

Answer 1:

Bibliographic Information

Medicinal chemistry of probimane and MST-16: comparison of anticancer effects between bisdioxopiperazines. Lu, Da-Yong; Huang, Min; Xu, Cheng-Hui; Zhu, Hong; Xu, Bin; Ding, Jian. School of Life Sciences, Shanghai University, Shanghai, Peop. Rep. China. *Medicinal Chemistry* (2006), 2(4), 369-375. Publisher: Bentham Science Publishers Ltd., CODEN: MCEHAJ ISSN: 1573-4064. Journal written in English. CAN 145:262672 AN 2006:672037 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Bisdioxopiperazines, including ICRF-154 and razoxane (ICRF-159, Raz), are a family of anticancer agents developed in the UK, specifically targeting neoplastic metastases. Two other bisdioxopiperazine derivs., probimane (Pro) and MST-16, were synthesized at the Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, China. To det. the similarities and differences between these agents in medical chem., we evaluated the antitumor and anti-metastatic effects of Pro and MST-16 in vitro and in vivo against a no. of human tumor cell lines and one of murine origin (Lewis lung carcinoma, LLC), and one human tumor xenograft (LAX-83) in nude mice. Our results show that Pro was cytotoxic to human tumor cell lines in vitro (IC50 < 50 μ M for 48 h), approx. 3 to 20-fold more than MST-16. Pro and MST-16 manifested more prolonged cytotoxicity than some other first-line anticancer drugs including 5-fluorouracil, vincristine and doxorubicin, and maintain their cytotoxic effects for 4 days in vitro. In animal expts., Pro and Raz were active against primary tumor growth (35-50 %) and significantly inhibited pulmonary metastasis of LLC (inhibition > 90 %) at dosage below LD5. Both Raz and Pro were effective in administration schedules of 1, 5 and 9 days. Both Raz (25-32 %) and Pro (55-60 %) caused statistically significant inhibition of the growth of LAX 83 (a human lung adenocarcinoma xenograft) in nude mice. In this model, Pro was more effective against LAX83 than Raz at equitoxic dosages. These findings suggest that Pro is active against more categories of tumors both in vivo and in vitrom, which in some circumstances may make it superior to the currently-used anticancer bisdioxopiperazines, including razoxane and MST-16.

Answer 2:

Bibliographic Information

Combination chemotherapy of human pancreatic tumor xenografts grown in nude mice. Duke, D. I.; Hellmann, K.; Hutchinson, G. E.; Pym, B. A. *Cancer Chemother. Dep., Imp. Cancer Res. Fund, London, UK.* Editor(s): Sordat, Bernard. *Immune-Defic. Anim., Int. Workshop Immune-Defic. Anim. Exp. Res.*, 4th (1984), Meeting Date 1982, 416-20. Publisher: Karger, Basel, Switz CODEN: 51ONAB Conference written in English. CAN 101:350 AN 1984:400350 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Various drug combinations, frequency of administration, and dosage schedules are examd. in an effort to maximize the chemotherapeutic response of human pancreatic tumor xenografts in mice. To be active against pancreatic cancer, chemotherapy should be administered at short intervals in a more or less continuous fashion.

Answer 3:

Bibliographic Information

Antitumor effects of two bisdioxopiperazines against two experimental lung cancer models in vivo. Lu Da-Yong; Xu Bin; Ding Jian Division of Anticancer Pharmacology, Shanghai Institute of Materia Medica, Shanghai Institutes of Biology Sciences, Chinese Academy of Sciences, Shanghai 201203, PR China. ludayong@sh163.net *BMC pharmacology* (2004), 4(1), 32. Journal code: 100967806. E-ISSN:1471-2210. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 15617579 AN 2005046076

MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

BACKGROUND: Probimane (Pro), an anti-cancer agent originating in China, was derived from razoxane (ICRF-159, Raz), a drug created in Britain, specifically targeting at cancer metastasis and as a cardioprotectant of anthracyclines. Pro and Raz are bisdioxopiperazine compounds. In this work, we evaluated the anti-tumor and anti-metastatic effects of Pro and Raz in vivo against two lung tumor models, one of murine origin (Lewis lung carcinoma, LLC) and one of human origin (LAX-83). **RESULTS:** After determining the lethal dosage of Pro and Raz, we assessed and compared the inhibitory effects of Pro and Raz against primary tumor growth and metastatic occurrences of LLC at the dosage of LD5. Pro and Raz were active against primary tumor growth and significantly inhibited pulmonary metastasis of LLC at same dose-ranges (inhibitory rates > 90 %). Both Raz and Pro were effective in 1, 5, and 9 day administration schedules. Three different schedules of Raz and Pro were effective against the primary tumor growth of LLC (35-50 %). The synergistic anticancer effect of Raz with bleomycin (Ble) (from 41.3 % to 73.3 %) was more obvious than those with daunorubicin (Dau) (from 33.1 % to 56.3 %) in the LLC tumor model. Pro was also seen to have synergistic anti-cancer effects with Ble in the LLC model. Both Raz and Pro inhibited the growth of LAX 83 in a statistically significant manner. **CONCLUSIONS:** These data suggest that both Raz and Pro may have anti-tumor potentiality and Raz and Pro have combinative effects with Ble or Dau. The potential targets of bisdioxopiperazines may include lung cancers, especially on tumor metastasis. The anti-cancer effects of Raz and Pro can be increased with the help of other anticancer drugs.

Answer 4:

Bibliographic Information

Monohydroxyethylrutoside, a dose-dependent cardioprotective agent, does not affect the antitumor activity of doxorubicin. van Acker S A; Boven E; Kuiper K; van den Berg D J; Grimbergen J A; Kramer K; Bast A; van der Vijgh W J Leiden Amsterdam Center for Drug Research, Division of Molecular Pharmacology, Department of Pharmacochemistry, Faculty of Chemistry, Vrije Universiteit, Amsterdam, The Netherlands Clinical cancer research : an official journal of the American Association for Cancer Research (1997), 3(10), 1747-54. Journal code: 9502500. ISSN:1078-0432. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 9815559 AN 199911117 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The cumulative dose-related cardiotoxicity of doxorubicin is believed to be caused by the production of oxygen-free radicals. 7-Monohydroxyethylrutoside (monoHER), a semisynthetic flavonoid and powerful antioxidant, was investigated with respect to the prevention of doxorubicin-induced cardiotoxicity in mice and to its influence on the antitumor activity of doxorubicin in vitro and in vivo. Non-tumor-bearing mice were equipped with a telemeter in the peritoneal cavity. They were given six weekly doses of 4 mg/kg doxorubicin i.v., alone or in combination with either 100 or 250 mg/kg monoHER i.p., 1 h prior to doxorubicin administration and for the following 4 days. Cardiotoxic effects were measured from electrocardiogram changes up to 2 weeks after treatment. Protection against cardiotoxicity was found to be dose dependent, with 53 and 75% protection, respectively, as calculated from the reduction in the increase in the ST interval. MonoHER and several other flavonoids with good antioxidant properties were tested for their antiproliferative effects in the absence or the presence of doxorubicin in A2780 and OVCAR-3 human ovarian cancer cells and MCF-7 human breast cancer cells in vitro. Some flavonoids were directly toxic at 50 and 100 microM, whereas others, including monoHER, did not influence the antiproliferative effects of doxorubicin at these concentrations. The influence of monoHER was further tested on the growth-inhibitory effect of 8 mg/kg doxorubicin i.v., given twice with an interval of 1 week in A2780 and OVCAR-3 cells that were grown as s.c. xenografts in nude mice. MonoHER, administered 1 h before doxorubicin in a dose schedule of 500 mg/kg i.p. 2 or 5 days per week, was not toxic and did not decrease the antitumor activity of doxorubicin. It can be concluded that monoHER showed a dose-dependent protection against chronic cardiotoxicity and did not influence the antitumor activity of doxorubicin in vitro or in vivo.

Answer 5:

Bibliographic Information

Distribution of ¹⁴C labeled at dioxopiperazine or methyl morpholine group of probimane by whole body autoradiography. Lu D Y; Xu B; Zhang X; Chen R T Shanghai Institute of Materia Medica, Chinese Academy of Sciences Zhongguo yao li xue bao = Acta pharmacologica Sinica (1993), 14(2), 171-3. Journal code: 8100330. ISSN:0253-9756. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Chinese. PubMed ID 8352014 AN 93355857 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Probimane (AT-2153) is a new anticancer compound. It was first developed in this Institute. It is effective against mouse tumors S37, S180, Lewis lung carcinoma, L1210 and human pulmonary adenocarcinoma heterotransplanted into nude mice. In the present work, ¹⁴C was labeled at central dioxopiperazine or methyl morpholine group of probimane 120 mg.kg⁻¹ was injected iv in mice bearing Lewis lung carcinoma by whole body autoradiography. The results showed that probimane was broken into at least two parts: a central part and a methyl morpholine group. The central part of compound hardly penetrated through the blood-brain barrier, but accumulated in the urinary bladder. The methyl morpholine group showed a high affinity to tumor tissue and accumulated in spleen, bone and liver.

Answer 6:

Bibliographic Information

Phase II study: treatment of non-Hodgkin's lymphoma with an oral antitumor derivative of bis(2,6-dioxopiperazine). Ohno R; Yamada K; Hirano M; Shirakawa S; Tanaka M; Oguri T; Kodera Y; Mitomo Y; Ikeda Y; Yokomaku S; + Department of Medicine, Nagoya University School of Medicine, Branch Hospital, Japan Journal of the National Cancer Institute (1992), 84(6), 435-8. Journal code: 7503089. ISSN:0027-8874. (CLINICAL TRIAL); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 1538420 AN 92167304 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

BACKGROUND: Although razoxane (ICRF-159), a derivative of bis(2,6-dioxopiperazine), has shown significant antitumor activity in several murine tumors, inadequate bioavailability has limited its clinical efficacy. Sobuzoxane (MST-16), another derivative of bis(2,6-dioxopiperazine), has shown activity against a broad spectrum of murine tumors and human tumor xenografts in nude mice and a lack of cross-resistance to vincristine, doxorubicin, cyclophosphamide, fluorouracil, etoposide, and mitomycin C. These findings suggest that MST-16 has a mode of cytotoxic activity different from that of other antitumor agents. **PURPOSE:** The present late phase II study was conducted to evaluate the clinical efficacy and toxicity of MST-16 in non-Hodgkin's lymphoma (NHL). **METHODS:** As part of a multi-institutional cooperative study, we conducted a study of MST-16 in 27 patients with NHL who were assessable for drug efficacy and toxicity. MST-16, a bis(2,6-dioxopiperazine) analogue and an inhibitor of topoisomerase II, was administered orally at a dose of 1600 mg/m² a day for 5-7 days at intervals of 2-3 weeks. **RESULTS:** Response consisted of one complete remission and seven partial remissions in 27 assessable patients. Response was achieved at a median of 13 days (range, 9-62 days) after initiation of therapy and lasted a median of 46 days (range, 29-155 days). Major toxic effects were leukopenia in 70% of the patients, thrombocytopenia in 44%, and gastrointestinal disorders in 37%. **CONCLUSIONS:** MST-16 was shown to be effective in NHL and deserves further clinical trial, since the drug shows little cross-resistance to available antitumor drugs. **IMPLICATIONS:** Phase II clinical studies of MST-16 in treatment of breast cancer, gastric cancer, and adult T-cell leukemia and lymphoma are also being conducted in Japan. Future trials of combination chemotherapy using MST-16 with other antitumor drugs are warranted in view of the additive effects observed in studies of MOLT-3 cells and studies of L1210 leukemia in mice.