

Answer 1:

### Bibliographic Information

**Activity of vincristine, L-ASP, and dexamethasone against acute lymphoblastic leukemia is enhanced by the BH3-mimetic ABT-737 in vitro and in vivo.** Kang, Min H.; Kang, Yun Hee; Szymanska, Barbara; Wilczynska-Kalak, Urszula; Sheard, Michael A.; Harned, Theresa M.; Lock, Richard B.; Reynolds, C. Patrick. Developmental Therapeutics Program, Childrens Hospital Los Angeles and University of Southern California (USC-CHLA) Institute for Pediatric Clinical Research, Los Angeles, CA, USA. *Blood* (2007), 110(6), 2057-2066. Publisher: American Society of Hematology, CODEN: BLOOAW ISSN: 0006-4971. Journal written in English. CAN 147:314135 AN 2007:1050782 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Defects in apoptosis signaling contribute to poor outcome in pediatric acute lymphoblastic leukemia (ALL), and overexpression of antiapoptotic Bcl-2 (Bcl-2 and Bcl-XL) family proteins has been obsd. in ALL. ABT-737 is a small-mol. BH3-mimetic that inhibits the antiapoptotic Bcl-2 family proteins. We evaluated the cytotoxicity of ABT-737 in combination with vincristine, dexamethasone, and L-asparaginase (VXL) in 7 ALL cell lines. Multilog synergistic cytotoxicity was obsd. in all 7 cell lines with ABT-737 plus L-asparaginase or vincristine, and in 5 of 7 cell lines with ABT-737 plus dexamethasone or VXL. In leukemia cells, but not in normal lymphocytes, ABT-737 plus L-asparaginase induced greater mitochondrial depolarization (JC-1 staining); mitochondrial cytochrome c release; activation of Bax, Bid, and caspases (immunoblotting); and eventually apoptosis (annexin V staining) than did either drug alone. In mouse xenografts derived from patients with ALL at diagnosis (ALL-7) or at relapse (ALL-19), event-free survival (EFS) was significantly enhanced with ABT-737 plus VXL relative to VXL or ABT-737 alone ( $P \leq .02$ ). Thus, ABT-737 synergistically enhanced VXL cytotoxicity in ALL cell lines via a mitochondrial death pathway and enhanced EFS in VXL-treated mice bearing ALL xenografts. Combining VXL with a BH3-mimetic warrants clin. investigation in ALL at relapse and potentially in chemotherapy-resistant ALL subgroups.

Answer 2:

### Bibliographic Information

**A study comparing endogenous protoporphyrin IX induced by 5-ALA and ALA-methyl ester with exogenous PpIX and PpIX dimethyl ester in photodynamic diagnosis of human nasopharyngeal carcinoma xenografts.** Manivasager, Vanaja; Yee, Karen Kar Lye; Heng, Paul Wan Sia; Soo, Khee Chee; Olivo, Malini. Division of Medical Sciences, National Cancer Centre, Singapore, Singapore. *International Journal of Oncology* (2006), 29(4), 997-1002. Publisher: International Journal of Oncology, CODEN: IJONES ISSN: 1019-6439. Journal written in English. CAN 147:183760 AN 2006:1098469 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

5-Aminolevulinic acid (5-ALA) and its esters have been under intense investigation to enhance the endogenous prodn. of protoporphyrin IX (PpIX) in tumor cells for the purpose of photodynamic diagnosis. In this study we have investigated the use of exogenous PpIX and its di-Me ester (PME) and compared the results with endogenous PpIX produced via 5-ALA and ALA Me ester (AME) in poorly differentiated NPC/CNE-2 nasopharyngeal carcinoma cells in both in vivo and in vitro systems. All prodrugs and photosensitizers were administered to tumor bearing balb/c nude mice either i.v. or topically. In vitro results show that 5-ALA induced more PpIX fluorescence when compared with AME in NPC/CNE-2 cells and PME showed better uptake than PpIX. In vivo results show that exogenous PpIX and PME show promise as good candidates as photosensitizers for photodynamic diagnosis as they exhibit significant selectivity between tumor tissue and normal tissue at 3 h. Modification of delivery vehicle used for application of exogenous PpIX and PME could allow for rapid uptake; better selectivity and localization of the photosensitizer.

Answer 3:

### Bibliographic Information

**Chemo- and radiation sensitivity of xenografted acute lymphoblastic leukemias-correlation to the expression of multidrug resistance proteins.** Fichtner, Iduna; Paal, Krisztina; Borgmann, Anja; Badiali, Lucia; Wurm, Reinhard; Henze, Guenter. Max Delbrueck Center for Molecular Medicine, Berlin, Germany. *Anticancer Research* (2003), 23(3B), 2657-2664. Publisher: International Institute of Anticancer Research, CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 140:87188 AN 2003:658895 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

The aim of our study was to characterize, for the first time, the chemo- and radiation sensitivity of seven pediatric acute lymphoblastic leukemias xenotransplanted into immunodeficient NOD/SCID mice and to correlate the findings with the expression of three drug resistance proteins, P-glycoprotein (P-gp), multidrug resistance-associated protein (MRP1) and lung resistance protein (LRP). Mice were treated with single drugs used in clinical protocols: daunorubicin, doxorubicin, cyclophosphamide, vincristine, cytarabine, asparaginase and methotrexate. Two ALL samples, established from primarily diagnosed patients, responded to 5 or 6 of the tested cytostatics, respectively, while 3 out of 5 ALLs from relapse patients were only sensitive towards 2-4 drugs tested. Daunorubicin was more efficient than doxorubicin. The response of xenografted ALL toward vincristine and cyclophosphamide was inversely correlated with the expression of P-gp, LRP and MRP1 ( $R^2=0.71$ ,  $0.70$  and  $0.64$  for vincristine and  $0.44$ ,  $0.70$  and  $0.60$  for cyclophosphamide). A good correlation could be detected between the expression of P-gp and LRP ( $R^2=0.88$ ), P-gp and MRP1 ( $R^2=0.75$ ) and LRP and MRP1 ( $R^2=0.90$ ). The highest co-expression of the drug resistance proteins in the leukemia ALL-SCID 6 coincided with a high resistance to radiation and chemotherapy. Prediction of the individual drug resistance profile of a patient on the basis of results from the ALL-SCID xenograft studies was not possible because of the relatively long time necessary and because of the changes in the expression of P-gp, LRP and MRP1 during the murine generations. We conclude that in the drug resistance phenotype of ALL not only the above mentioned proteins but a variety of different molecules are involved.

Answer 4:

#### Bibliographic Information

**Prolonged survival of allo- and xenografts of skin by means of an antitumor compound; L-asparaginase.** Bertelli, Aldo; Donati, L.; Trabucchi, E., Jr. *Inst. Pharmacol., Univ. Milan, Milan, Italy. Archivio Italiano di Patologia e Clinica dei Tumori* (1968), 11(3-4), 475-9. CODEN: AIPUAN ISSN: 0004-0266. Journal written in English. CAN 71:59023 AN 1969:459023 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

L-Asparaginase injected i.p. protected skin allo- and xenografts in mice. In controls, skin grafts performed between C 3H and C 57BL mice survived an av. of 8 days and those between Sprague-Dawley and C 57BL mice 5 days. In animals treated with L-asparaginase, 50% of allo- and xenografts were viable after 30 and 20 days respectively. During the L-asparaginase treatment, a striking drop of leukocytes (particularly lymphocytes) was observed. Lymph nodes and spleen showed involution. It is emphasized that for an effective antitumor effect the blockade of immune reactions may represent a negative factor.

Answer 5:

#### Bibliographic Information

**Comparison of antitumor effect of recombinant L-asparaginase with wild type one in vitro and in vivo.** Guo Qing-Long; Wu Min-Shu; Chen Zhen. Department of Physiology, China Pharmaceutical University, Nanjing 210009, China. qinglongguo@hotmail.com *Acta pharmacologica Sinica* (2002), 23(10), 946-51. Journal code: 100956087. ISSN:1671-4083. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 12370101 AN 2002613201 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

#### Abstract

AIM: To investigate the antitumor effect of recombinant L-asparaginase on the growth of several tumors such as P388, L1210, hepatocellular carcinoma (Heps), K562, P815, and sarcoma 180 (S180). METHODS: Tumor cells (K562, L1210, and P815) were cultured in vitro and the morphology of those cells was observed with inverse microscope and transmission electron microscope. MTT assay was performed to measure the cell proliferation and inhibition rate. DNA content was assayed by flow cytometry. According to protocols of transplant tumor research, mice were transplanted with tumor cells L1210, P388, Heps, and S180. The survival rate and weight of tumor were observed after the treatment of test drugs. RESULTS: The antitumor effects of L-asparaginase were observed in vitro with tumor cells K562, L1210, and P815 ( $P < 0.01$ ). In vivo experiments showed that ip administration of L-asparaginase significantly increased the survival rate and life span of mice with P388 or L1210 tumor cells ( $P < 0.01$ ). Tumor growth induced with Heps was also significantly suppressed. Furthermore, significant suppression of tumor growth was observed in mice induced with Heps and S180 by iv administration of L-asparaginase. CONCLUSION: Recombinant L-asparaginase markedly inhibited tumors tested in this study and the results strongly suggest that recombinant L-asparaginase has great potential for clinical treatment of these tumors.

Answer 6:

### Bibliographic Information

**In vitro and in vivo anti-leukemic efficacy of cyclic AMP modulating agents against human leukemic B-cell precursors.** Myers D E; Chandan-Langlie M; Chelstrom L M; Uckun F M University of Minnesota Biotherapy Program, Roseville 55113, USA Leukemia & lymphoma (1996), 22(3-4), 259-64. Journal code: 9007422. ISSN:1042-8194. 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 8819074 AN 96416168 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

### Abstract

We show that the adenylate cyclase activating diterpine, forskolin, the phosphodiesterase inhibitor, aminophylline, and the permeant cAMP analog dibutyryl cAMP inhibit the in vitro clonogenic growth of leukemic B-cell precursors. We also used a SCID mouse xenograft model of refractory human B-cell precursor leukemia to evaluate the anti-leukemic effect of aminophylline in vivo. Treatment with aminophylline (6 mg/kg bolus followed by 0.1-0.5 mg/kg/hour x 7 days) significantly prolonged the event-free survival of SCID mice (median survival of control mice, 39 days, N = 79; median survival of aminophylline-treated mice, 60 days, N = 10;  $P < 0.0001$  by log-rank test) and it was more effective than treatment with vincristine (median survival = 51 days, N = 5) or L asparaginase (median survival = 44 days, N = 5). However, aminophylline was not as effective as methylprednisolone (median survival: 103 days, N = 5). These results indicate that cAMP modulating agents may be useful in treatment of refractory human B-cell precursor leukemia.