

Answer 1:

Bibliographic Information

The bisphosphonate, zoledronic acid reduces experimental neuroblastoma growth by interfering with tumor angiogenesis.

Baeckman, Ulrika; Svensson, Aasa; Christofferson, Rolf H.; Azarbayjani, Faranak. Department of Medical Cell Biology, Children's Hospital, Uppsala University, Swed. *Anticancer Research* (2008), 28(3A), 1551-1558. Publisher: International Institute of Anticancer Research, CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 149:191332 AN 2008:861770 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: Zoledronic acid is a new member of the bisphosphonate (BP) class of compds., a family of closely related synthetic mols. originally derived from the naturally occurring pyrophosphate. These compds. that are potent inhibitors of bone resorption, have been shown to reduce the growth of several cancer cell lines in vitro, and can act as inhibitors of angiogenesis. The angiogenesis inhibitor TNP-470, a synthetic analog of the fungal antibiotic fumagillin, has been shown to inhibit the growth of multiple tumors in vivo, and is currently in Phase II clin. trials for cancer. **Materials and Methods:** The effects of daily s.c. (s.c.) administration of zoledronic acid (0.1 mg/kg) were compared with those of TNP-470 (15 mg/kg/day and 30 mg/kg every other day, s.c.) in a nude mouse xenograft model for the childhood cancer, neuroblastoma (NB). **Results:** Zoledronic acid reduced the tumor growth by 33% whereas TNP-470 was less effective and reduced the tumor growth by 26% and 11% for animals treated with 15 mg/kg/day and 30 mg/kg every other day, resp. **Anal. of angiogenesis** showed a significant redn. of the no. of vessels per grid and in vessel length in all the treatment groups. **Conclusion:** Zoledronic acid shows tumorstatic and angiostatic properties that might be beneficial in the treatment of solid tumors such as neuroblastoma.

Answer 2:

Bibliographic Information

RAD001 (Everolimus) inhibits growth of prostate cancer in the bone and the inhibitory effects are increased by combination with docetaxel and zoledronic acid.

Morgan, Todd M.; Pitts, Tiffany E. M.; Gross, Ted S.; Poliachik, Sandra L.; Vessella, Robert L.; Corey, Eva. Department of Urology, University of Washington School of Medicine, Seattle, WA, USA. *Prostate (Hoboken, NJ, United States)* (2008), 68(8), 861-871. Publisher: Wiley-Liss, Inc., CODEN: PRSTDS ISSN: 0270-4137. Journal written in English. CAN 149:118999 AN 2008:746751 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

INTRODUCTION: mTOR activity is increased in advanced prostate cancer (CaP) as a result of a high rate of PTEN mutations. RAD001 (Everolimus) is a new orally available mTOR inhibitor. The objective of our study was to evaluate the effects of RAD001 on the growth of CaP in the bone, both alone and in combination with docetaxel and zoledronic acid. **METHODS:** C4-2 CaP cells were injected into tibia of mice and the animals were treated with RAD001, docetaxel, and zoledronic acid alone or in combination. Histomorphometrical anal., serum PSA measurements, bone mineral d. (BMD), and μ CT were used to det. the effects of treatment on tumor and bone. **RESULTS:** All three agents alone decreased tumor vol., and RAD001 and docetaxel also decreased levels of serum PSA by 68% and 65%, resp. (both $P < 0.01$). Combinations of the agents were more effective in decreasing tumor vol. than single agents. Three-drug treatment showed the greatest effect: 64% inhibition vs. control ($P < 0.01$). Treatment with RAD001 interfered with the wt. loss assocd. with growth of this tumor in the bone (non-RAD001 groups: 4.0% decrease in body wt., $P = 0.0014$; RAD001 groups: increase of 3.6% in body wt., $P = 0.0037$). **CONCLUSIONS:** RAD001 inhibited growth of C4-2 cells in bone, an effect augmented by addn. of docetaxel and zoledronic acid. Moreover RAD001 had a significant impact on maintenance of body wt. RAD001 may hold promise for its effects on both metastatic CaP and the important syndrome of tumor cachexia.

Answer 3:

Bibliographic Information

A Novel Bioluminescent Mouse Model and Effective Therapy for Adult T-Cell Leukemia/Lymphoma. Shu, Sherry T.; Nadella, Murali V. P.; Dirksen, Wessel P.; Fernandez, Soledad A.; Thudi, Nanda K.; Werbeck, Jillian L.; Lairmore, Michael D.; Rosol, Thomas J. Arthur G. James Cancer Hospital and Solove Research Institute, The Ohio State University, Columbus, OH, USA. *Cancer Research* (2007), 67(24), 11859-11866. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 148:98915 AN 2007:1440170 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Adult T-cell /lymphomaleukemia (ATLL) is caused by human T-cell lymphotropic virus type 1 (HTLV-1). Approx. 80% of ATLL patients develop humoral hypercalcemia of malignancy (HHM), a life-threatening complication leading to a poor prognosis. Parathyroid hormone-related protein (PTHrP) and macrophage inflammatory protein-1 α (MIP-1 α) are important factors in the pathogenesis of HHM in ATLL and the expression of PTHrP can be activated by nuclear factor κ B (NF- κ B). NF- κ B is constitutively activated in ATLL cells and is essential for leukemogenesis including transformation of lymphocytes infected by HTLV-1. The authors' goal was to evaluate the effects of NF- κ B disruption by a proteasomal inhibitor (PS-341) and osteoclastic inhibition by zoledronic acid (Zol) on the development of ATLL and HHM using a novel bioluminescent mouse model. The authors found that PS-341 decreased cell viability, increased apoptosis, and down-regulated PTHrP expression in ATLL cells in vitro. To investigate the in vivo efficacy, nonobese diabetic/severe combined immunodeficient (NOD/SCID) mice were xenografted with ATLL cells and treated with vehicle control, PS-341, Zol, or a combination of PS-341 and Zol. Bioluminescent imaging and tumor cell count showed a significant redn. in tumor burden in mice from all treatment groups. All treatments also significantly reduced the plasma calcium concns. Zol treatment increased trabecular bone vol. and decreased osteoclast parameters. PS-341 reduced PTHrP and MIP-1 α expression in tumor cells in vivo. The authors' results indicate that both PS-341 and Zol are effective treatments for ATLL and HHM, which are refractory to conventional therapy. [*Cancer Res* 2007;67(24):11859-66].

Answer 4:

Bibliographic Information

A Cathepsin K Inhibitor Reduces Breast Cancer-Induced Osteolysis and Skeletal Tumor Burden. Le Gall, Celine; Bellahcene, Akeila; Bonnelye, Edith; Gasser, Juerg A.; Castronovo, Vincent; Green, Jonathan; Zimmermann, Johann; Clezardin, Philippe. UMR 664, IFR62, Institut National de la Sante et de la Recherche Medicale, Lyon, Fr. *Cancer Research* (2007), 67(20), 9894-9902. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 148:23925 AN 2007:1174361 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Osteoclasts mediate bone destruction in breast cancer skeletal metastases. Cathepsin K is a proteinase that is secreted by osteoclasts and degrades bone. Here, immunohistochem. revealed that cathepsin K was expressed not only by osteoclasts but also by breast cancer cells that metastasize to bone. Following intratibial injection with cathepsin K-expressing human BT474 breast cancer cells, tumor-bearing mice treated with a clin. dosing regimen of cathepsin K inhibitor (CKI; 50 mg/kg, twice daily) had osteolytic lesions that were 79% smaller than those of tumor-bearing mice treated with the vehicle. The effect of CKI was also studied in a mouse model in which the i.v. inoculation of human B02 breast cancer cells expressing cathepsin K leads to bone metastasis formation. Drug administration was started before (preventive protocol) or after (treatment protocol) the occurrence of osteolytic lesions. In treatment protocols, CKI (50 mg/kg, twice daily) or a single clin. dose of 100 μ g/kg zoledronic acid (osteoclast inhibitor) reduced the progression of osteolytic lesions by 59% to 66%. CKI therapy also reduced skeletal tumor burden by 62% compared with vehicle, whereas zoledronic acid did not decrease the tumor burden. The efficacy of CKI at inhibiting skeletal tumor burden was similar in the treatment and preventive protocols. By contrast, CKI did not block the growth of s.c. B02 tumor xenografts in animals. Thus, CKI may render the bone a less favorable microenvironment for tumor growth by inhibiting bone resorption. These findings raise the possibility that cathepsin K could be a therapeutic target for the treatment of bone metastases.

Answer 5:

Bibliographic Information

R115777 (Zarnestra)/zoledronic acid (Zometa) cooperation on inhibition of prostate cancer proliferation is paralleled by Erk/Akt inactivation and reduced Bcl-2 and Bad phosphorylation. Caraglia, Michele; Marra, Monica; Leonetti, Carlo; Meo, Giuseppina; D'Alessandro, Anna Maria; Baldi, Alfonso; Santini, Daniele; Tonini, Giuseppe; Bertieri, Raffaello; Zupi, Gabriella; Budillon, Alfredo; Abbruzzese, Alberto. Experimental Pharmacology Unit, National Cancer Institute of Naples "Fondazione G. Pascale", Naples, Italy. Journal of Cellular Physiology (2007), 211(2), 533-543. Publisher: Wiley-Liss, Inc., CODEN: JCLLAX ISSN: 0021-9541. Journal written in English. CAN 146:350848 AN 2007:400869 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Zoledronic acid (ZOL) has proved activity in bone metastases from prostate cancer through inhibition of mevalonate pathway and of prenylation of intracellular proteins. We have reported that ZOL synergizes with R115777 farnesyltransferase inhibitor (FTI, Zarnestra) in inducing apoptosis and growth inhibition on epidermoid cancer cells. Here, we have studied the effects of the combination of these agents in prostate adenocarcinoma models and, specifically, on androgen-independent (PC3 and DU145) and -dependent (LNCaP) prostate cancer cell lines. We have found that ZOL and R115777 were synergistic in inducing both growth inhibition and apoptosis in prostate adenocarcinoma cells. These effects were paralleled by disruption of Ras → Erk and Akt survival pathways, consequent decreased phosphorylation of both mitochondrial bcl-2 and bad proteins, and caspase activation. Finally, ZOL/R115777 combination induced cooperative effects also in vivo on tumor growth inhibition of prostate cancer xenografts in nude mice with a significant survival increase. These effects were paralleled by enhanced apoptosis and inactivation of both Erk and Akt. In conclusions, the combination between ZOL and FTI leads to enhanced anti-tumor activity in human prostate adenocarcinoma cells likely through a more efficacious inhibition of ras-dependent survival pathways and consequent bcl-related proteins-dependent apoptosis.

Answer 6:

Bibliographic Information

Administration of zoledronic acid enhances the effects of docetaxel on growth of prostate cancer in the bone environment. Brubaker, Kristen D.; Brown, Lisha G.; Vessella, Robert L.; Corey, Eva. Department of Biological and Allied Health Sciences, Bloomsburg University, Bloomsburg, PA, USA. BMC Cancer (2006), 6 No pp. given. Publisher: BioMed Central Ltd., CODEN: BCMACL ISSN: 1471-2407. <http://www.biomedcentral.com/content/pdf/1471-2407-6-15.pdf> Journal; Online Computer File written in English. CAN 145:39912 AN 2006:120688 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

After development of hormone-refractory metastatic disease, prostate cancer is incurable. The recent history of chemotherapy has shown that with difficult disease targets, combinatorial therapy frequently offers the best chance of a cure. In this study we have examd. the effects of a combination of zoledronic acid (ZOL), a new-generation bisphosphonate, and docetaxel on LuCaP 23.1, a prostate cancer xenograft that stimulates the osteoblastic reaction when grown in the bone environment. Intra-tibial injections of LuCaP 23.1 cells were used to generate tumors in the bone environment, and animals were treated with ZOL, docetaxel, or a combination of these. Effects on bone and tumor were evaluated by measurements of bone mineral d. and histomorphometrical anal. ZOL decreased proliferation of LuCaP 23.1 in the bone environment, while docetaxel at a dose that effectively inhibited growth of s.c. tumors did not show any effects in the bone environment. The combination of the drugs significantly inhibited the growth of LuCaP 23.1 tumors in the bone. In conclusion, the use of the osteolysis-inhibitory agent ZOL in combination with docetaxel inhibits growth of prostate tumors in bone and represents a potential treatment option.

Answer 7:

Bibliographic Information

Zoledronic acid cooperates with a cyclooxygenase-2 inhibitor and gefitinib in inhibiting breast and prostate cancer. Melisi, Davide; Caputo, Rosa; Damiano, Vincenzo; Bianco, Roberto; Veneziani, Bianca Maria; Bianco, A. Raffaele; De Placido, Sabino; Ciardiello, Fortunato; Tortora, Giampaolo. Cattedra di Oncologia Medica, Dipartimento di Endocrinologia e Oncologia Molecolare e Clinica, Universita di Napoli Federico II, Naples, Italy. Endocrine-Related Cancer (2005), 12(4), 1051-1058. Publisher: Society

for Endocrinology, CODEN: ERCAE9 ISSN: 1351-0088. Journal written in English. CAN 145:431 AN 2006:78820 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Biphosphonates (BPs) are widely used to inhibit osteoclastic activity in malignant diseases such as bone metastatic breast and prostate carcinoma. Recent studies reported that BPs could also cause a direct antitumor effect, probably due to their ability to interfere with several intracellular signaling molecules. The enzyme cyclooxygenase-2 (COX-2) and the epidermal growth factor receptor (EGFR) play an important role in the control of cancer cell growth and inhibitors of COX-2 and EGFR have shown antitumor activity in vitro and in vivo in several tumor types. We, and others, have previously shown that EGFR and COX-2 may be directly related to each other and that their selective inhibitors may have a cooperative effect. In the present study we have evaluated the combined effect of zoledronic acid, the most potent nitrogen-containing BP, with the COX-2 inhibitor SC-236 and the selective EGFR-tyrosine kinase inhibitor gefitinib, on breast and prostate cancer models in vitro and in xenografted nude mice. We show that combination of zoledronic acid with SC-236 and gefitinib causes a cooperative antitumor effect accompanied by induction of apoptosis and regulation of the expression of mitogenic factors, proangiogenic factors and cell cycle controllers both in vitro and in xenografted nude mice. The modulatory effect on protein expression and the inhibitory effect on tumor growth is much more potent when the three agents are used together. Since studies are ongoing to explore the antitumor effect of zoledronic acid, our results provide new insights into the mechanism of action of these agents and a novel rationale to translate this feasible combination treatment strategy into a clinical setting.

Answer 8:

Bibliographic Information

Cytotoxic effects of $\gamma\delta$ T cells expanded ex vivo by a third generation bisphosphonate for cancer immunotherapy. Sato, Kiyoshi; Kimura, Shinya; Segawa, Hidekazu; Yokota, Asumi; Matsumoto, Seiji; Kuroda, Junya; Nogawa, Masaki; Yuasa, Takeshi; Kiyono, Yasushi; Wada, Hiromi; Maekawa, Taira. Department of Transfusion Medicine and Cell Therapy, Kyoto University Hospital, Kyoto, Japan. International Journal of Cancer (2005), 116(1), 94-99. Publisher: Wiley-Liss, Inc., CODEN: IJCNAA ISSN: 0020-7136. Journal written in English. CAN 143:221972 AN 2005:566052 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Nitrogen-containing bisphosphonates (N-BPs), widely used to treat bone diseases, have direct antitumor effects via the inactivation of Ras proteins. In addition to the direct antitumor activities, N-BPs expand $\gamma\delta$ T cells, which exhibit major histocompatibility complex-unrestricted lytic activity. BPs accumulate intermediate metabolites which may be tumor antigens in target cells. The purpose of our study was to clarify the cytotoxicity of $\gamma\delta$ T cells expanded ex vivo by the most potent N-BP, zoledronate (ZOL). Especially, we focused on the importance of pretreatment against target cells also with ZOL; 1 μ M ZOL plus IL-2 increased the absolute number of $\gamma\delta$ T cells 298-768 fold for 14 days incubation. The small cell lung cancer and fibrosarcoma cell lines pretreated with 5 μ M ZOL showed a marked increase in sensitivity to lysis by $\gamma\delta$ T cells. While, untreated cell lines were much less sensitive to lysis by $\gamma\delta$ T cells. Video microscopy clearly demonstrated that $\gamma\delta$ T cells killed target cells pre-treated with ZOL within 3 h. Pretreatment with 80 μ g/kg ZOL also significantly enhanced the antitumor activity of $\gamma\delta$ T cells in mice xenografted with SBC-5 cells. These findings show that ZOL significantly stimulated the proliferation of $\gamma\delta$ T cells and that $\gamma\delta$ T cells required pre-treatment with ZOL for cytotoxic activity against target cells.

Answer 9:

Bibliographic Information

The third-generation bisphosphonate zoledronate synergistically augments the anti-Ph+ leukemia activity of imatinib mesylate. Kimura, Shinya; Kuroda, Junya; Maekawa, Taira. School of Medicine, Affiliated Hospital, Kyoto University, Japan. Ensho, Saisei (2004), 24(2), 113-117. Publisher: Nippon Ensho-Saisei Igakkai, CODEN: ENSHCC ISSN: 1346-8022. Journal written in Japanese. CAN 141:167358 AN 2004:450068 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Imatinib mesylate, a competitive inhibitor for of ABL tyrosine kinase, is highly active against Philadelphia-pos. (Ph+) chronic myelocytic leukemia. However, recent studies demonstrated the existence of primary and/or acquired imatinib-resistant Ph+ clones those would affect the treatment outcome. For the development of the strategies those strengthen the effect of imatinib, we selected Ras related proteins as an alternative mol. target, because these proteins enhance the oncogenetic property of BCR/ABL as downstream signaling effector. Based on the previous findings showing the inhibitory effect for Ras related proteins of the third-generation bisphosphonate, zoledronate (ZOL), we examd. its anti-leukemic potencies and the combination effect with imatinib against Ph+ leukemia both in vivo and in vitro. ZOL showed a time- and concn.-dependent antiproliferative effect in all examd. leukemic cell lines by inducing apoptosis. During the apoptotic execution, ZOL inactivated Ras related proteins via prevention of the posttranslational prenylation. The combination of imatinib and ZOL showed the synergistic anti-proliferative effects against Ph, leukemic cell lines in vitro, and, intriguingly, this combination could prolong the survival of mice xenografted with Ph, BV173 cell line in comparison with mice treated with imatinib or ZOL alone. These suggest that ZOL is a potent anti-leukemic agent that synergistically augments the effect of imatinib.

Answer 10:

Bibliographic Information

The third-generation bisphosphonate zoledronate synergistically augments the anti-Ph+ leukemia activity of imatinib mesylate. Kuroda, Junya; Kimura, Shinya; Segawa, Hidekazu; Kobayashi, Yutaka; Yoshikawa, Toshikazu; Urasaki, Yoshimasa; Ueda, Takanori; Enjo, Fumio; Tokuda, Harukuni; Ottmann, Oliver G.; Maekawa, Taira. Department of Transfusion Medicine and Cell Therapy, Kyoto University Hospital, Kyoto, Japan. *Blood* (2003), 102(6), 2229-2235. Publisher: American Society of Hematology, CODEN: BLOOAW ISSN: 0006-4971. Journal written in English. CAN 140:104474 AN 2003:736823 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Imatinib mesylate, a competitive inhibitor of Abl tyrosine kinase, is highly effective for the early stages of chronic myelogenous leukemia (CML), but remissions induced in advanced-phase CML and Philadelphia chromosome-pos. (Ph+) acute lymphoblastic leukemia tend to be relatively short-lived. Therefore, the search for agents that enhance the anti-Ph+ effect of imatinib mesylate is warranted. We investigated the combined effects of imatinib mesylate and the third-generation bisphosphonate zoledronate (ZOL) on Ph+ leukemias, because ZOL inhibited the prenylation of Ras-related proteins downstream of Bcr/Abl. First, we identified the potency of ZOL in vitro against human leukemic cell lines, including 2 Ph+ and a P-glycoprotein-overexpressing leukemic cell line. ZOL was also effective in vivo because as it prolonged the survival of nonobese diabetic/severe combined immunodeficient (NOD/SCID) mice who were given xenografts with Ph+ BV173 leukemic cells. Next, we showed the in vitro synergistic effects with ZOL and imatinib mesylate for Ph+ cell lines. ZOL combined with imatinib mesylate showed synergistic effects in vivo that prolonged the survival of mice inoculated with BV173. ZOL only minimally inhibited the growth of normal hematopoietic progenitors in vitro, and mice receiving ZOL or imatinib mesylate or both tolerated these treatments well. These findings indicate that ZOL is a potent antileukemic agent that augments synergistically the anti-Ph+ leukemia activity of imatinib mesylate.

Answer 11:

Bibliographic Information

The activity of zoledronic Acid on neuroblastoma bone metastasis involves inhibition of osteoclasts and tumor cell survival and proliferation. Peng Hongjun; Sohara Yasuyoshi; Moats Rex A; Nelson Marvin D Jr; Groshen Susan G; Ye Wei; Reynolds C Patrick; DeClerck Yves A Division of Hematology-Oncology, Department of Pediatrics, University of Southern California, USA *Cancer research* (2007), 67(19), 9346-55. Journal code: 2984705R. ISSN:0008-5472. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, N.I.H., EXTRAMURAL) written in English. PubMed ID 17909043 AN 2007588015 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Metastasis to the bone is seen in 56% of patients with neuroblastoma and contributes to morbidity and mortality. Using a murine model of bone invasion, we have reported previously that neuroblastoma cells invade the bone by activating osteoclasts. Here, we investigated the antitumoral and antiosteolytic activities of zoledronic acid, a bisphosphonate inhibitor of osteoclasts, in combination with cytotoxic chemotherapy in our model. We first show that zoledronic acid given at the same time (early prevention) or 2 weeks after tumor cell injection (late prevention) significantly prevented the formation of severe osteolytic lesions. It also prevented formation of these lesions when given 4 weeks after tumor cell injection (intervention) when combined with chemotherapy including cyclophosphamide and topotecan. The combination of zoledronic acid + cyclophosphamide/topotecan also significantly improved survival ($P < 0.001$). In mice treated with zoledronic acid, we observed a marked inhibition of osteoclasts inside the bone associated with a decrease in tumor cell proliferation and increase in tumor cell apoptosis. In vitro, zoledronic acid inhibited neuroblastoma cell proliferation and induced apoptosis, and these effects were significantly enhanced by the addition of 4-hydroxyperoxycyclophosphamide (4-HC). The proapoptotic effect of zoledronic acid and zoledronic acid in combination with 4-HC on tumor cells was associated with an increase in caspase-3 activity and a decrease in phosphorylated Bcl-2, Bcl-2, and Bcl-X(L) expression. Zoledronic acid inhibited the association of Ras with the plasma membrane and activation of c-Raf, Akt, and extracellular signal-regulated kinase 1/2. The data indicate that zoledronic acid, in addition to inhibiting osteoclasts, is active against tumor cells and suggest that zoledronic acid in combination with cytotoxic chemotherapy may be effective in children with neuroblastoma that has metastasized to the bone.

Answer 12:

Bibliographic Information

Effect of zoledronic acid on the doxycycline-induced decrease in tumour burden in a bone metastasis model of human breast cancer. Duivenvoorden W C M; Vukmirovic-Popovic S; Kalina M; Seidlitz E; Singh G Juravinski Cancer Centre, Hamilton, Ontario, Canada L8V 5C2 British journal of cancer (2007), 96(10), 1526-31. Journal code: 0370635. ISSN:0007-0920. (COMPARATIVE STUDY); (EVALUATION STUDIES); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 17437017 AN 2007289330 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Bone is one of the most frequent sites for metastasis in breast cancer patients often resulting in significant clinical morbidity and mortality. Bisphosphonates are currently the standard of care for breast cancer patients with bone metastasis. We have shown previously that doxycycline, a member of the tetracycline family of antibiotics, reduces total tumour burden in an experimental bone metastasis mouse model of human breast cancer. In this study, we combined doxycycline treatment together with zoledronic acid, the most potent bisphosphonate. Drug administration started 3 days before the injection of the MDA-MB-231 cells. When mice were administered zoledronic acid alone, the total tumour burden decreased by 43% compared to placebo treatment. Administration of a combination of zoledronic acid and doxycycline resulted in a 74% decrease in total tumour burden compared to untreated mice. In doxycycline- and zoledronate-treated mice bone formation was significantly enhanced as determined by increased numbers of osteoblasts, osteoid surface and volume, whereas a decrease in bone resorption was also observed. Doxycycline greatly reduced tumour burden and could also compensate for the increased bone resorption. The addition of zoledronate to the regimen further decreased tumour burden, caused an extensive decrease in bone-associated soft tissue tumour burden (93%), and sustained the bone volume, which could result in a smaller fracture risk. Treatment with zoledronic acid in combination with doxycycline may be very beneficial for breast cancer patients at risk for osteolytic bone metastasis.

Answer 13:

Bibliographic Information

The effect of zoledronic acid and osteoprotegerin on growth of human lung cancer in the tibias of nude mice.

Tannehill-Gregg S H; Levine A L; Nadella M V P; Iguchi H; Rosol T J Bristol-Myers Squibb Company, Pharmaceutical Research Institute, Evansville, IN, USA Clinical & experimental metastasis (2006), 23(1), 19-31. Journal code: 8409970. ISSN:0262-0898. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, N.I.H., EXTRAMURAL) written in English. PubMed ID 16715352 AN 2006612876 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The pathogenesis of bone metastases may require the activation of osteoclasts by tumor-secreted factors, which promote important interactions with the bone microenvironment. We utilized an intratibial model of bone metastasis with bioluminescent imaging (BLI) to measure the effect of osteoclast inhibition on the interaction of human lung cancer cells with bone, and on tumor growth. Mice were injected with luciferase-transduced tumor cells (HARA, human pulmonary squamous carcinoma) and divided into three groups: (1) untreated, (2) twice weekly treatment with the bisphosphonate zoledronic acid (ZOL), or (3) osteoprotegerin (OPG). Histomorphometry and imaging were used to evaluate tumor burden, and parameters of osteoclast activity. Mice in the treated groups had increased bone density and decreased osteoclast numbers in nontumor-bearing tibiae. There was greater than 60% reduction in mean tumor volume in both treatment groups when evaluated by histomorphometry ($P = 0.06$ [OPG], $P = 0.07$ [ZOL]). However, bioluminescent imaging failed to show a reduction in tumor burden due to wide variability in the data. Osteoclast numbers along tumor-associated bone were significantly increased compared to tumor-free bone, and were not reduced by either treatment. Plasma calcium concentration was increased in all groups. Plasma tartrate-resistant acid phosphatase 5b was reduced in both treatment groups. Plasma PTHrP was significantly increased in the untreated tumor-bearing group, but was not significantly different in the two treatment groups compared to normal mice. OPG or ZOL did not change tumor cell proliferation, but ZOL increased HARA cell apoptosis. OPG and ZOL reduced tumor growth in the tibiae of treated mice, however, PTHrP production by HARA cells may have resulted in a high concentration in the bone microenvironment, partially overriding the antiosteoclast effects of both OPG and ZOL.

Answer 14:

Bibliographic Information

Multimodal imaging analysis of tumor progression and bone resorption in a murine cancer model. Mouchess Maria L; Sohara Yasuyoshi; Nelson Marvin D Jr; DeClerck Yves A; Moats Rex A Division of Hematology Oncology, Department of Pediatrics, University of Southern California and the Saban Research Institute of Childrens Hospital Los Angeles, Los Angeles, California 90027, USA Journal of computer assisted tomography (2006), 30(3), 525-34. Journal code: 7703942. ISSN:0363-8715. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, N.I.H., EXTRAMURAL) written in English. PubMed ID 16778634 AN 2006376546 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

OBJECTIVE: This study evaluates the use of multimodal imaging to qualitatively and quantitatively measure tumor progression and bone resorption in a xenotransplanted tumor model of human neuroblastoma. **METHODS:** Human neuroblastoma cells expressing a luciferase reporter gene were injected into the femur of nu/nu mice. Tumor progression with and without zoledronic acid treatment was monitored using radiographs, D-luciferin-induced luminescence, micro-computer tomography (CT) and micro-magnetic resonance imaging (MRI). **RESULTS:** We observed a gradual increase in D-luciferin-based bioluminescence concomitant with detectable osteolytic lesions. Tumor growth was inhibited ($P=0.003-0.07$) with zoledronic acid treatment. Micro-CT analysis in vivo provided a method to quantify bone loss, and its prevention by zoledronic acid. High-resolution MRI images allowed the observation of tumor cells within the bone marrow cavity, as well as distant metastasis. **CONCLUSION:** Multimodal imaging allows to measure tumor growth and bone resorption simultaneously in vivo and also proved useful in the detection distant metastasis.

Answer 15:

Bibliographic Information

Evaluation of human fetal bone implants in SCID mice as a model of prostate cancer bone metastasis. Singh Arun S; Macpherson Gordon R; Price Douglas K; Schimel Daniel; Figg William D Medical Oncology Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD 20892, USA Oncology reports (2006), 15(3), 519-24. Journal code: 9422756. ISSN:1021-335X. (EVALUATION STUDIES); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 16465406 AN 2006079214 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The metastasis of prostate cancer cells to the bone marrow constitutes the major source of morbidity and mortality in prostate cancer. Studying this process has been hampered by the lack of preclinical models to evaluate novel therapeutics and to study the biology of the disease. One proposed model utilizes human fetal bone implants to serve as the target for prostate cancer cells injected via the tail vein. We employed this model to test the ability of zoledronic acid to prophylax and to treat bone metastases. To improve the rate of bone metastasis, we used two bone implants instead of one to evaluate the cell lines PC3 and PC3M, a more metastatic subline. For this purpose we generated the novel cell line PC3EGFPLuc, which can be used for luminescence and/or fluorescence imaging in vivo. We did not observe bone implant metastases in 52 mice, with 90 bone implants following tail vein injection of 1×10^6 PC3 or PC3M cells. Soft tissue lesions in the buttocks and hind limbs as well as cellular growth in the hindlimbs were observed via bioluminescence imaging. This evidence together with literature findings suggests that this model produces artifactual 'bone metastasis' lesions.

Answer 16:

Bibliographic Information

Administration of zoledronic acid enhances the effects of docetaxel on growth of prostate cancer in the bone environment. Brubaker Kristen D; Brown Lisha G; Vessella Robert L; Corey Eva Department of Biological and Allied Health Sciences, Bloomsburg University, Bloomsburg, PA, USA. kbrubake@bloomu.edu BMC cancer (2006), 6 15. Journal code: 100967800. E-ISSN:1471-2407. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 16417633 AN 2006065900 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

BACKGROUND: After development of hormone-refractory metastatic disease, prostate cancer is incurable. The recent history of chemotherapy has shown that with difficult disease targets, combinatorial therapy frequently offers the best chance of a cure. In this study we have examined the effects of a combination of zoledronic acid (ZOL), a new-generation bisphosphonate, and docetaxel on LuCaP 23.1, a prostate cancer xenograft that stimulates the osteoblastic reaction when grown in the bone environment. **METHODS:** Intra-tibial injections of LuCaP 23.1 cells were used to generate tumors in the bone environment, and animals were treated with ZOL, docetaxel, or a combination of these. Effects on bone and tumor were evaluated by measurements of bone mineral density and histomorphometrical analysis. **RESULTS:** ZOL decreased proliferation of LuCaP 23.1 in the bone environment, while docetaxel at a dose that effectively inhibited growth of subcutaneous tumors did not show any effects in the bone environment. The combination of the drugs significantly inhibited the growth of LuCaP 23.1 tumors in the bone. **CONCLUSION:** In conclusion, the use of the osteolysis-inhibitory agent ZOL in combination with docetaxel inhibits growth of prostate tumors in bone and represents a potential treatment option.

Answer 17:

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Efficacy of the third-generation bisphosphonate, zoledronic acid alone and combined with anti-cancer agents against small cell lung cancer cell lines. Comment in: Lung Cancer. 2005 Nov;50(2):271-2. PubMed ID: 16112774
Matsumoto Seiji; Kimura Shinya; Segawa Hidekazu; Kuroda Junya; Yuasa Takeshi; Sato Kiyoshi; Nogawa Masaki; Tanaka Fumihito; Maekawa Taira; Wada Hiromi Department of Thoracic Surgery, Faculty of Medicine, Kyoto University, Kyoto 606-8507, Japan Lung cancer (Amsterdam, Netherlands) (2005), 47(1), 31-9. Journal code: 8800805.
ISSN:0169-5002. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English.
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Abstract

Small cell lung cancer (SCLC) is one of the most aggressive types of cancers because of its early development of regional and distant metastases. Novel and more effective therapeutic strategies for the treatment of this disease are necessary. Bisphosphonates (BP), originally developed to treat bone disease, have recently been identified as attractive cancer therapeutic agents. In this study, we investigated the anti-proliferative effects of zoledronic acid (ZOL) as a single agent and in combination with other agents. ZOL inhibited both farnesylation and geranylgeranylation of RAS related proteins, induced apoptosis and inhibited the growth of eight out of twelve SCLC cell lines examined in vitro. ZOL also significantly inhibited SCLC tumor growth and SBC-3 cells transplanted subcutaneously into nude mice. Its suppressive effect has not been completed, the addition effect of ZOL with other agents was examined. ZOL augmented the effects of paclitaxel, etoposide, cisplatin and irinotecan synergistically, and imatinib mesylate additively. These findings indicate that ZOL and combined use of these agents may be promising therapeutic strategies for SCLC.

Answer 18:

Bibliographic Information

Use of zoledronate to treat osteoblastic versus osteolytic lesions in a severe-combined-immunodeficient mouse model. Lee Yu-Po; Schwarz Edward M; Davies Mark; Jo Mark; Gates Jeffrey; Zhang Xuguang; Wu Jing; Lieberman Jay R Department of Orthopaedic Surgery, David Geffen School of Medicine, Los Angeles, California 90095, USA
Cancer research (2002), 62(19), 5564-70. Journal code: 2984705R. ISSN:0008-5472. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 12359769 AN 2002609283
MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Prostate adenocarcinoma is associated with the formation of osteoblastic metastases in bone. It has been hypothesized that osteoclastic bone resorption is a critical component before the development of these osteoblastic lesions in bone. This observation has led researchers to test agents that inhibit osteoclastic activity to prevent or halt the formation of metastatic prostate cancer lesions in bone. Bisphosphonates inhibit osteoclast activity, and previous studies showed that they have the ability to reduce the osteolytic bone resorption associated with multiple myeloma and breast cancer. The objective of this study was to evaluate the efficacy of zoledronate in limiting the formation and/or progression of osteoblastic lesions produced by the injection of known prostate cancer cells (LAPC-9 and PC-3 cells) into the tibia of SCID mice. The mice were treated with either 30- micro g or 150- micro g doses of zoledronate before tumor implantation (pretreatment group), or at weekly intervals after tumor implantation (weekly treatment group), or weekly starting one month after tumor implantation (delayed-treatment group). The zoledronate was very effective in limiting the formation of osteolytic lesions in PC-3 implanted tibias by inhibiting osteoclast activity. Radiographic and histological analysis at weekly intervals revealed that osteolytic lesions developed in the control tibias by 2 weeks, and there was complete destruction of the cortical bone in much of the proximal tibias by 4 weeks. In the treatment groups, there was minimal cortical destruction noted in the weekly treatment groups at both doses, whereas mild cortical erosion was evident in the pretreatment groups, with more cortical destruction noted in the 30- micro g group compared with the 150- micro g group. Tartrate-resistant acid phosphatase (TRAP) staining showed that zoledronate decreased osteoclastic numbers and that there was a dose-dependent response.

In tibias implanted with the LAPC-9 cells, the zoledronate was not effective in halting the formation of the osteoblastic lesions. Radiographic and histological analysis revealed that osteoblastic lesions either had formed or were developing in 18 of 18 of the control tibias and 36 of 36 of the treated tibias at 8 weeks regardless of dose or treatment schedule. Furthermore, TRAP staining demonstrated that osteoblastic lesions had formed in the LAPC-9 tibias under conditions in which osteoclast numbers were significantly reduced. These results suggest that osteoclast activity may not be critical for the development of osteoblastic lesions associated with prostate tumor cells. Hence, bisphosphonates may not be ideal agents to prevent the formation of osteoblastic lesions associated with prostate cancer metastases to bone.

Answer 19:

Bibliographic Information

Myeloma interacts with the bone marrow microenvironment to induce osteoclastogenesis and is dependent on osteoclast activity. Yaccoby Shmuel; Pearse Roger N; Johnson Cherie L; Barlogie Bart; Choi Yongwon; Epstein Joshua Myeloma and Transplantation Research Center, University of Arkansas for Medical Sciences, Little Rock, AR 72205, USA British journal of haematology (2002), 116(2), 278-90. Journal code: 0372544. ISSN:0007-1048. 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 11841428 AN 2002127193 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Myeloma tumour growth, except in the most advanced stages of the disease, is restricted to the bone marrow. We used the severe combined immunodeficient-human (SCID-hu) host system, in which primary human myeloma cells grow in, disseminate to and interact with a human microenvironment, to study the interactions between myeloma cells and cells in the bone marrow microenvironment. We used inhibitors of osteoclast activity to determine the role of osteoclasts and their products in supporting myeloma cell growth. Treatment of myelomatous SCID-hu hosts with an inhibitor of osteoclast activity (pamidronate or zoledronate) or with a specific inhibitor of the receptor activator of NF-kappaB ligand (RANKL) halted myeloma-induced bone resorption, when present, and resulted in inhibition of myeloma cell growth and survival. In contrast, myeloma cells from patients with extramedullary disease had a different growth pattern in the SCID-hu hosts and were not inhibited by these interventions, indicating that, while still dependent on a human microenvironment, these cells no longer required the bone marrow microenvironment for survival. This study demonstrates the dependence of myeloma cells on osteoclast activity and their products, and highlights the importance of the myeloma-osteoclast-myeloma loop for sustaining the disease process. Breaking this loop may help control myeloma.