

Answer 1:

Bibliographic Information

Clinical and mechanistic aspects of glucocorticoid-induced chemotherapy resistance in the majority of solid tumors.

Zhang, Chengwen; Wenger, Till; Mattern, Juergen; Ilea, Septimia; Frey, Christian; Gutwein, Paul; Altevogt, Peter; Bodenmueller, Wolfram; Gassler, Nikolaus; Schnabel, Philipp A.; Dienemann, Hendrik; Marme, Alexander; Hohenfellner, Markus; Haferkamp, Axel; Pfitzenmaier, Jesco; Groene, Hermann-Josef; Kolb, Armin; Buechler, Peter; Buechler, Markus W.; Friess, Helmut; Rittgen, Werner; Edler, Lutz; Debatin, Klaus-Michael; Krammer, Peter H.; Rutz, Hans P.; Herr, Ingrid. Research Group Molecular OncoSurgery, University of Heidelberg, Heidelberg, Germany. *Cancer Biology & Therapy* (2007), 6(2), 278-287. Publisher: Landes Bioscience, CODEN: CBTAAO ISSN: 1538-4047. Journal written in English. CAN 147:479951 AN 2007:1039338 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Glucocorticoids have been used widely in conjunction with cancer therapy due to their ability to induce apoptosis in hematol. cells and to prevent nausea and emesis. However, recent data including ours, suggest induction of therapy-resistance by glucocorticoids in solid tumors, although it is unclear whether this happens only in few carcinomas or is a more common cell type specific phenomenon. We performed an overall statistical anal. of our new and recent data obtained with 157 tumor probes evaluated in vitro, ex vivo and in vivo. The effect of glucocorticoids on apoptosis, viability and cell cycle progression under diverse clin. important questions was examd. New in vivo results demonstrate glucocorticoid-induced chemotherapy resistance in xenografted prostate cancer. In an overall statistical anal. we found glucocorticoid-induced resistance in 89% of 157 analyzed tumor samples. Resistance is common for several cytotoxic treatments and for several glucocorticoid-derivs. and due to an inhibition of apoptosis, promotion of viability and cell cycle progression. Resistance occurred at clin. achievable peak plasma levels of patients under anti-emetic glucocorticoid therapy and below, lasted for a long time, after one single dose, but was reversible upon removal of glucocorticoids. Two nonsteroidal alternative anti-emetic agents did not counteract anticancer treatment and may be sufficient to replace glucocorticoids in cotreatment of carcinoma patients. These data demonstrate the need for prospective clin. studies as well as for detailed mechanistic studies of GC-induced cell-type specific pro- and anti-apoptotic signaling.

Answer 2:

Bibliographic Information

Preclinical Studies of TW-37, a New Nonpeptidic Small-Molecule Inhibitor of Bcl-2, in Diffuse Large Cell Lymphoma

Xenograft Model Reveal Drug Action on Both Bcl-2 and Mcl-1. Mohammad, Ramzi M.; Goustin, Anton Scott; Aboukameel, Amro; Chen, Ben; Banerjee, Sanjeev; Wang, Guoping; Nikolovska-Coleska, Zaneta; Wang, Shaomeng; Al-Katib, Ayad. Division of Hematology and Oncology, Department of Internal Medicine, Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI, USA. *Clinical Cancer Research* (2007), 13(7), 2226-2235. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 147:314436 AN 2007:369868 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

PURPOSE: Overexpression of Bcl-2 protein has been obsd. in more than 80% of B-cell lymphomas, including diffuse large cell lymphoma (DLCL), the most common subtype of non-Hodgkin's lymphoma. We have previously employed the natural product (-)-gossypol to test its therapeutic potential as a small-mol. inhibitor of Bcl-2 for the treatment of B-cell lymphomas. Exptl. Design: Recently, we have used a structure-based strategy to design a new class of potent small-mol. inhibitor acting on Bcl-2. One such lead compd. is the benzenesulfonyl deriv. TW-37, which was designed to target the BH3-binding groove in Bcl-2 where proapoptotic Bcl-2 proteins, such as Bak, Bax, Bid, and Bim bind. **RESULTS:** In our fluorescence polarization-based binding assays using recombinant Bcl-2, Bcl-XL, and Mcl-1 proteins, TW-37 binds to Bcl-2, Bcl-XL, and Mcl-1 with Ki values of 290, 1,110 and 260 nmol/L, resp. Hence, TW-37 is a potent inhibitor of Bcl-2 and has >3-fold selectivity over Bcl-XL. In vitro, TW-37 showed significant antiproliferative effect in a de novo chemoresistant WSU-DLCL2 lymphoma cell line and primary cells obtained from a lymphoma patient with no effect on normal peripheral blood lymphocytes. Coimmunopptn. expts. showed that TW-37 disrupted heterodimer formation between Bax or

truncated-Bcl-2 and antiapoptotic proteins in the order Mcl-1 > Bcl-2 >> Bcl-XL. As expected, TW-37 caused apoptotic death. Pre-exposure of lymphoma cells to TW-37 significantly enhanced the killing effect of cyclophosphamide-doxorubicin-vincristine-prednisone (CHOP) regimen. The max. tolerated dose of TW-37 in severe combined immunodeficient (SCID) mice was 40 mg/kg for three i.v. injections when given alone and 20 mg/kg, x3 when given in combination with CHOP. Using WSU-DLCL2-SCID mouse xenograft model, the addn. of TW-37 to CHOP resulted in more complete tumor inhibition compared with either CHOP or TW-37 alone. **CONCLUSIONS:** We conclude that the administration of TW-37, as a potent Bcl-2 and Mcl-1 inhibitor, to std. chemotherapy may prove an effective strategy in the treatment of B-cell lymphoma.

Answer 3:

Bibliographic Information

Glucocorticoids Suppress Tumor Angiogenesis and In vivo Growth of Prostate Cancer Cells. Yano, Akihiro; Fujii, Yasuhisa; Iwai, Aki; Kageyama, Yukio; Kihara, Kazunori. Department of Urology, Tokyo Medical and Dental University, Tokyo, Japan. *Clinical Cancer Research* (2006), 12(10), 3003-3009. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 145:241939 AN 2006:464146 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: Glucocorticoids, such as prednisone, hydrocortisone, and dexamethasone, are known to produce some clin. benefit for patients with hormone-refractory prostate cancer (HRPC). However, the underlying mechanisms by which glucocorticoids affect HRPC growth are not well established as yet. Here, we hypothesize that the therapeutic effect of glucocorticoids on HRPC can be attributed to a direct inhibition of angiogenesis through the glucocorticoid receptor by down-regulating two major angiogenic factors, vascular endothelial growth factor (VEGF) and interleukin-8 (IL-8). **Exptl. Design:** The effects of dexamethasone on VEGF and IL-8 expression and cell proliferation were examd. using DU145, which expresses glucocorticoid receptor. The effects of dexamethasone on DU145 xenografts were detd. by analyzing VEGF and IL-8 gene expression, microvessel d., and tumor vol. **Results:** Dexamethasone significantly down-regulated VEGF and IL-8 gene expression by 50% ($P < 0.001$) and 89% ($P < 0.001$), resp., and decreased VEGF and IL-8 protein prodn. by 55% ($P < 0.001$) and 74% ($P < 0.001$), resp., under normoxic condition. Similarly, hydrocortisone down-regulated VEGF and IL-8 gene expression. The effects of dexamethasone were completely reversed by the glucocorticoid receptor antagonist RU486. Even under hypoxia-like conditions, dexamethasone inhibited VEGF and IL-8 expression. In DU145 xenografts, dexamethasone significantly decreased tumor vol. and microvessel d. and down-regulated VEGF and IL-8 gene expression, whereas dexamethasone did not affect the in vitro proliferation of the cells. **Conclusion:** Glucocorticoids suppressed androgen-independent prostate cancer growth possibly due to the inhibition of tumor-assocd. angiogenesis by decreasing VEGF and IL-8 prodn. directly through glucocorticoid receptor in vivo.

Answer 4:

Bibliographic Information

Genistein sensitizes diffuse large cell lymphoma to CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy. Mohammad, Ramzi M.; Al-Katib, Ayad; Aboukameel, Amro; Doerge, Daniel R.; Sarkar, Fazlul; Kucuk, Omer. Division of Hematology and Oncology, Karmanos Cancer Institute, USA. *Molecular Cancer Therapeutics* (2003), 2(12), 1361-1368. Publisher: American Association for Cancer Research, CODEN: MCTOCF ISSN: 1535-7163. Journal written in English. CAN 140:246383 AN 2004:7917 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The incidence of non-Hodgkin's lymphoma (NHL) has been increasing and is now the leading cause of death in males aged 15-54. Diffuse large cell lymphoma (DLCL) is the most common subtype of NHL. These cells are notable for the high expression of the transcription factor nuclear factor kappa beta (NF- κ B), raising the possibility that constitutive activation of the NF- κ B pathway may

contribute to the poor prognosis of DLCL patients. Soy isoflavone genistein promotes apoptosis by decreasing NF- κ B activity. The combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) remains the std. therapy for DLCL with a cure rate of .apprx.40%. The WSU-DLCL2 cell line and its severe combined immunodeficient (SCID) xenograft have constitutively active NF- κ B which provides us with an excellent model in which to study NF- κ B modulation and CHOP sensitization by genistein. The antitumor activity of CHOP with or without a genistein was evaluated in our WSU-DLCL2 model. In vivo, WSU-DLCL2-bearing SCID mice received genistein alone (800 μ g kg⁻¹ day⁻¹, p.o. as gavages for 5 days), CHOP alone ("C", 40 mg/kg, i.v.; "H", 3.3 mg/kg, i.v.; "O", 0.5 mg/kg, i.v.; and "P", 0.2 mg/kg, every day for 5 days, p.o.), or genistein for 5 days followed by CHOP. Tumor growth inhibition (T/C), tumor growth delay (T - C), and log₁₀ kill for genistein, CHOP, and genistein followed by CHOP were 33.6%, 19.2%, and 5.2%; 7, 8, and 17 days; and 1.0, 1.2, and 2.6, resp. To begin elucidating the mechanism of genistein-induced sensitization of WSU-DLCL2 cells to CHOP chemotherapy in this xenograft mouse model, we studied the in vitro effect of genistein on WSU-DLCL2 growth inhibition, cell cycle, Bax:Bcl-2 ratio, NF- κ B DNA binding, and apoptosis in vitro. At 30 μ M, genistein inhibited the growth significantly, induced G2-M arrest, increased Bax:Bcl-2 ratio, decreased NF- κ B DNA binding, and induced apoptosis. Genistein also inhibited NF- κ B DNA binding in vivo, whereas CHOP enhanced it.

Our results show that genistein has growth modulatory effects on WSU-DLCL2 cells and enhances the antitumor activity of CHOP. Because soy isoflavone genistein is a widely available nutritional supplement, its use in combination with CHOP chemotherapy should be further explored in a clin. trial in patients with NHL.

Answer 5:

Bibliographic Information

The addition of bryostatin 1 to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy improves response in a CHOP-resistant human diffuse large cell lymphoma xenograft model. Mohammad, Ramzi M.; Wall, Nathan R.; Dutcher, Julie A.; Al-Katib, Ayad M. Division of Hematology and Oncology, Karmanos Cancer Institute Department of Internal Medicine, Wayne State University School of Medicine, Detroit, MI, USA. *Clinical Cancer Research* (2000), 6(12), 4950-4956. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 135:86680 AN 2001:83385 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The incidence of non-Hodgkin's lymphoma has been increasing at a rate of 4% per yr since 1950; more than 62,000 cases will be diagnosed in the United States in 2000. Diffuse large cell lymphoma (DLCL) is the prototype of curable non-Hodgkin's lymphoma. Empirically designed chemotherapy regimens did not increase the cure rate of 30-40% achieved by the original four-drug regimen introduced in the 1970s [cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)]. The authors studied the antitumor effects of the CHOP regimen alone or in combination with a unique protein kinase C activator, bryostatin 1, on a xenograft model for resistant DLCL in mice with severe combined immune deficiency (WSU-DLCL2-SCID). In this model, the efficacy of bryostatin 1 given at 75 μ g/kg, i.p., alone for 1 or 2 days [B(1 \times) and B(2 \times)] was compared with the efficacy of CHOP alone, bryostatin 1 + CHOP (B+CHOP) given concurrently, bryostatin 1 for 1 day followed by CHOP on day 2 [B(1 \times)-CHOP], and bryostatin 1 for 2 days followed by CHOP on day 3 [B(2 \times)-CHOP]. CHOP doses were as follows: (a) cyclophosphamide, 40 mg/kg, i.v.; (b) doxorubicin, 3.3 mg/kg, i.v.; (c) vincristine, 0.5 mg/kg, i.v.; and (d) prednisone, 0.2 mg/kg, every day for 5 days, p.o. Tumor growth inhibition (T/C), tumor growth delay (T-C), and log₁₀ kill for B(1 \times), B(2 \times), CHOP, B+CHOP, B(1 \times)-CHOP and B(2 \times)-CHOP were 49%, 39%, 25.8%, 15.1%, 14.6%, and 12%; 6, 7, 16, 25, 12, and 15 days; and 0.6, 0.5, 2.2, 3.6, 1.7, and 2.0, resp. To begin elucidating the mechanism whereby bryostatin 1 potentiated the effects of CHOP in the mouse model; the authors studied the effect of bryostatin 1 on Bax, Bcl-2, and poly(ADP-ribose) polymerase proteins in vitro and in vivo. Bax protein increased in a time-dependent manner without any measurable change in Bcl-2 expression.

However, significant cleavage of the preapoptotic marker poly(ADP-ribose) polymerase was not recorded, and the percentage of apoptotic cells detected by flow cytometry increased only slightly (.apprx.8%) after 96 h of bryostatin 1 exposure. The in vitro and in vivo results emphasize the superiority of combining bryostatin 1 with the CHOP regimen against the WSU-DLCL2 model. One possible mechanism may be the modulatory effects of bryostatin 1 on the Bax:Bcl-2 family of apoptosis-regulatory proteins. The use of this combination should be further explored clin. in the treatment of lymphoma.

Answer 6:

Bibliographic Information

Combination chemotherapy of human pancreatic tumor xenografts grown in nude mice. Duke, D. I.; Hellmann, K.; Hutchinson, G. E.; Pym, B. A. *Cancer Chemother. Dep., Imp. Cancer Res. Fund, London, UK. Editor(s): Sordat, Bernard. Immune-Defic. Anim., Int. Workshop Immune-Defic. Anim. Exp. Res., 4th (1984), Meeting Date 1982, 416-20. Publisher: Karger, Basel, Switz CODEN: 51ONAB Conference written in English. CAN 101:350 AN 1984:400350 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))*

Abstract

Various drug combinations, frequency of administration, and dosage schedules are examd. in an effort to maximize the chemotherapeutic response of human pancreatic tumor xenografts in mice. To be active against pancreatic cancer, chemotherapy should be administered at short intervals in a more or less continuous fashion.

Answer 7:

Bibliographic Information

In vivo MRS markers of response to CHOP chemotherapy in the WSU-DLCL2 human diffuse large B-cell lymphoma xenograft. Lee Seung-Cheol; Huang Ming Q; Nelson David S; Pickup Stephen; Wehrli Suzanne; Adegbola Onikepe; Poptani Harish; Delikatny Edward J; Glickson Jerry D *Molecular Imaging Laboratory, Department of Radiology, University of Pennsylvania, Philadelphia, PA 19104, USA NMR in biomedicine (2008), 21(7), 723-33. Journal code: 8915233. ISSN:0952-3480. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 18384181 AN 2008483384 In-process for MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))*

Abstract

To identify (1)H-MRS molecular biomarkers of early clinical therapeutic response in non-Hodgkin's lymphoma, an in vivo longitudinal study was performed on human non-Hodgkin's diffuse large B-cell lymphoma xenografts (WSU-DLCL2) grown in the flanks of female SCID mice. (31)P-MRS measurements, which have been demonstrated to be prognostic clinical indices of response (Arias-Mendoza et al. *Acad. Radiol.* 2004; 11: 368-376) but which provide lower spatial resolution, were included for comparison. The animals received CHOP (cyclophosphamide, hydroxydodoxorubicin, oncovin and prednisone) chemotherapy for three 1-week cycles, resulting in stable disease based on tumor volume. Localization of total choline and phosphorus metabolites in vivo was achieved with stimulated echo acquisition mode and image selected in vivo spectroscopy sequences, respectively. Significant decreases in lactate were detected by the selective multiple quantum coherence spectral editing technique after the first cycle of CHOP, whereas total choline and the phosphomonoester/nucleoside triphosphate ratio did not change until the third cycle. Ex vivo extract MRS of tumors corroborated the in vivo results. Histological staining with antibodies to Ki67 revealed a decrease in proliferation rate in CHOP-treated tumors that coincided with the decrease in lactate. This study demonstrates the utility of lactate as an early proliferation-sensitive indicator of therapeutic response in a mouse model of non-Hodgkin's lymphoma and serves as a basis for future clinical implementation of these methods. Copyright (c) 2008 John Wiley & Sons, Ltd.

Answer 8:

Bibliographic Information

In vivo monitoring response to chemotherapy of human diffuse large B-cell lymphoma xenografts in SCID mice by 1H and 31P MRS. Huang Ming Q; Nelson David S; Pickup Stephen; Qiao Hui; Delikatny E James; Poptani Harish; Glickson Jerry D *Molecular Imaging Laboratory, Department of Radiology, University of Pennsylvania, Philadelphia, PA 19104, USA Academic radiology (2007), 14(12), 1531-9. Journal code: 9440159. ISSN:1076-6332. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, N.I.H., EXTRAMURAL) written in English. PubMed ID*

18035282 AN 2007697395 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

RATIONALE AND OBJECTIVES: A reliable noninvasive method for in vivo detection of early therapeutic response of non-Hodgkin's lymphoma (NHL) patients would be of great clinical value. This study evaluates the feasibility of $(1)H$ and $(31)P$ magnetic resonance spectroscopy (MRS) for in vivo detection of response to combination chemotherapy of human diffuse large B-cell lymphoma (DLCL2) xenografts in severe combined immunodeficient (SCID) mice. **MATERIALS AND METHODS:** Combination chemotherapy with cyclophosphamide, hydroxy doxorubicin, Oncovin, prednisone, and bryostatin 1 (CHOPB) was administered to tumor-bearing SCID mice weekly for up to four cycles. Spectroscopic studies were performed before the initiation of treatment and after each cycle of the CHOPB. Proton MRS for detection of lactate and total choline was performed using a selective multiple-quantum-coherence-transfer (Sel-MQC) and a spin-echo-enhanced Sel-MQC (SEE-Sel-MQC) pulse sequence, respectively. Phosphorus-31 MRS using a nonlocalized, single-pulse sequence without proton decoupling was also performed on these animals. **RESULTS:** Significant decreases in lactate and total choline were detected in the DLCL2 tumors after one cycle of CHOPB chemotherapy. The ratio of phosphomonoesters to beta-nucleoside triphosphate (PME/betaNTP, measured by $(31)P$ MRS) significantly decreased in the CHOPB-treated tumors after two cycles of CHOPB. The control tumors did not exhibit any significant changes in either of these metabolites. **CONCLUSIONS:** This study demonstrates that $(1)H$ and $(31)P$ MRS can detect in vivo therapeutic response of NHL tumors and that lactate and choline offer a number of advantages over PMEs as markers of early therapeutic response.

Answer 9:

Bibliographic Information

Glucocorticoids suppress tumor lymphangiogenesis of prostate cancer cells. Yano Akihiro; Fujii Yasuhisa; Iwai Aki; Kawakami Satoru; Kageyama Yukio; Kihara Kazunori Department of Urology, Tokyo Medical and Dental University, Bunkyo-ku, Tokyo, Japan. yanoaki.uro@tmd.ac.jp Clinical cancer research : an official journal of the American Association for Cancer Research (2006), 12(20 Pt 1), 6012-7. Journal code: 9502500. ISSN:1078-0432. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 17062674 AN 2006628877 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

PURPOSE: Glucocorticoids such as prednisone, hydrocortisone, and dexamethasone are known to provide some clinical benefit for patients with hormone-refractory prostate cancer. However, the underlying mechanisms by which glucocorticoids affect hormone-refractory prostate cancer progression are not well established as yet. Our previous study has shown that glucocorticoids inhibit tumor angiogenesis possibly by down-regulation of vascular endothelial growth factor (VEGF) and interleukin 8. Here, we hypothesized that the therapeutic effect of dexamethasone on hormone-refractory prostate cancer can be partly attributed to a direct inhibition of lymphangiogenesis through the glucocorticoid receptor by down-regulating a major lymphangiogenic factor, VEGF-C. **EXPERIMENTAL DESIGN:** The effects of dexamethasone on the expression of VEGF-C and its receptor, VEGF receptor-3 (VEGFR-3), were examined using an androgen-independent human prostate cancer cell line, DU145, which expresses glucocorticoid receptor. The effects of dexamethasone on tumor-associated lymphangiogenesis in DU145 xenografts were determined by analyzing VEGF-C gene expression, lymphatic vessel density, and relative lymphatic vessel area. **RESULTS:** Dexamethasone significantly down-regulated VEGF-C gene expression and protein production by 48% ($P = 0.003$) and 44% ($P = 0.002$), respectively, under normoxic condition. Similarly, hydrocortisone down-regulated VEGF-C gene expression. The effects of dexamethasone were completely reversed by the glucocorticoid receptor antagonist RU486. Even under hypoxia-like conditions, dexamethasone inhibited VEGF-C gene expression. In DU145 xenografts, dexamethasone significantly down-regulated VEGF-C gene expression and decreased lymphangiogenesis. Dexamethasone did not affect VEGFR-3 gene expression in vitro and in vivo. **CONCLUSION:** Glucocorticoids suppressed tumor-associated lymphangiogenesis by down-regulating VEGF-C through glucocorticoid receptor in androgen-independent prostate cancer cells in vivo.

Answer 10:

Bibliographic Information

Preclinical studies of a nonpeptidic small-molecule inhibitor of Bcl-2 and Bcl-X(L) [(-)-gossypol] against diffuse large cell lymphoma. Mohammad Ramzi M; Wang Shaomeng; Aboukameel Amro; Chen Ben; Wu Xihan; Chen Jianyong; Al-Katib Ayad Department of Internal Medicine, Division of Hematology and Oncology, Karmanos Cancer Institute, Wayne State University School of Medicine, 724 HWCRC, 4100 John R. Street, Detroit, MI 48201, USA. Mohammad@karmanos.org Molecular cancer therapeutics (2005), 4(1), 13-21. Journal code: 101132535. ISSN:1535-7163. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 15657349 AN 2005030592 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Overexpression of Bcl-2/Bcl-X(L) protein has been observed in more than 80% of B-cell lymphomas. Diffuse large cell lymphoma (DLCL) is the most common subtype of non-Hodgkin's lymphoma. (-)-Gossypol, a natural product isolated from cottonseeds, was discovered as a potent small-molecule inhibitor of Bcl-2 and Bcl-X(L) proteins, with a Ki value in the nanomole per liter range for both. In vitro, (-)-gossypol showed significant growth inhibition effect against WSU-DLCL2 lymphoma cell line and fresh cells obtained from a lymphoma patient with no effect on normal peripheral blood lymphocytes. As expected (-)-gossypol induced complete cytochrome c release from mitochondria, increased caspases-3 and -9 activity, and caused apoptotic death without affecting protein levels of Bcl-2, Bcl-X(L), Bax, and Bak. The addition of cyclophosphamide-Adriamycin-vincristine-prednisolone (CHOP) regimen to lymphoma cells preexposed to (-)-gossypol enhanced killing significantly. The maximum tolerated dose of (-)-gossypol in severe combined immunodeficient (SCID) mice was 40 mg/kg for three i.v. injections when given alone and 20 mg/kg x 3 when given in combination with CHOP. Using WSU-DLCL2-SCID mouse xenograft model, the tumor growth inhibition, the tumor growth delay, and the log10 kill of mice treated with (-)-gossypol + CHOP were better than CHOP or (-)-gossypol alone. We conclude that adding Bcl-2/Bcl-X(L) small-molecule inhibitor to standard chemotherapy may prove an effective strategy in lymphoma therapy.

Answer 11:

Bibliographic Information

Comparative efficacy of immunosuppressive drugs in xenografting. Thomas F T; DeMasi R J; Araneda D; Marchman W; Alqaisi M; Larkin E W; Condie R M; Carobbi A; Thomas J M Department of Surgery, East Carolina University School of Medicine, Greenville, North Carolina Transplantation proceedings (1990), 22(3), 1083-5. Journal code: 0243532. ISSN:0041-1345. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 1693452 AN 90273489 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Answer 12:

Bibliographic Information

Clinical evaluation of the immunogenicity of horse and rabbit antihuman lymphocyte globulin in renal transplantation. Cerilli G J; Miller A; Hattan D Surgical forum (1970), 21 250-2. Journal code: 0337723. ISSN:0071-8041. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 4936976 AN 71291146 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))