

Answer 1:

Bibliographic Information

Phase II trial of cetuximab in combination with fluorouracil, leucovorin, and oxaliplatin in the first-line treatment of metastatic colorectal cancer. Taberner, Josep; Van Cutsem, Eric; Diaz-Rubio, Eduardo; Cervantes, Andres; Humblet, Yves; Andre, Thierry; Van Laethem, Jean-Luc; Soulie, Patrick; Casado, Esther; Verslype, Chris; Valera, Javier Sastre; Tortora, Giampaolo; Ciardiello, Fortunato; Kisker, Oliver; de Gramont, Aimery. Medical Oncology Service, Vall d'Hebron University Hospital, Barcelona, Spain. *Journal of Clinical Oncology* (2007), 25(33), 5225-5232. Publisher: American Society of Clinical Oncology, CODEN: JCONDN ISSN: 0732-183X. Journal written in English. CAN 148:253533 AN 2007:1464324 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: This phase II study investigated the efficacy and safety of cetuximab combined with standard oxaliplatin-based chemotherapy (infusional fluorouracil, leucovorin, and oxaliplatin [FOLFOX-4]) in the first-line treatment of epidermal growth factor receptor-expressing metastatic colorectal cancer (mCRC). **Patients and Methods:** The activity of cetuximab plus oxaliplatin was investigated in colon cancer cell lines and xenograft models. In the clinical study, patients with mCRC received on day 1 of a 14 day cycle, cetuximab (initial dose 400 mg/m² during week 1, then 250 mg/m² weekly) followed by FOLFOX-4 (oxaliplatin 85 mg/m² on day 1; leucovorin 200 mg/m² on days 1 and 2, followed by fluorouracil 400 mg/m² bolus then 600 mg/m² i.v. infusion during 22 h on days 1 and 2). **Results:** The preclinical studies confirmed the supra-additive activity of cetuximab to oxaliplatin. In the clinical study, 43 patients were included, with a median age of 65 years (range, 43 to 78 years). Response rates (RRs) were 79% (unconfirmed) and 72% (confirmed), with 95% disease control. Median progression-free survival (mPFS) and median duration of response were 12.3 and 10.8 mo, respectively. Ten patients (23%) underwent resection with curative intent of previously unresectable metastases. After a median follow-up of 30.5 mo, median overall survival (mOS) was 30.0 mo. Cetuximab did not increase the characteristic toxicity of FOLFOX-4 and was generally well tolerated. **Conclusion:** Cetuximab in combination with FOLFOX-4 is a highly active first-line treatment for mCRC, showing encouraging RR, mPFS, and mOS values. The treatment resulted in a high resectability rate, which could potentially result in an improved cure rate. This combination is under phase III development.

Answer 2:

Bibliographic Information

Mechanistic analysis and comparison of viral fusogenic membrane proteins for their synergistic effects on chemotherapy. Hoffmann, Dennis; Grunwald, Thomas; Kuete, Seraphin; Wildner, Oliver. Department of Molecular and Medical Virology, Ruhr-University Bochum; Institute of Microbiology and Hygiene, Bochum, Germany. *Cancer Biology & Therapy* (2007), 6(4), 510-518. Publisher: Landes Bioscience, CODEN: CBTAAO ISSN: 1538-4047. Journal written in English. CAN 147:479955 AN 2007:1039368 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Previously we demonstrated that the expression of fusogenic membrane proteins (FMG) of measles virus (MV-H/F) can synergistically enhance chemotherapy. In this study, we used median-effect analysis to evaluate whether the expression of respiratory syncytial virus (RSV-F), as well as vesicular stomatitis virus (VSV-G) can also synergistically enhance chemotherapy. Furthermore we elucidated by western blot analysis some molecular pathways that might be responsible for this effect. We showed in colorectal cancer cell lines that the expression of MV-H/F, but also of RSV-F, as well as VSV-G can synergistically enhance p53-independent clinically relevant chemotherapy (FOLFOX) over most of the cytotoxic dose range. In a subcutaneous HT-29 colorectal xenograft model, we demonstrated that the administration of replication-deficient adenovirus vectors encoding MV-H/F, RSV-G or VSV-G in combination with FOLFOX significantly enhanced treatment outcome when compared to the treatment with each compound individually. The anti-neoplastic efficacy of RSV-F was somewhat better than that of MV-H/F and both were statistically significantly more efficacious than VSV-G alone or in combination with chemotherapy. Treatment efficacy was further significantly improved when the replication-deficient FMG encoding vectors were trans-complemented for replication with a replication-restricted oncolytic adenovirus to improve tumor transduction efficiency. The combination of FMG expression, chemotherapy and trans-complementing oncolytic vectors resulted in a significantly better treatment

efficacy than treatment with its components as single- or double-agent therapy. Our data indicates that FMG expression (i.e., RSV-F and MV-H/F) in combination with chemotherapy and viral oncolysis warrants further investigations.

Answer 3:

Bibliographic Information

Dual biochemical modulation therapy using 5-FU, leucovorin and cisplatin on human rectal carcinoma xenografts in nude mouse. Shibusawa, Miki; Takata, Manabu; Kamiyama, Gouichi; Yokoyama, Noboru; Nakao, Kentaroh; Yoshizawa, Hiroto; Choh, Hiroto; Yasuda, Naokuni; Tsunoda, Yuko; et al. Dep. Surgery, Showa Univ. Sch. Med., Tokyo, Japan. Gan to Kagaku Ryoho (1996), 23(9), 1149-1152. Publisher: Gan to Kagaku Ryohosha, CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 125:185215 AN 1996:545435 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

This study examd. a combined treatment for colorectal carcinoma, the dual biochem. modulation therapy, consisting of 5-FU, Leucovorin (LV) and Cisplatin (CDDP). We compared the antitumor effects with other treatments: 5-FU alone, CDDP alone and 5-FU with LV. Primary diffuse infiltrated colorectal carcinoma is well known for its biol. malignancy and its lack of response to chemotherapy. We used SRM cells from a cell line of carcinoma of the rectum, and s.c. injected them into nude mice. The antitumor effects were estd. from the growth rate, inhibition rate and thymidylate synthetase inhibition rates in the tumor tissue. Results indicated that even if the concn. of 5-FU and LV were reduced by half, these combined with CDDP were more effective than other therapies. Dual biochem. modulation therapy is particularly promising because the redn. of the dosages would reduce the side effects while still serving as an excellent antitumor therapy.

Answer 4:

Bibliographic Information

The modulation by L-leucovorin of 5-fluorouracil antitumor activity on human colon carcinoma cells in vitro and in vivo. Kase, Suguru; Kubota, Tetsuro; Watanabe, Masahiko; Takahara, Tetsuya; Takeuchi, Tooru; Yamaguchi, Hiroshi; Furukawa, Toshiharu; Teramoto, Tatsuo; Kodaira, Susumu; et al. Sch. Med., Keio Univ., Tokyo, Japan. Surgery Today (1993), 23(7), 615-20. CODEN: SUTOE5 ISSN: 0941-1291. Journal written in English. CAN 120:180 AN 1994:180 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The authors investigated the modulating effect of L-leucovorin (LV) on the antitumor effect of 5-fluorouracil (5-FU) against human colon carcinoma cells (C-1) in vitro and human colon carcinoma xenografts (Co-4) in nude mice. The modulating effect of LV on 5-FU reached an optimal concn. of 40 - 80 $\mu\text{g}/\text{mL}$ in vitro which was detected by a colorimetric MTT assay. An optimal dose of 200 mg/kg was also obsd. in the nude mouse system. The modulating effect of LV increased according to the increment of thymidylate synthetase inhibition in vivo. Since the pharmacokinetic pattern of LV in the nude mice administered LV at 200 mg/kg was similar to that in patients treated with LV at a dose of 100 mg/m², this clin. method of administration was thought to be adequate for modulating the antitumor activity of 5-FU against clin. colon carcinomas.

Answer 5:

Bibliographic Information

Modulation by L-leucovorin of 1-hexylcarbamoyl-5-fluorouracil antitumor activity on human gastric and colon carcinomas serially transplanted into nude mice. Kubota, Tetsuro; Kase, Suguru; Furukawa, Toshiharu; Tanino, Hirokazu; Kuo, Tsong Hong; Saikawa, Yoshiro; Nishibori, Hideki; Ishibiki, Kyuya; Kitajima, Masaki; et al. Sch. Med., Keio Univ., Tokyo, Japan. Anticancer

Research (1992), 12(5), 1549-53. CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 118:52020 AN 1993:52020 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Exptl. biochem. modulation of 1-hexylcarbamoyl-5-fluorouracil (HCFU) with l-leucovorin (LV) was carried out using human gastric (H-111) and colon (Co-4) carcinoma xenografts serially transplanted into nude mice. Thirty-five or 70 mg/kg HCFU dissolved in 0.2 mL of 1% hydroxymethyl cellulose was administered orally daily for 3 wk except Sundays, and 50, 100, 200 or 300 mg/kg LV dissolved in 0.2 mL physiol. saline was administered po 30 min before administration of HCFU. The biochem. modulated antitumor activity was evaluated in terms of actual tumor wt., the relative mean tumor wt. and the degree of inhibition of thymidylate synthetase (TS) in the tumors at the end of the expts. Although 35 mg/kg HCFU was ineffective against gastric carcinoma H-111, combination with 200 or 300 mg/kg LV resulted in a pos. antitumor effect of HCFU on this strain without any increase of side effects in terms of body wt. loss and mouse mortality. The colon carcinoma strain Co-4 showed marginal sensitivity to HCFU (35 mg/kg) alone, but 50 or 100 mg/kg LV modulated the antitumor activity of HCFU on Co-4 to produce a significant pos. effect without any increase in toxicity, and HCFU administered with 100 mg/kg LV was more effective than the max. tolerated dose of HCFU (70 mg/kg) alone. The TS inhibition rate was closely related to the biochem. modulation of HCFU antitumor activity by LV, suggesting that the modulation involves an increase of the ternary complex of TS, 5,10-methylene tetrahydrofolate from LV and 5-fluorodeoxyuridine 5'-monophosphate (FdUMP). Combination of HCFU and LV is therefore thought to be useful in increasing the antitumor activity of HCFU on gastrointestinal carcinomas without enhancing its toxicity.

Answer 6:

Bibliographic Information

Therapeutic strategies for 5-fluorouracil-leucovorin based upon cellular metabolic characteristics in human colon adenocarcinoma xenografts. Houghton, J. A.; Williams, L. G.; Cheshire, P. J.; Houghton, P. J.; De Graaf, S. S. N. Dep. Pharmacol., St. Jude Child. Res. Hosp., Memphis, TN, USA. Editor(s): Curtius, Hans-Christoph; Ghisla, Sandro; Blau, Nenad. Chem. Biol. Pteridines, 1989 Proc. Int. Symp. Pteridines Folic Acid Deriv., 9th (1990), Meeting Date 1989, 1203-8. Publisher: de Gruyter, Berlin, Fed. Rep. Ger CODEN: 57FTAQ Conference written in English. CAN 115:149839 AN 1991:549839 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

In human colon adenocarcinoma xenografts in mice, [6R,S]leucovorin (I) increased the pools of reduced folates, an effect that was reversed upon stopping its infusion. I also increased the thymidylate synthase inhibition by 5-fluorouracil (II). The results are discussed in relation to the antitumor activity of I plus II.

Answer 7:

Bibliographic Information

Biochemical modulation applied to experimental cancer chemotherapy. Nakamura Y Department of Otolaryngology, Teikyo University, School of Medicine, Tokyo Nippon Jibiinkoka Gakkai kaiho (1996), 99(11), 1694-704. Journal code: 7505728. ISSN:0030-6622. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 8969073 AN 97123842 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The biochemical modulation (BCM) of the antitumor effect of 5-fluorouracil (5-FU) by leucovorin (LV) was studied with xenografts (MC-1, MC-3, MPC-2) by transplanting human tumors to nude mice and by human tumor clonogenic assay

(HTCA). For human tumor transplantation to nude mice, the dose of 5-FU was set at LD50 x 0.6 or LD50 x 0.8 and LV was given in three doses, 0.45, 0.15, 0.06 mg/body. Antitumor effects of combined administration of 5-FU and LV at the same time, as compared with that of administration of LV one hour before 5-FU, were examined. The relationship between the rate of inhibition of thymidylate synthetase (T.S) activity and 5-FU concentration in the neoplastic tissues was also examined. In HTCA the antitumor effects of 5-FU were examined by two methods: 1) limited contact for one four, and 2) continuous contact for two weeks. In the human tumor transplantation to nude mice, the BCM of the antitumor effect of 5-FU by LV was demonstrated in MC-1 and MPC-2. This BCM function of LV was enhanced by administering it one hour before 5-FU. The suitable LV dose was between 0.15 and 0.45 mg/body. Although there was a tendency for the rate of inhibition of T.S to be proportional to the tissue concentration of 5-FU, there was no significant relationship between the T.S inhibition rate and the antitumor effect. In HTCA, the BCM function of LV was suggested by the two-week-continuous contact method with MC-1 and MPC-2. Depending on the method of administering LV, the antitumor activity was higher with two-week continuous contact than with one-hour contact. In conclusion, the BCM effect of LV on the antitumor effect of 5-FU was revealed in MC-1 and MPC-2 strains. Further studies are needed to establish a standard for appropriate dosage and administration of LV.

Answer 8:

Bibliographic Information

Modulation by 1-leucovorin of 5-fluorouracil antitumor activity on human gastric carcinoma xenograft in nude mouse: preliminary report. Kase S; Kubota T; Furukawa T; Watanabe M; Teramoto T; Ishibiki K; Kitajima M
Department of Surgery, School of Medicine, Keio University, Tokyo, Japan Nippon Geka Gakkai zasshi (1993), 94(6), 659. Journal code: 0405405. ISSN:0301-4894. Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 8341253 AN 93341444 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Answer 9:

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_n and H₄PteGlu_n, 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_n and H₄PteGlu_n 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)