

Answer 1:

Bibliographic Information

Bortezomib (Velcade) Induces p27Kip1 Expression through S-Phase Kinase Protein 2 Degradation in Colorectal Cancer.

Uddin, Shahab; Ahmed, Maqbool; Bavi, Prashant; El-Sayed, Raafat; Al-Sanea, Nasser; AbdulJabbar, Alaa; Ashari, Luai H.; Alhomoud, Samar; Al-Dayel, Fouad; Hussain, Azhar R.; Al-Kuraya, Khawla S. Department of Human Cancer Genomic Research, Research Center, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia. *Cancer Research* (2008), 68(9), 3379-3388. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 148:486620 AN 2008:530633 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

S-phase kinase protein 2 (SKP2), an F-box protein, targets cell cycle regulators including cycle-dependent kinase inhibitor p27Kip1 via ubiquitin-mediated degrdn. SKP2 is frequently overexpressed in a variety of cancers. We investigated the role of SKP2 and its ubiquitin-proteasome pathway in colorectal carcinoma using a panel of cell lines, clin. samples, and the NUDE mouse model. Using immunohistochem. anal. on a large tissue microarray of 448 samples, an inverse assocn. of SKP2 expression with p27Kip1 protein levels was seen. A colorectal cancer (CRC) subset with high level of SKP2 and low level of p27Kip1 showed a decreased overall survival ($P = 0.0057$). Treatment of CRC cell lines with bortezomib or expression of small interfering RNA of SKP2 causes down-regulation of SKP2 and accumulation of p27Kip1. Furthermore, treatment of CRC cells with bortezomib causes apoptosis by involving the mitochondrial pathway and activation of caspases. In addn., treatment of CRC cells with bortezomib down-regulated the expression of XIAP, cIAP1, and survivin. Finally, treatment of CRC cell line xenografts with bortezomib resulted in growth inhibition of tumors in NUDE mice via down-regulation of SKP2 and accumulation of p27Kip1. Altogether, our results suggest that SKP2 and the ubiquitin-proteasome pathway may be potential targets for therapeutic intervention for treatment of CRC. [*Cancer Res* 2008;68(9):3379-88].

Answer 2:

Bibliographic Information

Effect of bortezomib used alone or in combination with arsenic trioxide on HL-60 cell xenograft in nude mice. Li, Li; Meng, Fan-yi; Fu, Yun-bi; Cai, Yan-xia; Sun, Qi-xin. Department of Hematology, Nanfang Hospital, Southern Medical University, Guangzhou, Peop. Rep. China. *Nanfang Yike Daxue Xuebao* (2007), 27(10), 1504-1506. Publisher: Nanfang Yike Daxue Xuebao Bianjibu, CODEN: NYDXAN ISSN: 1673-4254. Journal written in Chinese. CAN 148:345912 AN 2007:1359310 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The study assessed the antitumor efficacy and adverse effects of bortezomib either used alone or in combination with arsenic trioxide for transplanted tumor in nude mice. Nude mice bearing HL-60 cell xenografts were randomized into 4 groups to receive treatment with normal saline, bortezomib, arsenic trioxide, bortezomib plus arsenic trioxide. The tumor growth inhibition and general condition of the nude mice were obsd., and in situ TUNEL assay and immunohistochem. were performed on the transplanted tumors. Bortezomib alone and in combination with arsenic trioxide could both inhibit the growth of the transplanted tumors, prolong the survival of the nude mice, and induce cell apoptosis and growth inhibition of the HL-60 cells in vivo, and the combined administration exhibited even better effects. The administration was well tolerated with causing manifest vital organ damages in the mice. Bortezomib in combination with arsenic trioxide has significant antitumor effect in nude mice bearing HL-60 cell xenografts possibly by inducing HL-60 cell apoptosis and growth inhibition without producing no significant adverse effects.

Answer 3:

Bibliographic Information

Bortezomib Inhibits Nuclear Factor- κ B-Dependent Survival and Has Potent In vivo Activity in Mesothelioma.

Sartore-Bianchi, Andrea; Gasparri, Fabio; Galvani, Arturo; Nici, Linda; Darnowski, James W.; Barbone, Dario; Fennell, Dean A.; Gaudino, Giovanni; Porta, Camillo; Mutti, Luciano. Falck Division of Medical Oncology, Ca' Granda Hospital, Milan, Italy. *Clinical Cancer Research* (2007), 13(19), 5942-5951. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 148:205504 AN 2007:1104664 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

PURPOSE: Purpose of this study has been the assessment of nuclear factor- κ B (NF- κ B) as a survival factor in human mesothelial cells (HMC), transformed HMC and malignant mesothelioma (MMe) cells. We aimed at verifying whether the proteasome inhibitor Bortezomib could abrogate NF- κ B activity in MMe cells, leading to tumor cell death and may be established as a novel treatment for this aggressive neoplasm. **Exptl. Design:** In HMC and MMe cells, NF- κ B nuclear translocation and DNA binding were studied by electrophoretic mobility shift assay, following treatment with tumor necrosis factor- α (TNF- α). The IKK inhibitor Bay11-7082 was also tested to evaluate its effects on HMC, transformed HMC, and MMe cell viability upon exposure to asbestos fibers. Following Bortezomib treatment, cytotoxicity of MMe cells was evaluated by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, whereas apoptosis and cell-cycle blockade were investigated by high-content anal. Bortezomib was also given to mice bearing i.p. xenografts of MMe cells, and its effects on tumor growth were evaluated. **RESULTS:** Here, we show that NF- κ B activity is a constitutive survival factor in transformed HMC, MMe cells, and acts as a survival factor in HMC exposed to asbestos fibers. Bortezomib inhibits NF- κ B activity in MMe cells and induces cell cycle blockade and apoptosis in vitro as well as tumor growth inhibition in vivo. **CONCLUSIONS:** Inhibition of NF- κ B constitutive activation in MMe cells by Bortezomib resulted in in vitro cytotoxicity along with apoptosis and in vivo tumor regression. Our results support the use of Bortezomib in the treatment of MMe and has led to a phase II clin. trial currently enrolling in Europe.

Answer 4:

Bibliographic Information

Bortezomib Sensitizes Non-Hodgkin's Lymphoma Cells to Apoptosis Induced by Antibodies to Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand (TRAIL) Receptors TRAIL-R1 and TRAIL-R2. Smith, Mitchell R.; Jin, Fang; Joshi, Indira. Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA. *Clinical Cancer Research* (2007), 13(18, Pt. 2), 5528s-5534s. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 148:135235 AN 2007:1041639 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Non-Hodgkin's lymphoma (NHL) is an increasingly common disease that, despite advances in antibody-targeted therapy, still requires novel therapeutic approaches. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) activates a major nonmitochondrial pathway for tumor cell killing through binding to a receptor family, some activating and some decoy. Agonistic antibodies to the receptors TRAIL-R1 and TRAIL-R2 can mimic many of the effects of TRAIL. We are investigating the effects of such agonistic antibodies, mapatumumab directed at TRAIL-R1 and lexatumumab directed at TRAIL-R2, on NHL cell lines. These antibodies induce apoptosis through caspase-8 but also activate BID to involve the mitochondrial pathway and activate caspase-9. In addn., we find signaling through both the nuclear factor- κ B and c-Jun NH2-terminal kinase pathways. Because the proteasome inhibitor bortezomib also affects these pathways, we have investigated the combination of TRAIL-R antibodies and bortezomib and show enhanced apoptosis and signaling as well as enhanced killing of NHL cells in a severe combined immunodeficient mouse/human NHL cell line xenograft system. The combination of bortezomib and TRAIL signaling warrants further investigation as a therapeutic regimen. Understanding the multiple intracellular pathways of TRAIL activation may lead to rationally designed therapeutic trials.

Answer 5:

Bibliographic Information

Antimyeloma effects of arsenic trioxide are enhanced by melphalan, bortezomib and ascorbic acid. Campbell, Richard A.;

Sanchez, Eric; Steinberg, Jeffrey A.; Baritaki, Stavroula; Gordon, Melinda; Wang, Cathy; Shalitin, Dror; Chen, Haiming; Pang, Shen; Bonavida, Benjamin; Said, Jonathan; Berenson, James R. Institute for Myeloma & Bone Cancer Research, West Hollywood, The University of California, Los Angeles, CA, USA. *British Journal of Haematology* (2007), 138(4), 467-478. Publisher: Blackwell Publishing Ltd., CODEN: BJHEAL ISSN: 0007-1048. Journal written in English. CAN 147:479931 AN 2007:1032111 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Arsenic trioxide (ATO) induces apoptosis of malignant plasma cells through multiple mechanisms, including inhibition of DNA binding by nuclear factor kappa-B, a key player in the development of chemoresistance in multiple myeloma (MM). This activity suggests that ATO may be synergistic when combined with other active antimyeloma drugs. To evaluate this, we examd. the antimyeloma effects of ATO alone and in combination with bortezomib, melphalan and ascorbic acid (AA) both in vitro and in vivo using a severe combined immunodeficient (SCID)-hu murine myeloma model. Marked synergistic antimyeloma effects were demonstrated when human MM Los Angeles xenograft IgG lambda light chain (LAG λ -1) cells were treated in vitro with ATO and any one of these agents. SCID mice bearing human MM LAG λ -1 tumors were treated with single-agent ATO, bortezomib, melphalan, or AA, or combinations of ATO with either bortezomib or melphalan and AA. Animals treated with any of these drugs alone showed tumor growth and increases in paraprotein levels similar to control mice, whereas animals treated with ATO-contg. combinations showed markedly suppressed tumor growth and significantly reduced serum paraprotein levels. These in vitro and in vivo results suggest that addn. of ATO to other antimyeloma agents may result in improved outcomes for patients with relapsed or refractory MM.

Answer 6:

Bibliographic Information

Virus-associated tumor imaging by induction of viral gene expression. Fu, De-Xue; Tanhehco, Yvette C.; Chen, Jianmeng; Foss, Catherine A.; Fox, James J.; Lemas, Victor; Chong, Ja-Mun; Ambinder, Richard F.; Pomper, Martin G. Department of Oncology, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Medical Institutions, Baltimore, MD, USA. *Clinical Cancer Research* (2007), 13(5), 1453-1458. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 147:206634 AN 2007:230050 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

EBV and other herpesviruses are assocd. with a variety of malignancies. The EBV thymidine kinase (TK) is either not expressed or is expressed at very low levels in EBV-assocd. tumors. However, EBV-TK expression can be induced in vitro with several chemotherapeutic agents that promote viral lytic induction. The goal of this study is to image EBV-assocd. tumors by induction of viral TK expression with radiolabeled 2'-fluoro-2'-deoxy- β -D-5-iodouracil-arabinofuranoside (FIAU). Immunoblot, luciferase reporter assay, and in vitro assay with [¹⁴C]FIAU were used to show the effects of bortezomib on the induction of lytic gene expression of EBV-assocd. tumor cells. In vivo imaging and ex vivo biodistribution studies with [¹²⁵I]FIAU on EBV-assocd. tumors were done to visualize and confirm, resp., the EBV(+) tumor-specific effects of bortezomib. In vitro assays with [¹⁴C]FIAU and ex vivo biodistribution studies with [¹²⁵I]FIAU showed that uptake and retention of radiolabeled FIAU was specific for cells that express EBV-TK. Planar gamma imaging of EBV(+) Burkitt's lymphoma xenografts in severe combined immunodeficient mice showed [¹²⁵I]FIAU localization within tumors following treatment with bortezomib. These results indicate the feasibility of imaging chemotherapy-mediated viral lytic induction by radiopharmaceutical-based techniques such as single photon emission computed tomog. and positron emission tomog.

Answer 7:

Bibliographic Information

Suppression of the Hypoxia-Inducible Factor-1 Response in Cervical Carcinoma Xenografts by Proteasome Inhibitors. Birle, Diana C.; Hedley, David W. Division of Applied Molecular Oncology, Ontario Cancer Institute, Princess Margaret Hospital and University of Toronto, Toronto, ON, Can. *Cancer Research* (2007), 67(4), 1735-1743. Publisher: American Association for

Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 146:414439 AN 2007:181976
CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Exptl. data suggest therapeutic advantage from selective disruption of the hypoxia response. The authors recently found that the proteasome inhibitor bortezomib decreases tumor carbonic anhydrase IX (CAIX) expression in colon cancer patients and herein report a companion lab. study to test if this effect was the result of hypoxia-inducible factor (HIF) inhibition. Human cervical (SiHa and Me180) and colon (RKO) carcinoma cell lines were treated with bortezomib or the structurally unrelated proteasome inhibitor MG132 in normoxic and hypoxic conditions in vitro. Two different in vivo expts. investigated bortezomib effects after single dose (2 mg/kg, 24 h) or longer exposure in severe combined immunodeficient mice bearing SiHa xenografts. Treatment with either drug produced accumulation of HIF-1 α in vitro but strongly inhibited the prodn. of CAIX and vascular endothelial growth factor (VEGF) under hypoxia. This correlated with more than 10-fold redn. in HIF-1 transcriptional activity under hypoxic conditions. A similar effect of bortezomib was seen in vivo, using the nitroimidazole probe EF5 to define regions of tumor hypoxia and a triple immunofluorescence technique to measure the spatial distributions of HIF-1 α and CAIX. Plasma VEGF levels decreased by .apprx.90% during treatment with bortezomib, indicating that this agent can potently inhibit the hypoxia response in tumors.

Answer 8:

Bibliographic Information

Effect of Bortezomib on Human Neuroblastoma Cell Growth, Apoptosis, and Angiogenesis. Brignole, Chiara; Marimpietri, Danilo; Pastorino, Fabio; Nico, Beatrice; Di Paolo, Daniela; Cioni, Michela; Piccardi, Federica; Cilli, Michele; Pezzolo, Annalisa; Corrias, Maria Valeria; Pistoia, Vito; Ribatti, Domenico; Pagnan, Gabriella; Ponzoni, Mirco. Laboratory of Oncology, G. Gaslini Children's Hospital, Genoa, Italy. Journal of the National Cancer Institute (2006), 98(16), 1142-1157. Publisher: Oxford University Press, CODEN: JNCIEQ ISSN: 0027-8874. Journal written in English. CAN 146:287804 AN 2006:839748 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Bortezomib is a selective and reversible inhibitor of the 26S proteasome that shows potent antitumor activity in vitro and in vivo against several human cancers of adulthood. No data are available on bortezomib activity against human pediatric neuroblastoma. Ten neuroblastoma cell lines and suspensions of primary neuroblastoma cells from three patients were tested for sensitivity to bortezomib. Colony formation, cell proliferation, cell cycle progression, and apoptosis were evaluated by a clonogenic assay and by measuring 3H-thymidine incorporation, bromodeoxyuridine uptake, DNA fragmentation, and phosphatidylserine exposure and propidium iodide staining, resp. Angiogenesis was assessed by the chick embryo chorioallantoic membrane (CAM) assay. Two mouse xenograft models that mimic the growth and spread of neuroblastoma in humans were used to examine in vivo sensitivity of neuroblastoma to bortezomib. All statistical tests were two-sided. Bortezomib inhibited proliferation and colony formation of neuroblastoma cell lines in a time- and dose-dependent manner. The mean bortezomib concn. that caused 50% inhibition of growth was 6.1 nM (95% confidence interval [CI] = 0.9 to 11.3 nM) at 72 h. Bortezomib-treated neuroblastoma cells were arrested at G2/M and underwent apoptosis (mean percentage of apoptotic cells in four neuroblastoma cell lines treated with 20 nM bortezomib for 24 h ranged from 20% to 35%, and caspases were activated by two- to fivefold with respect to untreated cells). Similar results were obtained for primary neuroblastoma cells exposed to bortezomib. Bortezomib inhibited angiogenesis in CAMs stimulated by conditioned medium from neuroblastoma cell lines, by neuroblastoma xenografts, and by primary neuroblastoma biopsy specimens (microvessel area: 2.9×10^{-2} mm², 95% CI = 1.8×10^{-2} to 3.8×10^{-2} mm² in CAMs treated with biopsy specimens alone and 1.3×10^{-2} mm², 95% CI = 1×10^{-2} to 1.5×10^{-2} mm² in CAMs treated with biopsy specimens plus bortezomib, P = .024).

In both mouse models, mice treated with bortezomib lived statistically significantly longer than control mice (mean survival time in the pseudometastatic model: 74.2 vs. 50.3 days, P<.001; mean survival time in the orthotopic model: 72.3 vs. 50.6 days, P<.001). Bortezomib is an effective inhibitor of neuroblastoma cell growth and angiogenesis. These findings provide the rationale for further clin. investigation of bortezomib in pediatric neuroblastoma.

Answer 9:

Bibliographic Information

The combination of the proteasome inhibitor bortezomib and the Bcl-2 antisense molecule oblimersen sensitizes human B-cell lymphomas to cyclophosphamide. O'Connor, Owen A.; Smith, Emily A.; Toner, Lorraine E.; Teruya-Feldstein, Julie; Frankel, Stanley; Rolfe, Mark; Wei, Xiaohui; Liu, Shujun; Marcucci, Guido; Chan, Kenneth K.; Chanan-Khan, Asher. Department of Medicine, Lymphoma, and Developmental Chemotherapy Service, Laboratory of Experimental Therapeutics for Lymphoproliferative Disorders, Memorial Sloan Kettering Cancer Center, New York, USA. *Clinical Cancer Research* (2006), 12(9), 2902-2911. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 145:388835 AN 2006:532575 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: To det. whether the combination of the proteasome inhibitor bortezomib and the bcl-2 antisense mol. oblimersen can sensitize human lymphoma to cyclophosphamide. Exptl. Design: Cytotoxicity assays were conducted to det. if there was any additive or synergistic interaction between the combinations of bortezomib, oblimersen, and cyclophosphamide using a std. trypan blue exclusion assay. Based on these expts., in vivo expts. in severe combined immunodeficiency beige mice were done using human lymphoma xenografts in which different schedules were explored. Bcl-2 and oblimersen levels were detd. in treated tumors, some of which were resected at the end of the in vivo expt. and evaluated pathol. Results: The results suggest that the combination of bortezomib and oblimersen seem to interact in at least an additive fashion, and that the addn. of cyclophosphamide to this drug combination can markedly improve tumor cell kill. In addn., it seems that these drug combinations may be schedule-dependent, with a requirement for oblimersen pretreatment. Animals treated with the triplet drug combination in a schedule-dependent manner experienced pathol. complete regression of disease, which was not obsd. in other treatment cohorts. The addn. of bortezomib also seemed to increase the levels of intracellular oblimersen, which resulted in a marked redn. in Bcl-2. Histol. studies confirmed marked necrosis and caspase-3 activation only in the cohort receiving all three drugs. Conclusion: The use of Bcl-2-directed therapy and a proteasome inhibitor sensitizes human lymphoma cells to cytotoxic drugs like cyclophosphamide. This combination may offer new opportunities for integrating novel targeted therapies with conventional chemotherapy.

Answer 10:

Bibliographic Information

Inhibition of p38 α MAPK enhances proteasome inhibitor-induced apoptosis of myeloma cells by modulating Hsp27, Bcl-XL, Mcl-1 and p53 levels in vitro and inhibits tumor growth in vivo. Navas, T. A.; Nguyen, A. N.; Hideshima, T.; Reddy, M.; Ma, J. Y.; Haghazari, E.; Henson, M.; Stebbins, E. G.; Kerr, I.; O'Young, G.; Kapoun, A. M.; Chakravarty, S.; Mavunkel, B.; Perumattam, J.; Luedtke, G.; Dugar, S.; Medicherla, S.; Protter, A. A.; Schreiner, G. F.; Anderson, K. C.; Higgins, L. S. Scios, Inc., Fremont, CA, USA. *Leukemia* (2006), 20(6), 1017-1027. Publisher: Nature Publishing Group, CODEN: LEUKED ISSN: 0887-6924. Journal written in English. CAN 145:410153 AN 2006:488573 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Inhibition of p38 kinase blocks the prodn. of tumor-promoting factors in the multiple myeloma (MM) bone marrow microenvironment. Proteasome inhibitors MG132 and bortezomib have been shown to have direct cytotoxic effects on MM cells. We show that a selective inhibitor of p38 α , SCIO-469, enhances the ability of MG132 and bortezomib to induce the apoptosis of MM cells. Previously, we showed that p38 inhibition with SCIO-469 enhances MM cytotoxicity of bortezomib by inhibiting the transient expression and phosphorylation of Hsp27, a downstream target of p38. Here we show that continued treatment of MM cells with bortezomib leads to a SCIO-469-enhanced downregulation of Hsp27 and to increased MM apoptosis. Furthermore, we show that p38 inhibition enhances the bortezomib-induced MM apoptosis by upregulation of p53 and downregulation of Bcl-XL and Mcl-1. In a mouse xenograft plasmacytoma model of MM, we found that inhibiting p38 augments the effects of bortezomib in decreasing MM tumor growth in vivo. Thus, in addn. to its role in suppressing an activated MM microenvironment, co-treatment with a p38 inhibitor, such as SCIO-469, may enhance the cytotoxicity of bortezomib by modulating pro-apoptotic and anti-apoptotic factors in MM cells, suggesting great potential for co-therapy.

Answer 11:

Bibliographic Information

Anti-cancer effects of bortezomib against chemoresistant neuroblastoma cell lines in vitro and in vivo. Michaelis, Martin; Fichtner, Iduna; Behrens, Diana; Haider, Wolfram; Rothweiler, Florian; Mack, Andreas; Cinatl, Jaroslav; Doerr, Hans Wilhelm; Cinatl, Jindrich, Jr. Institut fuer Medizinische Virologie, Klinikum der Johann Wolfgang Goethe-Universitaet, Frankfurt am Main, Germany. *International Journal of Oncology* (2006), 28(2), 439-446. Publisher: International Journal of Oncology, CODEN: IJONES ISSN: 1019-6439. Journal written in English. CAN 145:95897 AN 2006:150396 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The proteasome inhibitor bortezomib (Velcade) was recently approved for the treatment of therapy-refractive multiple myeloma and is under investigation for numerous other types of cancer. A phase I clin. trial in pediatric patients resulted in tolerable toxicity. Since the emergence of chemoresistance represents one of the major drawbacks in cancer therapy, we investigated the influence of bortezomib on multi-drug resistant human neuroblastoma cell lines characterized by P-glycoprotein expression and p53 mutation. Nanomolar concns. of bortezomib inhibited the cell cycle and induced apoptosis in chemosensitive as well as in chemoresistant cell lines. In vivo growth of chemosensitive and chemoresistant neuroblastoma cell lines was inhibited to a similar extent. In addn., bortezomib inhibited vessel formation in neuroblastoma xenografts. These findings and the favorable toxicity profile of bortezomib in children make it reasonable to further pursue addnl. development of the drug for the treatment of neuroblastoma and other pediatric solid tumors.

Answer 12:

Bibliographic Information

The Potential Role of Proteasome Inhibitors in the Treatment of Lung Cancer. Bunn, Paul A., Jr. University of Colorado Cancer Center, Denver, CO, USA. *Clinical Cancer Research* (2004), 10(12, Pt. 2), 4263s-4265s. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal; General Review written in English. CAN 142:85493 AN 2004:511612 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A review. Bortezomib (PS-341, Velcade, Millennium Pharmaceuticals, Cambridge, MA) is a novel inhibitor of the proteasome. The proteasome plays a crit. role in the degrdn. and, therefore, regulation of many proteins involved in cell cycle regulation, apoptosis, and angiogenesis. Bortezomib inhibits the growth of lung cancer cell lines in vitro and in vivo in athymic nude mouse xenografts. Bortezomib produces a G2-M arrest, increases in cyclin A and cyclin B, increases in p21, and increases apoptosis in these preclin. models. Phase I studies established that a dose of 1.4 mg/m² given i.v. on days 1, 4, 8, and 11 of a 3-wk cycle produced acceptable toxicity and serum levels that resulted in proteasome inhibition. Phase II studies showed high-response rates in refractory multiple myeloma. These response rates were sufficiently high to allow accelerated approval of bortezomib by the Food and Drug Administration for this indication. Phase II trials in both non-small cell lung cancer and small cell lung cancer are in progress. A no. of Phase I combination studies are also underway. Hopefully, bortezomib will show sufficient activity in lung cancer to improve survival in this dread disease.

Answer 13:

Bibliographic Information

Kinematic modeling and its implication in longitudinal chemotherapy study of tumor physiology: ovarian xenograft mouse model and contrast-enhanced dynamic CT. Stantz, Keith M.; Liang, Yun; Hutchins, Gary D. Imaging Sciences, Indiana University School of Medicine, USA. *Proceedings of SPIE-The International Society for Optical Engineering* (2004), 5369 769-779. Publisher: SPIE-The International Society for Optical Engineering, CODEN: PSISDG ISSN: 0277-786X. Journal written in English. CAN 142:48583 AN 2004:431425 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The purpose of this study is to demonstrate that dynamic CT provides the necessary sensitivity to quantify tumor physiol. and differences in chemotherapeutic response. A compartmental mouse model utilizing measured contrast-enhanced dynamic CT scans is used to simulate systematic and statistical errors assocd. with tumor physiol.: perfusion, permeability (PS), fractional plasma vol. (fp), and fractional interstitial vol. The solute utilized is a small-mol.-wt. radio-opaque contrast agent (Isovue). For such an intravascular-interstitial medium, the kinematics simplifies to a two compartmental diffusive dominated set of coupled differential equations. Each combination of physiol. parameters is repeatedly simulated fifteen times from which statistical errors calcd. The fractional change relative to the true value (systematic error) and std. deviation (statistical error) are plotted as a function of PS, fp, scanner temporal resoln. and noise, and contrast media injection rates. By extrapolating from exptl. data found in literature, a relative change in PS and fp of approx. 40% is required. Thus, the longitudinal response of two chemotherapeutic drugs under investigation, i.e. proteasome and IMPDH inhibitors, are hypothesized to induce different physiol. responses. The first set of simulations varies PS from 0.05 to 0.40 mL/min/mL and fp from 0.01 to 0.07 mL/mL while holding all other physiol. parameters const. Errors in PS remain <3% while statistical errors for fp increase significantly as the vol. decreases toward 1-2%: errors remain <6% for fp>0.03 while increasing to >15% for fp<0.02. The second set of simulations are performed quantifying the relationship between scanner temporal resoln. and contrast media injection rate for various tumor permeabilities. For the majority of cases, the errors remain <5%. As PS approaches perfusion, a total error <6% can be maintained for a temporal resoln. ≤ 3 s, and an error <9% up to 5-7 s.

As the injection rate decreases from 2 mL/min down to 0.25 mL/min, inadequate sampling of the contrast dynamics necessary to decouple the physiol. parameters is lost increasing both systematic and statistical errors from 10% when sampling at 5 s in excess of 20-25% at a 9 s sampling rate. In each case, dynamic CT provides the necessary sensitivity to distinguish between the differing therapeutic responses of proteasome and IMPDH inhibitors.

Answer 14:

Bibliographic Information

Longitudinally quantitative 2-deoxy-2-[18F]fluoro-D-glucose micro positron emission tomography imaging for efficacy of new anticancer drugs: a case study with bortezomib in prostate cancer murine model. Zhang Yumin; Saylor Melissa; Wen Shenhua; Silva Matthew D; Rolfe Mark; Bolen Joseph; Muir Craig; Reimer Corinne; Chandra Sudeep Department of Imaging Sciences/Platform Technology, Millennium Pharmaceuticals, Inc., 45 Sidney St., Cambridge, MA, 02139, USA. yumin.zhang@mpi.com Molecular imaging and biology : MIB : the official publication of the Academy of Molecular Imaging (2006), 8(5), 300-8. Journal code: 101125610. ISSN:1536-1632. Journal; Article; (JOURNAL ARTICLE); (VALIDATION STUDIES) written in English. PubMed ID 16897318 AN 2006563015 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

PURPOSE: The aim of this study was to validate quantitative metabolic response of tumors to a treatment measured by longitudinal 2-deoxy-2-[(18)F]fluoro-D-glucose (FDG) micro positron emission tomography (microPET) as a robust tool for preclinical evaluation of new anticancer agents. **PROCEDURES:** Severe combined immunodeficiency mice with CWR22 xenografts were intravenously treated with bortezomib (Velcade) at 0.8 mg/kg on days 0, 3, 7, 10, and 14 and imaged with FDG microPET before, during and after treatment. Quantitative indices of tumor FDG uptake were developed. **RESULTS:** FDG microPET images successfully revealed the gradual reduction of tumor FDG uptake on day 4 onward despite no absolute tumor shrinkage. The standardized uptake values of FDG in tumors was reduced to 43% of the baseline values. Using the total tumor FDG uptake as the viable tumor burden, we found 86% tumor inhibition, compared to a 55% tumor growth inhibition in tumor volume measurement. **CONCLUSION:** FDG microPET imaging can provide an additional dimension of the efficacy of anticancer therapies that may otherwise be underestimated by tumor volume measurement.