Answer 1:

Bibliographic Information

Impact of Angiogenesis Inhibition by Sunitinib on Tumor Distribution of Temozolomide. Zhou, Qingyu; Guo, Ping; Gallo, James M. Department of Pharmaceutical Sciences, School of Pharmacy, Temple University, Philadelphia, PA, USA. Clinical Cancer Research (2008), 14(5), 1540-1549. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. AN 2008:270837 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

PURPOSE: As combination chemotherapy of antiangiogenic agents with conventional chemotherapeutic drugs continues to evolve, an understanding of the pharmacokinetic and pharmacodynamic variables assocd. with optimal treatment is needed. Thus, the effect of the multitargeted tyrosine kinase inhibitor sunitinib on tumor distribution of temozolomide was investigated to evaluate conditions for optimal combination chemotherapy. Exptl. Design: In mice bearing SF188V+ human glioma xenografts, measurements of temozolomide pharmacokinetic properties and sunitinib pharmacodynamic activities were evaluated, the latter including determinants for vascular normalization, including CD31, collagen IV, and α-SMA. RESULTS: Sunitinib given in a daily dose of either 10 or 40 mg/kg orally over 14 days increased temozolomide tumor distribution, as indicated by the tumor-to-plasma AUC ratio compared with control; however, only the 10 mg/kg group reached statistical significance ($P < 0.05$). From the pharmacodynamic anal., a "vascular normalization index" incorporating the microvessel d. (MVD) and protein expression of α-SMA and collagen IV was proposed as an indication of the no. of tumor vessels with relatively good quality, which was found to be significantly correlated with the unbound temozolomide AUC in tumor interstitial fluid ($P = 0.05$). Furthermore, both sunitinib-treated groups maintained the mol. balance between angiopoietins Ang-1 and Ang-2, suggesting a crit. role of angiopoietins in vascular normalization. CONCLUSIONS: Several important factors relevant to the antiangiogenic agent-induced tumor vascular normalization have been identified and incorporated into a vascular normalization index that may serve to correlate the angiogenic phenotype to the distribution of cytotoxic drugs in solid tumors.

Answer 2:

Bibliographic Information

Combining Agents that Target the Tumor Microenvironment Improves the Efficacy of Anticancer Therapy. Blansfield, Joseph A.; Caragacianu, Diana; Alexander, H. Richard, III; Tangrea, Michael A.; Morita, Shane Y.; Lorang, Dominique; Schafer, Peter; Muller, George; Stirling, David; Royal, Richard E.; Libutti, Steven K. Tumor Angiogenesis Section, Surgery Branch, National Cancer Institute, NIH, Bethesda, MD, USA. Clinical Cancer Research (2008), 14(1), 270-280. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 148:552920 AN 2008:8763 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

PURPOSE: Over the past 60 years, cytotoxic chemotherapy has targeted the cancer cell. Despite this, there have been few cancer cures. A new approach to cancer therapy is to target the multicellular biol. entity of the tumor microenvironment. Exptl. Design: Lenalidomide, an immunomodulatory drug, sunitinib, a tyrosine kinase inhibitor, and low-dose metronomic cyclophosphamide, were tested alone and in combination for their abilities to inhibit endothelial cell tube formation, rat aortic ring outgrowth, tumor growth, and metastatic development in mice. In addn., ectopic tumor lysates were evaluated for the presence of proangiogenic proteins. RESULTS: The three agents alone were shown to significantly inhibit endothelial cells' ability to form tubes and significantly inhibit the multicellular microenvironment in the rat aortic ring assay ($P < 0.01$ and $P < 0.001$). This effect was also significantly augmented when the agents were combined. Furthermore, the three-drug combination was able halt the progression of tumor growth almost completely in xenograft models of ocular melanoma, colon cancer, pancreatic cancer, and cutaneous melanoma. These agents significantly decrease the no. of proliferating cells in tumors, significantly increase the no. of cells undergoing active cell death in tumors, and significantly decrease the no. of blood vessels in treated tumors ($P < 0.05$). Combination therapy shows a decrease in the compensatory up-regulation of proangiogenic proteins after treatment when compared with single-agent therapy. CONCLUSIONS: This combination of agents causes an inhospitable microenvironment for tumor cells and shows great promise for use in the clinic.

Answer 3:

Bibliographic Information

Supra-additive antitumor effect of sunitinib malate (SU11248, Sutent) combined with docetaxel. A new therapeutic perspective in hormone refractory prostate cancer. Guerin, O.; Formento, P.; Lo Nigro, C.; Hofman, P.; Fischel, J. L.; Etienne-Grimaldi, M. C.; Merlano, M.; Ferrero, J. M.; Milano, G. Nice General Hospital, Nice, Fr. Journal of Cancer Research and Clinical Oncology (2008), 134(1), 51-57. Publisher: Springer, CODEN: JCROD7 ISSN: 0171-5216. Journal written in English. CAN 148:440375 AN 2007:1268849 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: Physiol. and mol. findings indicate over-expression of HER proteins and dysregulation of neo-angiogenesis during progression of advanced prostate cancer. The aim of this study was to test a novel rational therapeutic approach by combining docetaxel with an EGFR-targeting agent (cetuximab) and with an anti-angiogenic agent (sunitinib, SUTENT). Methods: Mice bearing well-established PC3 prostate tumors (mean tumor vol./treatment group .apprx.250 mm3) were treated every week with vehicle alone (controls), sunitinib (40 mg/kg/day, 5 days/wk for 3 wk, 0.2 mL p.o.), cetuximab (0.2 mg/kg/day, 5 days/wk for 3 wk, 0.2 mL i.p.) and docetaxel (10 mg/kg, 1 day/wk for 3 wk, 0.2 mL i.p.). Results: Each drug, administered as a single-agent, demonstrated comparable and moderate effects on tumor growth with approx. 50 % inhibition at the end of the 3-wk dosing schedule. Computed combination ratio (CR) values for tumor growth detd. on days 61, 68 and 75 after cell implantation indicated supra-additive effects for the sunitinib-docetaxel (1.53, 1.15 and 1.47, resp.) and sunitinib-cetuximab combinations (1.2, 1.32 and 1.14, resp.), and suggested additive effects only for the sunitinib-cetuximab-docetaxel combination (CR = 1). The effects on tumor growth were accompanied by a parallel diminution in tumor cell proliferation (Ki 67) and tumor vascularization (von Willebrandt factor). There were significantly higher pro-apoptotic effects (caspase-3 cleavage) obsd. for the sunitinib-docetaxel and sunitinib-docetaxel-cetuximab as compared to the other conditions. Conclusion: The supra-additive anti-tumor effect obsd. with the sunitinib-docetaxel combination might support innovative strategies in the management of advanced prostate cancer.

Answer 4:

Bibliographic Information

Sunitinib malate: oncolytic drug multitargeted tyrosine kinase inhibitor. McIntyre, J. A.; Castaner, J. Prous Science, Barcelona, Spain. Drugs of the Future (2005), 30(8), 785-792. Publisher: Prous Science, CODEN: DRFUD4 ISSN: 0377-8282. Journal; General Review written in English. CAN 145:327363 AN 2006:78290 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A review. Signal transduction via receptor tyrosine kinases (RTKs) is frequently dysregulated in malignant disease. Several type III split-kinase domain RTKs are expressed on tumor cells and directly affect tumor cell proliferation, as well as playing a prominent role in tumor angiogenesis. Inhibition of these RTKs represents an attractive therapeutic option in the treatment of human cancers. Sunitinib is an orally active, multi-targeted TK inhibitor. In in vitro and in vivo assays, sunitinib demonstrated potent inhibition of vascular endothelial growth factor (VEGF)-dependent Flk-1, platelet-derived growth factor receptor-β (PDGFR-β), Flt3 and Kit TKs. In mouse xenograft models, daily treatment with sunitinib resulted in growth inhibition of a variety of established human tumors. Synergistic activity in combination with other chemotherapeutic agents and radiotherapy was demonstrated in murine tumor models. Phase I and II clin. studies in patients with advanced solid tumors, AML, renal cell carcinoma and gastrointestinal stromal tumors (GIST) showed early evidence of efficacy and an acceptable toxicity profile. A phase III study in imatinib-refractory GIST patients was terminated early due to demonstrated efficacy compared with placebo, and a phase III study in renal cell carcinoma is ongoing.