

Answer 1:

Bibliographic Information

In vitro and in vivo reversal of resistance to 5-fluorouracil in colorectal cancer cells with a novel stealth double-liposomal formulation. Fanciullino, R.; Giacometti, S.; Mercier, C.; Aubert, C.; Blanquicett, C.; Piccerelle, P.; Ciccolini, J. EA3286-Laboratoire de Pharmacocinetique, Universite de la Mediterranee, Marseille, Fr. *British Journal of Cancer* (2007), 97(7), 919-926. Publisher: Nature Publishing Group, CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 148:205514 AN 2007:1104884 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Drug resistance is a major cause of treatment failure in cancer chemotherapy, including that with the extensively prescribed antimetabolite, 5-fluorouracil (5-FU). In this study, we tried to reverse 5-FU resistance by using a double-punch strategy: combining 5-FU with a biochem. modulator to improve its tumoral activation and encapsulating both these agents in one same stealth liposome. Expts. carried out in the highly resistant, canonical SW620 human colorectal model showed a up to 80% sensitization to 5-FU when these cells were treated with our liposomal formulation. Results with this formulation demonstrated 30% higher tumoral drug uptake, better activation with increased active metabolites including crit.-5-fluoro-2-deoxyuridine-5-monophosphate, superior inhibition (98%) of tumor thymidylate synthase, and subsequently, higher induction of both early and late apoptosis. Drug monitoring showed that higher and sustained exposure was achieved in rats treated with liposomal formulation. When examd. in a xenograft animal model, our dual-agent liposomal formulation caused a 74% redn. in tumor size with a mean doubling in survival time, whereas std. 5-FU failed to exhibit significant antiproliferative activity as well as to increase the lifespan of tumor-bearing mice. Taken collectively, our data suggest that resistance to 5-FU can be overcome through a better control of its intratumoral activation and the use of an encapsulated formulation. Published online 11 Sept. 2007.

Answer 2:

Bibliographic Information

Preclinical Auger and gamma radiation dosimetry for fluorodeoxyuridine-enhanced tumour proliferation scintigraphy with [123I]iododeoxyuridine. Buchegger, Franz; Vieira, Jean-Marc; Blaeuenstein, Peter; Dupertuis, Yves Marc; Schaffland, Andreas Oliver; Grannavel, Carine; de Tribolet, Nicolas; Slosman, Daniel Olivier; Bischof Delaloye, Angelika. Division of Nuclear Medicine, University Hospital of Lausanne CHUV, Lausanne, Switz. *European Journal of Nuclear Medicine and Molecular Imaging* (2003), 30(2), 239-246. Publisher: Springer-Verlag, CODEN: EJNMA6 ISSN: 1619-7070. Journal written in English. CAN 139:347493 AN 2003:66445 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Animal expts. have shown that short blocking of thymidine (dThd) synthesis with fluorodeoxyuridine (FdUrd) results in significantly increased DNA incorporation of [125I]iododeoxyuridine ([125I]IdUrd) in tumor and rapidly cycling tissues. Based on these results, we give an Auger and gamma radiation dosimetry est. for a scintigraphy study in glioblastoma patients using [123I]IdUrd. The Auger radiation dosimetry calcd. for patients is based on measurement of DNA-incorporated [125I]IdUrd in rapidly dividing tissues in nude mice xenografted with human glioblastoma. Further data obtained 0.5, 6 and 24 h after injection of [125I]IdUrd allowed calcn. of the addnl. gamma radiation exposure using MIRDOSE3.1. High gradients of radioactivity concn. between dividing and non-dividing tissues were obsd. 6 and 24 h after injection of [125I]IdUrd combined with FdUrd pretreatment. While the estd. Auger radiation absorbed doses of [123I]IdUrd in six rapidly cycling normal tissues in patients are low, the equiv. doses become significant with application of the recommended preliminary radiation weighting factor (WR) of 20 for stochastic effects of DNA-assocd. Auger radiation. Using the latter WR, extrapolation of the animal results to the proposed patient injection with 300 MBq [123I]IdUrd combined with FdUrd pretreatment indicates that the ED will be 5.42 mSv, including 1.67 mSv from Auger and 3.75 mSv from gamma radiation. The predicted Auger radiation ED for patients undergoing [123I]IdUrd scintigraphy will be significant if the enhancement of DNA incorporation that is achieved by means of FdUrd pretreatment is similar to that obtained in animals.

Answer 3:

Bibliographic Information

Fluorodeoxyuridine improves imaging of human glioblastoma xenografts with radiolabeled iododeoxyuridine. Dupertuis, Yves M.; Vazquez, Maria; Mach, Jean-Pierre; De Tribolet, Nicolas; Pichard, Claude; Slosman, Daniel O.; Buchegger, Franz. Divisions of Nuclear Medicine and Nutrition, University Medical Center of Geneva, Geneva, Switz. *Cancer Research* (2001), 61(21), 7971-7977. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 136:114834 AN 2001:832812 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Use of radiolabeled nucleotides for tumor imaging is hampered by rapid in vivo degrdn. and low DNA-incorporation rates. We evaluated whether blocking of thymidine (dThd) synthesis by 5-fluoro-2'-deoxyuridine (FdUrd) could improve scintigraphy with radio-dThd analogs, such as 5-iodo-2'-deoxyuridine (IdUrd). We first show in vitro that coincubation with FdUrd substantially increased incorporation of [125I]IdUrd and [3H]dThd in the three tested human glioblastoma lines. Flow cytometry anal. showed that a short coincubation with FdUrd (1 h) produces a signal increase per labeled cell. We then measured biodistribution 24 h after i.v. injection of [125I]IdUrd in nude mice s.c. xenografted with the three glioblastoma lines. Compared with animals given [125I]IdUrd alone, i.v. preadministration for 1 h of 10 mg/kg FdUrd increased the uptake of [125I]IdUrd in the three tumors 4.8-6.8-fold. Compatible with previous reports, there were no side effects in mice obsd. for 2 mo after receiving such a treatment. The tumor uptake of [125I]IdUrd was increased \leq 13.6-fold when FdUrd preadministration was stepwise reduced to 1.1 mg/kg. Uptake increases remained lower (between 1.7- and 5.8-fold) in normal proliferating tissues (i.e., bone marrow, spleen, and intestine) and negligible in quiescent tissues. DNA extn. showed that 72-80% of radioactivity in tumor and intestine was bound to DNA. Scintigraphy of xenografted mice was performed at different times after i.v. injection of 3.7 MBq [125I]IdUrd. Tumor detection was significantly improved after FdUrd preadministration while still equivocal after 24 h in mice given [125I]IdUrd alone. Furthermore, background activity could be greatly reduced by p.o. administration of KClO₄ in addn. to potassium iodide. We conclude that FdUrd preadministration may improve positron or single photon emission tomog. with cell division tracers, such as radio-IdUrd and possibly other dThd analogs.

Answer 4:

Bibliographic Information

Effect of administration of 5-(phenylselenenyl)acyclouridine, an inhibitor of uridine phosphorylase, on the antitumor efficacy of 5-fluoro-2'-deoxyuridine against murine colon tumor C26-10. Ashour, O. M.; Naguib, F. N. M.; Goudgaon, N. M.; Schinazi, R. F.; el Kouni, M. H. Center for AIDS Research, Comprehensive Cancer Center, Department of Pharmacology and Toxicology, University of Alabama at Birmingham, Birmingham, AL, USA. *Biochemical Pharmacology* (2000), 60(5), 687-692. Publisher: Elsevier Science Inc., CODEN: BCPCA6 ISSN: 0006-2952. Journal written in English. CAN 133:246875 AN 2000:526439 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The effect of co-administration of 5-(phenylselenenyl)acyclouridine (PSAU), a new uridine phosphorylase (UrdPase, EC 2.4.2.3) inhibitor, on the efficacy of 5-fluoro-2'-deoxyuridine (FdUrd) was tested against murine colon C26-10 tumor xenografts. In contrast to our previous results with human tumors, co-administration of PSAU with FdUrd decreased instead of increasing the efficacy of FdUrd against tumor growth. However, co-administration of PSAU with FdUrd (300 mg/kg/day) protected the mice completely from the 83% mortality induced by the same dose of FdUrd alone. Enzyme studies indicated that UrdPase in colon C26-10 tumors is responsible for the catabolism of FdUrd to 5-fluorouracil (FUra), as colon C26-10 tumors do not have thymidine phosphorylase (dThdPase, EC 2.4.2.4). In contrast, colon C26-10 tumors had extraordinarily high UrdPase activity (300 μ mol/min/mg protein), which was at least 200-fold higher than the highest UrdPase activity in any of the human xenografts we tested previously. Furthermore, the activities of UrdPase and orotate phosphoribosyltransferase (OPRTase, EC 2.4.2.10) were 192- and 2-fold higher, resp., while that of dihydrouracil dehydrogenase (EC 1.3.1.2) was 1000-fold lower in the tumor than in the host liver. It is suggested that FdUrd exerts its anticancer effects against colon C26-10 tumors mainly through the catabolism of FdUrd to FUra by UrdPase, which then could be anabolized to 5-fluorouridine 5'-monophosphate (FUMP) by OPRTase and ultimately to other toxic 5-fluorouridine nucleotides, hence inducing the obsd. FdUrd toxic effects. Co-administration of PSAU with FdUrd inhibited UrdPase and the catabolism of FdUrd to FUra. This would

result in the obsd. redn. of the antitumor efficacy of FdUrd. In addn., the increase in plasma uridine concn. induced by PSAU as well as the catabolism of FUra by the high dihydrouracil dehydrogenase activity in the liver also may have circumvented any residual FUra toxic effects against the host.

These results clearly demonstrate that the anticancer efficacy of the combination of UrdPase inhibitors and FdUrd is not general and is dependent largely on the type of tumor under treatment and the mode of FdUrd metab. in these tumors.

Answer 5:

Bibliographic Information

The effect of various therapeutic solutions including colloidal chromic 32P via an intratumoral injection on the tumor physiological parameters of AsPC-1 human pancreatic tumor xenografts in nude mice. Lee, Intae; Lee, Young H. Radiation Research Laboratory, Division of Radiation Research, UMDNJ-Robert Wood Johnson Medical School, Camden, NJ, USA. *Clinical Cancer Research* (1999), 5(10, Suppl.), 3139s-3142s. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 132:218943 AN 1999:740245 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

To overcome the physiol. barrier in solid tumors (i.e., tumor hypertension), a large vol. of material is required via an intratumoral injection. Alternatively, a method of redn. in tumor hypertension is also feasible. In this study, we focused on the physiol. response after an intratumoral infusion of various therapeutic agents. Tumor interstitial fluid pressure (TIFP) was intermittently monitored for up to 7 days after treatment using AsPC-1 human pancreatic tumors in nude mice. Macroaggregated albumin (MAA), colloidal chromic 32P (32P-CP), albumin, dexamethasone, 5-fluoro-2'-deoxyuridine, dextrose, saline, and trypan blue increased TIFP within .apprx.5 min, and TIFP returned to the original level within 1 h, except in the case of MAA and 32P-CP. We also found that the maximal uptake for AsPC-1 tumors in both the exponential and plateau growth phases occurred at .apprx.100 min postincubation; the max. value in the exponential growth phase was .apprx.2 times less than that of plateau growth phase ($P < 0.01$). Therefore, this study supports intralesional 32P-CP brachytherapy for nonresectional pancreatic cancer patients. This may offer a promising treatment modality for delivering high doses of tumor-selective radiation, mainly due to two physiol. mechanisms: (a) the high adherence of 32P-CP to the infused regions; and (b) redn. in either tumor blood flow or TIFP by this therapeutic colloid.

Answer 6:

Bibliographic Information

The alkylator treosulfan shows activity towards human renal-cell carcinoma in vivo and in vitro. Koepf-Maier, P. Institut fuer Anatomie, Freie Universitaet Berlin, Berlin, Germany. *In Vivo* (1998), 12(3), 275-288. Publisher: International Institute of Anticancer Research, CODEN: IVIVE4 ISSN: 0258-851X. Journal written in English. CAN 129:285676 AN 1998:550055 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Treosulfan (L-threitol-1,4-bismethanesulfonate, Ovastat) was tested on human renal tumor cells growing as xenografts in athymic nude mice and as monolayers in vitro, in comparison with clin. used cytostatic drugs (in vivo, cyclophosphamide, vinblastine, and 5-fluorouracil; in vitro, vinblastine and 5-fluoro-2'-deoxyuridine) which were administered at equitoxic or equiv. dose levels, resp. Four human renal tumor xenografts (N-U 2, N-U 26, MRI-H 121, KTCTL-1M) were investigated in vivo, and seven renal tumor cell lines (KTCTL-1M, KTCTL-2, KTCTL-26A, KTCTL-30, KTCTL-84, MRI-H 121, N-U 2) under in vitro conditions. The investigations of the four human renal tumor xenografts revealed that treosulfan is capable of inducing pronounced growth inhibitions ranging from 60-100% in comparison with untreated control tumors. In the xenografted renal-cell carcinoma KTCTL-1M, treosulfan administered at the highest dose level (1×3500 mg/kg) even effected a complete remission lasting for more than three weeks in all animals treated with this dose. It was more effective in the N-U 2 carcinoma growing in vivo than the comparative compds. cyclophosphamide and vinblastine. In the heterotransplanted renal-cell carcinoma N-U 26, treosulfan showed a similar activity as the two established cytostatic drugs tested

whereas, in the renal sarcoma MRI-H 121, both cyclophosphamide and vinblastine were slightly more effective than treosulfan. In four renal-cell carcinomas growing as monolayers in vitro (KTCTL-1M, KTCTL-2, KTCTL-84, N-U 2), treosulfan induced cell growth inhibitions by about 50% at peak plasma concn. in comparison with untreated control cultures. The IC₅₀ values ranged from 5×10^{-6} to 10^{-4} mol/L in all seven monolayer cultures investigated. 5-Fluoro-2'-deoxyuridine (floxuridine) was similarly active in vitro as treosulfan with respect to the molar concns.

inducing growth inhibition and to the IC₅₀ values, whereas vinblastine was more effective than treosulfan in most of the human renal tumor cell monolayers investigated. These results reveal the remarkable antitumor efficacy of treosulfan toward human renal-cell carcinomas, esp. under in vivo conditions. This activity was similarly high or even better than in cyclophosphamide and vinblastine. The in vitro data obtained in monolayer cultures also confirmed the remarkable antiproliferative activity of treosulfan in renal tumor cells, but did not mirror very well the pattern of antitumor activity obsd. in vivo.

Answer 7:

Bibliographic Information

Intratumoral chemotherapy with a sustained-release drug delivery system inhibits growth of human pancreatic cancer xenografts. Smith, Jill P.; Stock, Elizabeth; Orenberg, Elaine K.; Yu, Ning Y.; Kanekal, Sarathchandra; Brown, Dennis M. Dep. Medicine, Pennsylvania State Univ., Hershey, PA, USA. *Anti-Cancer Drugs* (1995), 6(6), 717-26. Publisher: Rapid Science Publishers, CODEN: ANTDEV ISSN: 0959-4973. Journal written in English. CAN 124:135020 AN 1996:49697 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

This study provides the first evidence that treatment of human pancreatic adenocarcinoma is markedly improved by the intratumoral administration of chemotherapeutic agents in a novel drug delivery system. The effect of chemotherapeutic agents delivered in a sustained-release, protein-based, injectable gel was evaluated on the growth of human pancreatic adenocarcinoma cell line, BxPC-3. In vitro chemosensitivity of BxPC-3 cells exposed for 24 or 72 h to fluorouracil (0.01-5 mM), cisplatin or doxorubicin (0.1-50 μ M) and floxuridine, vinblastine, mitomycin or paclitaxel (1.0-100 μ M) was compared with that of untreated cells. In vitro chemosensitivity was also studied with fluorouracil and mitomycin in the poorly differentiated PANC-1, human pancreatic cancer cell line. Survival was detd. after 7-10 days. All drugs decreased cell growth in a dose dependent fashion. The efficacy of fluorouracil, cisplatin and doxorubicin increased with prolonged exposure, rendering these drugs most appropriate for a sustained-release prepn. For in vivo studies, athymic nude mice bearing BxPC-3 xenografts were treated either with fluorouracil, cisplatin or doxorubicin in the therapeutic injectable gel contg. epinephrine or with vehicle alone administered intratumorally on days 1 and 4. After 28 days, the mice were sacrificed and tumors dissected and weighed. Tumors in mice treated with the injectable gel decreased in size by 72-79% compared with tumors in untreated controls and tumors treated with vehicle alone. Intratumoral injection of drug soln. and i.p. injection of drug in the injectable gel did not change tumor size compared with controls. In a drug-retention study, mice were injected intratumorally with [³H]fluorouracil either in the injectable gel or in soln. Sustained radioactivity was obsd. in tumors injected with the gel, and, conversely, greater radioactivity was detected in the liver and kidneys in mice receiving the radiolabeled soln.

These results suggest that the therapeutic injectable gel chemotherapy, when given intratumorally, may improve tumor response with less systemic toxicity in comparison with conventional systemic chemotherapy.

Answer 8:

Bibliographic Information

Enhancement of 5-fluoro-2'-deoxyuridine antitumor efficacy by the uridine phosphorylase inhibitor 5-(benzyloxybenzyl)barbituric acid acyclonucleoside. Ashour, Osama M.; Naguib, Fardos N. M.; Khalifa, Mohamed M. A.; Abdel-Raheem, Mahmoud H.; Panzica, Raymond P.; el Kouni, Mahmoud H. Dep. Pharmacology Toxicol., Univ. Alabama, Birmingham, AL, USA. *Cancer Research* (1995), 55(5), 1092-8. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 122:230279 AN 1995:405180 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

5-(Benzyloxybenzyl)barbituric acid acyclonucleoside (BBBA) was recently synthesized as a potent and specific inhibitor of uridine phosphorylase (EC 2.4.2.3), the enzyme responsible for the catabolism of 5-fluoro-2'-deoxyuridine (FdUrd) in many types of tumors that are deficient or have little thymidine phosphorylase (EC 2.4.2.4) activity. The effect of BBBA on modulating the antitumor efficacy of FdUrd was evaluated in vitro, against the human colon carcinomas DLD-1 and HCT-15 grown in culture, and in vivo, against DLD-1 grown as xenografts in anti-thymocyte serum immunosuppressed mice. The concns. of FdUrd that produced 50% growth inhibition after a 3-h exposure were 88 and 340 nM for HCT-15 and DLD-1, resp. BBBA alone, at all concns. tested, had no significant effect on the growth of DLD-1 and HCT-15 in culture. However, BBBA at 5, 10, 20, and 40 nM potentiated the cytotoxicity of FdUrd (340 nM; 3 h) against DLD-1 in culture by 20, 33, 55, and 63%, resp. Similarly, BBBA at 10 and 20 nM potentiated the cytotoxicity of FdUrd (88 nM; 3 h) against HCT-15 in culture by 37 and 45%, resp. In soft agar, BBBA (19 nM) also enhanced the cytotoxic effect of FdUrd (10 and 32 nM) against DLD-1 by 41 and 55%, resp., and against HCT-15 by 6 and 31%, resp. Increasing BBBA dose to 20 nM enhanced further the FdUrd (10 and 32 nM) cytotoxicity against DLD-1 by 76 and 77%, resp., and HCT-15 by 31 and 48%, resp. BBBA also potentiated the chemotherapeutic efficacy of FdUrd in anti-thymocyte serum immunosuppressed mice bearing DLD-1 xenografts with no apparent host toxicity. At a low tumor burden (2.5×10^6 cells/mouse), 2 days treatment with FdUrd alone (50 mg/kg/day \times 2) did not result in significant redn. in tumor vol. Coadministration of BBBA at 5 and 10 mg/kg/day \times 2 did not potentiate the efficacy of FdUrd over that achieved by FdUrd alone, but it significantly reduced the tumor vol. by 27 and 32%, resp., when compared with untreated controls. FdUrd alone at 150 mg/kg/day \times 2 reduced the tumor vol. by 29%. This redn.

in tumor vol. was enhanced 1.8-fold by coadministration of BBBA (10 mg/kg/day \times 2). At a higher tumor burden (5×10^6 cells/mouse) and 4 days treatment, BBBA at 10 and 30 mg/kg/day \times 4 reduced further the tumor vol. produced by FdUrd alone (200 mg/kg/day \times 4) by 1.2- and 1.4-fold, resp. At a higher dose of FdUrd (400 mg/kg/day \times 4), the potentiation by BBBA (10 and 30 mg/kg/day \times 4) was 1.6- and 3.4-fold, resp. Enzyme studies suggest that the lower sensitivity to FdUrd and the better potentiation of FdUrd cytotoxicity by BBBA in DLD-1 as compared to HCT-15 could be attributed to higher uridine phosphorylase activity in DLD-1. There were no significant differences between DLD-1 and HCT-15 in the activities of other enzymes involved in FdUrd metab. Enzyme studies also indicated that DLD-1 and HCT-15, in contrast to host tissues, contain no thymidine phosphorylase and have higher kinase activities towards FdUrd. Therefore, the enhancement of FdUrd antitumor efficacy by BBBA appears to be due to the specific inhibition of uridine phosphorylase. Such inhibition would selectively prevent catabolism and deactivation of FdUrd in the tumors but not in the host. The selective inhibition of FdUrd catabolism along with the higher thymidine kinase activities in the tumors would channel the metab. of FdUrd in the tumors towards anabolism and formation of its active metabolite 5-fluoro-dUMP to produce the selective toxicity of FdUrd. These findings may lead to a more successful use of FdUrd in cancer chemotherapy, esp. against tumors that lack thymidine phosphorylase.

Answer 9:

Bibliographic Information

Bromodeoxyuridine-mediated radiosensitization in human glioma: the effect of concentration, duration, and fluoropyrimidine modulation. McLaughlin, Patrick W.; Lawrence, Theodore S.; Seabury, Heather; Nguyen, Nguyen; Stetson, Phillip L.; Greenberg, Harry S.; Mancini, William R. Medical Center, University of Michigan, Ann Arbor, MI, USA. International Journal of Radiation Oncology, Biology, Physics (1994), 30(3), 601-7. CODEN: IOBPD3 ISSN: 0360-3016. Journal written in English. CAN 122:26860 AN 1995:235397 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The relative influence of duration of exposure, concn., and modulation by fluorodeoxyuridines (FdUrd) on the incorporation of 5-bromo-2-deoxyuridine (BrdUrd) into DNA of a human malignant glioma line (D-54) in vitro and in vivo was studied. In vitro studies, an established human malignant glioma line (D-54) was exposed to a clin. achievable concn. of BrdUrd to model i.v. (1 μ M BrdUrd) and intraarterial (4 μ M BrdUrd) conditions. The influence of modulation was assessed using 1 nM FdUrd. Incorporation of BrdUrd, radiosensitization, and cytotoxicity were detd. after 24, 72, and 120 h drug exposures. In in vivo studies, nude mice bearing D-54 xenografts were infused with BrdUrd at 100 mg/kg/day for 7 and 14 days or BrdUrd at 400 mg/kg/day for 5 days. The influence of modulation was assessed by combining 100 mg/kg/day of BrdUrd with 0.1, 0.3, and 1 mg/kg/day FdUrd for 7 days. Incorporation of BrdUrd into the DNA of tumor, gut, and marrow were detd. In vitro, thymidine replacement and radiosensitization were a function of concn., and incorporation began to plateau after 2 to 3 population doublings. Modulation with 1 nM FdUrd significantly increased incorporation. Radiosensitization was a linear function of thymidine replacement under all conditions tested. In vivo, infusion with 400

mg/kg/day for 5 days resulted in greater tumor incorporation ($10.3 \pm 0.4\%$ thymidine replaced) than treatment with 100 mg/kg/day for 14 days ($6.0 \pm 0.6\%$ of thymidine replaced). Infusion of FdUrd with BrdUrd increased normal tissue incorporation of BrdUrd, but failed to increase BrdUrd incorporation in tumor cells. These results suggest that relatively short, high dose rate infusions may be preferable to long, low dose rate infusions. The potential benefit of FdUrd modulation demonstrated *in vitro* may be difficult to realize using continuous systemic infusions.

Answer 10:

Bibliographic Information

The potential superiority of bromodeoxyuridine to iododeoxyuridine as a radiation sensitizer in the treatment of colorectal cancer. Lawrence, Theodore S.; Davis, Mary A.; Maybaum, Jonathan; Mukhopadhyay, Sunil K.; Stetson, Philip L.; Normolle, Daniel P.; McKeever, Paul E.; Ensminger, William D. Med. Cent., Univ. Michigan, Ann Arbor, MI, USA. Cancer Research (1992), 52(13), 3698-704. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 117:107414 AN 1992:507414 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Although the thymidine analogs 5-bromo-2'-deoxyuridine (BrdUrd) and 5-iodo-2'-deoxyuridine (IdUrd) have been used successfully as radiation sensitizers in clin. trials, it is not clear which of these agents is the more promising to pursue. To begin to assess this question with regard to colorectal cancer metastatic to the liver, a study was carried out using HT29 human colon cancer cells in culture and implanted in nude mice as xenografts. Cells and animals were treated with BrdUrd \pm the thymidylate synthase inhibitor 5-fluoro-2'-deoxyuridine (FdUrd), and the results compared to previous studies with IdUrd \pm FdUrd. Using cultured cells, it was found that FdUrd (at concns. of ≥ 10 nM) increased (a) the incorporation of BrdUrd into the DNA of cultured tumor cells, (b) BrdUrd-mediated radiosensitization, (c) BrdUrd-mediated increase in radiation-induced DNA damage, and (d) BrdUrd-mediated decrease in the repair of radiation-induced damage. The incorporation of BrdUrd was greater than or equal to the incorporation of IdUrd previously detd. under the same exposure conditions. Studies using nude mice bearing HT29 xenografts showed that FdUrd increased BrdUrd incorporation more into tumors than into the normal liver. Most tumor cells incorporated BrdUrd (labeling index after a 4-day infusion = 87%); in the liver, labeling was confined chiefly to nonparenchymal cells. In both the presence and absence of FdUrd, the incorporation of BrdUrd into tumors was significantly and consistently greater than the incorporation of IdUrd measured under the same conditions of drug administration (by a factor of 1.2-3.6). Furthermore, the administration of BrdUrd \pm FdUrd tended to produce less wt. loss and hematol. toxicity than IdUrd \pm FdUrd. BrdUrd may be superior to IdUrd as a radiation sensitizer in the treatment of colorectal cancer metastatic to the liver.

Answer 11:

Bibliographic Information

Antitumor effect of 2'-deoxy-5-fluorouridine conjugates against a murine thymoma and colon carcinoma xenografts. Krauer, Kenia G.; McKenzie, Ian F. C.; Pietersz, Geoffrey A. Austin Res. Inst., Austin Hosp., Heidelberg, Australia. Cancer Research (1992), 52(1), 132-7. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 116:98977 AN 1992:98977 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The conjugation of antineoplastic drugs to monoclonal antibodies reactive with tumor assocd. antigens conveys selective cytotoxicity, overcoming the systemic toxicities caused by drugs during std. chemotherapy. 2'-Deoxy-5-fluorouridine, a more potent deriv. of 5-fluorouracil, is an antimetabolite which exerts its cytotoxic action by inhibiting the enzyme thymidylate synthetase and as a result inhibits DNA synthesis. 2'-Deoxy-5-fluorouridine was successfully conjugated to anti-Ly-2.1 reactive with the murine thymoma ITT(1)75NS E3, 1-1, and 250-30.6 reactive with human colon cancer cells using the active ester of 2'-deoxy-5-fluoro-3'-O-succinoyluridine (5FdUrdsucc). *In vitro*, 5FdUrdsucc-anti-Ly-2.1 was selectively cytotoxic against ITT(1)75NS E3 murine thymoma cells at nanomolar concns. The human colon carcinoma cell LIM1899 was inhibited by 5FdUrdsucc-I-1 conjugates

in the range of 10⁻⁷-10⁻⁸ M, as were Colo 20222 cells by 5FdUrdsucc-250-30.6 conjugates. In vivo, 5FdUrdsucc conjugates were more effective than equiv. amts. of free 5FdUrdsucc. Against the ITT(1)75NS E3 murine thymoma, a single dose of 100 µg (5FdUrdsucc equiv.) 5FdUrdsucc-anti-Ly-2.1 resulted in 85% tumor inhibition compared to mean tumor size of control mice. Irrelevant 5FdUrdsucc conjugates failed to inhibit tumor growth. Multiple doses of 5FdUrdsucc-I-1 conjugate produced 50% growth inhibition of the moderately differentiated tumor LIM1899. In contrast, the human colon carcinoma Colo 205 was relatively resistant to free 5FdUrdsucc and 5FdUrdsucc-250-30.6 conjugates.

Answer 12:

Bibliographic Information

Fluorodeoxyuridine-mediated modulation of iododeoxyuridine incorporation and radiosensitization in human colon cancer cells in vitro and in vivo. Lawrence, Theodore S.; Davis, Mary A.; McKeever, Paul E.; Maybaum, Jonathan; Stetson, Philip L.; Normolle, Daniel P.; Ensminger, William D. Med. Cent., Univ. Michigan, Ann Arbor, MI, USA. Cancer Research (1991), 51(15), 3900-5. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 115:153988 AN 1991:553988 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A study was conducted to assess the potential of 5-fluoro-2'-deoxyuridine (FdUrd) to increase the incorporation and radiosensitizing properties of 5-iodo-2'-deoxyuridine (IdUrd) using HT29 human colon cancer cells both in vitro and in nude mice bearing these tumors as xenografts. The purpose of this study was to assess (a) whether FdUrd could increase IdUrd efficacy using clin. achievable concns. of drugs, (b) the relationship among radiosensitization, DNA damage and repair, and analog incorporation, and (c) whether FdUrd improved the selectivity of IdUrd incorporation into tumor cells compared to normal tissues. It was found that FdUrd, at clin. achievable concns. (1-100 nM), increased IdUrd incorporation under all conditions but particularly when the IdUrd concn. was ≤10 µM. FdUrd increased IdUrd-mediated radiosensitization in proportion to the increase in IdUrd incorporation. FdUrd potentiated the ability of IdUrd to increase radiation-induced DNA double-strand breaks and to slow their repair. When IdUrd alone (100 and 200 mg/kg/day) was infused into nude mice bearing tumors, the extent of thymidine replaced in the tumor was 1.6 (mean) and 2.5%, resp. The combination of FdUrd (0.1 mg/kg/day) and IdUrd (100 mg/kg/day) increased the incorporation in the tumor to 5.3% with less toxicity than that resulting from the use of 200 mg/kg/day of IdUrd alone. These data show that FdUrd is an effective biomodulator, because, for the same extent of normal tissue incorporation, the combination of IdUrd and FdUrd produces greater incorporation into the tumor compared to the use of IdUrd alone. Furthermore, it is suggested that the regional application of FdUrd with IdUrd, either through the use of regional infusions or in combination with focused irrads., could potentially improve the outcome of treatment of localized gastrointestinal cancer.

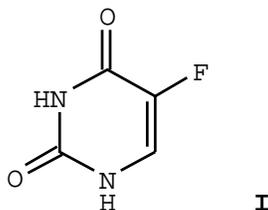
Answer 13:

Bibliographic Information

On the mechanism of cytotoxicity of fluorinated pyrimidines in four human colon adenocarcinoma xenografts maintained in immune-deprived mice. Houghton, Janet A.; Houghton, Peter J. Dep. Biochem., St. Jude Children's Res. Hosp., Memphis, TN, USA. Cancer (New York, NY, United States) (1980), 45(5), 1159-67. CODEN: CANCAR ISSN: 0008-543X. Journal written in English. CAN 95:35528 AN 1981:435528 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Three fluorinated pyrimidines, 5-fluorouracil (FUra)(I) [51-21-8], 5-fluorouridine (FUrd) [316-46-1], and 5-fluoro-2'-deoxyuridine (FdUrd) [50-91-9], were studied in 4 human colonic tumor xenograft lines. After equimolar dosages, the agent reaching the highest concn. in the tumor produced the highest level of fluorodeoxyuridylate (FdUMP) [134-46-3]; within a tumor line, the order of response to the three agents is related to the order of FdUMP-generation; the tumor-response did not correspond to the level of analog-incorporation into RNA; the measurement of levels of free FdUMP in tumors is a poor prognostic indicator of drug-response; and the levels of FdUMP in the tumors are maintained for considerable periods and appear to be dependent upon the maintenance of the levels of either FUra or FUrd, irres. of the parent agent administered.



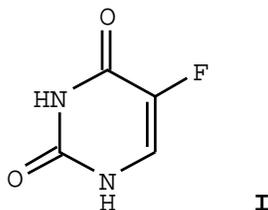
Answer 14:

Bibliographic Information

Biochemical determinants of responsiveness to 5-fluorouracil and its derivatives in xenografts of human colorectal adenocarcinomas in mice. Houghton, Janet A.; Maroda, Stephen J., Jr.; Phillips, John O.; Houghton, Peter J. Div. Biochem. Clin. Pharmacol., St. Jude Children's Res. Hosp., Memphis, TN, USA. *Cancer Research* (1981), 41(1), 144-9. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 94:95907 AN 1981:95907 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The level of thymidylate synthetase (EC 2.1.1.45) [9031-61-2] and its activity were measured in a series of human colorectal adenocarcinomas growing as xenografts in immune-deprived mice. Enzyme activity varied between 8.4 and 124 pmol/mg protein/h; within each tumor line, this activity correlated with the capacity to bind 3H-labeled 5-fluoro-2'-deoxyuridine 5'-monophosphate ([6-3H]FdUMP) [134-46-3], which varied between 0.16 and 1.68 pmol [6-3H]FdUMP bound per g tissue. Highest and lowest activities were measured in tumor lines that were insensitive to 5-fluorouracil (I) [51-21-8], 5-fluorouridine [316-46-1], and 5-fluoro-2'-deoxyuridine [50-91-9]. The ratio of the max. free FdUMP concn. to thymidine 5'-monophosphate synthetase-binding activity did not differentiate fluorinated pyrimidine-responsive lines from those innately insensitive. Max. potential binding of [6-3H]FdUMP in vitro was measured without addn. of dL-L-5,10-methylenetetrahydrofolate (CH₂FH₄) in cytosol from 2 tumor lines, both of which demonstrated some sensitivity to fluorinated pyrimidine therapy. The other 4 insensitive tumor lines required CH₂FH₄ to be added in order to attain max. [6-3H]FdUMP binding. Similar data were obtained using nitrocellulose membrane filtration to isolate both covalent and noncovalent complexes. Direct measurement of thymidine 5'-monophosphate synthetase activity after incubation of tumor cytosols with FdUMP, with or without added CH₂FH₄, showed that, in nonresponsive tumors, max. enzyme inhibition was achieved only in the presence of exogenous cofactor. It is suggested that the availability of cofactor may prove important in the formation of the ternary complex CH₂FH₄-thymidine 5'-monophosphate synthetase-FdUMP when high concns. of FdUMP are present for only short periods of time.



Answer 15:

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 16:

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 17:

Bibliographic Information

Changes of gene expression of thymidine phosphorylase, thymidylate synthase, dihydropyrimidine dehydrogenase after the administration of 5'-deoxy-5-fluorouridine, paclitaxel and its combination in human gastric cancer xenografts. Sakurai Yoichi; Yoshida Ikuo; Kamoshida Shingo; Inaba Kazuki; Isogaki Jun; Komori Yoshiyuki; Uyama Ichiro; Tsutsumi Yutaka Department of Surgery, Fujita Health University School of Medicine, Toyoake, Aichi 470-1192, Japan. ysakurai@fujita-hu.ac.jp Anticancer research (2008), 28(3A), 1593-602. Journal code: 8102988. ISSN:0250-7005. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 18630517 AN 2008455778 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

BACKGROUND: Although a variety of combination chemotherapies has been tested in gastric carcinoma, the most effective chemotherapeutic regimen and the precise mechanisms underlying anticancer agent combination have not yet been sufficiently elucidated. **MATERIALS AND METHODS:** Experimental chemotherapy was performed using human gastric carcinoma xenografts, MKN-45 and TMK-1, to examine the anticancer effects and gene expressions of the enzymes involved in 5-fluorouracil metabolism, thymidine phosphorylase (dThdPase), thymidylate synthase (TS) and dihydropyrimidine dehydrogenase (DPD). Nude mice were treated with 5'-deoxy-5-fluorouridine (5'-dFUrd), or paclitaxel alone or in combination. The in vivo antitumor effects on gene expressions of the enzymes were examined using the quantitative real-time RT-PCR method. **RESULTS:** The combined use of 5'-dFUrd and paclitaxel showed additive to synergistic antitumor effects on both gastric cancer xenografts. There were significant differences of the gene

expressions of dThdPase, TS, and DPD between the xenografts. The expression of dThdPase mRNA was consistently up-regulated by the administration of paclitaxel, while no constant direction of TS mRNA and DPD mRNA change was found in the xenografts. **CONCLUSION:** A synergistic antitumor effect of the combined administration of 5'-dFUrd and paclitaxel was found in gastric cancer xenografts and up-regulation of dThdPase mRNA may be an important underlying mechanism especially in tumors with high gene expression of this enzyme.

Answer 18:

Bibliographic Information

Increased preclinical efficacy of irinotecan and floxuridine coencapsulated inside liposomes is associated with tumor delivery of synergistic drug ratios. Harasym Troy O; Tardi Paul G; Harasym Natasha L; Harvie Pierrot; Johnstone Sharon A; Mayer Lawrence D Celator Pharmaceuticals Corp., Vancouver BC, V6P 6P2 Canada Oncology research (2007), 16(8), 361-74. Journal code: 9208097. ISSN:0965-0407. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 17913044 AN 2007592352 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Whether anticancer drug combinations act synergistically or antagonistically often depends on the ratio of the agents being combined. We show here that combinations of irinotecan and floxuridine exhibit drug ratio-dependent cytotoxicity in a broad panel of tumor cell lines in vitro where a 1:1 molar ratio consistently provided synergy and avoided antagonism. In vivo delivery of irinotecan and floxuridine coencapsulated inside liposomes at the synergistic 1:1 molar ratio (referred to as CPX-1) lead to greatly enhanced efficacy compared to the two drugs administered as a saline-based cocktail in a number of human xenograft and murine tumor models. When compared to liposomal irinotecan or liposomal floxuridine, the therapeutic activity of CPX-1 in vivo was not only superior to the individual liposomal agents, but the extent of tumor growth inhibition was greater than that predicted for combining the activities of the individual agents. In contrast, liposome delivery of irinotecan:floxuridine ratios shown to be antagonistic in vitro provided antitumor activity that was actually less than that achieved with liposomal irinotecan alone, indicative of in vivo antagonism. Synergistic antitumor activity observed for CPX-1 was associated with maintenance of the 1:1 irinotecan:floxuridine molar ratio in plasma and tumor tissue over 16-24 h. In contrast, injection of the drugs combined in saline resulted in irinotecan:floxuridine ratios that changed 10-fold within 1 h in plasma and sevenfold within 4 h in tumor tissue. These results indicate that substantial improvements in the efficacy of drug combinations may be achieved by maintaining in vitro-identified synergistic drug ratios after systemic administration using drug delivery vehicles.

Answer 19:

Bibliographic Information

The Hollow Fibre Assay as a model for in vivo pharmacodynamics of fluoropyrimidines in colon cancer cells. Temmink O H; Prins H-J; van Gelderop E; Peters G J Department of Medical Oncology, VU University Medical Center, Amsterdam, The Netherlands British journal of cancer (2007), 96(1), 61-6. Journal code: 0370635. ISSN:0007-0920. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 17179993 AN 2007016737 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The Hollow Fibre Assay (HFA) is usually applied as an early in vivo model for anti-cancer drug screening, but is potentially an excellent model for short-term in vivo pharmacodynamic studies. We used the model to study the in vivo role of thymidine phosphorylase/platelet-derived endothelial cell growth factor (TP/PD-ECGF) in the cytotoxicity and pharmacodynamics of TAS-102 in colon cancer cells. TAS-102 is a new oral drug formulation, which is composed of

trifluorothymidine (TFT) and thymidine phosphorylase inhibitor (TPI), which prevents TFT degradation. We compared the activity with Xeloda (capecitabine), which is activated by TP into 5FU. Hollow fibres filled with human Colo320 or Colo320TP1 colorectal cancer cells with deficient or high TP expression, respectively, were implanted subcutaneously (s.c.) at both flanks of BALB/c mice. The mice were treated orally over 5 days with TAS-102, TFT alone, 5'DFUR+/-TPI or capecitabine at their maximum tolerated dose (MTD). The cells were retrieved from the fibres and assayed for growth (MTT assay), cell cycle distribution (flow cytometry) and apoptosis induction (FragEL method). TAS-102 induced considerable growth inhibition (50%, $P < 0.01$) to both cell lines, which was completely abolished in the absence of TPI. Capecitabine and its metabolite 5'DFUR reduced proliferation of Colo320TP1 cells in the fibres significantly (down to 25-40%), but much less in Colo320 cells, whereas addition of TPI reduced the effect of 5'DFUR, although not completely. These differences in cytotoxic effects were reflected in the pharmacodynamic evaluation. TAS-102 induced a G2M-phase arrest (from 25 to 40%) and apoptosis (>8-fold), which was more pronounced in Colo320 than in Colo320TP1. Again, omission of TPI neutralised the effect of TAS-102. Similarly, 5'DFUR and capecitabine induced a significant G2M-phase arrest (up to 45%) in the Colo320TP1 cell line, but less pronounced in the parental Colo320. Addition of TPI to 5'DFUR reduced this effect to control levels.

Also induction of apoptosis was reduced in the presence of TPI. The data demonstrated that the HFA is excellently suited for studying short-term pharmacodynamic effects of fluoropyrimidines *in vivo*. TAS-102 is only effective in inducing cytotoxicity when systemic TPI is present, but acts against both low and high TP expressing colon cancer cells, while 5'DFUR needs cellular TP to exert significant activity.

Answer 20:

Bibliographic Information

Ratiometric dosing of anticancer drug combinations: controlling drug ratios after systemic administration regulates therapeutic activity in tumor-bearing mice. Comment in: *Mol Cancer Ther.* 2006 Jul;5(7):1639-40. PubMed ID: 16891448 Mayer Lawrence D; Harasym Troy O; Tardi Paul G; Harasym Natasha L; Shew Clifford R; Johnstone Sharon A; Ramsay Euan C; Bally Marcel B; Janoff Andrew S Celator Pharmaceuticals Corp., 1779 West 75th Avenue, Vancouver, BC, Canada V6P 6P2. Imayer@celatorpharma.com *Molecular cancer therapeutics* (2006), 5(7), 1854-63. Journal code: 101132535. ISSN:1535-7163. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 16891472 AN 2006468184 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Anticancer drug combinations can act synergistically or antagonistically against tumor cells *in vitro* depending on the ratios of the individual agents comprising the combination. The importance of drug ratios *in vivo*, however, has heretofore not been investigated, and combination chemotherapy treatment regimens continue to be developed based on the maximum tolerated dose of the individual agents. We systematically examined three different drug combinations representing a range of anticancer drug classes with distinct molecular mechanisms (irinotecan/floxuridine, cytarabine/daunorubicin, and cisplatin/daunorubicin) for drug ratio-dependent synergy. In each case, synergistic interactions were observed *in vitro* at certain drug/drug molar ratio ranges (1:1, 5:1, and 10:1, respectively), whereas other ratios were additive or antagonistic. We were able to maintain fixed drug ratios in plasma of mice for 24 hours after *i.v.* injection for all three combinations by controlling and overcoming the inherent dissimilar pharmacokinetics of individual drugs through encapsulation in liposomal carrier systems. The liposomes not only maintained drug ratios in the plasma after injection, but also delivered the formulated drug ratio directly to tumor tissue. *In vivo* maintenance of drug ratios shown to be synergistic *in vitro* provided increased efficacy in preclinical tumor models, whereas attenuated antitumor activity was observed when antagonistic drug ratios were maintained. Fixing synergistic drug ratios in pharmaceutical carriers provides an avenue by which anticancer drug combinations can be optimized prospectively for maximum therapeutic activity during preclinical development and differs from current practice in which dosing regimens are developed empirically in late-stage clinical trials based on tolerability.

Answer 21:

Bibliographic Information

Simultaneous determination of capecitabine and its metabolites by HPLC and mass spectrometry for preclinical and clinical studies. Guichard Sylvie M; Mayer Iain; Jodrell Duncan I Pharmacology and Drug Development Team, Cancer Research UK Centre, University of Edinburgh, Crewe Road, Edinburgh EH4 2XR, UK. Sylvie.guichard@cancer.org.uk Journal of chromatography. B, Analytical technologies in the biomedical and life sciences (2005), 826(1-2), 232-7. Journal code: 101139554. ISSN:1570-0232. Journal; Article; (JOURNAL ARTICLE); (VALIDATION STUDIES) written in English. PubMed ID 16198157 AN 2005550728 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

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

Answer 22:

Bibliographic Information

Enhancement of antitumor activity of 5'-deoxy-5-fluorouridine (Furtulon) by taxane in human gastric cancer xenografts. Sawada Noriaki; Nose Taeko; Ishikawa Tohru; Yutaka Tanaka Product Research Department, Chugai Pharmaceutical Co., Ltd., 200 Kajiwara, Kamakura, Kanagawa 247-8530, Japan. sawadanra@chugai-pharm.co.jp Oncology reports (2005), 14(1), 53-7. Journal code: 9422756. ISSN:1021-335X. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 15944767 AN 2005298644 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

5'-deoxy-5-fluorouridine (5'-DFUR, Furtulon) is activated to 5-fluorouracil (5-FU) by thymidine phosphorylase (dThdPase) highly expressed in many types of tumors. In previous studies, we demonstrated that taxanes (paclitaxel or docetaxel) up-regulated the tumor levels of dThdPase and enhanced the efficacy of 5'-DFUR in human colon and mammary xenograft models. In the present study, combination therapy of 5'-DFUR with taxanes in human gastric cancer xenograft models also showed, at the least, additive anti-tumor activity without significant augmentation of toxicity. Furthermore, paclitaxel up-regulated dThdPase expression in the tumor tissues as confirmed with ELISA and immunohistochemistry. These results suggest taxanes would potentiate the efficacy of 5'-DFUR by up-regulating the tumor levels of dThdPase in gastric xenograft models. Clinical trials of 5'-DFUR in combination with taxane against gastric cancer are warranted.

Answer 23:

Bibliographic Information

Correlations between antitumor activities of fluoropyrimidines and DPD activity in lung tumor xenografts. Takechi Teiji; Okabe Hiroyuki; Ikeda Kazumasa; Fujioka Akio; Nakagawa Fumio; Ohshimo Hideyuki; Kitazato Kenji; Fukushima Masakazu Cancer Research Laboratory, Product Lifecycle Management Department, Taiho Pharmaceutical Co., Ltd., 1-27 Kanda-Nishikicho, Chiyoda-ku, Tokyo 101-8444, Japan. ttakechi@taiho.co.jp Oncology reports (2005), 14(1), 33-9. Journal code: 9422756. ISSN:1021-335X. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 15944764 AN 2005298641 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

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

Answer 24:

Bibliographic Information

Sequential treatment with irinotecan and doxifluridine: optimal dosing schedule in murine models and in a phase I study for metastatic colorectal cancer. Mishima Hideyuki; Kato Takeshi; Yanagisawa Mieko; Tsujinaka Toshimasa; Nishisho Isamu; Tsujie Masaki; Fujimoto-Ouchi Kaori; Tanaka Yutaka; Kikkawa Nobuteru Department of Surgery, Osaka National Hospital, Osaka, Japan. hmishima@onh.go.jp Chemotherapy (2005), 51(1), 32-9. Journal code: 0144731. ISSN:0009-3157. (CLINICAL TRIAL); (CLINICAL TRIAL, PHASE I); (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 15767743 AN 2005178633 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

BACKGROUND: Irinotecan (CPT-11) and doxifluridine (5'-DFUR) are active agents against colorectal cancer. Each drug, however, has the possibility of causing diarrhea. **METHODS AND RESULTS:** First, we determined the optimal dosing regimen in murine models. CPT-11 (i.v., q2d x 3) and 5'-DFUR (p.o., qd x 14) were administered to mice bearing a human colorectal cancer xenograft model. Diarrhea was stronger in the simultaneously administered schedule but not much stronger in the sequentially administered schedule compared with monotherapies. Both schedules yielded similar antitumor efficacies. Next, we conducted a phase I study combining CPT-11 on days 1 and 15, and 5'-DFUR on days 3-14 and 17-28 every 5 weeks in 19 patients with metastatic colorectal cancer. The doses of CPT-11 ranged from 80 to 150 mg/m² and those of 5'-DFUR from 800 to 1,200 mg. Diarrhea of grade 3/4 developed in only 1 patient at 100 mg/m²/800-mg doses. Dose-limiting toxicities were hyperbilirubinemia and skipping doses due to fatigue at 150 mg/m²/1,200-mg doses. **CONCLUSION:** For the phase II study, the recommended dose was set at CPT-11 150 mg/m² and 5'-DFUR 800 mg. Copyright 2005 S. Karger AG, Basel.

Answer 25:

Bibliographic Information

A novel combination antimetabolite, TAS-102, exhibits antitumor activity in FU-resistant human cancer cells through a mechanism involving FTD incorporation in DNA. Emura Tomohiro; Suzuki Norihiko; Yamaguchi Masahiro; Ohshimo Hideyuki; Fukushima Masakazu Second Cancer Research Laboratory, Hanno Research Center, Taiho Pharmaceutical Co., Ltd., 1-27 Misugidai, Hanno-city, Saitama 357-8527, Japan. t-emura@taiho.co.jp International journal of oncology (2004), 25(3), 571-8. Journal code: 9306042. ISSN:1019-6439. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 15289858 AN 2004385335 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

TAS-102 is a new antimetabolite agent composed of a alpha, alpha, alpha-trifluorothymidine (FTD; 1 M) and thymidine phosphorylase inhibitor (TPI; 0.5 M). Here, we investigated the antitumor effect and mechanism of TAS-102 against 5-FU, or FdUrd, resistant human cancer cell lines. The respective tumor growth inhibition rate of orally administered FTD against 5-FU-resistant NUGC-3 was about 70% at a dose level of 200 mg/kg/day; this value was comparable to that against the parental NUGC-3. On the other hand, the tumor inhibition rates of 5-FU, FdUrd, and TS-1 against 5-FU-resistant NUGC-3 were lower than those against parental NUGC-3. Similar observations were made in an FdUrd-resistant human colorectal cancer cell line (DLD-1). TAS-102 was also effective in 5-FU-less sensitive human pancreatic cancer cell lines (PAN-12 and BxPC-3) and human esophagus cancer (T.T.) when compared with 5-FU or UFT. Our hypothesis was that a relatively short and high dosage of TAS-102 results in an additional mechanism of FTD incorporation into DNA other than thymidylate synthase (TS) inhibition. We then examined the effects of FTD on DNA at the cellular level. After treatment with FTD or FdUrd, the DNA fragmentation pattern was examined using filter elution and in situ nick translation. Treatment with FTD for 2 h resulted in marked DNA fragmentation. When the tumor cells were treated with FTD for 72 h or with FdUrd for 2 or 72 h, only a small amount of DNA fragmentation was observed, and the appearance of the tumor cells did not differ markedly from that of untreated cells. Moreover, the DNA fragmentation rate in the TAS-102 treatment group was significantly higher than that in the control group in vivo. These results suggest that when tumor cells are exposed to high concentrations of FTD for short periods of time, FTD manifests its antitumor activity primarily through the induction of DNA fragmentation after FTD incorporation into the DNA.

We conclude that TAS-102 is expected to manifest antitumor effects against 5-FU-resistant tumors that are similar to those exerted in 5-FU-sensitive tumors.

Answer 26:

Bibliographic Information**Rational combinations of trastuzumab with chemotherapeutic drugs used in the treatment of breast cancer.**

Comment in: J Natl Cancer Inst. 2004 May 19;96(10):725-7. PubMed ID: 15150294 PEGRAM Mark D; KONECNY Gottfried E; O'CALLAGHAN Carminda; BERYT Malgorzata; PIETRAS Richard; SLAMON Dennis J Division of Hematology/Oncology, Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles 90095-7077, USA Journal of the National Cancer Institute (2004), 96(10), 739-49. Journal code: 7503089. E-ISSN:1460-2105. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 15150302 AN 2004251719 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

BACKGROUND: Trastuzumab, a humanized anti-HER2 antibody, increases the clinical benefit of first-line chemotherapy in patients with metastatic breast cancers that overexpress HER2. We characterized interactions between trastuzumab and chemotherapeutic agents commonly used in the treatment of breast cancer. **METHODS:** Multiple drug effect/combination index isobologram analysis was used to study the efficacy of chemotherapeutic drug plus trastuzumab combinations tested against four HER2-overexpressing breast cancer cell lines (SK-BR-3, BT-474, MDA-MB-361, and MDA-MB-453). Combination index values were derived from parameters of the median effect plots, and statistical tests were used to determine whether the mean combination index values at multiple effect levels were statistically significantly different from a combination index value of 1.0. Values less than 1.0 indicate synergistic interactions, values greater than 1.0 indicate antagonistic interactions, and values equal to 1.0 indicate additive interactions. **RESULTS:** At a wide range of clinically achievable drug concentrations, synergistic interactions were observed in all four breast cancer cell lines for trastuzumab plus carboplatin (mean combination index values ranged from 0.32 [P<.001] to 0.53 [P<.001]), 4-hydroxycyclophosphamide (mean combination index values ranged from 0.38 [P<.001] to 0.73 [P =.010]), docetaxel (mean combination index values ranged from 0.30 [P<.001] to 0.62 [P<.001]), and vinorelbine (mean combination index values ranged from 0.24 [P<.001] to 0.78 [P<.034]). Additive interactions were observed in all four cell lines with trastuzumab plus doxorubicin, epirubicin, and paclitaxel. Interactions between trastuzumab and gemcitabine were synergistic at low concentrations of gemcitabine and antagonistic at high concentrations. A synergistic interaction was observed with a three-drug combination of docetaxel plus carboplatin plus trastuzumab in SK-BR-3 cells (mean combination index value = 0.09; P<.001).

CONCLUSION: Consistent synergistic interactions of trastuzumab plus carboplatin, 4-hydroxycyclophosphamide, docetaxel, or vinorelbine across a wide range of clinically relevant concentrations in HER2-overexpressing breast cancer cells indicate that these are rational combinations to test in human clinical trials.

Answer 27:

Bibliographic Information

Comparison of intraperitoneal continuous infusion of floxuridine and bolus administration in a peritoneal gastric cancer xenograft model. Inoue Kentaro; Onishi Hiraku; Kato Yoshinori; Michiura Taku; Nakai Koji; Sato Mutsuya; Yamamichi Keigo; Machida Yoshiharu; Nakane Yasushi Second Department of Surgery, Kansai Medical University, Osaka, Japan. inoueke@takii.kmu.ac.jp Cancer chemotherapy and pharmacology (2004), 53(5), 415-22. Journal code: 7806519. ISSN:0344-5704. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 15132129 AN 2004232877 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

PURPOSE: To identify the optimal schedule for intraperitoneal (i.p.) infusion of floxuridine (FUDR) against peritoneal micrometastases from gastric cancer. **METHODS:** The efficacy of continuous i.p. infusion of FUDR was compared with that of bolus i.p. administration in peritoneal gastric cancer (MKN45) xenografts. The FUDR continuous delivery system in this study was in the form of injectable poly(lactic-coglycolic) acid (PLGA) microspheres intended for i.p. injection. Animals were treated by continuous i.p. infusion using FUDR-loaded microspheres or bolus i.p. administration of FUDR. **RESULTS:** In vitro testing demonstrated that FUDR was released slowly from the microspheres at a rate of approximately 5% of the total encapsulated drug per day. In in vivo studies, the peritoneal level was found to persist and was approximately 5- to 50-fold higher than that of plasma for more than 2 weeks following a single injection of the microspheres. An in vitro MTT assay showed that exposure time clearly influenced the cytotoxic potency of FUDR. In vivo, continuous infusion was more effective against peritoneal tumor than bolus administration at equivalent doses. However, compared with bolus administration, toxicity was increased, resulting in a reduced maximum tolerated dose (MTD) with continuous infusion. When the treatment was carried out at each MTD (continuous 1 mg/kg, bolus 600 mg/kg), continuous infusion had no advantage in inhibiting tumor growth. **CONCLUSIONS:** Owing to the higher toxicity and the equal efficacy of continuous infusion compared with bolus administration, continuous infusion is not recommended in i.p. FUDR treatment.

Answer 28:

Bibliographic Information

Highly efficient DNA incorporation of intratumourally injected [125I]iododeoxyuridine under thymidine synthesis blocking in human glioblastoma xenografts. Buchegger Franz; Adamer Florence; Schaffland Andreas Oliver; Kosinski Marek; Grannavel Carine; Dupertuis Yves Marc; de Tribolet Nicolas; Mach Jean-Pierre; Delaloye Angelika Bischof Division of Nuclear Medicine, University Hospital of Lausanne, CHUV, Rue du Bugnon 46, CH-1011 Lausanne, Switzerland. Franz.Buchegger@chuv.hospvd.ch International journal of cancer. Journal international du cancer (2004), 110(1), 145-9. Journal code: 0042124. ISSN:0020-7136. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 15054880 AN 2004160671 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Intratumoural (i.t.) injection of radio-iododeoxyuridine (IdUrd), a thymidine (dThd) analogue, is envisaged for targeted Auger electron- or beta-radiation therapy of glioblastoma. Here, biodistribution of [(125I)]IdUrd was evaluated 5 hr after i.t. injection in subcutaneous human glioblastoma xenografts LN229 after different intravenous (i.v.) pretreatments with

fluorodeoxyuridine (FdUrd). FdUrd is known to block de novo dThd synthesis, thus favouring DNA incorporation of radio-I¹²⁵Urd. Results showed that pretreatment with 2 mg/kg FdUrd i.v. in 2 fractions 0.5 hr and 1 hr before injection of radio-I¹²⁵Urd resulted in a mean tumour uptake of 19.8% of injected dose (% ID), representing 65.3% ID/g for tumours of approx. 0.35 g. Tumour uptake of radio-I¹²⁵Urd in non-pretreated mice was only 4.1% ID. Very low uptake was observed in normal nondividing and dividing tissues with a maximum concentration of 2.9% ID/g measured in spleen. Pretreatment with a higher dose of FdUrd of 10 mg/kg prolonged the increased tumour uptake of radio-I¹²⁵Urd up to 5 hr. A competition experiment was performed in FdUrd pretreated mice using i.t. co-injection of excess dThd that resulted in very low tumour retention of [(125)I]dUrd. DNA isolation experiments showed that in the mean >95% of tumour (125)I activity was incorporated in DNA. In conclusion, these results show that close to 20% ID of radio-I¹²⁵Urd injected i.t. was incorporated in tumour DNA after i.v. pretreatment with clinically relevant doses of FdUrd and that this approach may be further exploited for diffusion and therapy studies with Auger electron- and/or beta-radiation-emitting radio-I¹²⁵Urd. Copyright 2004 Wiley-Liss, Inc.

Answer 29:

Bibliographic Information

Effects of introduction of dThdPase cDNA on sensitivity to 5'-deoxy-5-fluorouridine and tumor angiogenesis.

Kim Ryungsa; Murakami Shigeru; Toge Tetsuya Department of Surgical Oncology, Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima 734-8553, Japan. rkim@hiroshima-u.ac.jp International journal of oncology (2003), 22(4), 835-41. Journal code: 9306042. ISSN:1019-6439. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 12632076 AN 2003118325 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Human thymidine phosphorylase (dThdPase) is an angiogenic factor identical to platelet-derived endothelial cell growth factor (PD-ECGF). Thymidine phosphorylase is also a converting enzyme of the prodrug 5'-deoxy-5-fluorouridine (5'-DFUR) to 5-fluorouracil (5-FU) in tumors. To assess the role of dThdPase in targeting chemotherapy, we examined the relationship between the expression of dThdPase and the sensitivity of 5'-DFUR in cancer cell lines, and also examined whether transfection of dThdPase cDNA enhanced the drug-sensitivity to 5'-DFUR with or without angiogenesis in breast cancer cells. Thirteen human cancer cell lines consisting of 4 breast cancer, 6 gastric cancer, and 3 colon cancer cell lines were used. Expression of dThdPase was assessed by reverse transcriptase-polymerase chain reaction (RT-PCR) and enzyme-linked immunosorbent assay (ELISA). In vitro drug-sensitivity was assessed by MTT assay, and anti-tumor effect in vivo was assessed using nude mouse xenografts. Intratumoral microvessel density was evaluated by immunohistochemical staining to factor VIII related antigen. Transfection of dThdPase cDNA was performed using pcDNA3 expression vector encoding its cDNA by the lipofection method. An inverse relationship between the expression of dThdPase and the IC₅₀ values of 5'-DFUR was observed ($p=0.1278$, $\rho=-0.440$) in the 13 cancer cell lines. Transfection of dThdPase cDNA into MCF-7 breast cancer cells resulted in an approximately 2.6- and 10-fold increase of the expression of dThdPase mRNA and its enzyme activity, respectively, compared to the control vector alone. The sensitivity to 5'-DFUR in the transfected cells was increased approximately 20-fold compared to the parent cells and control vector alone, and the sensitivity to 5-FU was also somewhat increased. In contrast, the sensitivity to ADM, CDDP, and VP-16 was not different between the transfected and control cells.

In nude mice xenografts of the transfected cells, treatment with 5'-DFUR had a significant anti-tumor effect compared to those of the untreated transfected cells and control vector alone treated with 5'-DFUR ($p<0.01$). Intratumoral microvessel density in the transfected cells was not significantly increased with or without treatment with 5'-DFUR compared to control vector alone. The high expression of dThdPase was correlated with an increase in the sensitivity to 5'-DFUR in gastrointestinal and breast cancer cell lines. The introduction of dThdPase cDNA in breast cancer cells enhanced the sensitivity to 5'-DFUR without an increase of tumor angiogenesis, and targeting chemotherapy of dThdPase may be a good tumor-specific and personalized therapy for improving the poor prognosis of cancer patients who show high expressions of dThdPase.

Answer 30:

Bibliographic Information

Optimal dosing schedule in combination therapy with irinotecan and doxifluridine in a human colorectal cancer xenograft model. Yanagisawa Mieko; Ishikawa Tohru; Ouchi Kaori F; Tanaka Yutaka Dept. of Product Research, Nippon Roche Research Center Gan to kagaku ryoho. *Cancer & chemotherapy* (2003), 30(2), 223-30. Journal code: 7810034. ISSN:0385-0684. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 12610870 AN 2003098806 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

A combination therapy with CPT-11 and 5-FU/LV has been recently established as a first-line therapy for metastatic colorectal cancer. However, severe adverse effects have also been reported from this combination therapy, and a modality to reduce the adverse effects is desired. 5'-DFUR, a pro-drug of 5-FU, shows less myelotoxicity than 5-FU, and thus it may be a better partner to combine with CPT-11. However, since each drug has the possibility of inducing diarrhea, there is concern about their use in combination therapy. Therefore, in the present study, our aim was to establish an optimal schedule in murine models, which shows no increase in diarrhea but maintains potent antitumor activity. In non-tumor bearing mice, CPT-11 was given i.v. at 100 mg/kg/day q2d x 3, and 5'-DFUR was given p.o. at 172 mg/kg/day daily for 14 days. Each of these doses caused diarrhea in the single treatment. CPT-11 was administered simultaneously or sequentially with 5'-DFUR. With the simultaneously administered schedule, the diarrhea appeared stronger than that found in the CPT-11 single or in the 5'-DFUR single treatment groups. On the other hand, with the sequentially administered schedule the diarrhea was not much stronger than that found in the single agent treatment groups. When CPT-11 and 5'-DFUR administrations were separated by three-day intervals, the diarrhea was not augmented at all. In mice bearing human colorectal cancer COLO 205, the antitumor activity of CPT-11 in the combination with 5'-DFUR was additive in all of the examined schedules. The efficacy in the sequential schedule was the same as in the simultaneous schedule. These results suggest that a sequential administration schedule of CPT-11 and 5'-DFUR would be more tolerable than and equally efficacious to the simultaneous administration schedule. Clinical study of this sequential administration in combination therapy is warranted.

Answer 31:

Bibliographic Information

gamma-Hydroxybutyric acid and 5-fluorouracil, metabolites of UFT, inhibit the angiogenesis induced by vascular endothelial growth factor. Basaki Y; Chikahisa L; Aoyagi K; Miyadera K; Yonekura K; Hashimoto A; Okabe S; Wierzba K; Yamada Y Cancer Research Laboratory, Taiho Pharmaceutical Co., Ltd, Hanno City, Saitama, Japan. y-basaki@taiho.co.jp *Angiogenesis* (2001), 4(3), 163-73. Journal code: 9814575. ISSN:0969-6970. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 11911014 AN 2002178982 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

UFT, a drug composed of uracil and tegafur at the molar ratio of 4:1, is an orally active agent for the treatment of a wide variety of malignant tumours. Using a murine dorsal air sac (DAS) assay, we have previously shown that UFT and its metabolites, gamma-hydroxybutyric acid (GHB) and 5-fluorouracil (5-FU), inhibited the angiogenesis induced by murine renal cell carcinoma. Here we report that UFT was more effective than other fluorinated pyrimidines such as 5-FU and doxifluridine (5'-DFUR) in blocking the angiogenic responses elicited by five human cancer cell lines which produced high levels of vascular endothelial growth factor (VEGF), but no detectable fibroblast growth factor-2 (FGF-2) in vitro. In contrast, UFT was unable to block the angiogenic response to one human gastric cancer cell line which produced both VEGF and FGF-2 in vitro. However, the production or secretion of VEGF by these cells was unaffected by GHB and 5-FU treatment. Interestingly, GHB suppressed the chemotactic migration and tube formation of human umbilical vein endothelial cells (HUVECs) stimulated by VEGF, without inhibiting their DNA synthesis. Since GHB did not affect the FGF-2-driven activities in HUVECs, its action appears to be VEGF-selective. On the other hand, 5-FU inhibited DNA

synthesis and migration of HUVECs stimulated by both VEGF and FGF-2, and tube formation driven by VEGF, suggesting that 5-FU is cytotoxic to endothelial cells. The inhibitory effects of 5-FU, and especially those GHB, were reproduced under in vivo condition using the DAS assay. The VEGF-mediated angiogenesis was significantly inhibited by UFT, 5-FU, and especially by GHB. We propose that the selective inhibitory effects of GHB on VEGF-mediated responses of endothelial cells are involved in the anti-angiogenic activity of UFT.

Answer 32:

Bibliographic Information

Combined effects of docetaxel and fluoropyrimidines on tumor growth and expression of interleukin-6 and thymidine phosphorylase in breast cancer xenografts. Yamamoto S; Kurebayashi J; Kurosumi M; Kunisue H; Otsuki T; Tanaka K; Sonoo H Department of Breast and Thyroid Surgery, Kawasaki Medical School, Okayama, Japan Cancer chemotherapy and pharmacology (2001), 48(4), 283-8. Journal code: 7806519. ISSN:0344-5704. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 11710628 AN 2001665116 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

PURPOSE: Although several combination treatments with docetaxel and other antitumor agents have been tested in experimental and clinical studies, their synergistic effects are still ill-defined. The degree of synergism between docetaxel and two oral fluoropyrimidines, tegafur and 5'-deoxy-5-fluorouridine (5'-dFUrd), was investigated in the KPL-4 human breast cancer xenograft model. **METHODS:** Because this KPL-4 cell line secretes interleukin-6 (IL-6) and induces cachexia, the effects of the combined treatment on serum IL-6 levels and cachectic markers were investigated. In addition, the expression levels of thymidine phosphorylase (dThdPase), a key enzyme for converting 5'-dFUrd to 5-fluorouracil, were determined. Female nude mice bearing KPL-4 tumors were treated orally with 5'-dFUrd (60 mg/kg, five times a week) or tegafur (100 mg/kg, five times a week) and by intraperitoneal injection of docetaxel (5 or 10 mg/kg, once a week). **RESULTS:** Although docetaxel (5 mg/kg) alone did not decrease either tumor growth or serum IL-6 levels, docetaxel (5 mg/kg) plus 5'-dFUrd or tegafur enhanced tumor growth inhibition and decreased serum IL-6 levels more than 5'-dFUrd or tegafur alone. Docetaxel (5 mg/kg) alone slightly increased the percentage of dThdPase-positive tumor cells, but the combined treatment with docetaxel plus 5'-dFUrd or tegafur significantly decreased the percentage of dThdPase-positive cells in the KPL-4 tumors. **CONCLUSION:** These findings indicate that docetaxel may stimulate dThdPase expression in tumor tissues and may enhance the antitumor activity of oral fluoropyrimidines. In addition, combined treatment with docetaxel and oral fluoropyrimidines may decrease serum IL-6 levels and may ameliorate IL-6-induced cancer cachexia.

Answer 33:

Bibliographic Information

Schedule dependency of antitumor activity in combination therapy with capecitabine/5'-deoxy-5-fluorouridine and docetaxel in breast cancer models. Fujimoto-Ouchi K; Tanaka Y; Tominaga T Oncology, Nippon Roche Research Center, Kamakura, Kanagawa, Japan Clinical cancer research : an official journal of the American Association for Cancer Research (2001), 7(4), 1079-86. Journal code: 9502500. ISSN:1078-0432. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 11309360 AN 2001219498 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Docetaxel and capecitabine are being prescribed for the treatment of breast cancer. In this study, we tried to identify the optimal administration schedule in combination therapy with these anticancer drugs in human cancer xenograft models. Capecitabine was given p.o. daily for 2 weeks (days 1-14), whereas docetaxel was given i.v. on day 1, day 8, or day 15

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

Answer 34:

Bibliographic Information

Enhancement of sensitivity to capecitabine in human renal carcinoma cells transfected with thymidine phosphorylase cDNA. Morita T; Matsuzaki A; Tokue A Department of Urology, Jichi Medical School, Tochigi, Japan. moritatu@jichi.ac.jp International journal of cancer. Journal international du cancer (2001), 92(3), 451-6. Journal code: 0042124. ISSN:0020-7136. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 11291085 AN 2001218011 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The purpose of the present study was to examine directly the role of thymidine phosphorylase (TP) in the sensitivity of renal cell carcinoma (RCC) to a novel fluoropyrimidine carbamate, capecitabine. TP cDNA-transfected RCC are used in these experiments to provide a basis for improved therapeutic benefit in chemoimmunotherapy. Human RCC line KU2 cells were transfected with pcDNA3.1/zeo(+) with or without human TP cDNA by the lipofectin method. We established a clone transfected with pcDNA3.1/zeo(+)/TP (KU2-TP15) and a clone transfected with pcDNA3.1/zeo(+) as a control (KU2-C1). TP expression levels (mean +/- SD) examined by enzyme-linked immunosorbent assay (ELISA) were 1.3 +/- 0.14 U/mg protein in KU2, 1.6 +/- 0.57 U/mg protein in KU2-C1 and 216 +/- 25.6 U/mg protein in KU2-TP15. Immunohistochemical staining of subcutaneous tumors established in Balb/c nu/nu mice showed that KU2-TP15 was strongly positive for TP expression, whereas KU2 and KU2-C1 were negative. Sensitivities in vitro to 5-fluorouracil (5FU), 5'-deoxy-5-fluorouridine (5'DFUR) and capecitabine in KU2-TP15 were significantly enhanced compared with those in KU2 or KU2-C1. A moderate but statistically significant bystander effect was observed in vitro. KU2-TP15 tumors showed significant increase in the in vivo sensitivities to 5'DFUR and capecitabine as compared with the vehicle alone while KU2-C1 tumors did not. The difference in tumor-free rate in mice bearing KU2-TP15 at 2 months after the cessation of treatment was statistically significant between the capecitabine treatment group and the controls, the 5FU treatment group and the 5'DFUR treatment group. The present study clearly provides direct evidence for the role of TP in mediating the sensitivity of RCC to capecitabine. Copyright 2001 Wiley-Liss, Inc.

Answer 35:

Bibliographic Information

The design and synthesis of a new tumor-selective fluoropyrimidine carbamate, capecitabine. Shimma N; Umeda I; Arasaki M; Murasaki C; Masubuchi K; Kohchi Y; Miwa M; Ura M; Sawada N; Tahara H; Kuruma I; Horii I; Ishitsuka H Department of Chemistry, Nippon Roche Research Center, Kamakura City, Kanagawa, Japan.

nobuo.shimma@roche.com Bioorganic & medicinal chemistry (2000), 8(7), 1697-706. Journal code: 9413298. ISSN:0968-0896. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 10976516 AN 2001084495 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

To identify an orally available fluoropyrimidine having efficacy and safety profiles greatly improved over those of parenteral 5-fluorouracil (5-FU: 1), we designed a 5-FU prodrug that would pass intact through the intestinal mucosa and be sequentially converted to 5-FU by enzymes that are highly expressed in the human liver and then in tumors. Among various N4-substituted 5'-deoxy-5-fluorocytidine derivatives, a series of N4-alkoxycarbonyl derivatives were hydrolyzed to 5'-deoxy-5-fluorocytidine (5'-DFCR: 8) specifically by carboxylesterase, which exists preferentially in the liver in humans and monkeys. Particularly, derivatives having an N4-alkoxycarbonyl moiety with a C4-C6 alkyl chain were the most susceptible to the human carboxylesterase. Those were then converted to 5'-deoxy-5-fluorouridine (5'-DFUR: 4) by cytidine deaminase highly expressed in the liver and solid tumors and finally to 5-FU by thymidine phosphorylase (dThdPase) preferentially located in tumors. When administered orally to monkeys, a derivative having the N4-alkoxycarbonyl moiety with a C5 alkyl chain (capecitabine: 6) The highest AUC and Cmax for plasma 5'-DFUR. In tests with various human cancer xenograft models, capecitabine was more efficacious at wider dose ranges than either 5-FU or 5'-DFUR and was significantly less toxic to the intestinal tract than the others in monkeys.

Answer 36:

Bibliographic Information

Effect of a fluorinated pyrimidine on cachexia and tumour growth in murine cachexia models: relationship with a proteolysis inducing factor. Hussey H J; Todorov P T; Field W N; Inagaki N; Tanaka Y; Ishitsuka H; Tisdale M J Pharmaceutical Sciences Research Institute, Aston University, Birmingham, UK British journal of cancer (2000), 83(1), 56-62. Journal code: 0370635. ISSN:0007-0920. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 10883668 AN 200033872 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The fluorinated pyrimidine nucleoside, 5'-deoxy-5-fluorouridine (5'-dFUrd) has been shown to effectively attenuate the progress of cachexia in the murine adenocarcinomas MAC16 and colon 26 as well as in the human uterine cervical carcinoma xenograft, Yumoto. Although concomitant inhibition of tumour growth was observed in all three models this was not sufficient to account for the preservation of body weight. An attempt has been made to correlate the anti-cachectic activity of 5'-dFUrd with the presence of a tumour produced proteolysis-inducing factor (PIF), thought to be responsible for the development of cachexia in the MAC16 model. Two variants of colon 26 adenocarcinoma were employed, clone 20 which produces profound cachexia, and clone 5 which produces no change in body weight in recipient animals. Mice bearing the colon 26, clone 20 variant showed evidence for the presence of PIF in tumour, serum and urine, while there was no evidence for the presence of PIF in tumour or body fluids of mice bearing the clone 5 tumours. Treatment of animals bearing the clone 20 variant with 5'-dFUrd led to the disappearance of PIF from the tumour, serum and urine concomitant with the attenuation of the development of cachexia. The human cervical carcinoma, Yumoto, which also induced cachexia in recipient animals, showed expression of PIF in tumour, serum and urine in control and vehicle-treated mice, but was absent in mice treated with 5'-dFUrd. Thus in these experimental models cachexia appears to be correlated with the presence of PIF.

Answer 37:

Bibliographic Information

Evaluation of antitumor activity of etoposide administered orally for 21 consecutive days against human uterine

cancer subcutaneous and/or orthotopic xenografts in nude mice. Matsumoto S; Mashiba H; Okamoto K; Ekimoto H Anticancer Drugs Dept., Nippon Kayaku Co., Ltd Gan to kagaku ryoho. Cancer & chemotherapy (1999), 26(9), 1313-20. Journal code: 7810034. ISSN:0385-0684. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 10478185 AN 1999407623 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The antitumor activity of etoposide (ETP) against human uterine cancer cell lines were investigated in vitro and in vivo. The cytotoxic activity of ETP against HeLa S3, a human cervical cancer cell line, depended on exposure time. The survival rate with 24 h prolonged exposure was reduced to about 1/200 that with 6 h exposure. The time dependency of antitumor activity of ETP against HeLa S3 subcutaneously transplanted in nude mice was studied. The effect of 21 or 28 consecutive days oral administration was greater than that of 5 or 14 consecutive days. Furthermore, a longer administration schedule was less toxic. The antitumor activity of ETP administered orally for 21 consecutive days was compared with that of CDDP, CPT-11 and 5'-DFUR using both human uterine cancer cell lines (TCO-1, SIHA, UCC08JCK) transplanted subcutaneously in nude mice and human uterine cancer cell lines (HeLa S3, UCC08JCK) transplanted into the uterus of nude mice. ETP showed the same antitumor activity as CPT-11 and 5'-DFUR against TCO-1 and UCC08JCK, human uterine cancer cell lines transplanted subcutaneously in nude mice. ETP also showed anticancer activity against two cell lines transplanted into the uterus. The growth inhibition caused by ETP administered orally at 50 mg/kg against HeLa S3 transplanted subcutaneously was 36.7% while that against the same cell line transplanted into the uterus was 58.5%. 5'-DFUR also showed the same antitumor activity as ETP. These results suggest that long term oral administration of ETP is clinically useful for cervical cancer patients.

Answer 38:

Bibliographic Information

Induction of thymidine phosphorylase expression and enhancement of efficacy of capecitabine or 5'-deoxy-5-fluorouridine by cyclophosphamide in mammary tumor models. Endo M; Shinbori N; Fukase Y; Sawada N; Ishikawa T; Ishitsuka H; Tanaka Y Cytostatics Group, Nippon Roche Research Center, Kamakura, Kanagawa, Japan International journal of cancer. Journal international du cancer (1999), 83(1), 127-34. Journal code: 0042124. ISSN:0020-7136. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 10449619 AN 1999380236 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Thymidine phosphorylase (dThdPase) is an essential enzyme for the activation of the oral cytostatic drugs capecitabine (N(4)-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine, Xeloda(trade mark)) and its intermediate metabolite doxifluridine [5'-deoxy-5-fluorouridine (5'-dFUrd, Furtulon((R)))] to 5-fluorouracil (5-FUra) in tumors. In a previous study, we found that several cytostatics were able to up-regulate tumor levels of dThdPase in a human colon cancer xenograft model. In the present study, we confirmed that the administration of cytostatics used for breast cancer treatment, such as taxanes and cyclophosphamide (CPA), up-regulated the tumor level of dThdPase in mammary tumor models as well. Because the dThdPase up-regulation was observed even when CPA was given orally, we investigated further the usefulness of combination therapy with the 2 oral drugs, 5'-dFUrd/capecitabine and CPA in mammary tumor models. Daily oral administration of CPA up-regulated human dThdPase levels in the tumor tissue of mice bearing a human mammary tumor xenograft, MX-1, whereas in the small intestine and liver, it did not affect levels of pyrimidine nucleoside phosphorylases (PyNPase) including dThdPase and uridine phosphorylase. The preferential up-regulation of PyNPase activity in the tumor by CPA administration was also confirmed in mice bearing a syngeneic murine mammary adenocarcinoma, A755. In both models, combination therapy of 5'-dFUrd/capecitabine with CPA showed synergistic antitumor activity, without significant potentiation of toxicity. In contrast, treatment with CPA and either 5-FUra or UFT (a mixture of tegafur and uracil) in combination showed only additive activity. Our results suggest that CPA and capecitabine/5'-dFUrd, both available for oral administration, would be good partners, and that clinical trials with this drug combination against breast cancer are warranted. Copyright 1999 Wiley-Liss, Inc.

Answer 39:

Bibliographic Information

Antitumor activity of ZD1694 (tomudex) against human head and neck cancer in nude mouse models: role of dosing schedule and plasma thymidine. Cao S; McGuire J J; Rustum Y M Grace Cancer Drug Center, Roswell Park Cancer Institute, Buffalo, New York 14263, USA. scao@sc3101.med.buffalo.edu Clinical cancer research : an official journal of the American Association for Cancer Research (1999), 5(7), 1925-34. Journal code: 9502500. ISSN:1078-0432. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 10430100 AN 1999357169 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

We studied the antitumor activity and toxicity of ZD1694 (tomudex), a specific inhibitor of thymidylate synthase (TS), in nude mice bearing human head and neck squamous cell carcinoma A253 and FaDu xenografts. Mice were treated by single i.v. push (i.v. x 1), i.v. push once a week for 3 weeks (weekly x 3), and i.v. push once a day for 5 days (daily x 5), and the maximum tolerated doses (MTDs) of ZD1694 were 300 mg/kg, 60 mg/kg/week, and 30 mg/kg/day, respectively. ZD1694 was moderately active against both A253 and FaDu xenografts. Antitumor activity was schedule-dependent in both tumors: weekly x 3 > or = i.v. x 1 >> daily x 5. In contrast, the rank order of toxicity was daily x 5 >> weekly x 3 > or = i.v. x 1. ZD1694 at the MTD produced 20% complete tumor regression and 20% partial tumor regression (PR) with i.v. x 1 and weekly x 3 schedules and 12-day tumor growth delay with daily x 5 schedule against FaDu xenografts. No complete tumor regression was achieved with ZD1694 with any schedule against A253; a 20% PR, 40% PR, and 10-day tumor growth delay were observed with i.v. x 1, weekly x 3, and daily x 5 schedules, respectively. The data indicate that ZD1694 was slightly more effective against FaDu than against A253. Of interest and potential clinical importance was the observation that ZD1694 was still active at doses lower than the MTD (> or =1/3 MTD), which showed a high therapeutic index and wide safety margin. Study of ZD1694 compared with 5-fluorouracil and 5-fluoro-2'-deoxyuridine at the MTD revealed that the antitumor activity of ZD1694 was comparable with or superior to 5-fluorouracil and 5-fluoro-2'-deoxyuridine against both A253 and FaDu xenografts, with less toxicity. High plasma thymidine in mouse relative to human (approximately 1.3 microM and <0.1 microM, respectively) may complicate the study of antitumor activity and toxicity of TS inhibitors with human tumor xenografts grown in the mouse.

To test this hypothesis, we preadministered methoxypolyethyleneglycol-conjugated thymidine phosphorylase (MPEG-TPase; 2500 units/kg/dose) to reduce mouse plasma thymidine, then treated with various doses of ZD1694 using the daily x 5 or i.v. x 1 schedules in the A253 tumor model. MPEG-TPase significantly increased the toxicity of ZD1694; the MTD of ZD1694 plus MPEG-TPase was reduced 3- and 10-fold compared with ZD1694 alone for i.v. x 1 and daily x 5 schedules, respectively. However, preadministration of MPEG-TPase did not potentiate the antitumor activity of ZD1694 with either schedule. The data indicate that the study of TS inhibitors in rodent models may not be suitable for predicting a safe dose for clinical study. However, rodent models, particularly human tumor xenografts, are still useful models for evaluation of antitumor activity and schedule selection for TS inhibitors.

Answer 40:

Bibliographic Information

Antitumor effect of 22-oxacalcitriol on estrogen receptor-negative MDA-MB-231 tumors in athymic mice. Matsumoto H; Iino Y; Koibuchi Y; Andoh T; Horii Y; Takei H; Horiguchi J; Maemura M; Yokoe T; Morishita Y Second Department of Surgery, Gunma University School of Medicine, Maebashi, Gunma 371-8511, Japan Oncology reports (1999), 6(2), 349-52. Journal code: 9422756. ISSN:1021-335X. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 10023003 AN 1999148162 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The purpose of this study was to evaluate the usefulness of 22-oxacalcitriol (OCT) in the treatment of estrogen receptor (ER)-negative breast cancer. The antitumor effect of this agent and its effect combined with doxifluridine (5'-DFUR) on MDA-MB-231 tumors in female athymic mice were investigated. We also examined the effect of OCT on the expression of vascular endothelial growth factor (VEGF) which had been reported to generate angiogenesis in tumors. OCT significantly suppressed the growth of tumors without inducing hypercalcemia in a dose dependent manner. The effect of OCT combined with 5'-DFUR did not exceed the effect of a single agent therapy. The expressions of VEGF analyzed by enzyme-linked immunosorbent assay were significantly decreased in the OCT-treated group. These results suggest that OCT may partially suppress tumor growth by inhibiting neovascularization and it would likely have positive application as a treatment of ER-negative breast cancer.

Answer 41:

Bibliographic Information

Intrathecal 5-fluoro-2'-deoxyuridine (FdUrd) for the treatment of solid tumor neoplastic meningitis: an in vivo study. Nakagawa H; Yamada M; Fukushima M; Ikenaka K Department of Neurosurgery, Osaka Medical Center for Cancer and Cardiovascular Diseases (OMCC), Japan. hidemitsu@osaka.macnet.or.jp Cancer chemotherapy and pharmacology (1999), 43(3), 247-56. Journal code: 7806519. ISSN:0344-5704. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 9923556 AN 1999120431 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

To evaluate the possible intrathecal use of 5-fluoro-2'-deoxyuridine (FdUrd) for neoplastic meningitis, its antitumor activity and neurotoxicity in vivo were assessed. FdUrd at doses in the range 5-100 microg/animal was effective against meningeal carcinomatosis using Walker 256 carcinoma cells in rats and MM46 mammary cancer cells in mice and against meningeal gliomatosis using 203 glioma cells in mice. After four intrathecal injections, FdUrd at these doses also showed minimal neurotoxicity in the C57BL/6 mouse brain. To estimate the mechanism of FdUrd efficacy, thymidine phosphorylase (TPase) and thymidine kinase (TK), key enzymes in the metabolism of FdUrd, were measured in rat, mouse and normal human brain tissue, and in human brain tumor tissues and cerebrospinal fluid (CSF) from patients with malignant brain tumors including meningeal carcinomatosis. TPase levels were lower in brain and malignant brain tumors than in other organs and their tumors. Moreover, the activity of TPase in the gray matter of human brain, which faces the cerebrospinal fluid across the cortical surface and into which malignant cells invade in meningeal carcinomatosis, was lower than that in the white matter. TK was undetectable, and TPase was detected (at very low concentrations) in only 4 of 56 patients with brain tumors or meningeal carcinomatosis. These findings indicate that brain tissue and CSF are favorable sites for FdUrd chemotherapy because the rate of conversion of FdUrd to 5-FU would be minimal. In conclusion, FdUrd is potentially useful for intrathecal treatment of neoplastic meningitis from primary brain tumors and systemic cancer.

Answer 42:

Bibliographic Information

Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. Miwa M; Ura M; Nishida M; Sawada N; Ishikawa T; Mori K; Shimma N; Umeda I; Ishitsuka H Nippon Roche Research Centre, Kanagawa, Japan European journal of cancer (Oxford, England : 1990) (1998), 34(8), 1274-81. Journal code: 9005373. ISSN:0959-8049. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 9849491 AN 1999066353 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Capecitabine (N4-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine) is a novel oral fluoropyrimidine carbamate, which is converted to 5-fluorouracil (5-FU) selectively in tumours through a cascade of three enzymes. The present study investigated tissue localisation of the three enzymes in humans, which was helpful for us to design the compound. Carboxylesterase was almost exclusively located in the liver and hepatoma, but not in other tumours and normal tissue adjacent to the tumours. Cytidine (Cyd) deaminase was located in high concentrations in the liver and various types of solid tumours. Finally, thymidine phosphorylase (dThdPase) was also more concentrated in various types of tumour tissues than in normal tissues. These unique tissue localisation patterns enabled us to design capecitabine. Oral capecitabine would pass intact through the intestinal tract, but would be converted first by carboxylesterase to 5'-deoxy-5-fluorocytidine (5'-dFCyd) in the liver, then by Cyd deaminase to 5'-deoxy-5-fluorouridine (5'-dFUrd) in the liver and tumour tissues and finally by dThdPase to 5-FU in tumours. In cultures of human cancer cell lines, the highest level of cytotoxicity was shown by 5-FU itself, followed by 5'-dFUrd. Capecitabine and 5'-dFCyd had weak cytotoxic activity only at high concentrations. The cytotoxicity of the intermediate metabolites 5'-dFCyd and 5'-dFUrd was suppressed by inhibitors of Cyd deaminase and dThdPase, respectively, indicating that these metabolites become effective only after their conversion to 5-FU. Capecitabine, which is finally converted to 5-FU by dThdPase in tumours, should be much safer and more effective than 5-FU, and this was indeed the case in the HCT116 human colon cancer and the MX-1 breast cancer xenograft models.

Answer 43:

Bibliographic Information

Antitumor activities of a novel fluoropyrimidine, N4-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine (capecitabine).

Ishikawa T; Fukase Y; Yamamoto T; Sekiguchi F; Ishitsuka H Cytostatics Group, Nippon Roche Research Center, Kamakura, Kanagawa, Japan Biological & pharmaceutical bulletin (1998), 21(7), 713-7. Journal code: 9311984. ISSN:0918-6158. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 9703255 AN 1998366815 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Capecitabine (N4-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine) is a novel fluoropyrimidine carbamate that was synthesized for the purpose of finding antitumor drugs with improved safety and efficacy profiles compared with those of 5-fluorouracil (5-FUra) and doxifluridine (5'-deoxy-5-fluorouridine, 5'-dFUrd). The present study compared the antitumor activities of the compound with those of other fluoropyrimidines in 12 human cancer xenograft models and their antimetastatic activities in murine tumor models. The antitumor efficacy of capecitabine was greater than those of 5'-dFUrd, UFT (a mixture of tegafur and uracil) and 5-FUra. Capecitabine was also much safer, particularly much less toxic to the intestinal tract, than the other compounds, indicating higher therapeutic indices. The therapeutic indices of capecitabine, 5'-dFUrd and 5-FUra were >40, >20 and 2.0 against the human CXF280 colon cancer xenograft, the most sensitive line to the fluoropyrimidines so far tested, and 5.1, 1.5, and <1.5 against the human HCT116 colon cancer xenograft with ordinary sensitivity, respectively. In addition, capecitabine, as well as 5'-dFUrd, selectively suppressed the spontaneous metastasis of mouse Lewis lung carcinoma in mice at extremely low doses, 32-64 fold lower than their minimum effective dose (MED) against the primary tumor growth. Capecitabine was even more antimetastatic than 5'-dFUrd. These results indicate that capecitabine has high therapeutic potential.

Answer 44:

Bibliographic Information

Positive correlation between the efficacy of capecitabine and doxifluridine and the ratio of thymidine phosphorylase to dihydropyrimidine dehydrogenase activities in tumors in human cancer xenografts.

Ishikawa T; Sekiguchi F; Fukase Y; Sawada N; Ishitsuka H Cytostatics Group, Nippon Roche Research Center, Kamakura-City, Kanagawa, Japan Cancer research (1998), 58(4), 685-90. Journal code: 2984705R. ISSN:0008-5472. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 9485021 AN 1998143552 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Capecitabine (N4-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine) is a new fluoropyrimidine carbamate, which is converted to 5-fluorouracil (5-FUra) selectively in tumors through the intermediate metabolite 5'-deoxy-5-fluorouridine (5'-dFUrd, doxifluridine). 5'-dFUrd is metabolized to 5-FUra by thymidine phosphorylase (dThdPase) located in high levels in various types of solid tumors from patients, whereas 5-FUra generated is catabolized to dihydrofluorouracil by dihydropyrimidine dehydrogenase (DPD). The present study investigated whether the efficacy of capecitabine and its intermediate metabolite 5'-dFUrd correlates with levels of these enzymes in various human cancer xenograft models. Capecitabine and 5'-dFUrd were highly effective and inhibited tumor growth by more than 50% in 18 of 24 xenograft lines (75%) and 15 of 24 xenograft lines (63%), respectively, whereas 5-FUra and a mixture of tegafur and uracil were effective only in 1 of 24 (4.2%) and 5 of 24 (21%), respectively. The efficacy of capecitabine correlated with dThdPase activity. However, capecitabine was effective even in tumors with lower levels of dThdPase if DPD levels were also lower. In contrast, it was not as effective even in tumors with sufficient levels of dThdPase if DPD levels were very high. The efficacy of capecitabine consequently correlated very well with and depended on the ratio of these two enzymes in tumors. These results indicate that capecitabine might exert its efficacy through 5-FUra generated in tumor tissues but not through that generated in normal organs. On the other hand, there was no correlation between the efficacy of a mixture of tegafur and uracil and these enzyme activities in tumors. The efficacy of capecitabine would be optimized by selecting patients who have tumors with a high ratio of dThdPase to DPD activities.

Answer 45:

Bibliographic Information

Efficacy of combination chemotherapy of cyclophosphamide and 5'-deoxy-5-fluorouridine in a mammary tumor xenograft model, MX-1. Endo M; Fujimoto-Ouchi K; Matsumoto T; Tanaka Y; Ishitsuka H Nippon Roche Research Center Gan to kagaku ryoho. Cancer & chemotherapy (1997), 24(10), 1295-301. Journal code: 7810034. ISSN:0385-0684. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 9279349 AN 97425299 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Efficacy of long-term combination chemotherapy of cyclophosphamide (CPA) and 5'-deoxy-5-fluorouridine (5'-DFUR), both of which have been widely used as chemotherapeutics against breast cancer patients, was examined in a mammary tumor xenograft model, MX-1. 5'-DFUR suppressed the tumor growth over a long period and prolonged the survival, although it did not reduce the initial tumor burden, CPA induced the disappearance of the tumor burden temporarily. However, CPA became ineffective despite continuation of treatment, and induced the recurrence of the tumor. The combination of these two drugs dramatically reduced the tumor burden, and suppressed the recurrence of the tumor over a long period. The tumor recurring during CPA monotherapy was resistant to CPA but susceptible to 5'-DFUR, which could be a reason for the long-lasting activity of the combination therapy. These results indicate that CPA and 5'-DFUR monotherapies have different modes of antitumor activities in the long-term therapy model, and that these drugs in combination would have better therapeutic advantage than each drug given individually.

Answer 46:

Bibliographic Information

The influence of BIBW22BS, a dipyridamole derivative, on the antiproliferative effects of 5-fluorouracil, methotrexate and gemcitabine in vitro and in human tumour xenografts. Erratum in: Eur J Cancer 1996 Jan;32A(1):185 Jansen W J; Pinedo H M; van der Wilt C L; Feller N; Bamberger U; Boven E Department of Medical Oncology, Amsterdam, Netherlands European journal of cancer (Oxford, England : 1990) (1995), 31A(13-14), 2313-9. Journal code: 9005373. ISSN:0959-8049. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 8652262 AN 96262872 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Dipyridamole is known as a potent inhibitor of facilitated diffusion-mediated nucleoside transport as well as a modulator of 'classical' multidrug resistance. BIBW22BS, a derivative of dipyridamole, has been found to be 20- to 100-fold more potent in the reversal of multidrug resistance when compared to the parent compound. In parallel, we studied the efficacy of BIBW22BS in the modulation of the antiproliferative effects of 5-fluorouracil, methotrexate and gemcitabine in human cancer cell lines. BIBW22BS, at non-toxic concentrations up to 1.0 microM, increased the antiproliferative effects of 5-fluorouracil 2- to 6-fold in seven of the eight colon cancer cell lines tested in a dose-dependent manner. The addition of 1.0 microM BIBW22BS to methotrexate resulted in a slight increase in the antiproliferative effects, but inhibited the activity of gemcitabine 30- to 100-fold in various cancer cell lines. In vitro, no notable difference was found between BIBW22BS and dipyridamole in their capacity to modulate the activity of the antimetabolites studied. BIBW22BS did not affect the growth inhibition induced by 5-fluorouracil or gemcitabine in human tumour xenografts grown subcutaneously in nude mice. We confirmed the higher potency of BIBW22BS when compared to dipyridamole in the reversal of drug resistance in the Pgp-positive COLO 320 cell line.

Answer 47:

Bibliographic Information

Augmentation of chemotherapeutic efficaciousness of UFT by oral l-leucovorin--growth-inhibitory activity of combination against human tumor xenograft. Saito H; Okabe H; Nakano K; Fujioka A; Toko T; Takeda S; Unemi N Anticancer and Antimicrobials Research Lab., Taiho Pharmaceutical Co., Ltd Gan to kagaku ryoho. Cancer & chemotherapy (1995), 22(13), 1919-25. Journal code: 7810034. ISSN:0385-0684. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 7487121 AN 96083692 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Combination chemotherapy with FUra and LV has been reported as a useful treatment for patients suffering from colon carcinoma. Usually, both FUra and LV are administered by intravenous infusion, but not orally. UFT, an anti-neoplastic agent consisting of FT and uracil, is widely used for oral administration in Japan. Using human tumor xenografts of 10 cell lines, we evaluated the efficacy of UFT combined with l-LV, which is the active form of LV, by oral administration. Combined treatment of UFT with l-LV was more effective than UFT alone on the growth suppression of colon carcinoma (KM 20 C, Col-1) and mammary carcinoma (H-31, MX-1). When 1.85 mg/kg (5.55 mg/m²) of LV was given to tumor bearing mice, the antitumor activity of UFT was augmented and at a dose of 5.56 mg/kg (16.7 mg/m²) of LV, it was significantly augmented. Among various 5-FU derivatives, such as UFT, 5'-DFUR or FUra, combined treatment using UFT with l-LV was the most effective by oral administration. l-LV did not improve the anti-tumor efficacy or toxicity of 5'-DFUR. l-LV seemed to augment the anti-tumor activity of FUra, but not significantly. These results suggest that combination chemotherapy of UFT with LV is a promising approach for the clinical treatment of human colon cancer.

Answer 48:

Bibliographic Information

Interferon alpha and 5'-deoxy-5-fluorouridine in colon cancer: effects as single agents and in combination on growth of xenograft tumours. Laurent P L; Tevæearai H T; Eliason J F; Givel J C; Odartchenko N Swiss Institute for Experimental Cancer Research, Epalinges European journal of cancer (Oxford, England : 1990) (1994), 30A(12), 1859-65. Journal code: 9005373. ISSN:0959-8049. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 7880618 AN 95186248 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Interferon-alpha (IFN-alpha) enhances the activity of the 5-fluorouracil (5-FU) prodrug 5'-deoxy-5-fluorouridine (5'-dFUrd) in colorectal cancer cells in vitro by upregulating the enzyme pyrimidine nucleoside phosphorylase (PNPase), which is responsible for converting 5'-dFUrd to 5-FU. We examined whether such enhancement also occurs in vivo using human colorectal xenografts in nude mice. The Co-115 line has high basal levels of PNPase and the enzyme level was increased in tumours from mice treated for 3 weeks with 50,000 IU/day (5 days/week) of IFN-alpha A/D. The prodrug 5'-dFUrd (200 mg/day, 5 days/week) had a much greater antitumour activity than 5-FU had when it was used at an approximately equitoxic dose (20 mg/day, 5 days/week). However, because of the high activity of 5'-dFUrd as a single agent, no enhancement by IFN-alpha A/D was observed. Studies on xenografts of WiDr cells indicated that this line is much less sensitive to 5'-dFUrd. However, treatment of animals with IFN-alpha A/D at doses of 75,000 IU/day or 150,000 IU/day resulted in significant inhibition of WiDr tumour growth. Combination treatment with 75 mg/kg/day or 150 mg/kg/day of 5'-dFUrd resulted in enhanced antitumour activity, particularly at the higher dose of IFN-alpha A/D. Synergy of this drug combination was confirmed by isobologram analysis. Analysis of PNPase levels in WiDr tumours, excised from mice treated with IFN-alpha A/D, demonstrated that the enzyme activity was increased by IFN-alpha in a dose-dependent manner. Slight increases were also seen in normal liver and intestine from the same animals. Our results indicate that modulation of converting enzymes for anticancer prodrugs by cytokines could be a novel therapeutic strategy for combination therapy of colorectal cancer.

Answer 49:

Bibliographic Information

Remarkable antitumor activity of 5'-deoxy-5-fluorouridine in human colorectal tumor xenografts. De Cesare M; Pratesi G; De Braud F; Zunino F; Stampino C G Division of Experimental Oncology B, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy Anticancer research (1994), 14(2A), 549-54. Journal code: 8102988. ISSN:0250-7005. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 8017859 AN 94288536 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

5'-Deoxy-5-fluorouridine (doxifluridine) is a prodrug of 5-fluorouracil (5FU) selectively activated by tumor cells. Since in clinical studies the side effects of doxifluridine differed after intravenous (i.v.) or oral administration, and oral route was the most promising in preclinical studies with murine models, in this study the drug was tested orally against a panel of human colorectal tumor xenografts with varying degrees of sensitivity to 5FU. Doxifluridine efficacy was comparable to that of 5FU when it was delivered according to a weekly schedule, but it was statistically higher when it was delivered more frequently. Impressive tumor inhibition (between 90 and 97%) was achieved in 4 out of 5 tumor lines after treatments delivered twice a week or daily 5 times a week. No difference in 5FU activity was observed between weekly and biweekly treatments, or between oral and i.v. injections. Moreover, in one tumor line in which different dosages of doxifluridine were investigated, a marked antitumor effect was obtained with a wide range of tolerated doses (4000-8000 mg/kg). Overall, these data indicated that doxifluridine is well tolerated when given orally and frequently. Using an adequate schedule, the prodrug has a better therapeutic efficacy against a variety of human colon cancer models than 5FU.

Answer 50:

Bibliographic Information

A comparative study of the antitumor activities of 5'-deoxy-5-fluorouridine and its prodrug trimethoxybenzoyl-5'-deoxy-5-fluorocytidine (Ro09-1390) on human digestive organ cancer xenograft lines transplanted into nude mice. Nio Y; Kimura H; Tsubono M; Tseng C C; Kawabata K; Masai Y; Hayashi H; Araya S; Meyer C; Fukumoto M First Department of Surgery, Kyoto University Faculty of Medicine, Japan Anti-cancer drugs (1992), 3(4), 387-93. Journal code: 9100823. ISSN:0959-4973. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 1421435 AN 93043401 MEDLINE (Copyright (C) 2008 U.S. National Library

of Medicine on SciFinder (R))

Abstract

5'-Deoxy-5-fluorouridine (5'-DFUR) is one of the oral fluoropyrimidines widely used in the treatment of gastric, colorectal and breast cancers in Japan. 5'-DFUR is converted to 5-fluorouracil by pyrimidine nucleoside phosphorylase in the tumor. 5'-DFUR has toxic effects on the intestine and may cause severe diarrhea. Trimethoxybenzoyl-5'-deoxy-5-fluorocytidine (Ro09-1390) is a prodrug of 5'-DFUR, which was developed to reduce the intestinal toxicity of 5'-DFUR. The present study was designed to assess the antitumor activity and spectrum of Ro09-1390, and to compare its efficacy with that of 5'-DFUR. Six digestive organ cancer xenograft lines (two gastric, one esophageal, one colorectal, one gall bladder and one bile duct cancers) were s.c. transplanted into nude mice. The agents were orally administered daily for 14 days at doses of 0.08-0.64 mmol/kg (1-8 times the maximal clinical dose of 5'-DFUR). Both 5'-DFUR and Ro09-1390 significantly inhibited the growth of two gastric cancer lines, and the IC₅₀'s for Ro09-1390 in both lines were lower than the respective values for 5'-DFUR. The esophageal, colorectal, gall bladder and bile duct cancer lines, however, were resistant to both agents. 5'-DFUR at 0.64 mmol/kg significantly inhibited the growth of these cancers, but with high mortality, and most mice receiving this dose died within 14 days after the start of therapy, suffering from severe diarrhea and body weight loss. Ro09-1390 at the same dose resulted in low mortality, but evidenced similarly low antitumor activity. (ABSTRACT TRUNCATED AT 250 WORDS)

Answer 51:

Bibliographic Information

Antitumor activity of 5'-deoxy-5-fluorouridine in human digestive organ cancer xenografts and pyrimidine nucleoside phosphorylase activity in normal and neoplastic tissues from human digestive organs. Nio Y; Kimura H; Tsubono M; Tseng C C; Kawabata K; Masai Y; Hayashi H; Meyer C; Fukumoto M; Tobe T First Department of Surgery, Kyoto University Faculty of Medicine, Japan Anticancer research (1992), 12(4), 1141-6. Journal code: 8102988. ISSN:0250-7005. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 1386969 AN 92368128 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

5'-Deoxy-5-fluorouridine (5'-DFUR) is believed to be metabolized to 5-fluorouracil (5-FU) by pyrimidine nucleoside phosphorylase (PyNPase). PyNPase activity is reported to be higher in neoplastic tissues than in normal tissues, and this has been proposed as an explanation for the selective cytotoxicity of 5'-DFUR against tumors. In the present study, PyNPase activity was measured in 95 neoplastic and normal specimens from human digestive organ tissues. In specimens from the esophagus, stomach, intestine and pancreas, PyNPase activity was higher in neoplastic tissues than in normal tissues. However, PyNPase activity in non-malignant liver tissues, especially cirrhotic liver tissues, was much higher than in the normal tissues of the other digestive organs. PyNPase activity in non-malignant liver tissues was as high as in primary liver tumors, and PyNPase activity in metastatic liver tumors was lower than in primary tumors and non-malignant cirrhotic tissues. The in vivo antitumor activities of oral 5'-DFUR and intravenous 5-FU were also assessed in 6 human digestive organ cancer xenograft lines transplanted subcutaneously in nude mice, and the relationship between the in vivo antitumor effects of 5'-DFUR and PyNPase activity in the tumors was assessed. However, there was no statistically significant correlation between them. Although the in vivo antitumor effect of intravenous 5-FU correlated significantly with the in vitro sensitivity of the tumors to 5-FU (assessed by DNA synthesis inhibition assay), the in vivo effects of 5'-DFUR did not correlate with the in vitro sensitivity to 5-FU. It is suggested that: (a) the liver may be the major site for metabolizing 5'-DFUR to 5-FU, and (b) measuring PyNPase activity in the tumor may not be a useful indicator for chemotherapy with 5'-DFUR.

Answer 52:

Bibliographic Information

Comparative studies on the antitumor activity of fluorinated pyrimidine derivatives against human bladder, cervical and ovarian cancer xenografts in nude mice. Miwa M; Sekiguchi F; Akaza H; Tokita H; Nitta K; Adachi S; Kanazawa K; Ishitsuka H Dept. of Oncology and Immunology, Nippon Roche Research Center, Japan Gan to kagaku ryoho. Cancer & chemotherapy (1991), 18(10), 1579-86. Journal code: 7810034. ISSN:0385-0684. (COMPARATIVE STUDY); (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 1831339 AN 91336740 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Fluorinated pyrimidines given orally were examined for their antitumor activity with 11 human cancer xenograft models (4 bladder, 4 cervical and 3 ovarian cancers). The drugs were evaluated to be effective when they inhibited tumor growth over 58%. UFT was not effective against all of 11 cancer xenografts tested. 5-Fluorouracil (5-FU) was effective against only one bladder cancer xenograft among 6 cancer xenografts tested. On the other hand, 5'-deoxy-5-fluorouridine (5'-DFUR) was effective against one bladder, 3 cervical and one ovarian cancer xenografts. The Antitumor activity of 5'-DFUR was correlated with the enzyme activity of pyrimidine nucleoside phosphorylase, which is an essential enzyme for phosphorolysis of 5'-DFUR to 5-FU.

Answer 53:

Bibliographic Information

Relationship between dose rate of [6RS]Leucovorin administration, plasma concentrations of reduced folates, and pools of 5,10-methylenetetrahydrofolates and tetrahydrofolates in human colon adenocarcinoma xenografts. Houghton J A; Williams L G; de Graaf S S; Cheshire P J; Rodman J H; Maneval D C; Wainer I W; Jadaud P; Houghton P J Department of Biochemical and Clinical Pharmacology, St. Jude Children's Research Hospital, Memphis, Tennessee 38101 Cancer research (1990), 50(12), 3493-502. Journal code: 2984705R. ISSN:0008-5472. 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 2140289 AN 90254623 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

[6RS]Leucovorin (5-formyltetrahydrofolate; 5-CHO-H4PteGlu) administered in different regimens in combination with 5-fluorouracil (FUra) has increased the response rates to FUra in patients with colon adenocarcinoma. Using preclinical models of human colon adenocarcinomas as xenografts in immune-deprived mice, the effect of the rate of administration of racemic [6RS]leucovorin on the concentration-time profile of reduced folates in plasma, size of intratumor pools of 5,10-methylenetetrahydrofolates (CH₂-H4PteGlu) and tetrahydrofolates (H4PteGlu), and the distribution of their polyglutamate species have been examined. Bolus injection i.v., or 4-h or 24-h infusion of [6RS]leucovorin (500 mg/m²) yielded similar concentration profiles of the biologically active [6S] and inactive [6R] isomers of 5-CHO-H4-PteGlu and 5-methyltetrahydrofolate (5-CH₃-H4PteGlu) in mouse plasma to those previously reported in humans, but with more rapid elimination half-lives (t_{1/2} = 11 to 16 min, 23 to 41 min, and 30 to 35 min, respectively). Thus, reduced folates remained elevated in plasma during the period of [6RS]leucovorin administration. In HxELC2 and HxGC3 tumors, pools of CH₂-H4PteGlu and H4PteGlu were increased from 350% to 700% of control, but only during [6RS]leucovorin infusion. Intracellular levels subsequently declined rapidly, similar to the loss of reduced folates from plasma. Increasing the rate of [6RS]leucovorin delivery by decreasing the time for administration from a 24-h to a 4-h infusion did not further increase the intratumor pools of CH₂-H4PteGlu and H4PteGlu, suggesting saturation in the cellular metabolism of [6RS]leucovorin. In HxGC3 tumors, CH₂-H4PteGlu₄₋₅ were elevated more rapidly than in line HxELC2, which accumulated predominantly a shorter chain length species following i.v. bolus injection.

During the 4-h infusion schedule, di- and triglutamate species in particular accumulated in both tumors with no elevation in CH₂-H4PteGlu₅ until the infusion was discontinued, when this species increased as the shorter chain length forms were declining. However, during the 24-h infusion of [6RS]leucovorin, CH₂-H4PteGlu₃₋₅ were elevated in tumors. Since these species have been reported to increase the binding affinity of [6-3H]5-fluorodeoxyuridine monophosphate ([6-3H]FdUMP) to thymidylate synthase, and intratumor pools of CH₂-H4PteGlu and H4PteGlu were elevated during the 24-h infusion

of [6RS]leucovorin, this was considered to be the preferred schedule for administration.(ABSTRACT TRUNCATED AT 400 WORDS)

Answer 54:

Bibliographic Information

Fluoropyrimidine metabolism in human head and neck cancer xenografts and murine colon tumors.

Laurensse E J; Braakhuis B J; Pinedo H M; Peters G J Department of Oncology, Free University Hospital, Amsterdam, the Netherlands Advances in experimental medicine and biology (1989), 253B 327-34. Journal code: 0121103. ISSN:0065-2598. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 2532861 AN 90119199 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Answer 55:

Bibliographic Information

Value of in vivo tissue testing in predicting the clinical response to regional perfusion chemotherapy in colorectal cancer patients with liver metastases.

Schmitz R; Krakamp B; Mennigen R; Barkun J; Klauke H II. Department of Surgery, University of Cologne Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft ... [et al] (1989), 165(7), 546-7. Journal code: 8603469. ISSN:0179-7158. (CLINICAL TRIAL); (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE); (RANDOMIZED CONTROLLED TRIAL) written in English. PubMed ID 2526381 AN 89317860 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Answer 56:

Bibliographic Information

MTX-5-FU combination therapy compared to FUDR monotherapy in nude mice. Zanea-Wangler E; Schmitz R; Kessler J; Ploss H J II. Surgical Department, University of Cologne Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft ... [et al] (1989), 165(7), 544-6. Journal code: 8603469. ISSN:0179-7158. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 2526380 AN 89317859 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Answer 57:

Bibliographic Information

The antiproliferative effects of fluoropyrimidine derivatives against human tumor xenografts in a subrenal capsule assay.

Nishiyama M; Takagami S; Kirihara Y; Saeki T; Hirabayashi N; Nosoh Y; Niimoto M; Hattori T Department of Surgery, Hiroshima University, Japan The Japanese journal of surgery (1988), 18(6), 725-8. Journal code: 1302176. ISSN:0047-1909. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 2977626 AN 89236816 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The antiproliferative effects of the fluoropyrimidine derivatives, 5-fluorouracil (5-FU), 1-(2-tetrahydrofuryl)-5-fluorouracil (Tegafur), UFT, 1-hexylcarbonyl-5-fluorouracil (HCFU), and 5'-deoxy-5-fluorouracil (5'DFUR), were investigated in a 4 day subrenal capsule assay. The antiproliferative effects against two human tumor xenografts established in athymic mice were examined after treatment with three different doses of each anticancer agent, and the adequate dose of each

anticancer agent in this experimental system was estimated as: 473 mg/kg for Tegafur, 433 mg/kg for UFT, 50 mg/kg for HCFU and 185 mg/kg for 5'DFUR, respectively. A comparative study of the antiproliferative effects of fluoropyrimidine derivatives was carried out against 7 xenografts. According to our criteria of positive tumor response, the effective rates were: 1 of 7 (14.3 per cent) by 5-FU, 2 of 7 (28.6 per cent) by Tegafur, 2 of 7 (28.6 per cent) by UFT, 1 of 6 (16.7 per cent) by HCFU, and 1 of 4 (25.0 per cent) by 5'DFUR, respectively. Although no statistical differences were demonstrated between the agents, the utility of a chemosensitivity test before clinical use was suggested.

Answer 58:

Bibliographic Information

Enhanced therapeutic efficacy of 5'deoxy-5-fluorouridine in 5-fluorouracil resistant head and neck tumours in relation to 5-fluorouracil metabolising enzymes. Peters G J; Braakhuis B J; de Bruijn E A; Laurensse E J; van Walsum M; Pinedo H M Department of Oncology, Free University Hospital, Amsterdam, The Netherlands British journal of cancer (1989), 59(3), 327-34. Journal code: 0370635. ISSN:0007-0920. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 2522792 AN 89194072 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Four human head and neck xenograft (HNX) tumour lines grown in nude mice and two murine colon carcinomas (Colon 26 and 38) were tested for their sensitivity to 5-fluorouracil (5-FU) and its prodrug 5'deoxy-5-fluorouridine (Doxifluridine, 5'd-FUR). 5-FU sensitivity at the maximum tolerated dose (MTD) showed the following pattern; HNX-DU less than HNX-KE = HNX-E = HNX-G less than Colon 26 much less than Colon 38. The sensitivity pattern to 5'd-FUR was: HNX-DU less than HNX-G less than HNX-E less than HNX-KE less than Colon 38 less than Colon 26. For HNX-KE, HNX-E and Colon 26 an increase in therapeutic efficacy was observed with 5'd-FUR as compared to 5-FU; Colon 38 was as sensitive to 5'd-FUR as to 5-FU. Plasma pharmacokinetics of 5'd-FUR and 5-FU were comparable in normal and nude mice. Metabolism of 5-FU and 5'd-FUR was studied in the tumours. Conversion of 5'd-FUR to 5-FU was highest in Colon 26 and 15-20 times lower in HNX-DU, HNX-KE and Colon 38. The Km for 5'd-FUR in all tumours was 1-2 mM. Further anabolism of 5-FU to fluorouridine (FUR) was 5-10 times higher than that of 5-FU to FUR in HNX tumours and 3 times in the colon tumours. 5-FU conversion to FUMP via FUR had the following pattern: Colon 26 much greater than HNX-DU greater than HNX-G greater than HNX-E greater than HNX-KE much greater than Colon 38; of 5-FU to FdUMP via FUDr: Colon 26 greater than HNX-DU = HNX-KE greater than HNX-E greater than HNX-G = Colon 38; and that of 5-FU to FUMP catalysed by orotate phosphoribosyl transferase (OPRT); Colon 26 greater than or equal to Colon 38 greater than HNX-KE greater than HNX-E = HNX-DU = HNX-G. Only those tumours with a relatively high activity of OPRT were sensitive to 5'd-FUR. Colon 26, which has a very high rate of pyrimidine nucleoside phosphorylase, showed a relatively high increase in the therapeutic efficacy. It is concluded that a low rate of pyrimidine nucleoside phosphorylase is enough to convert 5'd-FUR to 5-FU; further anabolism of 5-FU catalysed by OPRT may be limiting and explain the differential sensitivity.

Answer 59:

Bibliographic Information

Effects of alternating chemotherapy with 2 non-cross-resistant drug combinations on human alimentary and breast cancer xenografts in nude mice. Fujita F; Fujita M; Yamauchi T; Sakamoto Y; Shimozuma K; Inaba H; Taguchi T Gan to kagaku ryoho. Cancer & chemotherapy (1987), 14(5 Pt 1), 1297-304. Journal code: 7810034. ISSN:0385-0684. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 2953311 AN 87212073 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Despite the recent advances made in the development of anticancer drugs, any single chemotherapy treatment has only limited effects on cancers of the stomach, colon and breast, so that the combined use of multiple drugs is necessary for the treatment of solid tumors. In our previous studies with human gastrointestinal and breast cancers xenografted into nude mice, combination therapy with mitomycin C (MMC) and 5'-deoxy-5-fluorouridine (5'-DFUR) [I] or cisplatin (CDDP), vindesine (VDS) and 5'-DFUR [II] produced higher response rates than single-agent therapy with any one of these drugs. In the present study, the effectiveness of alternating chemotherapy with the combination regimens I and II was evaluated using 3 lines of cancer xenografts with special emphasis on relapse-free survival. Even in untreated controls, different influences of these cancers on the host as well as differences in their growth rates resulted in delayed tumor death in breast cancer (H-31) compared with pancreas (H-48) and colon (H-110) cancers. Four cycles of the regimen I drug combination failed to prolong life due to toxic side effects in every cancer line. In H-48 cancer, although regimen I alternated with regimen II achieved an inhibition rate (IR) of 96% with tumor shrinkage, 2 of 7 mice died of toxicity. In H-110 cancer, which is only sensitive to VDS, 4 cycles of regimen II alone produced an IR of 83.5%, which was slightly superior to alternating chemotherapy. In H-31 cancer, which retains considerable sensitivity to CDDP, MMC and 5'-DFUR, mice treated with alternating chemotherapy starting from regimen I for a total of 5 cycles attained a maximal IR of over 99% including disappearance of the tumor in 6 of 7 mice during the treatment course, and at the end of the experiment (20th week), all had survived with one in a relapse-free state, compared with the control group which had only 2 survivors.

Thus, cyclic delivery of two non-cross-resistant drug combinations with optimal treatment doses and timing prevented toxic effects and induced long-term survival without relapse. Also, this appears to be the first study that has evaluated the effects of cancer chemotherapy in a human solid tumor-nude mouse system according to survival rate.

Answer 60:

Bibliographic Information

Combination chemotherapy with 3 or 4 drugs on human breast and gastrointestinal cancer xenografts in nude mice (II). Fujita F; Fujita M; Sakamoto Y; Shimozuma K; Inaba H; Taguchi T Gan to kagaku ryoho. Cancer & chemotherapy (1987), 14(5 Pt 1), 1252-9. Journal code: 7810034. ISSN:0385-0684. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 2953310 AN 87212065 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Because of the limited effects of single-agent chemotherapy for solid tumors, combination therapy was employed in an attempt to enhance the clinical effects. Following our former report in which the combination effects of mitomycin C (MMC) and 5'-deoxy-5-fluorouridine (5'-DFUR) were clarified, combined applications of 4 drugs, vindesine (VDS), methotrexate (MTX), cisplatin (CDDP) and 5'-DFUR against 3 lines of human breast cancer (H-62, H-31, H-71), and one line each of gastric cancer (H-55) and colon cancer (H-110) xenografted into nude mice were evaluated in comparison with CAF (cyclophosphamide, adriamycin and 5-FU) therapy which is commonly used for breast cancer. Treatment was initiated in groups of 7 mice each when the mean tumor volume of subcutaneous tumors had reached about 100mm³, and the therapeutic effect was evaluated in terms of the inhibition rate (I.R.). A synergistic effect is said to exist when the combination therapy is superior to each single drug therapy at the maximal tolerated dose. Combination therapy with 3 drugs (VDS, CDDP and 5'-DFUR) or 4 drugs (VDS, CDDP, MTX and 5'-DFUR) achieved an I.R. of over 98%, i.e., a marked effect with tumor shrinkage, in 3 lines of tumors (H-55, H-31 and H-62). Moreover, remarkable effects were shown even in the other 2 lines which were insensitive to every single-agent therapy, the I.R. values being 85.7% (H-71) and 78.5% (H-110). A synergistic effect was obtained in 3 of the 5 lines examined. These combination therapies were histologically superior to therapies employing each single-drug therapy or CAF therapy. The side effects for combination of these 3 or 4 drugs evaluated by body weight loss were transient and equivalent to maximal dose of VDS or CDDP. Clinically, it is thought that these combined therapies of 3 or 4 drugs will bring about a considerable response in practice.

Answer 61:

Bibliographic Information

Evaluation by multiple regression analysis of factors influencing the chemosensitivity of human tumors xenografted into nude mice. Fujita F; Fujita M; Hirai T; Taguchi T Gan to kagaku ryoho. Cancer & chemotherapy (1987), 14(3 Pt 1), 618-25. Journal code: 7810034. ISSN:0385-0684. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 2950823 AN 87155358 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The chemosensitivity of human cancer lines is thought to be expressed as a result of contributions by various interacting factors. Multiple regression analyses were performed in order to clarify the weighting of factors responsible for the chemosensitivity of 15 human cancers xenografted into nude mice. Inhibition rates of 11 anticancer agents predetermined for each line of human cancer were used as the criterion variables. As the explanatory variables, 9 parameters characteristic of each cancer or cancer-bearing mouse were selected as follows; grade of differentiation, vascularity, percentage necrosis, volume doubling time, labeling index, LDH activity, tissue/serum LDH ratio, thymidine phosphorylase activity and serum CEA. By applying this analysis with stepwise deletion, the estimated multiple regression equations for drug sensitivity were clarified for each drug. Although all equations were composed of different factors and their partial regression coefficients varied from drug to drug, those among analogous drugs such as FT-207 and UFT, or MMC and M-83 had similar factors. The equations for M-83, ACNU and ADR consisted of a number of parameters with a sufficiently high coefficient of determination of over 80%. Even in cases of MXT that showed no significant factor upon simple correlation analysis, an equation with 7 factors revealed a coefficient of determination of 0.83. The estimated values of effectiveness for these drugs showed remarkable coincidence with each actual value. For some drugs, the in vivo mode of action was inferred through this analysis.

Answer 62:

Bibliographic Information

Combination chemotherapy of human gastrointestinal and breast cancer xenografts in nude mice with 5'-deoxy-5-fluorouridine and mitomycin C. Fujita F; Fujita M; Shimozuma K; Taguchi T Nippon Gan Chiryō Gakkai shi (1986), 21(7), 1386-96. Journal code: 7505713. ISSN:0021-4671. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 2946789 AN 87059413 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Answer 63:

Bibliographic Information

Combined therapy of polyamine antimetabolites and antitumor drugs for human gastric cancer xenotransplanted into nude mice. Fujimoto S; Igarashi K; Shrestha R D; Miyazaki M; Endoh F; Ohta M; Togawa Y; Okui K The Japanese journal of surgery (1986), 16(2), 133-9. Journal code: 1302176. ISSN:0047-1909. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 2941608 AN 86255011 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Antitumor therapies using polyamine antimetabolites combined with 1-(4-amino-2-methyl-5-pyrimidyl)methyl-3(2-chloroethyl)-3-nitrosourea (ACNU) or fluorinated pyrimidines for human gastric cancer xenotransplanted into nude mice were studied to determine inhibiting post-therapeutic regrowth of the tumor after cessation of antitumor treatments with polyamine antimetabolites alone. ACNU 20 mg/kg, fluorinated pyrimidine, 5-FU 52.8 mg/kg and 5'-deoxy-5-fluorouridine (5'-DFUR) 100 mg/kg as well as polyamine antimetabolites, alpha-difluoromethylornithine (DFMO) 1000 mg/kg and methylglyoxal-bis-guanylhydrazone (MGBG) 50 mg/kg were given intraperitoneally for 5 successive days. When DFMO and MGBG were combined with ACNU, the post-therapeutic

regrowth was definitely inhibited, while combined treatments with 5-FU or 5'-DFUR did not inhibit the regrowth. Post-therapeutic DNA biosynthesis was suppressed in mice given DFMO, MGBG plus ACNU. On the contrary, in mice treated with DFMO, MGBG plus 5-FU or 5'-DFUR, suppression of DNA biosynthesis was not observed. Tumor tissue spermine levels in the DFMO, MGBG plus 5-FU or 5'-DFUR group remained unchanged, compared to those in the DFMO + MGBG group. In mice given DFMO, MGBG plus ACNU, however, spermine levels were markedly depressed; and the ACNU alone depressed also the tissue spermine levels. These different results between nitrosourea and fluorinated pyrimidines may relate to mechanisms of action of these antitumor drugs.

Answer 64:

Bibliographic Information

Anticancer treatment with a combination of antimetabolites of polyamine and pyrimidine. Fujimoto S; Shrestha R D; Igarashi K; Miyazaki M; Endoh F; Shimura T; Sugawara H; Takahashi O; Kawata S; Ohta M; + Gan to kagaku ryoho. *Cancer & chemotherapy* (1985), 12(10), 2024-9. Journal code: 7810034. ISSN:0385-0684. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 2932057 AN 86024325 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

A combined efficacy of the polyamine antimetabolites, alpha-difluoromethylornithine (DFMO) and methylglyoxal-bis-guanylhydrazine (MGBG) with two fluorinated pyrimidines was studied. DFMO, MGBG, 5-FU and 5'-deoxy-5-fluorouridine (5'-DFUR) were administered intraperitoneally to BALB/c nu/nu mice bearing xenotransplanted human gastric cancer for 5 consecutive days. Similar antitumor efficacies were observed in 3 groups treated with DFMO plus MGBG, DFMO, MGBG plus 5-FU as well as DFMO, MGBG plus 5'-DFUR. The two groups on 5-FU or 5'-DFUR alone did not differ in antitumor effects from the control, although reasonable levels of 5-FU were involved in tumor tissues. Hepatic and splenic 5-FU levels after 5-FU administration were significantly higher than those after 5'-DFUR, and marked decrease in mouse body weight was caused by 5-FU alone as well as 5-FU plus polyamine antimetabolites for 5 consecutive days. DNA biosynthesis and spermine levels in the tumor tissues on day 2 after cessation of the treatments dropped in 3 groups with DFMO plus MGBG, DFMO, MGBG plus 5'-DFUR as well as DFMO, MGBG plus 5-FU, while on day 6 there was little difference between the control and treated groups. These data suggest that combination with 5-FU or 5'-DFUR does not enhance the antitumor activity of polyamine antimetabolites by this experimental regimen.

Answer 65:

Bibliographic Information

Antitumor activity of a new fluoropyrimidine derivative, 5'-deoxy-5-fluorouridine, against murine and human experimental tumors. Fujimoto S; Wang Y; Inoue K; Ogawa M *Japanese journal of cancer research : Gann* (1985), 76(7), 644-50. Journal code: 8509412. ISSN:0910-5050. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 3161854 AN 85288581 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

5'-Deoxy-5-fluorouridine (5'-DFUR) was evaluated for antitumor activity against four murine tumors (L1210 leukemia, P388 leukemia, Lewis lung carcinoma, and B16 melanoma) and a human mammary carcinoma (MX-1) xenografted in athymic mice. Intraperitoneal administration of 5'-DFUR was ineffective against B16 melanoma implanted intraperitoneally and showed less marked antitumor activity against P388 and L1210 leukemias implanted intraperitoneally or intravenously as compared with that of 5-fluorouracil (5-FU) or 1-(2-tetrahydrofuryl)-5-fluorouracil (FT-207), while oral administration of 5'-DFUR showed a similar or superior antitumor activity to that of 5-FU or FT-207 against L1210 leukemia implanted subcutaneously. 5'-DFUR showed a marked antitumor activity against MX-1 implanted subcutaneously and also showed slight antitumor activity against Lewis lung carcinoma implanted subcutaneously, while

5-FU and FT-207 did not show any significant antitumor activity against these tumors. These results suggest that 5'-DFUR may be worthy of clinical trial against solid tumors, especially cancers of the breast.

Answer 66:

Bibliographic Information

Effects of 5'-deoxy-5-fluorouridine on human gastrointestinal and breast cancers xenografted to nude mice.

Fujita F; Fujita M; Taguchi T Gan to kagaku ryoho. Cancer & chemotherapy (1984), 11(8), 1635-43. Journal code: 7810034. ISSN:0385-0684. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in Japanese. PubMed ID 6236751 AN 84305913 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

As a preclinical secondary screening trial, the efficacy of a new derivative of 5-fluorouracil, 5'-deoxy-5-fluorouridine (5'-DFUR), on 15 human cancers xenografted serially to nude mice of BALB/c background was evaluated in comparison with two other derivatives, tegafur and UFT. Oral administration of 123 mg/kg/day of 5'-DFUR, 25-30 times, produced effective inhibition in 5 out of 7 gastric cancers, 2 out of 3 colorectal cancers, all 3 of breast cancers and 1 out of 2 pancreatic cancers, totalling 11 out of 15 cancer lines (73%) examined. In some cases shrinkage of tumors was noted without any noticeable side effects. Although an increased dose of 185 mg/kg/day of 5'-DFUR resulted in more prominent inhibition on all 9 tumors tested, some animals suffered from severe loss of body weight or diarrhea. Comparative experiments with of equimolar doses of 5'-DFUR(123 mg/kg) and FT-207(100 mg/kg) showed that the inhibition rate of the former was higher than that of the latter in all 8 lines of cancers examined. Six experiments in particular (2 gastric, 1 colorectal, 2 breast and 1 pancreatic cancers), showed that 5'-DFUR statistically sustained more effective suppression. Direct comparisons of 5'-DFUR and UFT were also made in 5 experiments in which 3 cancers were more sensitive to the former drug. Promising results in clinical trials can be expected with the new drug 5'-DFUR for these kinds of cancers.