ANTI-CANCER EFFECTS OF ARTEMISININ- ABSTRACTS


Willmar Schwabe Award 2006: antiplasmodial and antitumor activity of artemisinin--from bench to bedside.

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Secondary metabolites from plants serve as defense against herbivores, microbes, viruses, or competing plants. Many medicinal plants have pharmacological activities and may, thus, be a source for novel treatment strategies. During the past 10 years, we have systematically analyzed medicinal plants used in traditional Chinese medicine and focused our interest on Artemisia annua L. (qinhao, sweet wormwood). We found that the active principle of Artemisia annua L., artemisinin, exerts not only antimalarial activity but also profound cytotoxicity against tumor cells. The inhibitory activity of artemisinin and its derivatives towards cancer cells is in the nano- to micromolar range. Candidate genes that may contribute to the sensitivity and resistance of tumor cells to artemisinins were identified by pharmacogenomic and molecular pharmacological approaches. Target validation was performed using cell lines transfected with candidate genes or corresponding knockout cells. The identified genes are from classes with diverse biological functions; for example, regulation of proliferation (BUB3, cyclins, CDC25A), angiogenesis (vascular endothelial growth factor and its receptor, matrix metalloproteinase-9, angiostatin, thrombospondin-1) or apoptosis (BCL-2, BAX, NF-kappaB). Artesunate triggers apoptosis both by p53-dependent and -independent pathways. Antioxidant stress genes (thioredoxin, catalase, gamma-glutamylcysteine synthetase, glutathione S-transferases) as well as the epidermal growth factor receptor confer resistance to artesunate. Cell lines overexpressing genes that confer resistance to established antitumor drugs (MDR1, MRP1, BCRP, dihydrofolate reductase, ribonucleotide reductase) were not cross-resistant to artesunate, indicating that artesunate is not involved in multidrug resistance. The anticancer activity of artesunate has also been shown in human xenograft tumors in mice. First encouraging experience in the clinical treatment of patients suffering from uveal melanoma calls for comprehensive clinical trials with artesunate for cancer treatment in the near future.

PMID: 17354163 [PubMed - indexed for MEDLINE]


Inhibition of glutathione S-transferases by antimalarial drugs possible implications for circumventing anticancer drug resistance.
A strategy to overcome multidrug resistance in cancer cells involves treatment with a combination of the antineoplastic agent and a chemomodulator that inhibits the activity of the resistance-causing protein. The aim of our study was to investigate the effects of antimalarial drugs on human recombinant glutathione S-transferase (GSTs) activity in the context of searching for effective and clinically acceptable inhibitors of these enzymes. Human recombinant GSTs heterologously expressed in Escherichia coli were used for inhibition studies. GST A1-1 activity was inhibited by artemisinin with an IC(50) of 6 microM, whilst GST M1-1 was inhibited by quinidine and its diastereoisomer quinine with IC(50)s of 12 microM and 17 microM, respectively. GST M3-3 was inhibited by tetracycline only with an IC(50) of 47 microM. GST P1-1 was the most susceptible enzyme to inhibition by antimalarials with IC(50) values of 1, 2, 1, 4, and 13 microM for pyrimethamine, artemisinin, quinine, quinidine, and tetracycline, respectively. The IC(50) values obtained for artemisinin, quinine, quinidine, and tetracycline are below peak plasma concentrations obtained during therapy of malaria with these drugs. It seems likely, therefore, that GSTs may be inhibited in vivo at doses normally used in clinical practice. Using the substrate ethacrynic acid, a diuretic drug also used as a modulator to overcome drug resistance in tumour cells, GST P1-1 activity was inhibited by tetracycline, quinine, pyrimethamine and quinidine with IC(50) values of 18, 27, 45 and 70 microM, respectively. The ubiquitous expression of GSTs in different malignancies suggests that the addition of nontoxic reversing agents such as antimalarials could enhance the efficacy of a variety of alkylating agents. Copyright 2001 Wiley-Liss, Inc.


**Effects of artemisinin and its derivatives on growth inhibition and apoptosis of oral cancer cells.**

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BACKGROUND: Artemisinin is of special biological interest because of its outstanding antimalarial activity. Recently, it was reported that artemisinin has antitumor activity. Its derivatives, artesunate, arteether, and artemeter, also have antitumor activity against melanoma, breast, ovarian, prostate, CNS, and renal cancer cell lines. Recently, monomer, dimer, and trimer derivatives were synthesized from deoxoartemisinin, and the dimers and the trimers were found to have much more potent antitumor activity than the monomers. METHODS: We evaluated the antitumor activity of artemisinin and its various derivatives (dihydroartemisinin, dihydroartemisinin 12-benzoate, 12-(2'-hydroxyethyl) deoxoartemisinin, 12-(2'-ethylthio) deoxoartemisinin dimer, deoxoartemisinin trimer) in comparison with paclitaxel (Taxol), 5-fluorouracil (5-FU), cisplatin in vitro. RESULTS: In this study, the deoxoartemisinin trimer had the most potent antitumor effect (IC(50) = 6.0 microM), even better than paclitaxel (IC(50) =
13.1 microM), on oral cancer cell line (YD-10B). In addition, it induced apoptosis through a caspase-3-dependent mechanism. CONCLUSION: The deoxoartemisinin trimer was found to have greater antitumor effect on tumor cells than other commonly used chemotherapeutic drugs, such as 5-FU, cisplatin, and paclitaxel. Furthermore, the ability of artemisinin and its derivatives to induce apoptosis highlights their potential as chemotherapeutic agents, for many anticancer drugs achieve their antitumor effects by inducing apoptosis in tumor cells. (c) 2006 Wiley Periodicals, Inc.

PMID: 17163469 [PubMed - indexed for MEDLINE]


**Microarray expression profiles of angiogenesis-related genes predict tumor cell response to artemisinins.**

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Artemisinin (ARS) and its derivatives are used for the second-line therapy of malaria infections with Plasmodium falciparum and P. vivax. ARSs also reveal profound antitumor activity in vitro and in vivo. In the present investigation, we correlated the mRNA expression data of 89 angiogenesis-related genes obtained by microarray hybridization from the database of the US National Cancer Institute with the 50% growth inhibition concentration values for eight ARSs (ARS, arteether (ARE), artesunate (ART), artemisetene, arteanuine B, dihydroartemisinylester stereoisomers 1 and 2). The constitutive expression of 30 genes correlated significantly with the cellular response to ARSs. By means of hierarchical cluster analysis and cluster image mapping expression, profiles were identified that determined significantly the cellular response to ART, ARE, artemether and dihydroartemisinylester stereoisomer 1. We have exemplarily validated the microarray data of six out of these 30 genes by real-time RT-PCR in seven cell lines. The fact that sensitivity and resistance of tumor cells could be predicted by the mRNA expression of angiogenesis-related genes indicate that ARSs reveal their antitumor effects at least in part by inhibition of tumor angiogenesis. As many chemopreventive drugs exert antiangiogenic features, ARSs might also be chemopreventive in addition to their cytotoxic effects.

PMID: 16432535 [PubMed - indexed for MEDLINE]


**Oral artemisinin prevents and delays the development of 7,12-dimethylbenz[a]anthracene (DMBA)-induced breast cancer in the rat.**

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Artemisinin, a compound isolated from the sweet wormwood Artemisia annua L., has previously been shown to have selective toxicity towards cancer cells in vitro. In the present experiment, we studied the potential of artemisinin to prevent breast cancer development in rats treated with a single oral dose (50mg/kg) of 7,12-dimethylbenz[a]anthracene (DMBA), known to induce multiple breast tumors. Starting from the day immediately after DMBA treatment, one group of rats was provided with a powdered rat-chow containing 0.02% artemisinin, whereas a control group was provided with plain powdered food. For 40 weeks, both groups of rats were monitored for breast tumors. Oral artemisinin significantly delayed (P<.002) and in some animals prevented (57% of artemisinin-fed versus 96% of the controls developed tumors, P<.01) breast cancer development in the monitoring period. In addition, breast tumors in artemisinin-fed rats were significantly fewer (P<.002) and smaller in size (P<.05) when compared with controls. Since artemisinin is a relatively safe compound that causes no known side effects even at high oral doses, the present data indicate that artemisinin may be a potent cancer-chemoprevention agent.

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Synergistic cytotoxicity of artemisinin and sodium butyrate on human cancer cells.

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BACKGROUND: Butyric acid is a short chain fatty acid produced by large bowel bacterial flora. It serves as an antiinflammatory agent and nutrient for normal colon cells. Butyric acid has also been shown to induce apoptosis in colon and many other cancer cells. Artemisinin is a compound extracted from the wormwood Artemisia annua L. It has been shown to selectively kill cancer cells in vitro and to be effective in treating animal and human cancer. We and others have found that the artemisinin analog, dihydroartemisinin (DHA), kills cancer cells by apoptosis. In the present study, the efficacy of a combined treatment of DHA and butyric acid at low doses in killing cancer cells was investigated. MATERIALS AND METHODS: Molt-4 cells (a human lymphoblastoid leukemia cell line) and freshly isolated human lymphocytes, cultured in complete RPMI-1640 medium, were first incubated with 12 microM of human holotransferrin at 37 degrees C in a humid atmosphere of 5% CO2 for one hour to enhance the iron concentration in the cells. Cells from each cell type were then divided into 20 flasks. These flasks were grouped into four sets of five cultures each. Zero, 5, 10 or 20 microM of DHA was added, respectively, to these sets and the cells were incubated at 37 degrees C for one hour. Zero, 1, 5, 10, or 20 mM of sodium butyrate was then added to the five cultures of each set, respectively. Thus, the treatments involved a combination of 4 doses of DHA and 5 doses of sodium butyrate. The cells were counted immediately before the addition of DHA, and at 24 and 48 hours after the addition of sodium butyrate. RESULTS: DHA alone at the 24-hour time-point and 20 microM concentration significantly reduced the number of Molt-4 cells in the culture by approximately 40% (p < 0.001, compared to non-treated control), whereas it did not significantly
affect the number of normal human lymphocytes. Similarly, 1 mM sodium butyrate alone at 24 hours reduced the number of Molt-4 cells by approximately 32% (p < 0.001, compared to non-treated control), without significantly affecting normal human lymphocytes. The combination of 20 microM DHA and 1 mM sodium butyrate killed all Molt-4 cells at the 24-hour time-point and did not significantly affect lymphocytes. CONCLUSION: DHA in combination with butyric acid acts synergistically at low doses. The combination may provide a less toxic, inexpensive and effective cancer chemotherapy. PMID 16309236.


Enhancement of cytotoxicity of artemisinins toward cancer cells by ferrous iron.


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Iron(II) heme-mediated activation of the peroxide bond of artemisinins is thought to generate the radical oxygen species responsible for their antimalarial activity. We analyzed the role of ferrous iron in the cytotoxicity of artemisinins toward tumor cells. Iron(II)-glycine sulfate (Ferrosanol) and transferrin increased the cytotoxicity of free artesunate, artesunate microencapsulated in maltosyl-beta-cyclodextrin, and artemisinin toward CCRF-CEM leukemia and U373 astrocytoma cells 1.5- to 10.3-fold compared with that of artemisinins applied without iron. Growth inhibition by artesunate and ferrous iron correlated with induction of apoptosis. Cell cycle perturbations by artesunate and ferrous iron were not observed. Treatment of p53 wild-type TK6 and p53 mutated WTK1 lymphoblastic cells showed that mutational status of the tumor suppressor p53 did not influence sensitivity to artesunate. The effect of ferrous iron and transferrin was reversed by monoclonal antibody RVS10 against the transferrin receptor (TfR), which competes with transferrin for binding to TfR. CCRF-CEM and U373 cells expressed TfR in 95 and 48% of the cell population, respectively, whereas TfR expression in peripheral mononuclear blood cells of four healthy donors was confined to 0.4-1.3%. This indicates that artemisinins plus ferrous iron may affect tumor cells more than normal cells. The IC(50) values for a series of eight different artemisinin derivatives in 60 cell lines of the U.S. National Cancer Institute were correlated with the microarray mRNA expression of 12 genes involved in iron uptake and metabolism by Kendall's tau test to identify iron-responsive cellular factors enhancing the activity of artemisinins. This pointed to mitochondrial aconitase and ceruloplasmin (ferroxidase).

PMID: 15336316 [PubMed - indexed for MEDLINE]


Artemisinin induces apoptosis in human cancer cells.
BACKGROUND: Artemisinin is a chemical compound extracted from the wormwood plant, Artemisia annua L. It has been shown to selectively kill cancer cells in vitro and retard the growth of implanted fibrosarcoma tumors in rats. In the present research, we investigated its mechanism of cytotoxicity to cancer cells. MATERIALS AND METHODS: Molt-4 cells, in complete RPMI-1640 medium, were first incubated with 12 microM of human holotransferrin at 37 degrees C in a humid atmosphere of 5% CO2 for one hour. This enhanced the iron supply to the cells. The cells were then pelleted and transferred to a complete RPMI-1640 containing 200 microM of an analog dihydroartemisinin (DHA) and incubation was started (0 h). In addition, some culture samples were treated with holotransferrin alone and some (controls) were assayed without neither holotransferrin nor DHA treatment. Cells were counted and DNA diffusion assay was used to evaluate apoptosis and necrosis in each sample at 0 h and at 1, 2, 4 and 8 h of incubation. RESULTS: DHA treatment significantly decreased cell counts and increased the proportion of apoptosis in cancer cells compared to controls (chi2 = 4.5, df=1, p<0.035). Addition of holotransferrin significantly further decreased cell counts (chi2 = 4.5, df=1, p<0.035) and increased apoptosis (chi2 = 4.5, df=1, p<0.035). No necrotic cells were observed. CONCLUSION: This rapid induction of apoptosis in cancer cells after treatment with DHA indicates that artemisinin and its analogs may be inexpensive and effective cancer agents.

PMID: 15330172 [PubMed - indexed for MEDLINE]


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In this tutorial review, an effort towards presentation of a comprehensive account of the recent developments on various kinds of artemisinin derivatives including artemisinin dimers, trimers and tetramers has been made and their efficacy towards malaria parasites and different cancer cells lines was compared with that of artemisinins, and various other anti-malarial and anti-cancer drugs. It is expected that this review will provide first-hand information on artemisinin chemistry to organic/medicinal chemists, and pharmacologists working on anticancer and anti-malarial drug development.

PMID: 20111769 [PubMed - in process]

Artemisinin blocks prostate cancer growth and cell cycle progression by disrupting Sp1 interactions with the cyclin-dependent kinase-4 (CDK4) promoter and inhibiting CDK4 gene expression. FREE FULL TEXT

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Artemisinin, a naturally occurring component of Artemisia annua, or sweet wormwood, is a potent anti-malaria compound that has recently been shown to have anti-proliferative effects on a number of human cancer cell types, although little is known about the molecular mechanisms of this response. We have observed that artemisinin treatment triggers a stringent G1 cell cycle arrest of LNCaP (lymph node carcinoma of the prostate) human prostate cancer cells that is accompanied by a rapid down-regulation of CDK2 and CDK4 protein and transcript levels. Transient transfection with promoter-linked luciferase reporter plasmids revealed that artemisinin strongly inhibits CDK2 and CDK4 promoter activity. Deletion analysis of the CDK4 promoter revealed a 231-bp artemisinin-responsive region between -1737 and -1506. Site-specific mutations revealed that the Sp1 site at -1531 was necessary for artemisinin responsiveness in the context of the CDK4 promoter. DNA binding assays as well as chromatin immunoprecipitation assays demonstrated that this Sp1-binding site in the CDK4 promoter forms a specific artemisinin-responsive DNA-protein complex that contains the Sp1 transcription factor. Artemisinin reduced phosphorylation of Sp1, and when dephosphorylation of Sp1 was inhibited by treatment of cells with the phosphatase inhibitor okadaic acid, the ability of artemisinin to down-regulate Sp1 interactions with the CDK4 promoter was ablated, rendering the CDK4 promoter unresponsive to artemisinin. Finally, overexpression of Sp1 mostly reversed the artemisinin down-regulation of CDK4 promoter activity and partially reversed the cell cycle arrest. Taken together, our results demonstrate that a key event in the artemisinin anti-proliferative effects in prostate cancer cells is the transcriptional down-regulation of CDK4 expression by disruption of Sp1 interactions with the CDK4 promoter.

PMID: 19017637 [PubMed - indexed for MEDLINE]


Artemisinin reduces human melanoma cell migration by down-regulating alpha V beta 3 integrin and reducing metalloproteinase 2 production.


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Artemisinin and its derivatives are well known antimalarial drugs, particularly useful after resistance to traditional antimalarial pharmaceuticals has started to occur in Plasmodium
falciparum. In recent years, anticancer activity of artemisinin has been reported both in vitro and in vivo. Artemisinin has inhibitory effects on cancer cell growth and anti-angiogenetic activity. In the present investigation, we analyzed the inhibitory effects of artemisinin on migratory ability of melanoma cell lines (A375P and A375M, low and medium metastatic properties, respectively). We demonstrate that artemisinin induces cell growth arrest in A375M, and affects A375P cells viability with cytotoxic and growth inhibitory effects, while it was not effective in contrasting proliferation of other tumor cell lines (MCF7 and MKN). In addition, artemisinin affected the migratory ability of A375M cells by reducing metalloproteinase 2 (MMP-2) production and down-regulating alpha v beta 3 integrin expression. These findings introduce a potential of artemisinin as a chemotherapeutic agent in melanoma treatment.

PMID: 18956140 [PubMed - indexed for MEDLINE]


Artemisinin selectively decreases functional levels of estrogen receptor-alpha and ablates estrogen-induced proliferation in human breast cancer cells. FREE FULL TEXT.

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MCF7 cells are an estrogen-responsive human breast cancer cell line that expresses both estrogen receptor (ER) alpha and ERbeta. Treatment of MCF7 cells with artemisinin, an antimalarial phytochemical from the sweet wormwood plant, effectively blocked estrogen-stimulated cell cycle progression induced by either 17beta-estradiol (E(2)), an agonist for both ERs, or by propyl pyrazole triol (PPT), a selective ERalpha agonist. Artemisinin strongly downregulated ERalpha protein and transcripts without altering expression or activity of ERbeta. Transfection of MCF7 cells with ERalpha promoter-linked luciferase reporter plasmids revealed that the artemisinin downregulation of ERalpha promoter activity accounted for the loss of ERalpha expression. Artemisinin treatment ablated the estrogenic induction of endogenous progesterone receptor (PR) transcripts by either E(2) or PPT and inhibited the estrogenic stimulation of a luciferase reporter plasmid driven by consensus estrogen response elements (EREs). Chromatin immunoprecipitation assays revealed that artemisinin significantly downregulated the level of endogeneous ERalpha bound to the PR promoter, whereas the level of bound endogeneous ERbeta was not altered. Treatment of MCF7 cells with artemisinin and the pure antiestrogen fulvestrant resulted in a cooperative reduction of ERalpha protein levels and enhanced G(1) cell cycle arrest compared with the effects of either compound alone. Our results show that artemisinin switches proliferative human breast cancer cells from expressing a high ERalpha:ERbeta ratio to a condition in which ERbeta predominates, which parallels the physiological state linked to antiproliferative events in normal mammary epithelium.

PMID: 18784357 [PubMed - indexed for MEDLINE]

The antiviral activities of artemisinin and artesunate.

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Traditional Chinese medicine commands a unique position among all traditional medicines because of its 5000 years of history. Our own interest in natural products from traditional Chinese medicine was triggered in the 1990s, by artemisinin-type sesquiterpene lactones from Artemisia annua L. As demonstrated in recent years, this class of compounds has activity against malaria, cancer cells, and schistosomiasis. Interestingly, the bioactivity of artemisinin and its semisynthetic derivative artesunate is even broader and includes the inhibition of certain viruses, such as human cytomegalovirus and other members of the Herpesviridae family (e.g., herpes simplex virus type 1 and Epstein-Barr virus), hepatitis B virus, hepatitis C virus, and bovine viral diarrhea virus. Analysis of the complete profile of the pharmacological activities and molecular modes of action of artemisinin and artesunate and their performance in clinical trials will further elucidate the full antimicrobial potential of these versatile pharmacological tools from nature.

PMID: 18699744 [PubMed - indexed for MEDLINE]


Experimental therapy of hepatoma with artemisinin and its derivatives: in vitro and in vivo activity, chemosensitization, and mechanisms of action.

FREE FULL TEXT


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PURPOSE: ART and its derivatives, clinically used antimalarial agents, have recently shown antitumor activities. However, the mechanisms underlying these activities remain unclear. This study was designed to determine their antitumor efficacy and underlying mechanisms of action in human hepatoma cells. EXPERIMENTAL DESIGN: The in vitro cytotoxicities of ART, DHA, artemether, and artesunate were compared in human hepatoma cells, HepG2 (p53 wild-type), Huh-7 and BEL-7404 (p53 mutant), and Hep3B (p53 null), and a normal human liver cell line, 7702. Based on their activity and specificity, ART and DHA were further investigated for their in vitro and in vivo antitumor effects and their effects on the protein expression of genes associated with cell proliferation and apoptosis. RESULTS: ART and DHA exerted the greatest cytotoxicity to hepatoma cells but significantly lower cytotoxicity to normal liver cells. The compounds inhibited cell proliferation, induced G(1)-phase arrest, decreased the levels of cyclin D1, cyclin E, cyclin-dependent kinase 2, cyclin-dependent kinase 4, and E2F1, and increased the levels of Cip1/p21 and Kip1/p27. They induced apoptosis, activated caspase-3, increased the
Bax/Bcl-2 ratio and poly(ADP-ribose) polymerase, and down-regulated MDM2. In mice bearing HepG2 and Hep3B xenograft tumors, ART and DHA inhibited tumor growth and modulated tumor gene expression consistent with in vitro observations. DHA increased the efficacy of the chemotherapeutic agent gemcitabine. CONCLUSIONS: ART and DHA have significant anticancer effects against human hepatoma cells, regardless of p53 status, with minimal effects on normal cells, indicating that they are promising therapeutics for human hepatoma used alone or in combination with other therapies.

PMID: 18765544 [PubMed - indexed for MEDLINE]

**ANTI-CANCER EFFECTS OF ARTESUNATE ABSTRACTS**


Artesunate inhibits angiogenesis and downregulates vascular endothelial growth factor expression in chronic myeloid leukemia K562 cells.

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Artesunate (ART), a semi-synthetic derivative of artemisinin extracted from the Chinese herb Artemisia annua, is a safe and effective antimalarial drug. In the present investigation, we analyzed the inhibitory effects of ART on angiogenesis and on VEGF production in chronic myeloid leukemia (CML) K562 cells in vitro and in vivo. In order to analyze the effect of ART on VEGF secretion in K562 cells, we examined the level of VEGF secreted in conditioned media (CM) by ELISA assay. The result showed that ART could decrease the VEGF level in CM of K562 cells, even at a lower concentration (2 micromol/l, P<0.01). The inhibitory effect of in vitro angiogenesis was tested on aortic sprouting in fibrin gel. ART could effectively suppress the stimulating angiogenic ability of CM by pretreated with K562 cells for 48 h in a time-dependent manner (days 3-14). The antiangiogenic effect of ART was further evaluated in vivo in chicken chorioallantoic membrane (CAM) neovascularization model. The result indicated that the stimulating angiogenic activity was decreased in response to the K562 cells treated with ART or the CM from K562 cells pretreated with ART in a dose-dependent manner (3-12 micromol/l). Furthermore, we analyzed the level of VEGF expression by western blot and detected the form of VEGF mRNA by RT-PCR in K562 cells. The experiments showed that ART could inhibit the VEGF expression, correlated well with the level of VEGF secreted in CM. These findings suggest that ART might present potential antileukemia effect as a treatment for CML therapy, or as an adjunct to standard chemotherapeutic regimens.

PMID: 17581794 [PubMed - indexed for MEDLINE]
Artesunate in the treatment of metastatic uveal melanoma--first experiences.

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Artesunate (ART) is a derivative of artemisinin, the active principle of the Chinese herb Artemisia annua L. Artesunate is approved for the treatment of multidrug-resistant malaria and has an excellent safety profile. It has been shown that Artesunate, apart from its anti-malarial activity, has cytotoxic effects on a number of human cancer cell lines, including leukemia, colon cancer and melanoma. We report on the first long-term treatment of two cancer patients with ART in combination with standard chemotherapy. These patients with metastatic uveal melanoma were treated on a compassionate-use basis, after standard chemotherapy alone was ineffective in stopping tumor growth. The therapy-regimen was well tolerated with no additional side effects other than those caused by standard chemotherapy alone. One patient experienced a temporary response after the addition of ART to Fotemustine while the disease was progressing under therapy with Fotemustine alone. The second patient first experienced a stabilization of the disease after the addition of ART to Dacarbazine, followed by objective regressions of splenic and lung metastases. This patient is still alive 47 months after first diagnosis of stage IV uveal melanoma, a situation with a median survival of 2-5 months. Despite the small number of treated patients, ART might be a promising adjuvant drug for the treatment of melanoma and possibly other tumors in combination with standard chemotherapy. Its good tolerability and lack of serious side effects will facilitate prospective randomized trials in the near future.

PMID: 16273263 [PubMed - indexed for MEDLINE]

Inhibition of angiogenesis in vivo and growth of Kaposi's sarcoma xenograft tumors by the anti-malarial artemesunate.


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Artesunate (ART) is a semi-synthetic derivative of the sesquiterpene artemisinin used for the second line therapy of malaria infections with Plasmodium falciparum. ART also inhibits growth of many transformed cell lines. In the present investigation, we show that ART inhibited the growth of normal human umbilical endothelial cells and of KS-IMM cells that we have established from a Kaposi's sarcoma lesion obtained from a renal transplant patient. The growth...
inhibitory activity correlated with the induction of apoptosis in KS-IMM cells. Apoptosis was not observed in normal endothelial cells, which, however, showed drastically increased cell doubling times upon ART treatment. ART strongly reduced angiogenesis in vivo in terms of vascularization of Matrigel plugs injected subcutaneously into syngenic mice. We conclude that ART represents a promising candidate drug for the treatment of the highly angiogenic Kaposi's sarcoma. As a low-cost drug, it might be of particular interest for areas of Kaposi's sarcoma endemics. ART could be useful for the prevention of tumor angiogenesis.

PMID: 15548382 [PubMed - indexed for MEDLINE]


The anti-malarial artesunate is also active against cancer.

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Artesunate (ART) is a semi-synthetic derivative of artemisinin, the active principle of the Chinese herb Artemisia annua. ART reveals remarkable activity against otherwise multidrug-resistant Plasmodium falciparum and P. vivax malaria. ART has now been analyzed for its anti-cancer activity against 55 cell lines of the Developmental Therapeutics Program of the National Cancer Institute, USA. ART was most active against leukemia and colon cancer cell lines (mean GI50 values: 1.11+/-0.56 microM and 2.13+/-0.74 microM , respectively). Non-small cell lung cancer cell lines showed the highest mean GI50 value (25.62+/-14.95 microM) indicating the lowest sensitivity towards ART in this test panel. Intermediate GI50 values were obtained for melanomas, breast, ovarian, prostate, CNS, and renal cancer cell lines. Importantly, a comparison of ART's cytotoxicity with those of other standard cytostatic drugs showed that ART was active in molar ranges comparable to those of established anti-tumor drugs. Furthermore, we tested CEM leukemia sub-lines resistant to either doxorubicin, vincristine, methotrexate, or hydroxyurea which do not belong to the N.C.I. screening panel. None of these drug-resistant cell lines showed cross resistance to ART. To gain insight into the molecular mechanisms of ART's cytotoxicity, we used a panel of isogenic Saccaromyces cerevisiae strains with defined genetic mutations in DNA repair, DNA checkpoint and cell proliferation genes. A yeast strain with a defective mitosis regulating BUB3 gene showed increased ART sensitivity and another strain with a defective proliferation-regulating CLN2 gene showed increased ART resistance over the wild-type strain, wt644. None of the other DNA repair or DNA check-point deficient isogenic strains were different from the wild-type. These results and the known low toxicity of ART are clues that ART may be a promising novel candidate for cancer chemotherapy.

PMID: 11251172 [PubMed - indexed for MEDLINE]

Anti-cancer effects of artesunate in a panel of chemoresistant neuroblastoma cell lines.


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Artemisinin derivatives are well-tolerated anti-malaria drugs that also exert anti-cancer activity. Here, we investigated artemisinin and its derivatives dihydroartemisinin and artesunate in a panel of chemosensitive and chemoresistant human neuroblastoma cells as well as in primary neuroblastoma cultures. Only dihydroartemisinin and artesunate affected neuroblastoma cell viability with artesunate being more active. Artesunate-induced apoptosis and reactive oxygen species in neuroblastoma cells. Of 16 cell lines and two primary cultures, only UKF-NB-3(r)CDDP(1000) showed low sensitivity to artesunate. Characteristic gene expression signatures based on a previous analysis of artesunate resistance in the NCI60 cell line panel clearly separated UKF-NB-3(r)CDDP(1000) from the other cell lines. l-Buthionine-S,R-sulfoximine, an inhibitor of GCL (glutamate-cysteine ligase), resensitised in part UKF-NB-3(r)CDDP(1000) cells to artesunate. This finding together with bioinformatic analysis of expression of genes involved in glutathione metabolism showed that this pathway is involved in artesunate resistance. These data indicate that neuroblastoma represents an artesunate-sensitive cancer entity and that artesunate is also effective in chemoresistant neuroblastoma cells.

PMID: 19698702 [PubMed - indexed for MEDLINE]