-3.3 mg/kg) for 2 wk, repeated every 21 days for 3 cycles, produced complete regressions of Daoy xenografts; however, daily exposure was required to achieve complete regressions of Rh30 xenografts. It is concluded that effective intermittent schedules of exposure to topotecan, based on biochem. parameters, can be identified. The clin. utility of each schedule will depend on the relative antitumor effect compared to the toxic effect on the bone marrow, which usually limits administration of topotecan to patients.

Answer 31:

### Bibliographic Information

**Potent and broad antitumor effects of DX-8951f, a water-soluble camptothecin derivative, against various human tumors xenografted in nude mice.** Kumazawa, Eiji; Jimbo, Takeshi; Ochi, Yusuke; Tohgo, Akiko. New Product Research Lab. IV, Daiichi Pharmaceutical Co., Ltd., Tokyo, Japan. *Cancer Chemotherapy and Pharmacology* (1998), 42(3), 210-220. Publisher: Springer-Verlag, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 129:117542 AN 1998:468186 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

The therapeutic efficacy of the camptothecin (CPT) deriv. DX-8951f against human tumor xenografts was evaluated in nude mice. Its activity was compared with those of CPT-11 and other CPT derivs. Against both gastric adenocarcinoma SC-6 and its CPT-11-resistant variant, SC-6/CPT-11, DX-8951f demonstrated superior anti-tumor activity and anti-tumor activity over a broader range of doses than did CPT-11, SK&F104864, and GG-211. DX-8951f at 75 mg/kg was effective (growth inhibition rate, IR,  $\geq 58\%$ ) against 15 of 16 lines of human cancers examd. and exhibited excellent anti-tumor activity (IR  $\geq 80\%$ ) against 14 of these lines. CPT-11 exhibited anti-tumor activity with IR values of  $\geq 58\%$  against 11 lines and with IR values  $\geq 80\%$  against only 8 of the same tumors. DX-8951f was effective in inhibiting the growth of an SN-38-resistant tumor and some P-glycoprotein-expressing tumors, but CPT-11 was not.

Answer 32:

### Bibliographic Information

**Relationship between topotecan systemic exposure and tumor response in human neuroblastoma xenografts.** Zamboni, William C.; Stewart, Clinton F.; Thompson, Joyce; Santana, Victor M.; Cheshire, Pamela J.; Richmond, Lois B.; Luo, Xiaolong; Poquette, Catherine; Houghton, Janet A.; Houghton, Peter J. Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, TN, USA. *Journal of the National Cancer Institute* (1998), 90(7), 505-511. Publisher: Oxford University Press, CODEN: JNCIEQ ISSN: 0027-8874. Journal written in English. CAN 129:36173 AN 1998:244431 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Topotecan is a topoisomerase I inhibitor with activity against xenografts of childhood solid tumors and established clin. activity against neuroblastoma and rhabdomyosarcoma. We have studied the relationship between systemic exposure to and the antitumor activity of topotecan lactone (the active form of the drug) in the xenograft models. Furthermore, we detd. whether the responses seen in these models occur at systemic exposure levels that are tolerable in children. Neuroblastoma xenografts derived from the tumors of six different patients were established s.c. in immune-deprived mice. Topotecan was administered by i.v. bolus injection 5 days a week for 2 consecutive weeks, repeated every 21 days for three cycles. The min. daily doses that induced complete responses (CRs) and partial responses (PRs) were detd. Topotecan lactone pharmacokinetic studies were performed in both tumor-bearing and nontumor-bearing mice. The min. doses assocd. with CRs and PRs in four of the six neuroblastoma xenografts were 0.61 and 0.36 mg/kg body wt., resp. The topotecan lactone single-day systemic exposures assocd. with these doses were 88 and 52 ng · hr/mL, resp. There was an approx. sixfold difference in topotecan lactone systemic exposure (290 ng · hr/mL vs. 52 ng · hr/mL) assocd. with achieving CRs in the least-sensitive and most-sensitive tumors, resp. Neuroblastoma xenografts are highly sensitive to topotecan therapy, and responses in mice are achieved at systemic exposures similar to those that are clin. effective and tolerable in children. These results support the concept of deriving preclin. data relating systemic exposure to antitumor activity in xenograft models. Such data may be valuable in making informed decisions regarding the clin. development of new agents.

Answer 33:

### Bibliographic Information

**Topotecan in advanced colorectal cancer.** Creemers, G. J. Ziekenhuis Walcheren, Vlissingen, Neth. *Seminars in Oncology* (1997), 24(6, Suppl. 20), S20/42-S20/48. Publisher: W. B. Saunders Co., CODEN: SOLGAV ISSN: 0093-7754. Journal; General Review written in English. CAN 128:175686 AN 1998:60581 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

A review with 36 refs. Colorectal cancer is the 3rd most common cause of cancer-related death in both men and women. Surgery is the primary form of treatment, with >90% of patients surviving  $\geq 5$  yr. The remaining patients have metastatic disease, for which treatment options are limited. The fluoropyrimidine 5-fluorouracil elicits favorable tumor response rates in patients with metastatic disease, but has little impact on survival. Based on the observation that colorectal tumors have increased levels of topoisomerase I relative to normal tissue, investigations have focused on the camptothecin derivs., particularly topotecan, as an effective treatment.

Topotecan demonstrated antitumor activity in preclin. studies, causing significant growth delay of xenografts in thymectomized, irradiated mice. Clin. studies with topotecan have not yielded as promising results, with response rates of approx. 7%-10%, but modifications in dosage schedule or combinations with other agents may enhance antitumor activity.

Answer 34:

### **Bibliographic Information**

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

### **Abstract**

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

Answer 35:

### **Bibliographic Information**

**Intermittent exposure of medulloblastoma cells to topotecan produces growth inhibition equivalent to continuous exposure.** Danks, Mary K.; Pawlik, Cynthia A.; Whipple, David O.; Wolverton, Judith S. Department of Molecular Pharmacology, St. Jude Children's Research Hospital, Memphis, TN, USA. *Clinical Cancer Research* (1997), 3(10), 1731-1738. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 127:326137 AN 1997:695948 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### **Abstract**

Camptothecin analogs such as topotecan increase the no. of covalent topoisomerase I-DNA complexes, which, in turn, have been proposed to initiate apoptosis. If induction of apoptosis by the camptothecins is, in fact, dependent on the formation of topoisomerase I-DNA complexes, then it would be of clin. relevance to identify schedules of exposure to the camptothecins that maximize the formation of these complexes but minimize the total amt. of the drug administered. The time and dose dependence of topoisomerase I-DNA complex formation was detd. by incubating Daoy pediatric medulloblastoma cells in vitro with topotecan at concns. equiv. to those achievable in the plasma clin. (10, 50, or 200 nM) and measuring the no. of complexes present in cells incubated for 15 min to 48 h with the drug. Regardless of the concn. of topotecan used, covalent topoisomerase I-DNA complexes were maximal within 15 min following addn. of the lactone form of topotecan to the tissue culture medium. After 2 h of exposure to topotecan, complexes had

decreased from max. to approx. half of that value. Few, if any, complexes were detectable with topotecan incubations of 24-48 h. Growth inhibition studies showed that the IC<sub>50</sub>s of topotecan for the Daoy cell line ( $2.2 \times 10^{-9}$  M) and also for a second pediatric medulloblastoma cell line, SJ-Med3 ( $3.6 \times 10^{-9}$  M), exposed to topotecan 8 h daily for 5 days or continuous exposure were equiv. The decrease in topoisomerase I-DNA complexes between 15 min and 1 h was consistent with a pH-dependent re-equilibration of topotecan to the less active hydroxyacid form of the drug. The decrease in complexes after a 2-48-h incubation with the drug was attributable neither to biol. inactivation of topotecan as shown by sequential growth inhibition studies nor to a decrease in amt. of topoisomerase I in the drug-treated cells. Indirect immunofluorescence labeling of topoisomerase I in Daoy cells incubated for 48 h with 10 nM topotecan showed a redistribution of nucleolar topoisomerase I.

We are currently evaluating the antitumor effect of intermittent repetitive exposures to topotecan in mice bearing Daoy cells as a xenograft. The clin. utility of each effective schedule of exposure will depend on whether the therapeutic index of repetitive intermittent exposure to the drug is more or less favorable than the therapeutic index of continuous exposure.

Answer 36:

### Bibliographic Information

#### **Topotecan increases topoisomerase II $\alpha$ levels and sensitivity to treatment with etoposide in schedule-dependent process.**

Whitacre, Cecilia M.; Zborowska, Elizabeth; Gordon, Nahida H.; Mackay, Wilma; Berger, Nathan A. Department of Medicine, and Cancer Center, Case Western Reserve University School of Medicine, Cleveland, OH, USA. *Cancer Research* (1997), 57(8), 1425-1428. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 126:325111 AN 1997:269603 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

To elucidate the effect of topoisomerase (Topo) I inhibitors in the modulation of Topo II levels and sensitivity to Topo II-directed drugs, athymic mice bearing SW480 human cancer xenografts were treated with simultaneous, subsequent, or distant doses of topotecan and etoposide. This in vivo study demonstrates that simultaneous administration of topotecan and etoposide results in an antagonistic response. In contrast, inhibition of Topo I by topotecan results in a compensatory increase in Topo II $\alpha$  levels assocd. with increasing sensitivity of tumors to subsequent treatment with the Topo II inhibitor etoposide. Furthermore, we show that Topo II $\alpha$  levels decline 5 days after the last dose of topotecan, resulting in restoration of the original response of the xenografts to etoposide. Thus, this study emphasizes the crit. role of schedule dependency to optimize the effectiveness of combination chemotherapy with Topo I and Topo II inhibitors.

Answer 37:

### Bibliographic Information

**Treatment of central nervous system xenografts with camptothecins.** Friedman, Henry S.; Houghton, Peter J. Department of Pediatrics, Duke University Medical Center, Durham, NC, USA. *Annals of the New York Academy of Sciences* (1996), 803(Camptothecins), 210-212. Publisher: New York Academy of Sciences, CODEN: ANYAA9 ISSN: 0077-8923. Journal written in English. CAN 126:139597 AN 1997:109267 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

The camptothecins 9-aminocamptothecin, topotecan, and CPT-11 were active against central nervous system xenografts in athymic mice transplanted with glioma, ependymoma, or medulloblastoma.

Answer 38:

### Bibliographic Information

**Topoisomerase I inhibition by the camptothecin analog GI147211C: from the laboratory to the clinic.** Besterman, Jeffrey M. Department of Cell Biology, Glaxo Research Laboratories, Research Triangle Park, NC, USA. *Annals of the New York Academy of Sciences* (1996), 803(Camptothecins), 202-209. Publisher: New York Academy of Sciences, CODEN: ANYAA9 ISSN: 0077-8923. Journal; General Review written in English. CAN 126:194709 AN 1997:109266 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

A review with 13 refs. on the effort to create through total synthesis a novel., potent and water-sol. camptothecin analog, GI147211C. GI147211C is a specific inhibitor of DNA topoisomerase I. Compared with topotecan, GI147211C is approx. 3 times as potent in the cleavable complex assay and approx. twice as sol. in aq. medium. Human tumor cell line cytotoxicity assays indicated that GI147211C was approx. 3-5 times more potent than topotecan, while both compds. were relatively insensitive to the multidrug resistance P-glycoprotein. In in vivo preclin. antitumor activity of GI147211C was compared to topotecan in an array of human tumor xenograft models in nude mice. In general, GI147211C was able to induce regression of established tumors, whereas topotecan was not. Microscopic evaluation of necropsied tissues indicated that drug-induced toxicity was mild, primarily limited to the gastrointestinal tract, and was comparable for both GI147211C and topotecan. A summary of Phase I clin. trials is given.

Answer 39:

#### Bibliographic Information

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

#### Abstract

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

Answer 40:

#### Bibliographic Information

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

**Abstract**

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

Answer 41:

**Bibliographic Information****Successful local regional therapy with topotecan of intraperitoneally growing human ovarian carcinoma xenografts.**

Pratesi, G; Tortoreto, M; Corti, C; Giardini, R; Zunino, F. Divisions of Experimental Oncology B, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy. *British Journal of Cancer* (1995), 71(3), 525-8. CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 122:255667 AN 1995:484791 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

The therapeutic effects of i.p. topotecan, a water-sol. camptothecin analog, were investigated in two models of human ovarian carcinoma xenografted i.p. into nude mice: the IGROV-1 tumor, which originated from an untreated patient, and the A2780 tumor, selected for resistance in vitro to cisplatin (A2780DDP). In IGROV-1 tumor-bearing mice, the optimal dose (10 mg kg<sup>-1</sup>) of topotecan, given i.p. every 4 days for four occasions markedly increased survival time over control mice (300 T/C%) and cured 4/9 mice, and such effects were not achieved by any of the clin. available drugs tested, i.e. cisplatin, carboplatin and doxorubicin delivered i.p. according to their optimal doses and schedules. In the treatment of A2780DDP tumor-bearing mice, topotecan was very effective since, at dose levels of 6.6 and 10 mg kg<sup>-1</sup> every 4 days for four occasions, 15/18 mice survived more than 100 days, and most of them (12/15) were tumor free. The high responsiveness of this tumor to topotecan might be related to the elevated expression of the target enzyme topoisomerase I. From these results, i.p. treatment with topotecan appears to be a promising approach in the therapy of refractory ovarian cancer confined to the peritoneal cavity.

Answer 42:

**Bibliographic Information****Activity of 9-dimethylaminomethyl-10-hydroxycamptothecin against pediatric and adult central nervous system tumor xenografts.**

Friedman, Henry S.; Houghton, Peter J.; Schold, S. Clifford; Keir, Stephen; Bigner, Darell D. Department Pediatrics, Duke University Medical Center, Durham, NC, USA. *Cancer Chemotherapy and Pharmacology* (1994), 34(2), 171-4. CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 121:169972 AN 1994:569972 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

The activity of 9-dimethylaminomethyl-10-hydroxycamptothecin (topotecan) was evaluated against a panel of xenografts derived from ependymomas (D528 EP, D612 EP), childhood high-grade gliomas (D-456 MG, D-212 MG), adult high-grade gliomas (D-245 MG, D-54 MG), and medulloblastomas (D425 Med) growing s.c. and i.c. (intracranially) in athymic nude mice. Topotecan was given at a dose of 1.9 mg/kg by i.p. injection in 0.9% saline using a vol. of 90 mL/m<sup>2</sup> on days 1-5 and 8-12, which represents the dose lethal to 10% of treated animals. Topotecan was active in the therapy of all s.c. xenografts tested, with growth delays ranging from 6.3 days in D-54 MG to 55.7 days in D528 EP. Topotecan produced statistically significant tumor regressions in D425 Med, D-456 MG, D-245 MG, D528 EP, and D612 EP. No tumor regression was seen in any control animal. Statistically significant increases in median survival were seen in the two i.c. xenografts - D-456 MG (28.6% increase) and D-54 MG (39% increase) - treated with topotecan. These studies suggest that topotecan may be an important new addn. to the therapy of central nervous system tumors.

Answer 43:

### Bibliographic Information

**Potentiation of radiation response in human carcinoma cells in vitro and murine fibrosarcoma in vivo by topotecan, an inhibitor of DNA topoisomerase I.** Kim, Jae Ho; Kim, Sang Hie; Kolozsvary, Andrew; Khil, Mark S. Dep. Radiat. Oncol., Henry Ford Hosp., Detroit, MI, USA. International Journal of Radiation Oncology, Biology, Physics (1992), 22(3), 515-18. CODEN: IOBPD3 ISSN: 0360-3016. Journal written in English. CAN 116:169130 AN 1992:169130 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

DNA topoisomerase I, a nuclear enzyme important for solving topol. problems arising during DNA replication, has been identified as a principal target of a plant alkaloid, 20(s)-camptothecin. In view of the profound biochem. effects of camptothecin and its analogs on DNA replication and the differential cytotoxic effects on human tumors in xenografts, expts. were performed to det. whether topotecan, a camptothecin analog, would potentiate the radiation effects on human carcinoma cells in culture and murine fibrosarcoma in mice. Cell culture studies showed that a dose dependent redn. in cell survival was obtained with a 4 h exposure of the drug following irradiation of cells. No enhancement of cell killing was seen when cells were treated with the drug before irradiation. Preliminary in vivo tumor studies showed a significant radiosensitizing effect of topotecan that was both drug dose (20 mg/kg) and time sequence (4 h before irradiation) dependent. There was no enhanced skin reaction following the combined treatments.

Answer 44:

### Bibliographic Information

**Comparison of efficacy and toxicity profile between intraperitoneal and intravenous topotecan in human ovarian cancer xenografts.** Yi Xiao-fang; Fan Shi-ming; Yao Ming; Feng You-ji Department of Gynecology, The Hospital of Obstetrics and Gynecology, Fudan University, Shanghai 200011, China Beijing da xue xue bao. Yi xue ban = Journal of Peking University. Health sciences (2006), 38(1), 88-91. Journal code: 101125284. ISSN:1671-167X. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 16415975 AN 2006025220 In-process for MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

### Abstract

**OBJECTIVE:** To compare the therapeutic and toxic profile of topotecan given intraperitoneally with intravenously in human ovarian cancer xenografted into athymic nude mice. **METHOD:** Eighty female Balb-c/nu-nu mice were randomized assigned into eight groups (n=10). Xenografts resulted from intramesentery injection of cultured human ovarian cancer cells SKOV3 in athymic mice. Onset of intraperitoneal treatment with either topotecan or cisplatin (7.5 mg/kg) was on day 7. Animals scheduled for topotecan i.p. received intraperitoneal application of topotecan (1.5 mg/kg x 2, 3.0 mg/kg x 2, 6.0 mg/kg x 2 or 10.0 mg/kg x 1). Animals scheduled for topotecan i.v. received intravenous administration of topotecan (6.0 mg/kg x 2 or 10.0 mg/kg x 1). Two weeks after drug application animals were killed. Tumor growth inhibition were assessed and compared with untreated mice and cisplatin intraperitoneally administered mice. Acute toxicity was

determined by loss of body weight. Cell cycle division and apoptosis after drug administration was determined by flow cytometric analysis. **RESULTS:** In a panel of ten tumour xenografts, intraperitoneal topotecan was significantly more effective than intravenous administration. The toxicity profile suggested a better tolerability in terms of weight loss after intraperitoneal administration than cisplatin control. Topotecan 10.0 mg/kg i.p. per day (1 day) schedule was an optimal treatment for ovarian cancer and well tolerated by mice with no signs of acute toxicity. Topotecan and cisplatin induce cells G0-G1 arrest and apparent apoptosis. No significant difference among mice treated with topotecan intraperitoneally or intravenously or cisplatin was observed in term of apoptosis and cell cycle perturbation. **CONCLUSION:** The results may have implications for the future design of clinical studies on intraperitoneal application of topotecan. It suggests that apoptosis and cell cycle perturbation play an limited role in the mechanism of topotecan administration.

Answer 45:

#### **Bibliographic Information**

**Preclinical and phase I study of oxaliplatin and topotecan in combination in human cancer.** Tortora G; Ciardiello F; Damiano V; De Laurentiis M; Matano E; Pepe S; Pensabene M; Catalano G; De Placido S; Bianco A R Dipartimento di Endocrinologia e Oncologia Molecolare e Clinica, Universita di Napoli Federico II, Italy. gtortora@unina.it *Annals of oncology* : official journal of the European Society for Medical Oncology / ESMO (2002), 13(3), 392-8. Journal code: 9007735. ISSN:0923-7534. (CLINICAL TRIAL); (CLINICAL TRIAL, PHASE I); (COMPARATIVE STUDY); (EVALUATION STUDIES); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 11996469 AN 2002256342 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

#### **Abstract**

**BACKGROUND:** DNA damage caused by platinum agents is frequently followed by induction of topoisomerase I, providing a rationale for use of platinum-based compounds with topoisomerase I inhibitors. **MATERIALS AND METHODS:** We studied the effect of a sequential schedule of oxaliplatin on day 1 and topotecan on days 2-5, in human colon and ovarian cancer cells in vitro, in nude mice bearing human cancer xenografts and finally in cancer patients in a phase I trial. **RESULTS:** We demonstrated a supra-additive effect of this combination on inhibition of colony formation and induction of apoptosis in vitro. We then demonstrated that the two agents in combination markedly inhibit tumor growth in nude mice. We translated these results into a clinical setting, conducting a phase I study in cancer patients with oxaliplatin 85 mg/m<sup>2</sup> on day 1 and topotecan at doses escalating from 0.5 to 1.5 mg/m<sup>2</sup> on days 2-5. Sixty cycles of treatment were administered to 18 patients affected prevalently by ovarian and colorectal cancer. Combination with topotecan 1.5 mg/m<sup>2</sup> caused a dose-limiting toxicity. Therefore the maximum tolerated dose of topotecan was 1.25 mg/m<sup>2</sup>, at which six patients experienced a mild hematological and gastrointestinal toxicity. We also obtained evidence of clinical activity, particularly in ovarian cancer. **CONCLUSIONS:** Our results provide a solid biological and clinical rationale for a phase II trial at the recommended doses of oxaliplatin 85 mg/m<sup>2</sup> and topotecan 1.25 mg/m<sup>2</sup>, possibly in ovarian cancer patients.

Answer 46:

#### **Bibliographic Information**

**Successful therapy of subcutaneously growing human hepatoblastoma xenografts with topotecan.** Warmann S W; Fuchs J; Wilkens L; Gratz K F; von Schweinitz D; Mildenerger H Department of Pediatric Surgery, Medical School Hannover, Carl-Neuberg-Str.1, 30625 Hannover, Germany. warmann.steven@mh-hannover.de *Medical and pediatric oncology* (2001), 37(5), 449-54. Journal code: 7506654. ISSN:0098-1532. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 11745873 AN 2001696310 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

#### **Abstract**

**BACKGROUND:** Human hepatoblastoma is an infrequent liver tumor in children. Although many hepatoblastomas can be treated adequately with well-defined treatment regimens, problems still persist with advanced and non-resectable tumors; in these cases, an effective chemotherapy is necessary to improve the patients' prognosis. This underlines the need for alternative anti-tumor agents in the treatment of human hepatoblastoma. The aim of this study was to investigate the therapeutic effects of topotecan, a water-soluble camptothecin analog (topoisomerase-I-antagonist), in an in vivo model of three human hepatoblastomas xenografted subcutaneously into nude mice. **PROCEDURE:** Hepatoblastoma cell suspensions from three children were transplanted subcutaneously into nude mice NMRI (nu/nu). Treatment with topotecan was initiated when the tumors reached a volume between 50 and 80 mm<sup>3</sup>. A dose of 6.6 mg/kg of topotecan were given intraperitoneally every 4 days on four occasions. The tumor volume development and alpha-fetoprotein alterations were measured and statistically analyzed. After the treatment, the tumors were investigated histologically and by immunohistochemistry. **RESULTS:** There was a significant reduction of tumor growth in all treated tumor xenografts vs. untreated control groups (mean relative volume 3.1 vs. 47.4; P = 0,0015-0,0079). Serum alpha-fetoprotein levels were reduced in all three cell lines, in two of them significantly (mean 44,535 kU/l vs. 228,883 kU/l; P = 0.005-0.246). Histologically, the tumor necrosis rates were higher and immunohistochemistry showed lower proliferation activities in the treated tumor xenografts vs. the control groups. **CONCLUSION:** The data show that topotecan is an effective agent in the treatment of human hepatoblastoma xenografts. From these results, treatment with topotecan appears to be a promising alternative in the pre- and postoperative therapy of patients suffering from human hepatoblastoma Copyright 2001 Wiley-Liss, Inc.