

Answer 1:

Bibliographic Information

Amrubicin, a novel 9-aminoanthracycline, enhances the antitumor activity of chemotherapeutic agents against human cancer cells in vitro and in vivo. Hanada, Mitsuharu; Noguchi, Toshihiro; Yamaoka, Takashi. Pharmacology Research Laboratories, Drug Research Division, Dainippon Sumitomo Pharma Co., Ltd, 3-1-98, Kasugadenaka, Konohana-ku, Osaka, Japan. *Cancer Science* (2007), 98(3), 447-454. Publisher: Blackwell Publishing Asia Pty Ltd., CODEN: CSACCM ISSN: 1347-9032. Journal written in English. CAN 146:266424 AN 2007:262575 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Amrubicin, a completely synthetic 9-aminoanthracycline deriv., is an active agent in the treatment of untreated extensive disease-small-cell lung cancer and advanced non-small-cell lung cancer. Amrubicin administered i.v. at 25 mg/kg substantially prevented the growth of five of six human lung cancer xenografts established in athymic nude mice, confirming that amrubicin as a single agent was active in human lung tumors. To survey which antitumor agent available for clin. use produces a synergistic interaction with amrubicin, we examd. the effects in combinations with amrubicinol, an active metabolite of amrubicin, of several chemotherapeutic agents in vitro using five human cancer cell lines using the combination index (CI) method of Chou and Talalay. Synergistic effects were obtained on the simultaneous use of amrubicinol with cisplatin, irinotecan, gefitinib and trastuzumab, with CI values after 3 days of exposure being <1. Additive effect was obsd. with the combination contg. vinorelbine with CI values indistinguishable from 1, while the combination of amrubicinol with gemcitabine was antagonistic. All combinations tested in vivo were well tolerated. The combinations of cisplatin, irinotecan, vinorelbine, trastuzumab, tegafur/uracil, and to a lesser extent, gemcitabine with amrubicin caused significant growth inhibition of human tumor xenografts without pronouncedly enhancing body wt. loss, compared with treatment using amrubicin alone at the max. tolerated dose. Growth inhibition of tumors by gefitinib was not antagonized by amrubicin. These results suggest that amrubicin appears to be a possible candidate for combined use with cisplatin, irinotecan, vinorelbine, gemcitabine, tegafur/uracil or trastuzumab.

Answer 2:

Bibliographic Information

Amrubicin hydrochloride. Nukiwa, Toshihiro. Department of Respiratory Oncology and Molecular Medicine, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan. *Bunshi Kokyukibyō* (2002), 6(6), 547-552. Publisher: Sentan Igakusha, CODEN: BUKOFC ISSN: 1342-436X. Journal; General Review written in Japanese. CAN 139:94492 AN 2002:941973 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A review. A new antitumor agent amrubicin hydrochloride induces cell growth inhibition by stabilizing topoisomerase II-DNA complex at mouse exptl. tumors and human tumor xenografts such as small cell lung cancer is reviewed including its structure, its active metabolite and its pharmacokinetics.

Answer 3:

Bibliographic Information

Evaluation of amrubicin with a 5 day administration schedule in a mouse model. Noguchi, Toshihiro; Ichii, Shinji; Morisada, Shinya; Yamaoka, Takashi; Yanagi, Yoshikazu. Research Center, Sumitomo Pharmaceuticals Co., Ltd., Japan. *Gan to Kagaku Ryoho* (1999), 26(9), 1305-1312. Publisher: Gan to Kagaku Ryohosha, CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 132:117202 AN 1999:634563 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

It was reported that amrubicin hydrochloride (9-aminoanthracycline; SM-5887), showed a higher therapeutic activity than doxorubicin against human tumor xenografts implanted into nude mice with a single treatment schedule. In order to find a more effective treatment schedule, the efficacy, toxicity and pharmacokinetic properties with a 5 consecutive day treatment schedule were investigated. The total amt. of the max. tolerated dose and tumor growth inhibiting activity with a 5 day schedule was found to be higher than with a single administration. High levels of amrubicinol, the active metabolite of amrubicin, was detected in the tumor tissue. It was thus assumed that the improved efficacy with the 5-day schedule resulted from the high accumulation of amrubicinol. Bone marrow suppression at the MTD with the 5 day schedule was severer than with a single dose, but recovery was rapid, similar to that following a single dose. In conclusion, it was demonstrated that a 5 day treatment schedule was more effective than a single administration.

Answer 4:

Bibliographic Information

Tumor-selective distribution of an active metabolite of the 9-aminoanthracycline amrubicin. Noguchi, Toshihiro; Ichii, Shinji; Morisada, Shinya; Yamaoka, Takashi; Yanagi, Yoshikazu. Research Center, Sumitomo Pharmaceuticals Co., Ltd., Osaka, Japan. Japanese Journal of Cancer Research (1998), 89(10), 1061-1066. Publisher: Japanese Cancer Association, CODEN: JJCREP ISSN: 0910-5050. Journal written in English. CAN 130:90041 AN 1998:727094 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The disposition and metab. of amrubicin in human-tumor-xenograft-bearing mice were studied in comparison with those of doxorubicin. Amrubicinol, a 13-hydroxy metabolite of amrubicin, which is 10-100-fold more cytotoxic than amrubicin, was detected as a major metabolite in blood and tissues, and aglycons of amrubicin were also detected. A pharmacokinetic study revealed that amrubicin had a smaller distribution vol. and a shorter half-life than doxorubicin. In several normal tissues, the levels of amrubicin and amrubicinol were lower than those of doxorubicin. In contrast, the tumor levels of amrubicinol in the mice treated with amrubicin were higher than those of doxorubicin in the mice treated with that drug, in tumors that are sensitive to amrubicin. The results suggest that the potent therapeutic activity of amrubicin is caused by the selective distribution of its highly active metabolite, amrubicinol, in tumors.

Answer 5:

Bibliographic Information

In vivo efficacy and tumor-selective metabolism of amrubicin to its active metabolite. Noguchi, Toshihiro; Ichii, Shinji; Morisada, Shinya; Yamaoka, Takashi; Yanagi, Yoshikazu. Research Center, Sumitomo Pharmaceuticals Co., Ltd., Osaka, Japan. Japanese Journal of Cancer Research (1998), 89(10), 1055-1060. Publisher: Japanese Cancer Association, CODEN: JJCREP ISSN: 0910-5050. Journal written in English. CAN 130:90181 AN 1998:727093 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The tissue distribution of the antitumor anthracycline antibiotic amrubicin in 7 human tumor xenografts implanted into nude mice was studied in order to identify the principal factors detg. its therapeutic efficacy. There was a good correlation between the level of the metabolite amrubicinol in the tumor and the in vivo efficacy. High metab. of amrubicin to amrubicinol was detected in tumor tissue homogenates, esp. in cell lines highly sensitive to amrubicin in vivo. In contrast to amrubicin, amrubicinol had less tumor-selective toxicity in these human tumor xenograft models. These data indicate that the tumor-selective metab. of amrubicin to amrubicinol resulted in a tumor-selective disposition of amrubicinol, leading to good efficacy in vivo.