

Answer 1:

Bibliographic Information

Proteasome Inhibition Activates Epidermal Growth Factor Receptor (EGFR) and EGFR-Independent Mitogenic Kinase Signaling Pathways in Pancreatic Cancer Cells. Sloss, Callum M.; Wang, Fang; Liu, Rong; Xia, Lijun; Houston, Michael; Ljungman, David; Palladino, Michael A.; Cusack, James C., Jr. Authors' Affiliations: Division of Surgical Oncology, Harvard Medical School, Boston, Massachusetts General Hospital, Massachusetts and Nereus Pharmaceuticals, San Diego, CA, USA. *Clinical Cancer Research* (2008), 14(16), 5116-5123. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. AN 2008:976367 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

PURPOSE: In the current study, we investigate the activation of antiapoptotic signaling pathways in response to proteasome inhibitor treatment in pancreatic cancer and evaluate the use of concomitant inhibition of these pathways to augment proteasome inhibitor treatment responses. **Exptl. Design:** Pancreatic cancer cell lines and mouse flank xenografts were treated with proteasome inhibitor alone or in combination with chemotherapeutic compds. (gemcitabine, erlotinib, and bevacizumab), induction of apoptosis and effects on tumor growth were assessed. The effect of bortezomib (a first-generation proteasome inhibitor) and NPI-0052 (a second-generation proteasome inhibitor) treatment on key pancreatic mitogenic and antiapoptotic pathways [epidermal growth factor receptor, extracellular signal-regulated kinase, and phosphoinositide-3-kinase (PI3K)/AKT] was detd. and the ability of inhibitors of these pathways to enhance the effects of proteasome inhibition was assessed in vitro and in vivo. **RESULTS:** Our data showed that proteasome inhibitor treatment activates antiapoptotic and mitogenic signaling pathways (epidermal growth factor receptor, extracellular signal-regulated kinase, c-Jun-NH2-kinase, and PI3K/AKT) in pancreatic cancer. Addnl., we found that activation of these pathways impairs tumor response to proteasome inhibitor treatment and inhibition of the c-Jun-NH2-kinase and PI3K/AKT pathways increases the antitumor effects of proteasome inhibitor treatment. **CONCLUSION:** These preclin. studies suggest that targeting proteasome inhibitor-induced antiapoptotic signaling pathways in combination with proteasome inhibition may augment treatment response in highly resistant solid organ malignancies. Further evaluation of these novel treatment combinations in clin. trials is warranted.

Answer 2:

Bibliographic Information

Inhibitory effect of bevacizumab on the angiogenesis and growth of retinoblastoma. Lee, Sun Young; Kim, Dong-Kyu; Cho, Jae Hyung; Koh, Jae-Young; Yoon, Young Hee. Department of Ophthalmology, College of Medicine, Asan Medical Center, University of Ulsan, Seoul, S. Korea. *Archives of Ophthalmology* (Chicago, IL, United States) (2008), 126(7), 953-958. Publisher: American Medical Association, CODEN: AROPAW ISSN: 0003-9950. Journal written in English. AN 2008:918594 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Objective: To evaluate the potential effect of bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), on the angiogenesis and tumor growth of retinoblastoma in vitro and in vivo. **Methods:** The antiangiogenic effects of bevacizumab were evaluated in a coculture of a Y-79 human retinoblastoma cell line and a human umbilical vein endothelial cell line by means of a cell proliferation assay kit and a VEGF ELISA. The Y-79 xenotransplanted nude mice were treated with bevacizumab i.p. twice weekly for 4 wk, during which each tumor was measured once a week. The mice were then euthanized, and the wt. of each tumor and its microvessel d. were detd. via CD34 immunohistochem. staining. **Results:** The mean (std. error of the mean) increased human umbilical vein endothelial cell proliferation, when cocultured with Y-79 (156% [1%]), was suppressed 58% (5%) by the blockage of VEGF induced by bevacizumab. By causing a 2-fold redn. in microvessel d. in the Y-79 xenograft model, bevacizumab induced a 75% redn. in the growth of the retinoblastomas without producing significant systemic toxicity. **Conclusions and Clin. Relevance:** Treatment with bevacizumab suppressed the angiogenesis and growth of retinoblastoma in vitro and in vivo. Bevacizumab is likely to be of benefit in the treatment of retinoblastoma.

Answer 3:

Bibliographic Information

Disruption of signaling through SEK1 and MKK7 yields differential responses in hypoxic colon cancer cells treated with oxaliplatin. Vasilevskaya, Irina A.; Selvakumaran, Muthu; O'Dwyer, Peter J. Abramson Family Cancer Center, University of Pennsylvania, Philadelphia, PA, USA. *Molecular Pharmacology* (2008), 74(1), 246-254. Publisher: American Society for Pharmacology and Experimental Therapeutics, CODEN: MOPMA3 ISSN: 0026-895X. Journal written in English. AN 2008:822744 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Transcriptional changes in response to hypoxia are regulated in part through mitogen-activated protein (MAP) kinase signaling to activator protein 1 (AP-1), and thus contribute to resistance of cancer cells to therapy, including platinum compds. A key role for JNK in pro-apoptotic signaling in hypoxic cells has previously been established. Here we analyze hypoxic signaling through MAPK kinases to AP-1/c-Jun in the HT29 colon adenocarcinoma cell line, and observe activation of stress-activated pathways mediated predominantly by SEK1 and MKK7. In transient transfection assays, introduction of dominant-neg. constructs for both MKK7 and SEK1 abolished hypoxia-induced AP-1 activation. Functional studies of the pathway using HT29-derived cell lines stably expressing mutant SEK1 or MKK7 showed impaired activation of Jun NH2-terminal kinase (JNK) and AP-1 in response to hypoxia, more marked in MKK7-deficient than SEK1-deficient cells. Inhibition of SEK1 rendered hypoxic cells more sensitive to oxaliplatin in vitro, whereas the opposite effect was obsd. in MKK7-deficient cells. The mutant cell lines grown as mouse xenografts were treated with oxaliplatin, bevacizumab, or both. The SEK1-deficient tumors exhibited greater sensitivity to all treatments, whereas MKK7-deficient cells were resistant in vivo, consistent with in vitro observations. These data support a pos. contribution of MKK7/JNK to oxaliplatin cytotoxicity and identify SEK1 as a potential target for reversal of hypoxic resistance to oxaliplatin.

Answer 4:

Bibliographic Information

Effects of bevacizumab and cisplatin on human lung adenocarcinoma A549/DDP xenografts in nude mice. Dai, Ming; Luo, Rong-cheng; Zheng, Da-yong; Lu, Cheng-wei; Ding, Xue-mei. Center of Oncology, Nanfang Hospital, Southern Medical University, Guangzhou, Peop. Rep. China. *Nanfang Yike Daxue Xuebao* (2007), 27(9), 1402-1405. Publisher: Nanfang Yike Daxue Xuebao Bianjibu, CODEN: NYDXAN ISSN: 1673-4254. Journal written in Chinese. AN 2007:1193293 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The objective is to explore the effects of bevacizumab with or without cisplatin (DDP) on the growth of lung adenocarcinoma A549/DDP cell xenografts in mice. The objective is to explore the effects of bevacizumab with or without cisplatin (DDP) on the growth of lung adenocarcinoma A549/DDP cell xenografts in mice. Human lung cancer A549/DDP cells was s.c. transplanted in to 25 nude mice, which were randomly divided into control group (group A), bevacizumab group (group B), DDP group (group C), combined treatment group (group D) and half-dose combined treatment group (group E). After corresponding treatments for 4 consecutive weeks, the tumor inhibition rate was evaluated, tumor microvessel d. (MVD) measured with immunohistochem., and the mRNA expression of apoptosis-assocd. gene (bcl-2) and multidrug resistance genes (LRP and GST- π) assessed by RT-PCR. The tumor growth inhibition rates in groups B, D, and E with bevacizumab treatment were 20.96%, 51.67% and 50.95%, resp., and the two combined treatment groups showed better effects. MVD in these 3 groups were 18.6 \pm 1.14, 13.6 \pm 1.14, and 14.4 \pm 0.55, resp., and no significant difference was found in MVD between DDP group and the control group. Compared with the control group, the 3 bevacizumab-treated groups showed decreased expression of bcl-2 genes in A549/DDP tumors at a comparable amplitude, and LRP and GST- π mRNA expression showed no significant differences between the 5 groups. Bevacizumab has synergetic inhibitory effect with conventional chemotherapy against lung adenocarcinoma A549/DDP cell xenografts in mice by inhibiting angiogenesis of the tumor, and may enhance the sensitivity of A549/DDP cells to DDP by inducing cell apoptosis.

Answer 5:

Bibliographic Information

Androgen Receptor Blockade in Experimental Combination Therapy of Pancreatic Cancer. Konduri, Srivani; Schwarz, Margaret A.; Cafasso, Danielle; Schwarz, Roderich E. Department of Surgery, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, Divisions of Surgical Oncology and Surgical Sciences, The Cancer Institute of New Jersey, New Brunswick, NJ, USA. *Journal of Surgical Research* (2007), 142(2), 378-386. Publisher: Elsevier, CODEN: JSGRA2 ISSN: 0022-4804. Journal written in English. CAN 148:112427 AN 2007:1073190 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: Reports on hormone receptor expression of pancreatic cancer (PaCa) cells and treatment responses to antihormonal therapy are still conflicting. Methods: Eight human PaCa cell lines were tested for androgen receptor (AR) protein levels by Western blot anal. Cell proliferation in vitro was measured by sulforhodamine B anal. AR agonists and inhibitors included dihydrotestosterone (DHT), testosterone (T), and flutamide (Flu). In vivo therapy of nude mouse xenografts tested Flu with gemcitabine (Gem) and/or bevacizumab (Bev). Results: Seven of eight human PaCa cell lines expressed detectable AR protein. Median relative expression compared with the AR pos. control LnCaP was 21% (range: 16 to 63). Growth stimulation by DHT or T was minor (<20%); inhibition by Flu varied greatly and did not correlate to AR levels. Even in the sensitive cell line Panc1, Flu failed to increase Gem toxicity in vitro. However, in vivo Flu therapy resulted in significant growth inhibition of Panc-1 tumors. Flu/Gem treatment did not enhance the effect; Bev/Flu/Gem triple therapy had the greatest effect (P = 0.06 compared to Flu/Gem). Flu alone did not affect apoptotic activity, but decreased the tumor cell proliferative index (P = 0.04); in combination with Gem, Flu reduced the tumor cell d. (P = 0.02). Conclusions: The majority of PaCa cell lines express AR at various levels, but most fail to show an in vitro antiproliferative response to AR inhibition. The strong antitumor effect of flutamide in vivo is not significantly enhanced in combination with gemcitabine or bevacizumab, suggesting primarily monotherapy benefit potential of AR blockade in susceptible PaCa.

Answer 6:

Bibliographic Information

Mda-7 in Combination with Bevacizumab Treatment Produces a Synergistic and Complete Inhibitory Effect on Lung Tumor Xenograft. Inoue, Satoshi; Hartman, Amanda; Branch, Cynthia D.; Bucana, Corazan D.; Bekele, Benjamin N.; Stephens, L. Clifton; Chada, Sunil; Ramesh, Rajagopal. Department of Thoracic and Cardiovascular Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX, USA. *Molecular Therapy* (2007), 15(2), 287-294. Publisher: Nature Publishing Group, CODEN: MTOHCK ISSN: 1525-0016. Journal written in English. CAN 147:335808 AN 2007:1030800 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor (VEGF), has shown antitumor activity by inhibiting tumor angiogenesis in preclin. and clin. studies. However, bevacizumab monotherapy does not induce complete tumor regression. Thus, addnl. treatments must be combined with bevacizumab to promote tumor regression. The authors previously showed that melanoma differentiation assocd. gene-7 (mda-7) protein exerts potent antitumor and antiangiogenic activity. Here, they investigated the therapeutic effects of mda-7 in combination with bevacizumab using lung cancer as a model. In vitro, treatment of human umbilical vein endothelial cells with conditioned medium from Ad-mda7 plus bevacizumab-treated lung tumor cells showed reduced VEGF ligand-receptor binding, and decreased cell survival, resulting in growth arrest and apoptosis. In vivo, treatment of s.c. lung tumor xenografts with bevacizumab plus Ad-mda7 resulted in tumor growth inhibition and improved survival compared to tumor growth in control mice. Furthermore, tumors in all the Ad-mda7 plus bevacizumab-treated mice completely regressed, and these were tumor free through the study's end. Mol. anal. showed enhanced tumor cell apoptosis and reduced VEGF and CD31 expression in Ad-mda7 plus bevacizumab-treated tumors. Thus, Ad-mda7 and bevacizumab treatment produces a synergistic and complete therapeutic effect against human lung cancer.

Answer 7:

Bibliographic Information

In vivo VEGF imaging with radiolabeled bevacizumab in a human ovarian tumor xenograft. Nagengast, Wouter B.; de Vries, Elisabeth G.; Hospers, Geke A.; Mulder, Nanno H.; de Jong, Johan R.; Hollema, Harry; Brouwers, Adrienne H.; van Dongen, Guus A.; Perk, Lars R.; Lub-de-Hooge, Marjolijn N. Department of Medical Oncology, University of Groningen and University Medical Center Groningen, Groningen, Neth. *Journal of Nuclear Medicine* (2007), 48(8), 1313-1319. Publisher: Society of Nuclear Medicine, CODEN: JNMEAQ ISSN: 0161-5505. Journal written in English. CAN 147:481989 AN 2007:1007718 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Vascular endothelial growth factor (VEGF), released by tumor cells, is an important growth factor in tumor angiogenesis. The humanized monoclonal antibody bevacizumab blocks VEGF-induced tumor angiogenesis by binding, thereby neutralizing VEGF. Our aim was to develop radiolabeled bevacizumab for noninvasive in vivo VEGF visualization and quantification with the single γ -emitting isotope ^{111}In and the PET isotope ^{89}Zr . Methods: Labeling, stability, and binding studies were performed. Nude mice with a human SKOV-3 ovarian tumor xenograft were injected with ^{89}Zr -bevacizumab, ^{111}In -bevacizumab, or human ^{89}Zr -IgG. Human ^{89}Zr -IgG served as an aspecific control antibody. Small-animal PET and microCT studies were obtained at 24, 72, and 168 h after injection of ^{89}Zr -bevacizumab and ^{89}Zr -IgG (3.5 ± 0.5 MBq, 100 ± 6 μg , 0.2 mL [mean \pm SD]). Small-animal PET and microCT images were fused to calc. tumor uptake and compared with ex vivo biodistribution at 168 h after injection. ^{89}Zr - and ^{111}In -bevacizumab ex vivo biodistribution was compared at 24, 72, and 168 h after injection (2.0 ± 0.5 MBq each, 100 ± 4 μg in total, 0.2 mL). Results: Labeling efficiencies, radiochem. purity, stability, and binding properties were optimal for the radioimmunoconjugates. Small-animal PET showed uptake in well-perfused organs at 24 h and clear tumor localization from 72 h onward. Tumor uptake detd. by quantification of small-animal PET images was higher for ^{89}Zr -bevacizumab-namely, 7.38 ± 2.06 %ID/g compared with 3.39 ± 1.16 %ID/g (percentage injected dose per g) for human ^{89}Zr -IgG ($P = 0.011$) at 168 h and equiv. to ex vivo biodistribution studies. Tracer uptake in other organs was seen primarily in liver and spleen. ^{89}Zr - and ^{111}In -bevacizumab biodistribution was comparable. Conclusion: Radiolabeled bevacizumab showed higher uptake compared with radiolabeled human IgG in a human SKOV-3 ovarian tumor xenograft. Noninvasive quant. small-animal PET was similar to invasive ex vivo biodistribution.

Radiolabeled bevacizumab is a new tracer for noninvasive in vivo imaging of VEGF in the tumor microenvironment.

Answer 8:

Bibliographic Information

Antitumor activity of capecitabine and bevacizumab combination in a human estrogen receptor-negative breast adenocarcinoma xenograft model. Higgins, Brian; Kolinsky, Kenneth; Linn, Michael; Adames, Violeta; Zhang, Yu-E.; Moisa, Carlos; Dugan, Ute; Heimbrosk, David; Packman, Kathryn. Department of Discovery Oncology, Hoffmann-La Roche Inc., Nutley, NJ, USA. *Anticancer Research* (2007), 27(4B), 2279-2287. Publisher: International Institute of Anticancer Research, CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 147:439706 AN 2007:994186 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: Capecitabine and bevacizumab have each been shown to inhibit tumor growth. Their combination failed to improve survival in a phase III trial of metastatic breast cancer (MBC), although it should be noted patients had been heavily pretreated with anthracyclines and taxanes. Our aim was to evaluate whether combination treatment would increase tumor growth inhibition and survival in a breast cancer model. Materials and Methods: Mice bearing KPL-4 human estrogen receptor-neg. breast adenocarcinoma xenografts were given capecitabine orally daily for 14 days at the max. tolerated dose (MTD) or half MTD, alone or with 5 mg/kg i.p. bevacizumab twice weekly. Results: Tumor growth inhibition (TGI) and increased life span (ILS) were superior in the combination groups vs. monotherapy ($p < 0.05$). TGI and ILS were significantly improved in the high- vs. low-dose capecitabine combination ($p < 0.05$). Conclusion: Capecitabine in combination with bevacizumab provides a basis for pursuing the combination for first-line treatment of MBC.

Answer 9:

Bibliographic Information

Bevacizumab plus 5-fluorouracil induce growth suppression in the CWR-22 and CWR-22R prostate cancer xenografts.

Hung, Huynh. Laboratory of Molecular Endocrinology, Division of Cellular and Molecular Research, National Cancer Centre, Singapore, Singapore. *Molecular Cancer Therapeutics* (2007), 6(8), 2149-2157. Publisher: American Association for Cancer Research, CODEN: MCTOCF ISSN: 1535-7163. Journal written in English. CAN 147:268498 AN 2007:905665 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Prostate cancer is the most common malignancy in men. Although patients with metastatic prostate cancer can benefit from androgen ablation, most of them will die of prostate cancer progression to an androgen-refractory state. In the present study, the effects of docetaxel, bevacizumab, 5-fluorouracil (5-FU), bevacizumab plus docetaxel, and bevacizumab plus 5-FU on the growth of human CWR-22 (androgen-dependent) and CWR-22R (androgen-independent) prostate carcinoma xenografts were investigated. We report that i.p. administration of 10 mg/kg docetaxel at 1-wk interval, 5 mg/kg bevacizumab once every 2 wk, or 12.5 mg/kg 5-FU, bevacizumab/docetaxel, or bevacizumab/5-FU weekly to severe combined immunodeficient mice bearing prostate cancer xenografts (12 mice per treatment group) for 21 days resulted in 22.5±8%, 23±7%, 31±8%, 22±6%, and 81±5% growth inhibition, resp. Greatest growth suppression was obsd. in bevacizumab/5-FU treatment. Bevacizumab/5-FU-induced growth suppression was assocd. with redn. in microvessel d., inhibition of cell proliferation; up-regulation of phosphatase and tensin homolog, p21Cip1/Waf1, p16INK4a, and p27Kip1; hypophosphorylation of retinoblastoma protein; and inhibition of Akt/mammalian target of rapamycin pathway. Our data indicate that bevacizumab/5-FU effectively inhibits angiogenesis and cell cycle progression and suggest that bevacizumab/5-FU may represent an alternative treatment for patients with prostate cancer.

Answer 10:

Bibliographic Information

Putting the brakes on angiogenesis through a novel VEGF-KLH (kinoid) vaccine. Nair, Jayakumar R.; Bansal, Sanjay; Lee, Kelvin P. Department of Immunology, Roswell Park Cancer Institute, Buffalo, NY, USA. *Expert Review of Vaccines* (2007), 6(4), 491-496. Publisher: Future Drugs Ltd., CODEN: ERVXAX ISSN: 1476-0584. Journal written in English. CAN 148:98665 AN 2007:840676 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Angiogenesis, the growth of new blood vessels, is essential for tumor growth and metastasis. Of the several known angiogenic factors, VEGF is an important mediator of tumor-induced angiogenesis and represents a potential target for innovative anticancer therapy. Recently, humanized monoclonal anti-VEGF antibody (bevacizumab) has been approved by the US FDA for combinatorial therapies with cytotoxic drugs in metastatic colorectal cancer. However, adverse side effects and enormous costs are assocd. with the use and delivery of bevacizumab. In the study under evaluation, Rad et al. demonstrated an alternative approach by using active immunization in mice with a novel VEGF-kinoid vaccine. The authors obsd. that the antitumor effects elicited by their vaccine were as effective as bevacizumab in xenografted-tumor mouse models.

Answer 11:

Bibliographic Information

Anti-tumor effects of bevacizumab in combination with paclitaxel on head and neck squamous cell carcinoma. Fujita, Kyoko; Sano, Daisuke; Kimura, Machiko; Yamashita, Yukiko; Kawakami, Mariko; Ishiguro, Yukari; Nishimura, Goshi; Matsuda, Hideki; Tsukuda, Mamoru. Department of Biology and Function in Head and Neck, City University Graduate School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama, Japan. *Oncology Reports* (2007), 18(1), 47-51. Publisher: Oncology Reports, CODEN:

OCRPEW ISSN: 1021-335X. Journal written in English. CAN 147:320967 AN 2007:826593 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Human tumors are dependent on angiogenesis for growth, and the vascular endothelial growth factor (VEGF) is a major regulator of this process. Bevacizumab (Avastin), a monoclonal antibody directed against VEGF, has shown promise in treating a variety of cancers. In this study, we first examd. the anti-tumor effects of bevacizumab on head and neck squamous cell carcinoma (HNSCC). Then we examd. the effects of bevacizumab combined with paclitaxel, a chemotherapeutic agent, in HNSCC. This is the first demonstration of the anti-tumor effects of bevacizumab on HNSCC. In vitro, bevacizumab did not show any antiproliferative effects against the HNSCC cell lines. However, in vivo, bevacizumab showed dramatic anti-tumor effects against HNSCC tumor xenografts in mice. In addn., treatment with a bevacizumab-paclitaxel combination resulted in a remarkable inhibition of the HNSCC tumor xenografts, compared to the effects of each agent sep. A decreased blood vessel d. and an increased apoptotic index were seen in the shrunken tumors. These results suggest that bevacizumab in combination with paclitaxel could have useful clin. application in HNSCC.

Answer 12:

Bibliographic Information

The Anti-VEGF Antibody Bevacizumab Potently Reduces the Growth Rate of High-Risk Neuroblastoma Xenografts.

Segerstroem, Lova; Fuchs, Dieter; Baeckman, Ulrika; Holmquist, Kajsa; Christofferson, Rolf; Azarbayjani, Faranak. Childhood Cancer Research Unit, Department of Women and Child Health, Karolinska Institutet, Stockholm, Swed. Pediatric Research (2006), 60(5), 576-581. Publisher: Lippincott Williams & Wilkins, CODEN: PEREBL ISSN: 0031-3998. Journal written in English. CAN 146:98820 AN 2006:1075817 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Neuroblastoma (NB) is a rapidly growing, well-vascularized childhood cancer that often presents with metastases. The overall five-year survival in NB is approx. 45% despite multimodality treatment, and therefore there is a clin. need for new therapeutic strategies. NB frequently overexpresses the angiogenic factor VEGF (vascular endothelial growth factor). The aim of this study was to investigate the effect of bevacizumab (Avastin, Genentech/Roche), a humanized anti-VEGF-A antibody, on NB growth in three different xenograft models, chosen to resemble high-risk NB. The human NB cell lines SK-N-AS, IMR-32 and SH-SY5Y, which are poorly differentiated and overexpress VEGF-A, were injected s.c. in immunodeficient mice. Bevacizumab was given i.p. twice weekly at 5 mg/kg body wt., starting at a tumor vol. of 0.3 mL. Bevacizumab significantly ($p < 0.01-0.05$) reduced NB growth in vivo without toxicity by causing a 30-63% redn. of angiogenesis, but had no effect on NB cell survival in vitro. Serum concns. of VEGF-A increased two- to six-fold during bevacizumab therapy which did not result in faster tumor growth compared with control animals. Based on our exptl. data we suggest consideration of bevacizumab in treatment of high-risk NB that does not respond to conventional therapy and that overexpresses VEGF.

Answer 13:

Bibliographic Information

Molecular targeted therapies for colorectal cancer.

Mizunuma, Nubuyuki. Gastrointestian Center, Cancer Institute Ariake Hospital, Japanese Foundation for Cancer Research, Japan. Drug Delivery System (2006), 21(1), 52-57. Publisher: Nippon DDS Gakkai Jimukyoku, CODEN: DDSYEI ISSN: 0913-5006. Journal; General Review written in Japanese. CAN 145:255613 AN 2006:203709 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A review. In the past decade the median duration of survival with advanced colorectal cancer has increased from 12 mo to nearly 24

mo. Oxaliplatin and irinotecan are widely used in combination with 5-FU and leucovorin as FOLFOX (FU/LV+oxaliplatin) therapy or FOLFIRI (FU/LV+CPT-11) therapy. Recently two monoclonal antibodies showed significant activity for advanced colorectal cancer. Cetuximab is a chimeric IgG1 monoclonal antibody that binds to EGFR. Cetuximab has significant activity when given in combination with CPT-11 or FOLFOX (FU/LV+oxaliplatin) chemotherapy. Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in in vitro models of angiogenesis. Administration of Bevacizumab to xenotransplant models of colon cancer in nude (athymic) mice caused redn. of microvascular growth and inhibition of metastatic disease progression. Bevacizumab also had significant activity combined with FL(FU/LV), IFL(CPT/FU/LV) and FOLFOX(Oxal/FU/LV). These mol. target agents are going to the mainstay of the new era of cancer treatments.

Answer 14:

Bibliographic Information

Dynamic contrast-enhanced and diffusion MRI show rapid and dramatic changes in tumor microenvironment in response to inhibition of HIF-1 α using PX-478. Jordan, Benedicte F.; Runquist, Matthew; Raghunand, Natarajan; Baker, Amanda; Williams, Ryan; Kirkpatrick, Lynn; Powis, Garth; Gillies, Robert J. Department of Biochemistry, University of Arizona Health Sciences Center, Tucson, AZ, USA. Neoplasia (Ann Arbor, MI, United States) (2005), 7(5), 475-485. Publisher: Neoplasia Press Inc., CODEN: NEOPFL ISSN: 1522-8002. Journal written in English. CAN 143:109227 AN 2005:590289 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

PX-478 is a new agent known to inhibit the hypoxia-responsive transcription factor, HIF-1 α , in exptl. tumors. The current study was undertaken in prepn. for clin. trials to det. which noninvasive imaging endpoint(s) is sensitive to this drug's actions. Dynamic contrast-enhanced (DCE) and diffusion-weighted (DW) magnetic resonance imaging (MRI) were used to monitor acute effects on tumor hemodynamics and cellularity, resp. Mice bearing human xenografts were treated either with PX-478 or vehicle, and imaged over time. DW imaging was performed at three b values to generate apparent diffusion coeff. of water (ADC_w) maps. For DCE-MRI, a macromol. contrast reagent, BSA-Gd-DTPA, was used to det. vascular permeability and vascular vol. fractions. PX-478 induced a dramatic redn. in tumor blood vessel permeability within 2 h after treatment, which returned to baseline by 48 h. The anti-VEGF antibody, Avastin, reduced both the permeability and vascular vol. PX-478 had no effect on the perfusion behavior of a drug-resistant tumor system, A-549. Tumor cellularity, estd. from ADC_w, was significantly decreased 24 and 36 h after treatment. This is the earliest significant response of ADC to therapy yet reported. Based on these preclin. findings, both of these imaging endpoints will be included in the clin. trial of PX-478.

Answer 15:

Bibliographic Information

Assessment of bevacizumab conjugated to Cy5.5 for detection of head and neck cancer xenografts. Withrow K P; Newman J R; Skipper J B; Gleysteen J P; Magnuson J S; Zinn K; Rosenthal E L Department of Surgery, Division of Otolaryngology - Head and Neck Surgery, University of Alabama at Birmingham, Birmingham, AL 35294-0012, USA Technology in cancer research & treatment (2008), 7(1), 61-6. Journal code: 101140941. ISSN:1533-0346. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, N.I.H., EXTRAMURAL); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 18198926 AN 2008046145 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Optical fluorescent technology has the potential to deliver real time imaging of cancer into the operating room and the clinic. To determine the efficacy of fluorescently labeled anti-vascular endothelial growth factor (VEGF) antibody to be used as a cancer specific optical contrast agent to guide surgical resections, we evaluated the sensitivity and specificity

of this agent to detect microscopic residual disease in a preclinical model of head and neck squamous cell carcinoma (HNSCC). Using a flank murine model, mice were xenografted with SCC-1 tumor cells and injected with anti-VEGF antibody (bevacizumab) conjugated to an optically active fluorophore (Cy5.5). Tumors underwent sub-total resections and were assessed for the presence of residual disease by fluorescent stereomicroscopy. Expected positive and negative biopsies were taken according to the presence or absence of fluorescence, respectively. Histology was used to confirm the presence or absence of disease. Biopsies taken from areas of fluorescence within the wound bed (n=18) were found to be histologically malignant in all but one biopsy. Samples taken from a non-fluorescing tumor bed (n=15) were found to be histologically benign in 11 of 15. These findings correlated with a sensitivity and specificity of 80.9% and 91.7%, respectively. This data supports previous data presented by this group and supports further investigation of fluorescently labeled anti-tumor antibodies to detect disease in the surgical setting.