

Answer 1:

### Bibliographic Information

**Enhancement of semustine-induced cytotoxicity by chlorpromazine and caffeine in a human melanoma xenograft.** Osieka, R.; Glatte, P.; Pannenbaecker, R.; Schmidt, C. G. West Ger. Tumor Cent., Inn. Universitaetsklin. Poliklin., Essen, Fed. Rep. Ger. Cancer Treatment Reports (1986), 70(10), 1167-71. CODEN: CTRRDO ISSN: 0361-5960. Journal written in English. CAN 105:218411 AN 1986:618411 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

In a xenograft model of human melanoma (in athymic mice), the antineoplastic activity of semustine [13909-09-6] was enhanced by the concurrent administration of chlorpromazine [50-53-3] and caffeine [58-08-2]. This enhancement of semustine activity was attributed to increased drug retention by the tumor tissue (detd. with <sup>14</sup>C-labeled semustine) and to increased DNA damage (detd. by alk. elution patterns). DNA damage was also increased in the mouse bone marrow cells. These results are discussed in relation to previously reported results in a randomized clin. trial.

Answer 2:

### Bibliographic Information

**Induced and inherent resistance to alkylating agents in human small-cell bronchial carcinoma xenografts.** Berman, R.; Steel, G. G. Radiother. Res. Unit, Inst. Cancer Res., Sutton, UK. British Journal of Cancer (1984), 49(4), 431-6. CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 100:203254 AN 1984:203254 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Inherent and induced resistance was investigated in human small-cell lung cancer xenografts. Specimens from patients were established in immune suppressed mice; the sensitivity of the xenografts to cyclophosphamide [50-18-0], MeCCNU [13909-09-6], and melphalan [148-82-3] was detd. Clin. chemosensitivity data were available in 2 cases and inherent differences in sensitivity were noted both in the xenografts and clin. Radioactively-labeled melphalan uptake studies were performed with these 2 xenografts. A no. of different strategies to induce resistance were explored. Only 1 method proved to be successful and in only 1 of the xenografts; this was with cyclophosphamide. The induced resistant line was characterized in terms of the time course of its prodn., the degree of induced resistance, the growth rate, the cross-resistance pattern and stability of the phenotype; the possibility of altered antigenicity was also examd.

Answer 3:

### Bibliographic Information

**Primary and acquired resistance to alkylating agents in heterotransplants of human melanomas and colon carcinomas.** Osieka, Rainhardt; Schmidt, Carl G. Innere Klin., West German Tumor Cent., Essen, Fed. Rep. Ger. Proceedings of the International Workshop on Nude Mice (1982), Volume Date 1979, 3rd(Vol. 2), 675-84. CODEN: PIWMDW ISSN: 0171-1784. Journal written in English. CAN 98:119257 AN 1983:119257 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Heterotransplants of human neoplasms onto athymic nude mice was used to screen new antineoplastic agents for activity against specific types of cancer. A variety of agents with diverse mechanisms of action, AMSA (NSC-249992) [51264-14-3], anguidine (NSC-141537) [2270-40-8], Baker's antifol (NSC-139105) [41191-04-2], maytansine (NSC-153858) [35846-53-8], and PALA

(NSC-224131) [51321-79-0], were ineffective against a battery of 3 human colon carcinoma heterotransplants and gave few responses against colon carcinoma in phase I and II clin. trials. Screening results also provide the initial basis for anal. of drug resistance mechanisms. Human colon cancer heterotransplant CX-3 (BE) can only be cured by methyl-CCNU [13909-09-6], whereas all other alkylating agents tested were ineffective. In a similar fashion, patterns of resistance to alkylating agents were established for 5 lines of malignant melanoma from patients who received DTIC [4342-03-4], cis-platinum [15663-27-1], and isophosphamide [3778-73-2] either singly or in combination during the course of their treatment. Partial remissions of patients correlated with transient regressions in the heterotransplantation system. With the new method of alk. elution modified for in vivo anal. by use of microfluorometric DNA detns., the development and removal of DNA damage was monitored. Absence of DNA damage at all times correlated with drug resistance. Resistance in a patient previously sensitive to the combination of isophosphamide and cis-platinum was paralleled in the heterotransplantation system. Sensitivity to cis-platinum and isophosphamide was also abolished after 3 transplant generations when initially sensitive tumors that had regrown after treatment with either drug were selected for propagation.

Answer 4:

#### **Bibliographic Information**

**Molecular pharmacology on human cancer xenografts.** Osieka, R.; Becher, R.; Schmidt, C. G. Westdsch. Tumorzent., Innere Universitaetsklin. Poliklin., Essen, Fed. Rep. Ger. Editor(s): Bastert, Gunther B.; Fortmeyer, Hans Peter; Schmidt-Matthiesen, Heinrich. Thymusaplastic Nude Mice Rats Clinial Oncol., Proc. Symp. (1981), Meeting Date 1979, 513-27. Publisher: Fischer, Stuttgart, Fed. Rep. Ger CODEN: 46XEAJ Conference written in English. CAN 96:115594 AN 1982:115594 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### **Abstract**

The effect of neoplasm inhibitors on human colorectal cancers xenografted into nude mice and on human malignant melanoma heterotransplants is reported. The xenograft system provides 2 advantages over conventional murine tumor models; 1) screening new antineoplastic agents with ref. to specific types of cancer yields information on the spectrum of clin. activity previously available only through phase I-II clin. trials, and 2) with some limitations inherent to biochem. assays on tumor material, mechanisms of primary and acquired resistance can be explored with the system providing the classification into sensitive and resistant tumors and also serving as a source of readily available tumor material. Biochem. studies were limited to the actions of alkylating agents on DNA as their presumptive target mol. In addn. the effect of hyperthermia on human colon cancer xenografts in conjunction with chemotherapy was investigated with specific attention paid to synergism and(or) cross resistance among the 2 modes of treatment.

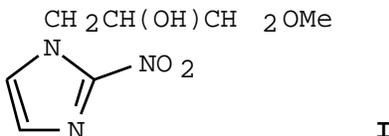
Answer 5:

#### **Bibliographic Information**

**Enhanced cell killing in Lewis lung carcinoma and a human pancreatic-carcinoma xenograft by the combination of cytotoxic drugs and misonidazole.** Stephens, T. C.; Courtenay, V. D.; Mills, J.; Peacock, J. H.; Rose, C. M.; Spooner, D. Div. Radiother., Inst. Cancer Res., Sutton/Surrey, UK. British Journal of Cancer (1981), 43(4), 451-7. CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 95:73397 AN 1981:473397 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### **Abstract**

Misonidazole (I) [13551-87-6] (1 mg/g s.c.) substantially enhanced cytotoxicity of melphalan [148-82-3], cyclophosphamide [50-18-0], CCNU [13010-47-4], 5-FU [51-21-8], or vincristine [57-22-7] in mice bearing Lewis lung carcinoma. However, no enhancement was obsd. with bleomycin [11056-06-7], VP16-213 [33419-42-0], or cis-dichlorodiammineplatinum [15663-27-1]. The same level of enhancement by I of the cyclophosphamide effect was seen with both cell survival and growth delay endpoints of tumor response. I also enhanced the effect of melphalan, cyclophosphamide, and methyl-CCNU [13909-09-6] in human pancreatic adenocarcinoma xenograft; the cis-dichlorodiammineplatinum effect was not enhanced.



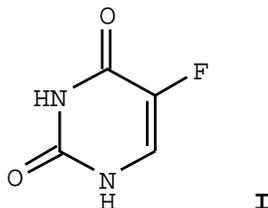
Answer 6:

### Bibliographic Information

**Chemotherapeutic sensitivity of human colorectal tumor xenografts.** Kopper, L.; Lapis, K.; Hegedus, C. 1st Inst. Pathol. Exp. Cancer Res., Semmelweis Med. Univ., Budapest, Hung. *Oncology* (1980), 37(Suppl. 1, Dev. Cancer Chemother.), 42-50. CODEN: ONCOBS ISSN: 0030-2414. Journal written in English. CAN 94:95948 AN 1981:95948 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Studies were made of the therapeutic response of 6 human colorectal tumor lines serially transplanted in immunosuppressed mice. The tumors with adenomatous structure showed greater sensitivity against different cytotoxic agents than the gelatinous ones. Among the drugs, 5-FU (I) [51-21-8], 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) [154-93-8], and NSC 95441 (1-[2-chloroethyl-(3)-methylcyclohexyl-1-nitrosourea) [13909-09-6] had high activities producing not only temporary but long-term regressions. BCNU showed maximal activity when given as a single oral administration. 5-FU sensitive and insensitive lines showed an equal uptake and incorporation of radiolabeled 5-FU. Both the uptake rate and the growth of nontreated and treated tumors in the same host revealed the influence of host-defense mechanisms on tumor progression.



Answer 7:

### Bibliographic Information

**Comparison of antitumor activities of nitrosourea derivatives against mammary breast carcinoma (MX-1) in nude mice.** Inoue, Katsuhiko; Fujimoto, Shuichi; Ogawa, Makoto. Div. Clin. Chemother., Cancer Chemother. Cent., Tokyo, Japan. *Gann* (1980), 71(5), 686-91. CODEN: GANNA2 ISSN: 0016-450X. Journal written in English. CAN 94:273 AN 1981:273 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

The antitumor activities of 6 nitrosourea derivs. against the xenograft of mammary breast carcinoma transplanted in nude mice (MX-1) were evaluated. A single treatment with ACNU [55661-38-6] (40 mg/kg, i.v.) induced 92% tumor regression, compared to 73% and 69% tumor regression induced by MCNU [58994-96-0] (15 mg/kg, i.v.) and CCNU [13010-47-4] (50 mg/kg, i.v.), resp. GANU [58484-07-4], 2-[3-(2-chloroethyl)-3-nitrosoureido]-2-deoxyl-D-glucopyranose (DCNU) [54749-90-5], and 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea (MeCCNU) [13909-09-6] were less effective. To evaluate the antitumor activity of the drugs, the predetd. dose lethal to 0.10 of the BDF1 mice (LD10) was employed for each drug as a std. therapeutic dose to nude

mice; doses higher than LD10 and 0.25 or 0.50 of the LD10 were also give. Apparently, the LD10 in BDF1 mice could be employed as a std. therapeutic dose in the chemotherapy of nude mice.

Answer 8:

#### **Bibliographic Information**

**The combination of methyl-CCNU and irradiation: cell survival studies on a human tumor xenograft.** Bateman, Angela E.; Fu, Karen K.; Towse, G. D. W. Radiother. Res. Dep., Inst. Cancer Res., Sutton/Surrey, UK. International Journal of Radiation Oncology, Biology, Physics (1979), 5(9), 1545-8. CODEN: IOBPD3 ISSN: 0360-3016. Journal written in English. CAN 92:69674 AN 1980:69674 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### **Abstract**

Methyl-CCNU [13909-09-6] 3 h before  $\gamma$ -irradn. was the most effective time schedule of those tested on a human tumor xenograft in mice. This pretreatment decreased the D0 of the radiation survival curve from 231 to 135 rad without any effect on the shoulder of the curve.

Answer 9:

#### **Bibliographic Information**

**Evaluation of cytotoxic agents in human colonic tumor xenografts and mouse gastrointestinal tissues using a 3H-thymidine fractional incorporation assay.** Houghton, J. A.; Houghton, P. J. Dep. Radiopharmacol., Inst. Cancer Res., Sutton/Surrey, UK. European Journal of Cancer (1965-1981) (1979), 15(5), 763-9. CODEN: EJCAAH ISSN: 0014-2964. Journal written in English. CAN 91:101741 AN 1979:501741 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### **Abstract**

Drug-induced changes in thymidine-3H fractional incorporation (TFI) in 4 human colonic xenograft lines and mouse gastrointestinal tissues were related to the growth inhibition and host toxicity, resp. The combinations of actinomycin D [50-76-0] with cyclophosphamide [50-18-0] and methylCCNU [13909-09-6] with pentamethylmelamine [16268-62-5] were examd. by the TFI assay. Both combinations showed greater than additive activity against only 1 of the 3 xenograft lines in which they were tested. The TFI assay allowed more rapid evaluation of drug activity and was more sensitive than growth delay studies. It also gave quant. measurement of cytotoxic activity in gastrointestinal tissues after sublethal dose levels.

Answer 10:

#### **Bibliographic Information**

**Chemotherapy studies with human colon cancer xenografts in nude mice.** Osieka, R. West German Cancer Cent., Univ. Essen, Essen, Fed. Rep. Ger. Editor(s): Siegenthaler, Walter; Luethy, Ruedi. Curr. Chemother., Proc. Int. Congr. Chemother., 10th (1978), Meeting Date 1977, 2 1149-51. Publisher: Am. Soc. Microbiol., Washington, D. C CODEN: 37XLA2 Conference written in English. CAN 89:190953 AN 1978:590953 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### **Abstract**

The activity of neoplasm inhibitors against 3 human colon cancer xenografts was tested in nude mice. Of the 9 agents tested, only NSC-95441 (methyl-CCNU) [13909-09-6], NSC-178248 (chlorozotocin) [54749-90-5], and Baker's antifol (triazinate) [41191-04-2] had any activity. The mechanism of action of the drugs was explored. Hyperthermia could not overcome resistance to methyl-CCNU,

although hyperthermia inhibited 1 tumor line. Thus, the new tumor model using nude mice is a very selective screening model for testing the effect of neoplasm inhibitors on specific types of neoplasia such as colon cancer.

Answer 11:

#### Bibliographic Information

**DNA cross-linking by in vivo treatment with 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea of sensitive and resistant human colon carcinoma xenografts in nude mice.** Thomas, Cornelius B.; Osieka, Rainhardt; Kohn, Kurt W. Lab. Mol. Pharmacol., Natl. Cancer Inst., Bethesda, MD, USA. Cancer Research (1978), 38(8), 2448-54. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 89:157436 AN 1978:557436 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

The DNA alk. elution technique was adapted to permit measurements of effects of drugs on DNA in solid tumors. Human colon carcinoma xenografts in nude mice were treated with a single i.p. injection of 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea [13909-09-6], and the effects on the DNA were followed for 19 h. Drug doses in the pharmacol. range produced redns. in DNA alk. elution rates in assays in which X-ray was used to introduce a std. frequency of single-strand breaks. These changes in alk. elution rate were attributed to the prodn. of both DNA interstrand and DNA-protein cross-links, which were distinguished from each other on the basis of the extent to which the effect on elution could be reversed by proteinase K. Cross-linking increased for about 8 h after treatment with little change thereafter up to 19 h. A drug-resistant tumor line exhibited substantially less cross-linking than did a drug-sensitive line at all time points examd.

Answer 12:

#### Bibliographic Information

**Sensitivity of a human tumor xenograft in nude (athymic) mice to various clinically-active drugs.** Ovejera, Artemio A.; Houchens, David P.; Barker, Anna D. Battelle, Columbus Lab., Columbus, OH, USA. Proceedings of the International Workshop on Nude Mice (1977), 2 451-60. CODEN: PIWMDW ISSN: 0171-1784. Journal written in English. CAN 89:100164 AN 1978:500164 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

The regression of human colon tumor grown in nude mice was obsd. after administration of Me CCNU [13909-09-6] but not after 5-fluorouracil [51-21-8], cyclophosphamide [50-18-0], mitomycin C [50-07-7], 5-fluoro-2'-deoxyuridine [50-91-9], or methotrexate [59-05-2]. 5-Fluorouracil, cyclophosphamide, and mitomycin C elicited the retardation of the growth rate of this tumor. Methotrexate was without effect.

Answer 13:

#### Bibliographic Information

**Chemotherapy of human colon cancer xenografts in athymic nude mice.** Osieka, Rainhardt; Houchens, David P.; Goldin, Abraham; Johnson, Randall K. Lab. Chem. Pharmacol., Natl. Cancer Inst., Bethesda, MD, USA. Cancer (New York, NY, United States) (1977), 40(5, Suppl.), 2640-50. CODEN: CANCAR ISSN: 0008-543X. Journal written in English. CAN 89:36566 AN 1978:436566 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

Xenografts of human colon cancer in nude mice reproduce many features of the original tumor specimen and could be expected to predict drug response for colon cancer with more specificity than previously used screens. NIH-Swiss nude mice bearing s.c. trocar implants of tumor tissue were used in these studies. Three serially transplantable lines of human colon cancer (designated °HT°, °CA°, and °BE°), which range in their degree of differentiation from well-differentiated adenocarcinoma to undifferentiated carcinoma, were used for drug testing. Treatment was delayed until tumors had reached 60-600 mg in mass to correspond to advanced tumors in patients. Drugs being developed for clin. trial by NCI were selected for testing against the xenografts based on promising activity against transplantable murine tumor lines and difference in mechanism of action. Two antimetabolites, PALA [60342-56-5] and Baker's antifol [41191-04-2], a mitotic spindle poison, maytansine [35846-53-8], and a DNA intercalating agent, AMSA [63949-13-3], produced no significant regression in any of the 3 colon xenograft lines. From the group of nitrosoureas, methyl CCNU [13909-09-6] and chlorozotocin [54749-90-5] were tested. Me CCNU caused no regression of line HT, a transient response of line CA and complete regressions of line BE. Chlorozotocin also caused regression of line BE but had no effect on the other tumor lines. The results of chemotherapy studies with human colon cancer xenografts in nude mice reflect the clin. situation where few objective responses are achieved with presently available chemotherapy. Information about activity against colon cancer of a new drug may be gained by testing the drug against a panel of human colon cancer xenografts. Careful clin. followup studies and parallel studies with xenograft systems should establish the correlation between individual clin. response and response in the xenograft system.

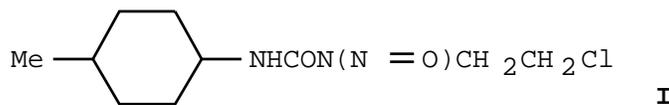
Answer 14:

### Bibliographic Information

**Differential repair of 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea-induced DNA damage in two human colon tumor cell lines.** Erickson, Leonard C.; Osieka, Rainhardt; Kohn, Kurt W. Natl. Cancer Inst., NIH, Bethesda, MD, USA. Cancer Research (1978), 38(3), 802-8. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 88:147129 AN 1978:147129 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Two human colon tumor cell lines were examd. for their responses to 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea (I) [13909-09-6] treatment when maintained as cultured cell lines and xenograft tumors in nude mice. One tumor line, HT, was resistant to I treatment both in tissue culture and in vivo. The other tumor line, BE, was sensitive to I treatment in vitro and in vivo. The DNA of tissue-cultured cells treated with I was examd. by alk. elution for DNA damage. I was found to produce DNA strand breaks and DNA cross-links in both cells types. The DNA cross-links appear to be completely repaired in the resistant HT line over the 48-h period following drug removal, but in the sensitive BE line little or no cross-link repair was obsd. during this interval.



Answer 15:

### Bibliographic Information

**Chemotherapy of cell-line-derived human colon carcinomas in mice immunosuppressed with antithymocyte serum.** Tibbetts, Lance M.; Chu, Ming Y.; Hager, Jean C.; Dexter, Daniel L.; Calabresi, Paul. Dep. Med., Brown Univ., Providence, RI, USA. Cancer (New York, NY, United States) (1977), 40(5, Suppl.), 2651-9. CODEN: CANCAR ISSN: 0008-543X. Journal written in English. CAN 88:115007 AN 1978:115007 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

An in vivo model is described for assessing the antitumor activity of chemotherapeutic agents. Tumors derived from human colon carcinoma cell lines injected into antithymocyte serum (ATS) immunosuppressed mice were used. In this system, both antitumor

effects and host toxicity can be quantitated, permitting calcn. of a therapeutic Index. Compared with other xenograft models, the present system is simple. Expts. are completed in less than 2 wk, and the use of cultured cell lines allows in vitro studies to be performed. The in vitro sensitivities of 1 colon cell line to 22 chemotherapeutic agents and of 4 cell lines to 3 agents is reported. Four drugs used in treating colon cancer (mitomycin C [50-07-7], 5-fluorouracil [51-21-8], BCNU [154-93-8], methyl-CCNU [13909-09-6]) showed antitumor activity in vivo in this system. Each had a low therapeutic index.

Answer 16:

#### **Bibliographic Information**

**Modulation of mammalian O6-alkylguanine-DNA alkyltransferase in vivo by O6-benzylguanine and its effect on the sensitivity of a human glioma tumor to 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea.** Dolan M E; Stine L; Mitchell R B; Moschel R C; Pegg A E Division of Hematology-Oncology, University of Chicago Medical Center, IL 60637 Cancer communications (1990), 2(11), 371-7. Journal code: 8916730. ISSN:0955-3541. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 2242301 AN 91054942 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

#### **Abstract**

Experiments were carried out in mice and hamsters to determine whether the activity of the DNA repair protein, O6-alkylguanine-DNA alkyltransferase, in tissues and tumors was reduced by treatment with O6-benzylguanine in vivo. Following intraperitoneal injection of O6-benzylguanine, there was a rapid and complete loss of alkyltransferase activity in both livers and kidneys of mice and hamsters. The activity in mouse tissues was slowly restored, reaching pretreatment activities at 16 hr and 72 hr after injection of O6-benzylguanine at 10 mg/kg or 126 mg/kg, respectively. The activity in hamster liver was restored at a significantly lower rate, reaching less than 20% pretreatment activity 72 hr after treatment with 100 mg/kg of O6-benzylguanine. The efficient reduction of alkyltransferase activity by O6-benzylguanine was in sharp contrast to the inability of O6-methylguanine to bring about similar reductions. Activities dropped to about 55% of pretreatment activities in several mouse organs 4 hr after treatment with 126 mg/kg of O6-methylguanine compared to a more than 90% reduction in activity in animals after treatment with O6-benzylguanine. The sensitivity of SF767 cells to meCCNU after treatment with O6-benzylguanine was increased substantially. Furthermore, treatment of nude mice carrying SF767 tumor with 60 mg/kg of O6-benzylguanine prior to either 7.5 or 15 mg/kg of meCCNU led to significant inhibition of tumor growth. These studies indicate that O6-benzylguanine is a suitable compound for use in experiments to examine the role of the alkyltransferase protein in vivo in counteracting the effects of alkylating agents.(ABSTRACT TRUNCATED AT 250 WORDS)

Answer 17:

#### **Bibliographic Information**

**Response of human colon carcinoma xenografts to recombinant human tumor necrosis factor (TNF).** Osieka R; Glatte P; Niederle N; Schmidt C G Department of Medical Oncology, University of Essen Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft ... [et al] (1989), 165(7), 552-4. Journal code: 8603469. ISSN:0179-7158. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 2749495 AN 89317864 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Answer 18:

#### **Bibliographic Information**

**Chemosensitization by chlorpromazine (CPZ) and caffeine (C) in human melanoma xenografts sensitive or resistant to methyl-CCNU (semustine).** Osieka R; Glatte P; Schmidt C G West German Tumor Center, University

of Essen Strahlentherapie und Onkologie : Organ der Deutschen Röntgengesellschaft ... [et al] (1989), 165(7), 526-8. Journal code: 8603469. ISSN:0179-7158. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 2749491 AN 89317849 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Answer 19:

#### **Bibliographic Information**

**Increased cytotoxicity of 1-(2-chloroethyl)-1-nitroso-3(4-methyl)-cyclohexylurea by pretreatment with O6-methylguanine in resistant but not in sensitive human melanoma cells.** Dempke W; Nehls P; Wandl U; Soll D; Schmidt C G; Osieka R Journal of cancer research and clinical oncology (1987), 113(4), 387-91. Journal code: 7902060. ISSN:0171-5216. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 3597524 AN 87250917 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

#### **Abstract**

Cells from a resistant ("Gr II") and a sensitive ("Str") human melanoma xenograft were incubated in vitro with O6-methylguanine for 2 h, subsequently treated with 1-(2-chloroethyl)-1-nitroso-3(4-methyl)-cyclohexylurea (MeCCNU) for 1 h and then plated in soft agar. In the resistant cells the O6-methylguanine pretreatment (2 mM) yielded an increase in sensitivity towards MeCCNU by a factor of 7.5. In the sensitive melanoma cells pretreatment with O6-methylguanine did not increase cytotoxicity. Human bone marrow cells from three normal donors were similarly pretreated with O6-methylguanine and MeCCNU. There was a clear increase in MeCCNU-induced cytotoxicity. We conclude, that while O6-methylguanine does potentiate the action of MeCCNU in resistant melanoma cells, the therapeutic usefulness of this treatment strategy may be limited.

Answer 20:

#### **Bibliographic Information**

**O6-Alkylguanine-DNA alkyltransferase activity correlates with the therapeutic response of human rhabdomyosarcoma xenografts to 1-(2-chloroethyl)-3-(trans-4-methylcyclohexyl)-1-nitrosourea.** Brent T P; Houghton P J; Houghton J A Proceedings of the National Academy of Sciences of the United States of America (1985), 82(9), 2985-9. Journal code: 7505876. ISSN:0027-8424. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 3857628 AN 85190621 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

#### **Abstract**

Immune-deprived female CBA/CaJ mice bearing xenografts of six different human rhabdomyosarcoma lines were treated with 1-(2-chloroethyl)-3-(trans-4-methylcyclohexyl)-1-nitrosourea (MeCCNU). Tumor responses were compared with levels of O6-methylguanine-DNA methyltransferase activity because of evidence indicating that repair of DNA interstrand cross-link precursors, mediated by the transferase, may be an important determinant of MeCCNU cytotoxicity. Levels of methyltransferase in tumor extracts were measured by determining the loss of O6-methylguanine from 3H-labeled methylated DNA. Five of the six tumor lines examined showed either no response to MeCCNU or regrowth after an incomplete response. In each instance, the extent of tumor regression correlated with the level of O6-methylguanine-DNA methyltransferase activity in tumor extracts. The single highly drug sensitive line was totally devoid of the activity. These results suggest that O6-methylguanine-DNA methyltransferase levels in human tumor cells may be a clinically useful predictor of sensitivity to the chloroethylnitrosoureas.

Answer 21:

**Bibliographic Information**

**Studies on drug resistance in a human melanoma xenograft system.** Osieka R Cancer treatment reviews (1984), 11 Suppl A 85-98. Journal code: 7502030. ISSN:0305-7372. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 6539651 AN 84233878 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

**Abstract**

Alkylating agents and their functional analogues belong to the most useful antineoplastic drugs in the treatment of disseminated malignant melanoma. In conjunction with an open clinical phase II trial evaluating the combination of cisplatin and ifosfamide, 17 melanoma xenograft lines were established from patients often refractory to dacarbazine (DTIC). These xenograft lines were exposed to cisplatin, dacarbazine, dibromodulcitol, ifosfamide, methyl-CCNU, mitomycin C, and malonato-diaminocyclohexane-platinum II (PHM) at the respective LD 10/30 doses. Growth delay values less than 2 corresponded in 26/27 instances with progressive disease, whereas values greater than 2 corresponded in only 10/13 instances with achievement of a no-change status or a partial remission of the donor patient's disease. Among the panel of DNA-damaging agents tested, cross-resistance was incomplete. Some xenograft lines revealed unique chemosensitivity patterns in contrast to a uniform pattern of drug resistance in others (pleiotropic or multidrug resistance). The data confirm independently of results obtained in the phase II study that the combination of cisplatin and ifosfamide is effective against malignant melanoma refractory to dacarbazine. Suboptimal drug exposure, repeated up to 21 transplant generations, was employed to induce secondary resistance to either dacarbazine, melphalan or methyl-CCNU in a melanoma xenograft line originally quite sensitive to drug treatment. When the resistant sublines were exposed to the other agents, only partial cross-resistance was observed. Tumour volume responses to treatment with dacarbazine correlated with persisting DNA damage assayed 24 h after in vivo drug exposure in a sensitive line and the absence of such lesions in a resistant line.

Answer 22:

**Bibliographic Information**

**Therapeutic evaluation of five nitrosoureas in a human melanoma xenograft system.** Osieka R; Glatte P; Pannenbacker R; Schmidt C G Cancer chemotherapy and pharmacology (1983), 11(3), 147-52. Journal code: 7806519. ISSN:0344-5704. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 6227420 AN 84055725 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

**Abstract**

The development of nitrosoureas has switched from more lipophilic derivatives to congeners with higher water-solubility, since this property was presumably associated with a decrease in myelosuppression. We have compared the therapeutic efficacy of clinically well-known lipophilic nitrosoureas BCNU, CCNU, and MeCCNU with the recently introduced water-soluble nitrosoureas chlorozotocin (CZT) and hydroxyethyl-CNU (HeCNU), using a human melanoma xenograft system. There were considerable differences in tumor-inhibitory activity, with HeCNU ranking first and CZT last, and the rank order was similar for drug-induced lethality or bone marrow damage (in terms of reduced cellularity or macromolecular DNA damage). When the doses are expressed as percentages of the corresponding LD10/30 values, CZT ranks last and HeCNU low among conventional nitrosoureas. We conclude that water-solubility is not associated with reduced myelosuppression and that other guidelines will have to be adopted for rational development of nitrosoureas.

Answer 23:

**Bibliographic Information**

**Enhancement of MeCCNU potency (chemosensitization) by misonidazole in a human melanoma xenograft system.** Osieka R; Glatte P; Haedecke U; Schmidt C G *Strahlentherapie* (1982), 158(10), 620-9. Journal code: 1260024. ISSN:0039-2073. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in German. PubMed ID 7179344 AN 83094247 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

#### Abstract

In addition to the well-known radiosensitizing properties of misonidazole its potential for chemosensitization has been investigated recently. According to results obtained mostly with conventional murine tumor systems, the degree of such chemosensitization depends on the particular tumor system, the type of antineoplastic agent and the dose of misonidazole employed. Our experiments were conducted with a human melanoma transplanted onto (nu/nu) mice. At the dose level of 1 g/kg misonidazole toxicity was enhanced by a factor of about 3, whereas antineoplastic activity was enhanced only by a factor of about 1.8. Therefore, the usefulness of such chemosensitization remains limited, especially since under clinical circumstances this dose of misonidazole would cause unacceptable neurotoxicity. The retention of radioactivity from <sup>14</sup>C-MeCCNU is increased in neoplastic as well as in normal tissues by a factor of 1.3. DNA interstrand crosslinks measured 24 hours after drug exposure, however, are increased by a factor of about 2. Despite their nonselective reaction at the level of molecular pharmacology, drugs with sensitizing or protective properties may well constitute a valuable addition to the serial synthesis of chemical congeners in drug development. The use of oxazaphosphorines is quoted as an example where selective protection from urotoxicity is afforded by sodium-2-mercaptoethanesulfonate.

Answer 24:

#### Bibliographic Information

**Use of the agar diffusion chamber for the exposure of human tumor cells to drugs.** Selby P J; Steel G G *Cancer research* (1982), 42(11), 4758-62. Journal code: 2984705R. ISSN:0008-5472. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 7127312 AN 83024783 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

#### Abstract

Human melanoma xenografts in immune-deprived mice have been used to assess the value of the agar diffusion chamber for chemosensitivity testing. Tumor cells were treated with melphalan, Adriamycin, or methyl trans-1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea either as solid tumors growing in mice or as suspensions in agar in i.p. diffusion chambers. Survival of clonogenic human tumor cells was measured by the agar diffusion chamber assay in both cases. Cell survival curves were log-linear for treatment of tumor cells in vivo or in the chambers. For melphalan the slopes of survival curves were significantly greater for treatment in the chambers than as solid tumors in vivo, but for methyl trans-1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea or Adriamycin, they were indistinguishable. Experiments with [<sup>14</sup>C]melphalan showed that the levels of drug achieved were less inside the diffusion chambers than in the tumors in vivo so that the sensitivity of tumor cells to melphalan was much greater when they were treated in chambers. The differences in drug exposure and in cellular chemosensitivity between chambers and tumors suggest caution in the interpretation of drug testing using this system, but the log-linear nature of the dose-response curves is an important feature which may be useful in the eventual development of optimal chemosensitivity testing systems.

Answer 25:

#### Bibliographic Information

**The spectrum of chemosensitivity of two human pancreatic carcinoma xenografts.** Courtenay V D; Mills J; Steel

G G British journal of cancer (1982), 46(3), 436-9. Journal code: 0370635. ISSN:0007-0920. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 6215052 AN 83022865 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Answer 26:

#### **Bibliographic Information**

**In vitro chemosensitivity tests on xenografted human melanomas.** Bateman A E; Selby P J; Steel G G; Towse G D British journal of cancer (1980), 41(2), 189-98. Journal code: 0370635. ISSN:0007-0920. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 7370159 AN 80175232 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

#### **Abstract**

An in vitro chemosensitivity test has been applied to malignant melanoma cells from 5 patients. The tumour cells were first grown as xenografts in immune-suppressed mice, so that the results of the in vitro test could be compared with precise measurements of the sensitivity of the melanoma cells when exposed to chemotherapeutic drugs in vivo in the mouse. The in vitro assay involved exposing the tumour cells to each of 8 drugs, after which cell survival was determined by colony assay in soft agar. Dose-response curves were obtained and the surviving fraction at drug levels estimated to be achieved in man was used as a measure of in vitro drug sensitivity. Significant differences among the 8 drugs were detected, and these accorded with clinical experience. The correlation of in vivo (in the mouse) and in vitro sensitivities to Melphalan and MeCCNU was also significant.

Answer 27:

#### **Bibliographic Information**

**Human brain tumor transplantation into nude mice.** Shapiro W R; Basler G A; Chernik N L; Posner J B Journal of the National Cancer Institute (1979), 62(3), 447-53. Journal code: 7503089. ISSN:0027-8874. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 216838 AN 79112596 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

#### **Abstract**

Seven human brain tumors were transplanted into the brains (6/7 takes) and subcutaneous tissues (7/7 takes) of athymic nude mice. Compared to experimental animal brain tumors, these tumors, taken directly from patients in the operating room and transplanted, grew more slowly in the mice; their growth rates following explant generally paralleled those in the patients. A rough correlation was seen between the degree of the tumor's malignancy and both successful take and rate of growth following explant. The tumors' growth rates increased during serial transplantation after explant. Two tumors developed into long-term serial lines; both came from gliosarcomas. Preliminary chemotherapy experiments with these two lines demonstrated different chemosensitivities. One line was very sensitive to the nitrosoureas and resistant to procarbazine; the other line was more sensitive to procarbazine than to the nitrosoureas. This model permits study of the biologic behavior of human brain tumors growing intracerebrally and subcutaneously in nude mice.