Intravenous Artesunate

Integrative Oncology and survival Chronic Infections

Brenden Cochran ND, Virginia Osborne ND,
Paul Anderson ND

Artesunate

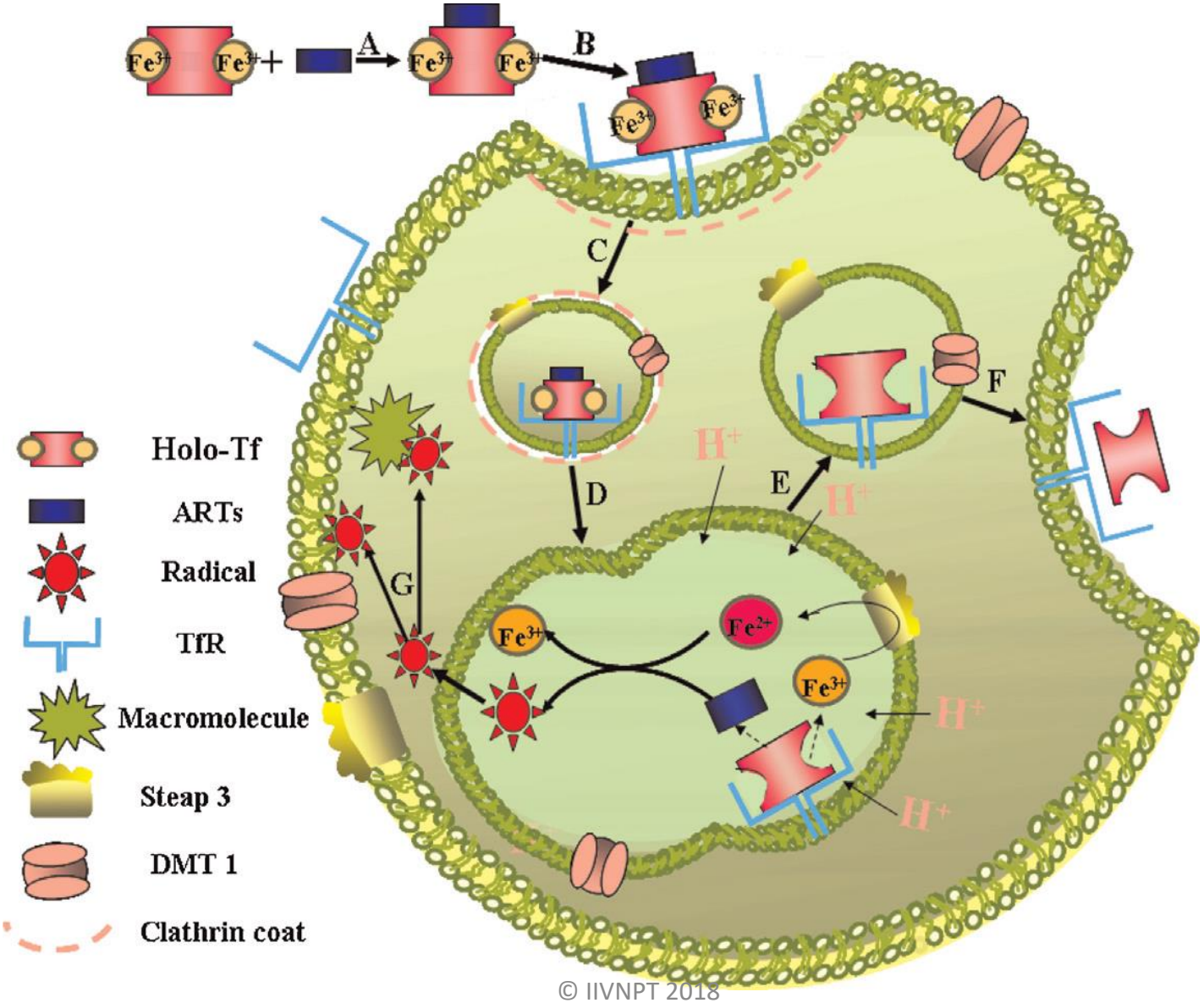
- Artesunate (ART), a derivative of artemisinin, can be a potent and selective antitumor agent as well as antimicrobial agent.
- Importantly, ART has produced a dose-dependent tumor regression in an in vivo pancreatic cancer xenografts model.
- **The in vivo antitumor activity of ART was similar to that of gemcitabine.**
- ART is considered to produce a ROS burst which may alter cancer cell activity.
- Additionally ART appears to be a synergist with oxidative therapies such as high dose ascorbic acid.
- Potential COX-2 inhibitor
  - **Artesunate inhibits the growth and induces apoptosis of human gastric cancer cells by downregulating COX-2. (Onco Targets Ther 2015 Apr 16;8:845-54)**

ART Pharmacokinetics

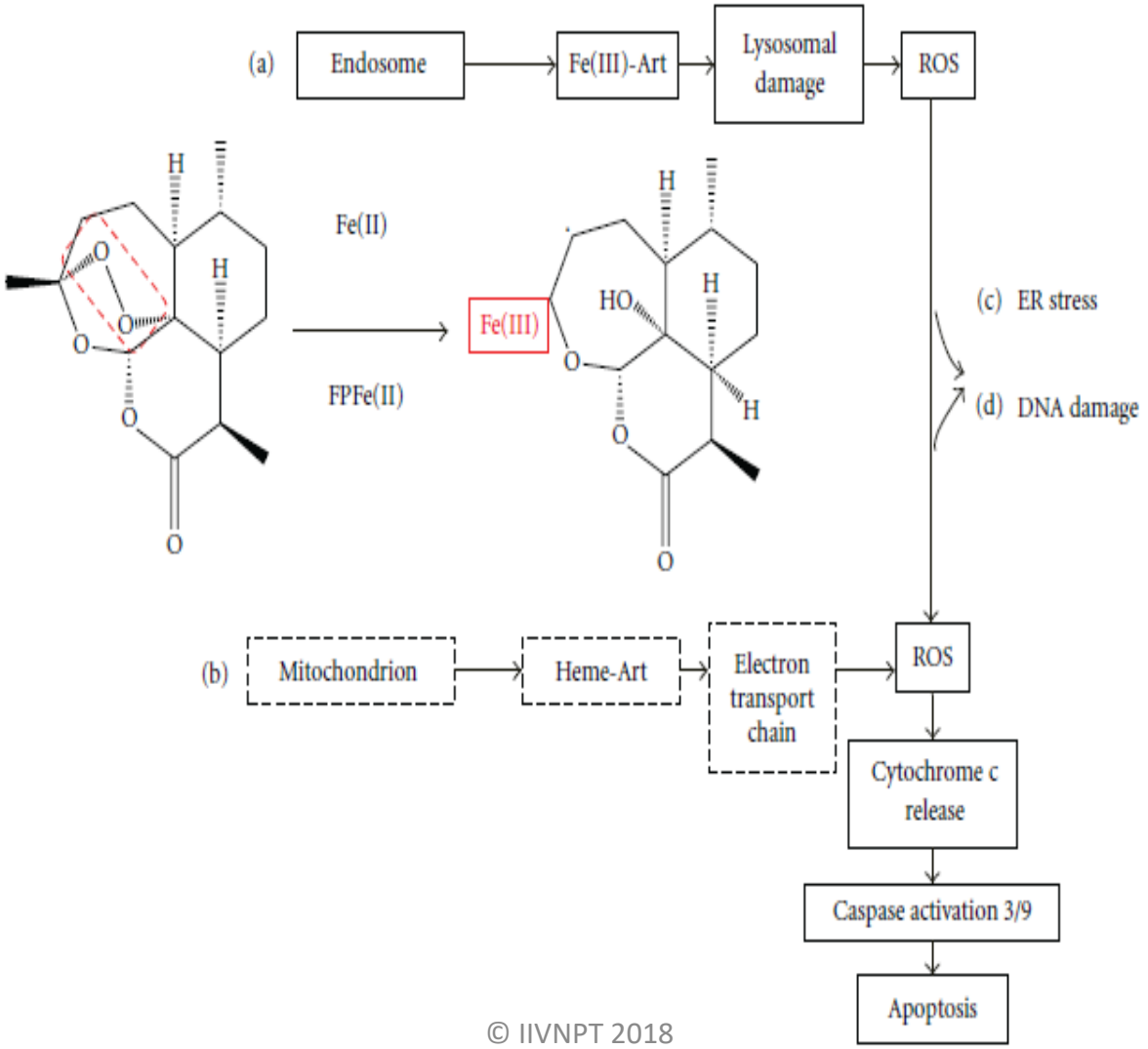
Abstract

- The pharmacokinetics of good manufacturing process injection of artesunate (AS) were evaluated after single doses at 0.5, 1, 2, 4, and 8 mg/kg with a 2-minute infusion in 40 healthy subjects. Drug concentrations were analyzed by validated liquid chromatography and mass spectrometry system (LC-MS/MS) procedures. The drug was immediately converted to dihydroartemisinin (DHA), with elimination half-lives ranging 0.12-0.24 and 1.15-2.37 hours for AS and DHA, respectively. Pharmacokinetic model-dependent analysis is suitable for AS, whereas DHA fits both model-dependent and -independent methods. Although DHA concentration was superior to that of AS with a 1.12-1.87 ratio of area under the curve (AUC)(DHA/AS), peak concentration of AS was much higher than that of DHA, with a 2.80- to 4.51-fold ratio of peak concentration (C(max AS/DHA)). Therefore, AS effectiveness has been attributed not only to its rapid hydrolysis to DHA, but also to itself high initial C(max).
- Li Q, Cantilena LR, Leary KJ, Saviolakis GA, Miller RS, Melendez V, Weina PJ. Pharmacokinetic profiles of artesunate after single intravenous doses at 0.5, 1, 2, 4, and 8 mg/kg in healthy volunteers: a phase I study.Am J Trop Med Hyg. 2009 Oct;81(4):615-21. PMID: 19815876

Yan Yang, Xiaomin Zhang, Xiofen Wang, et. Enhanced delivery of artemisinin and its analogues to cancer cells by their adducts with human serum transferrin. International Journal of Pharmaceutics. 2014, March 2014, 467 (1-2):113-122 doi:10.1016/j.ijpharm.2014.03.044



Maria P. Crespo-Ortiz and Ming Q.Wei. Antitumor Activity of Artemisinin and Its Derivatives: From aWell-Known Antimalarial Agent to a Potential Anticancer Drug .Journal of Biomedicine and Biotechnology. Volume 2012, Article ID 247597, 18 pages. doi:10.1155/2012/247597



J. Biol Chem. Artesunate induces cell death in human cancer in human cancer cells via enhancing lysosomal function and lysosomal degradation of ferritin. 2014 Nov. 28;289(48):33425-41. doi: 10.1074/jbc.M114.564567. Epub 2014 Oct 10
Yang ND, Tan SH, Shi Y, et al

In summary, our study demonstrates that ART treatment activates lysosomal function and **then promotes ferritin degradation, subsequently leading to the increase of lysosomal iron that is utilized by ART for its cytotoxic effect on cancer cells.**

ART and CMV Virus

From the Abstract:

"This is the first report of treatment of cytomegalovirus infection with artesunate, for a stem cell transplant recipient with a newly identifie foscarnet-resistant and ganciclovirresistant DNA polymerase L776M mutation. Artesunate treatment resulted in a 1.7–2.1-log reduction in viral load by treatment day 7, with a viral half-life of 0.9–1.9 days, indicating a highly effective block in viral replication."

Shapira MY, et. Al. Artesunate as a Potent Antiviral Agent in a Patient with Late Drug-Resistant Cytomegalovirus Infection after Hematopoietic Stem Cell Transplantation. Clinical Infectious Diseases 2008; 46:1455–7

ART and CMV Virus

And a cell line study bore out the superiority of Artesunate over other Artemesia compounds in CMV:

Flobinus A. Stability and antiviral activity against human cytomegalovirus of artemisinin derivatives. J. Antimicrob. Chemother. (2014) 69 (1): 34-40. doi: 10.1093/jac/dkt346

ART and Bacteria

"Artemisinin and nine of its semisynthetic derivatives were tested for antibacterial activity against anaerobic, facultative anaerobic, microaerophilic and aerobic bacteria. Only anaerobic bacteria and gonococci showed sensitivity to artemisinin derivatives."

Shoeb HA, Tawfik AF, Shibl AM, el-Feraly FS. Antimicrobial activity of artemisinin and its derivatives against anaerobic bacteria. Journal of Chemotherapy (Florence, Italy) [1990, 2(6):362-367] (PMID:2128751)

Improving quality of life oncology?

Maria P. Crespo-Ortiz and Ming Q.Wei. Antitumor Activity of Artemisinin and Its Derivatives: From aWell-Known Antimalarial Agent to a Potential Anticancer Drug .Journal of Biomedicine and Biotechnology. Volume 2012, Article ID 247597, 18 pages. doi:10.1155/2012/247597

Abstract: Improvement of quality of life and survival of cancer patients will be greatly enhanced by the development of highly effective drugs to selectively kill malignant cells. Artemisinin and its analogs are naturally occurring antimalarials which have shown potent anticancer activity. In primary cancer cultures and cell lines, their antitumor actions were by inhibiting cancer proliferation,metastasis, and angiogenesis. In xenograft models, exposure to artemisinins substantially reduces tumor volume and progression…

Multiple myeloma and Diffuse large B-cell lymphoma

Eur J Haematol. 2013 Oct;91(4):339-46. doi: 10.1111/ejh.12176. Epub 2013 Aug 20.

Lymphoma and myeloma cells are highly sensitive to growth arrest and apoptosis induced by artesunate.

Holien T, Olsen OE, Misund K, Hella H, Waage A, Rø TB, Sundan A.

Author information

Department of Cancer Research and Molecular Medicine, KG Jebsen Center for Myeloma Research, Norwegian University of Science and Technology, Trondheim, Norway.

Abstract

OBJECTIVES:

The use of new drugs has improved the treatment of multiple myeloma and diffuse large B-cell lymphoma (DLBCL). Nevertheless, over time many patients relapse and develop resistance to treatment, and efforts are needed to overcome drug resistance. The widely used malaria drug artesunate has been reported to have antitumor activity, and we aimed to test the effects of artesunate on a panel of myeloma and lymphoma cells.

METHODS:

Myeloma and DLBCL cell lines were treated with artesunate **in vitro**. The effects of artesunate treatment were evaluated using ATP content measurements for proliferation and annexin V/propidium iodide labeling for apoptosis. Western blotting was used to look for artesunate-induced protein changes. In addition, we measured artesunate effects on patient myeloma cells in the presence of bone marrow stromal cells.

RESULTS:

Artesunate treatment efficiently inhibited cell growth and induced apoptosis in cell lines. Apoptosis was induced concomitantly with downregulation of MYC and anti-apoptotic Bcl-2 family proteins, as well as with cleavage of caspase-3. The IC50 values of artesunate in cell lines varied between 0.3 and 16.6 μm. Furthermore, some primary myeloma cells were also sensitive to artesunate at doses around 10 μm. Concentrations of this order are pharmacologically relevant as they can be obtained in plasma after intravenous administration of artesunate for malaria treatment.

CONCLUSION:

Our findings indicate that artesunate is a potential drug for treatment of multiple myeloma and DLBCL at doses of the same order as currently in use for treatment of malaria without serious adverse effects.

Gliomas and Malignant Brain Tumors

Oncol Rep. 2016 Aug;36(2):984-90. doi: 10.3892/or.2016.4847. Epub 2016 Jun 2.

Artesunate attenuates glioma proliferation, migration and invasion by affecting cellular mechanical properties.

Lian S[1], Shi R[2], Huang X[3], Hu X[2], Song B[2], Bai Y[4], Yang B[2], Dong J[5], Du Z[6], Zhang Y[5], Jia J[7], Ma N[1], Guo G[1], Wang M[1].

Abstract

Glioma is one of the most common malignant brain tumors. Current chemotherapy is far from providing satisfactory clinical outcomes for patients with glioma. More efficient drugs are urgently needed. Artesunate (ART) is clinically used as an anti-malarial agent and exhibits potent antiproliferative activity as a traditional Chinese medicine. In addition, ART has been shown to exert a profound cytotoxic effect on various tumor cell lines, presenting a novel candidate for cancer chemotherapy. However, its anticancer effect on glioma by altering cell biomechanical properties remains unclear. The present study aimed to identify the anticancer effects of ART on human glioma SHG44 cells by assessing cell proliferation, migration/invasion, the expression of claudin-1 and the biomechanical properties of ART-treated SHG44 cells. The proliferation of the SHG44 cells was assessed by MTT assay. The cell apoptosis was detected by flow cytometry. For cell migration and invasion assays, the Transwell was used. The expression of the gene claudin-1 was detected by polymerase chain reaction. The cell membrane and biomechanical properties, as targets of ART action, were investigated by atomic force microscopy (AFM). ART significantly inhibited the proliferation of SHG44 cells in a dose- and time-dependent manner. After treatment with 30 mg/l ART, the level of cell apoptosis was significantly increased (from 6.88±0.062 to 23.7±4.16%). Furthermore, the cell migration and invasion abilities of the SHG44 cells were markedly inhibited after treatment with 30 mg/l ART. Compared with the control group (0 mg/l ART), the SHG44 cells treated with 30 mg/l ART exhibited upregulated expression of claudin-1, increased adhesive force (from 2,400±300 to 3,600±500 pN), increased high connection among SHG44 cells, increased cytomembrane roughness (from 0.118±0.011 to 0.269±0.015 µm) and reduced elasticity (from 23±8 to 3.5±1.1 MPa). The present study demonstrated that ART could alter the biomechanical properties of the glioma cells to inhibit cell proliferation, migration and invasion.

Lymphoblastic leukemia and lymphoma

Sichuan Da Xue Xue Bao Yi Xue Ban. 2009 Nov;40(6):1038-43.

[Inhibitive effect of artesunate on human lymphoblastic leukemia/lymphoma cells].

[Article in Chinese]

Zeng Y, Ni X, Meng WT, Wen Q, Jia YQ.

Source

Department of Hematology, West China Hospital, Sichuan University, Chengdu 610041, China.

Abstract

OBJECTIVE:

To test the effect of Artesunate (ART) on the proliferation of Raji cells, Jurkat cells and acute lymphoblastic leukemia (ALL) primary cells; to determine the synergistic antiproliferation effect between ART and Vincristine (VCR) or Cytarabine(Ara-C) on Raji and Jurkat cells; and to explore the mechanism of ART induced apoptosis of tumor cells in vitro.

METHODS:

MTT assay was performed to detect the inhibition of proliferation of Raji, Jurkat, and ALL primary cells. The cells were exposed to ART at various concentrations with or without VCR or Ara-C. The morphological changes of Raji and Jurkat cells were observed under light microscopy after Wright-Giemsa dyeing and electron transmission microscopy. The mitochondria transmenbrane potential was measured by Rhodamine 123 staining. Colorimetric method was used to measure the activities of caspase-3 in those tumor cells.

RESULTS:

ART inhibited the proliferation of Raji cells, Jurkat cells and ALL primary cells. The cytotoxicity of ART on Raji cells and Jurkat cells at a low concentration increased when combined with VCR or Ara-C. Apoptosis in Raji cells and Jurkat cells appeared after exposure to ART. Raji cells and Jurkat cells exposed to ART showed mitochondria transmembrane potential collapse. ART increased the caspase-3 activities of Raji, Jurkat and ALL primary cells.

CONCLUSION:

ART alone or combined with chemotherapy drugs could inhibit the proliferation of B/T lymphocytic tumor cell lines as well ALL primary cells in vitro, probably through the mechanism of apoptosis, which suggest that ART is likely to be a potential drug in the treatment of leukemia/lymphoma.

Ovarian Cancer

Acta Pharmacol Sin. 2007 Jul;28(7):1045-56.

Dihydroartemisinin is an inhibitor of ovarian cancer cell growth.

Jiao Y, Ge CM, Meng QH, Cao JP, Tong J, Fan SJ.

Author information

School of Radiology and Public Health, Soochow University, Suzhou 215123, China.

Abstract

AIM:

To investigate the anticancer activity of dihydroartemisinin (DHA), a derivative of antimalaria drug artemisinin in a panel of human ovarian cancer cell lines.

METHODS:

Cell growth was determined by the MTT viability assay. Apoptosis and cell cycle progression were evaluated by a DNA fragmentation gel electro-phoresis, flow cytometry assay, and TUNEL assay; protein and mRNA expression were analyzed by Western blotting and RT-PCR assay.

RESULTS:

Artemisinin and its derivatives, including artesunate, arteether, artemether, arteannuin, and DHA, exhibit anticancer growth activities in human ovarian cancer cells. Among them, DHA is the most effective in inhibiting cell growth. Ovarian cancer cell lines are more sensitive (5-10-fold) to DHA treatment compared to normal ovarian cell lines. DHA at micromolar dose levels exhibits a dose- and time-dependent cytotoxicity in ovarian cancer cell lines. Furthermore, DHA induced apoptosis and G2 cell cycle arrest, accompanied by a decrease of Bcl-xL and Bcl-2 and an increase of Bax and Bad.

CONCLUSION:

The promising results show for the first time that **DHA inhibits the growth of human ovarian cancer cells.** The selective inhibition of ovarian cancer cell growth, apoptosis induction, and G2 arrest provide in vitro evidence for further studies of DHA as a possible anticancer drug in the clinical treatment of ovarian cancer.

Ovarian Cancer + Cisplatin

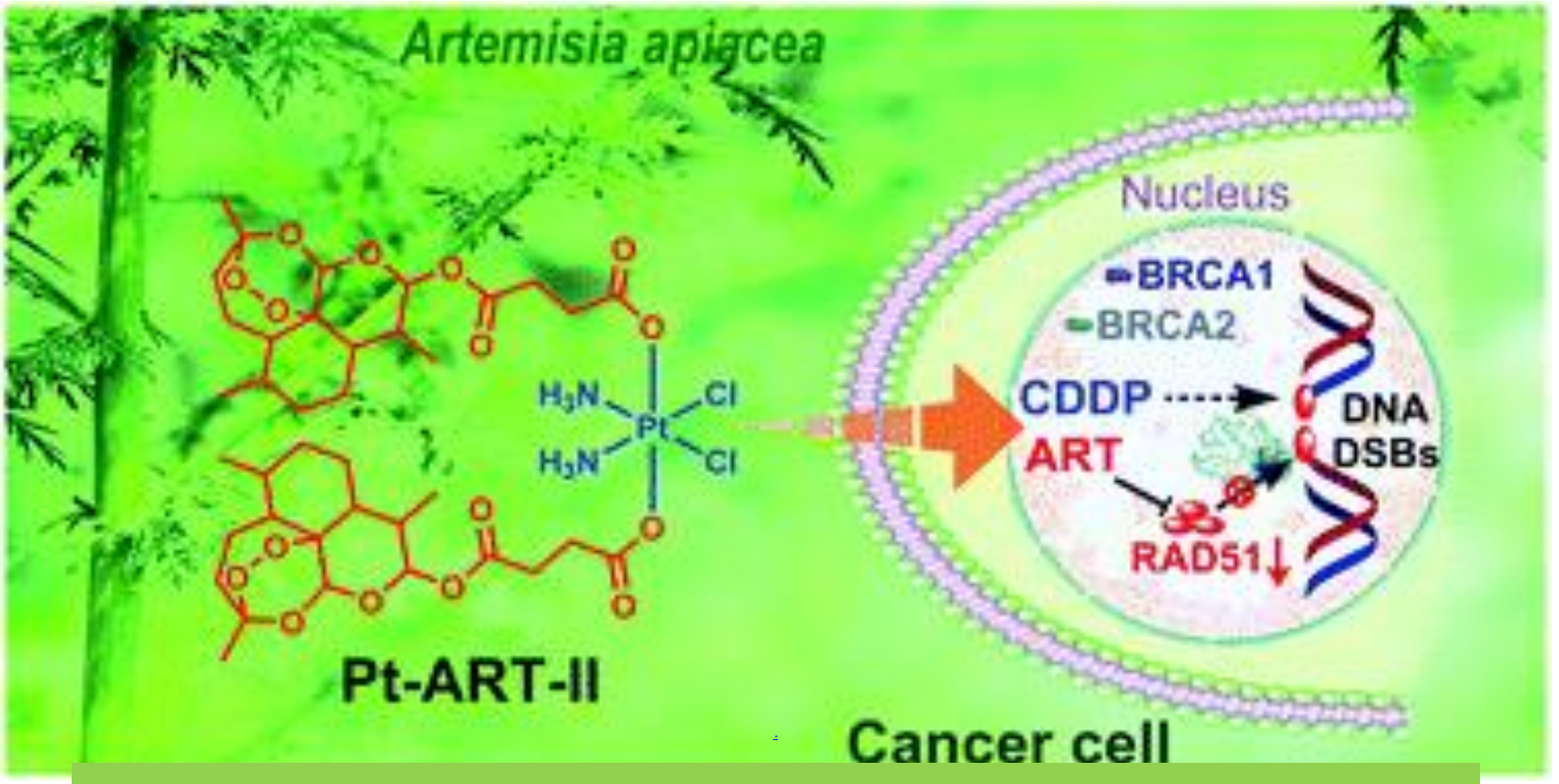
Cancer Biol Ther. 2015 Jul;15.

Artesunate Sensitizes Ovarian Cancer Cells to Cisplatin by Downregulating RAD51

Wang B, Hou D, Liu Q, Wu T, et al

Artesunate, a semi-synthetic derivative of arteminisin originally developed for the treatment of malaria, has recently been shown to possess antitumor properties. One of the cytotoxic effects of artesunate on cancer cells is mediated by induction of oxidative stress and DNA double-strand breaks (DSBs). We report here that in addition to inducing oxidative stress and DSBs, artesunate can also downregulate RAD51 and impair DSB repair in ovarian cancer cells. We observed that the formation of RAD51 foci and homologous recombination repair (HRR) were significantly reduced in artesunate-treated cells. As a consequence, artesunate and cisplatin synergistically induced DSBs and inhibited the clonogenic formation of ovarian cancer cells. Ectopic expression of RAD51 was able to rescue the increased chemosensitivity conferred by artesunate, confirming that the **chemosensitizing effect of artesuante is at least partially mediated by the downregulation of RAD51.** Our results indicated that artesunatecan compromise the repair of DSBs in ovarian cancer cells, and thus could be employed as a sensitizing agent in chemotherapy.

Artesunate BRCA1 and BRCA2



Chem Commun. 2018 Sep. 19.
Toward rational design of RAD51-targeting prodrugs: platinum-artesunate conjugates with enhanced cytotoxicity against BRAC-proficient ovarian and breast cancer cells
Zhang S, Yuan H et al

Artesunate + Allicin in Osteosarcoma

Asian Pac J Cancer Prev. 2013;14(8):4615-4619. doi:http://dx.doi.org/10.7314/APJCP2013.14.8.4615 Epub 2013.

The synergistic Anticancer Effect of Artesunate Combined with Allicin in Osteosarcoma Cell Line in Vitro and in Vivo.

Wei Jiang, Yong Huang, Jing-Peng Wang, Xiao-Yun Yu, Lin-Yi Zhang

Abstract

Background: Artesunate, extracted from *Artemisia annua*, has been proven to have anti-cancer potential. Allicin, diallyl thiosulfinate, the main biologically active compound derived from garlic, is also of interest in cancer treatment research. This object of this report was to document synergistic effects of artesunate combined with allicin on osteosarcoma cell lines *in vitro* and *in vivo*. Methods: After treatment with artesunate and allicin at various concentrations, the viability of osteosarcoma cells was analyzed by MTT method, with assessment of invasion and motility, colony formation and apoptosis. Western Blotting was performed to determine the expression of caspase-3/9, and activity was also detected after drug treatment. Moreover, in a nude mouse model established with orthotopic xenograft tumors, tumor weight and volume were monitored after drug administration via the intraperitoneal (i.p.) route. Results: The viability of osteosarcoma cells in the combination group was significantly decreased in a concentration and time dependent manner; moreover, invasion, motility and colony formation ability were significantly suppressed and the apoptotic rate was significantly increased through caspase-3/9 expression and activity enhancement in the combination group. Furthermore, suppression of tumor growth was evident *in vivo*. Conclusion: Our results indicated that artesunate and allicin in combination exert synergistic effects on osteosarcoma cell proliferation and apoptosis.

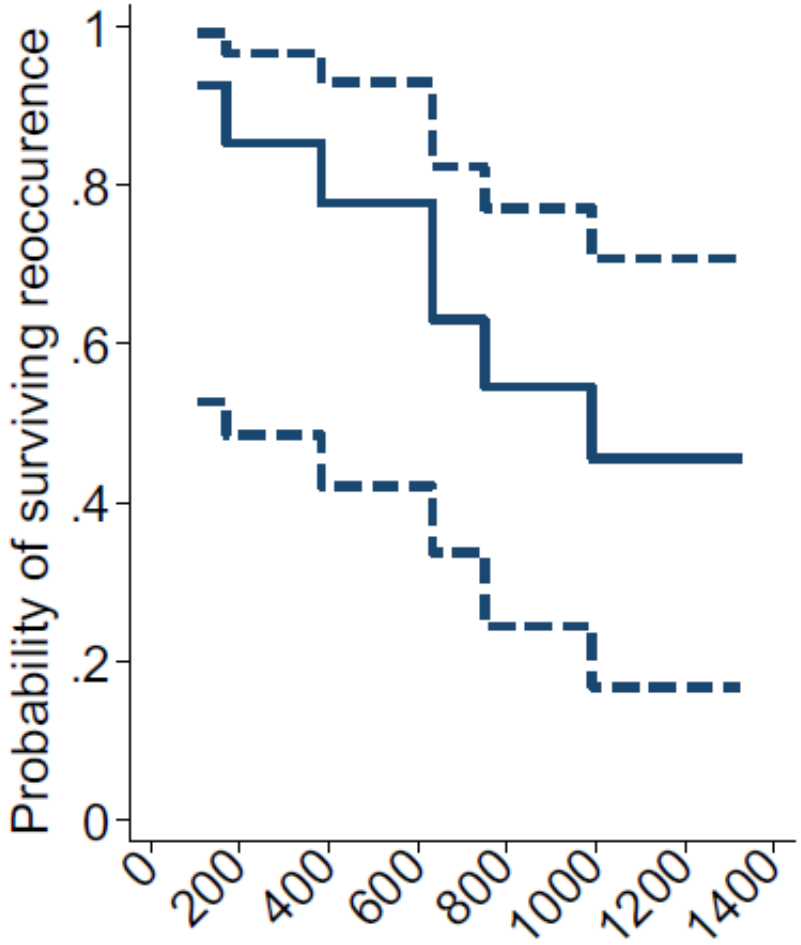
Colon Cancer

EBioMedicine. 2015 Jan;2(1):82-90. doi:10.1016/j.ebiom.2014.11.010

A Randomised, Double Blind, Placebo-Controlled Pilot Study of Oral Artesunate Therapy for Colorectal Cancer

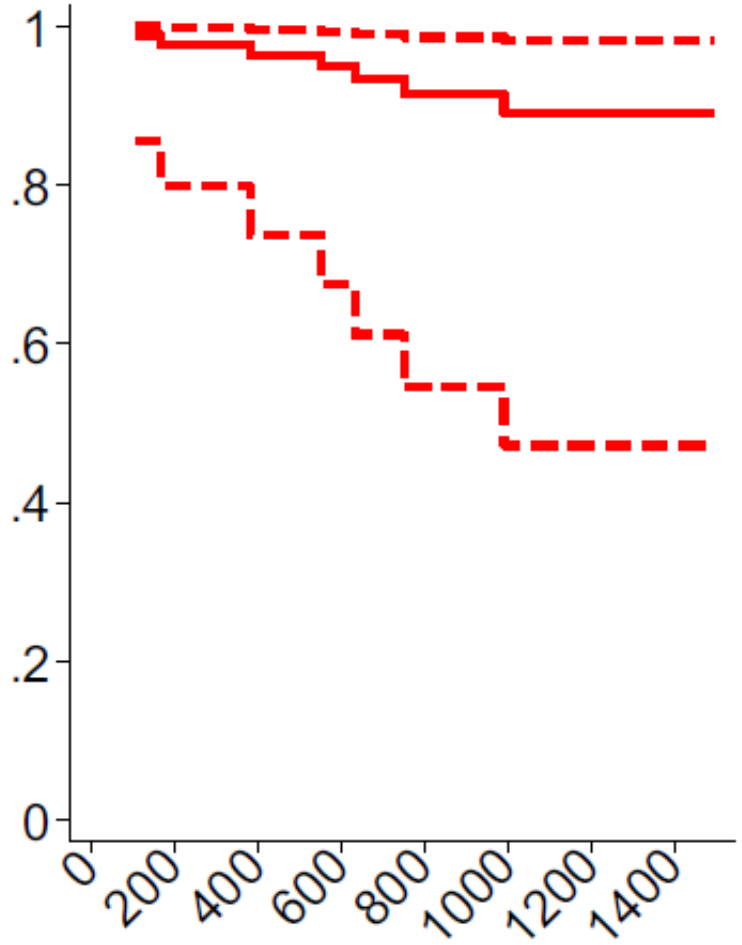
Sanjeev Krishna, Senthil Genapathi, Irina Chis Ster, Mohamed Saeed, Matt Cowan, Caroline Finalyson, et al

- N = 23 (Artesunate = 11, Placebo= 12)
- Intervention with 200 mg oral Artesunate daily for 14 days and stopped 48-72 hours prior to surgery
- No patients on Artesunate had increase CEA values, 3 placebo increased
- One case showed ~75% fall in CEA in 2 weeks with ART alone.
- Side effects: Neutropenia, Anemia (less then 22%)



Surv(1yrs)=0.78(95%CI(0.46, 0.92))
Surv(2yrs)=0.63(95%CI(0.32, 0.83))
Surv(3yrs)=0.45(95%CI(0.18, 0.70))

Placebo



Surv(1yrs)=0.96(95%CI(0.74, 0.99))
Surv(2yrs)=0.93(95%CI(0.61, 0.99))
Surv(3yrs)=0.89(95%CI(0.47, 0.98))

Artesunate

Rhabdomyosarcoma

Carcinogenesis. 2015

Artesunate induces ROS- and p38 MAPK-mediated apoptosis and counteracts tumor growth in vivo in embryonal rhabdomyosarcoma cells.

Phase 1 Intravenous Artesunate

Cancer Chemother Pharmacol. 2018 Mar; 81(3).

A phase 1 study of intravenous artesunate in patients with advanced solid tumor malignancies

Deeken JF, Wang H, Hartley M, et al.

Abstract

PURPOSE:

The artemisinin class of anti-malarial drugs has shown significant anti-canceractivity in pre-clinical models. Proposed anti-cancer mechanisms include DNA damage, inhibition of angiogenesis, TRAIL-mediated apoptosis, and inhibition of signaling pathways. We performed a phase I study to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of intravenous artesunate (IV AS).

METHODS:

Patients were enrolled in an accelerated titration dose escalation study with planned dose levels of 8, 12, 18, 25, 34 and 45 mg/kg given on days 1 and 8 of a 21-day cycle. Toxicities were assessed using the NCI CTCAE (ver. 4.0), and response was assessed using RECIST criteria (version 1.1). Pharmacokinetic (PK) studies were performed during cycle 1.

RESULTS:

A total of 19 pts were enrolled, 18 of whom were evaluable for toxicity and 15 were evaluable for efficacy. DLTs were seen at dosages of 12 (1 of 6 patients), 18 (1 of 6) and 25 mg/kg (2 of 2), and were neutropenic fever (Gr 4), hypersensitivity reaction (Gr 3), liver function test abnormalities (Gr 3/4) along with neutropenic fever, and nausea/vomiting (Gr 3) despite supportive care. The MTD was determined to be 18 mg/kg. No responses were observed, while four patients had stable disease, including three with prolonged stable disease for 8, 10, and 11 cycles, for a disease control rate of 27%. PK parameters of AS and its active metabolite, dihydroartemisinin (DHA), correlated with dose.

CONCLUSION:

The MTD of intravenous artesunate is 18 mg/kg on this schedule. Treatment was well tolerated. Modest clinical activity was seen in this pre-treated population.

Maria P. Crespo-Ortiz and Ming Q.Wei. Antitumor Activity of Artemisinin and Its Derivatives: From aWell-Known Antimalarial Agent to a Potential Anticancer Drug .Journal of Biomedicine and Biotechnology. Volume 2012, Article ID 247597, 18 pages. doi:10.1155/2012/247597

Table 3: Drug interactions of artemisinins.

Drug combination	Cancer/cell line	Effect
DHA + Temozolomide	Rat C6 glioma cells	Increased apoptosis, ROS Induced necrosis
DHA + Cyclophosphamide	Lewis lung carcinoma	Increased apoptosis, decreased VEGF receptor KDR/flk-1 Apoptosis
DHA + Cisplatin	Human non-small cell lung cancer (A549)	Decreased metastasis
DHA + Gemcitabine	Pancreas (Panc-1)	Inhibition of proliferation, decreased cyclin D1 Increased apoptosis, increased Bax/Bcl2 ratio, activation of caspase 3
	Hepatoma (cell panel)	Increased growth inhibition by 45%
DHA + Butyric acid	Human lymphoblastoid leukemia (Molt-4)	Synergistic. Depletion of cancer cells
DHA + Radiation	Glioma cells U373MG	Increased cytotoxicity Inhibition of radiation-induced GST
DHA + Carboplatin	Ovarian cancer cells (A2780, OVCAR-3)	Increased growth inhibition through death receptor and mitochondrial mediated pathways
DHA + TRAIL	Prostate cancer (DU145, PC-3, LNCaP)	Increased apoptosis extrinsic and intrinsic pathways
ART/DHA + Doxorubicin + Pirarubicin	Leukemia (K562/adr) Small cell lung cancer (GLC4/adr)	Synergistic
ART + Lenalidomide	Lung (A549) and breast (MCF-7)	Decreased IC50 by 48%
ART + Oxiplatin	Colon (HT 1116)	Additive. Sensitising effect
ART + Gemcitabine	Breast (MCF-7)	Additive
	Lung (A549)	Additive
ATM + Oxiplatin ATM + Thalidomide ATM + Gemcitabine	Colon (HCTl16, SW480) Breast (MCF-7)	All additive
ARS + Hyperbaric oxygen (HBO_2)	Molt-4 human leukemia	22% decrease in growth
ARS + Doxorubicin	Colon cancer(HT29)	Predicted as antagonic, mediated by activation of NF-κB/overexpression of Pgp
ARS + Oxiplatin	Colon (HCTl16, SW480)	Antagonism
ARS + Thalidomide		Additive
ARS + Gemcitabine	Breast (MCF-7)	Antagonism

DHA: Dihydroartemisinin

ART: Artesunate

ARS: Artemisinin

ATM: Artemisone

ART and Chemo?

Prostate Cancer

Phytomedicine. 2015 Dec 15;22(14):1223-31. doi: 10.1016/j.phymed.2015.11.001. Epub 2015 Nov 10.

Activity of Artemisia annua and artemisinin derivatives, in prostate carcinoma.

Michaelsen FW[1], Saeed ME[2], Schwarzkopf J[3], Efferth T[4].

- 80 year old male presenting with abdominal pain, weakness, and fever in January 2014. Hospitalized February 2014 for acute renal failure.
  - Multiple skeletal metastasis, without hepatic metastasis
  - Previous treatment with low dose 7.5 gram vitamin C and glutathione
  - Staged as pT3bN1M1 graded with Gleason score (4+4) = 8.
  - PSA >800 ug/l
  - Treated with 50 mg bicalutamide x 14 days then Artemesinin annua 250 mg per day.
  - PSA dropped from the start of Artemesinin from 580.3 to 0.98 ug/l until August 2014.
    - Also CRP dropped
  - Then August 2014 PSA started to increased and by January 2015 reached 1245 ug/l.
  - Upon rising levels the researchers switch to IV Artesunate in August with no benefit.

Conclusion: Artemisinin works and then resistance can develop.

Artesunate and Light?

Storage: Keep away from light!
Infusions: Short! 10-15 min!

J Pharm Pharmacol. 1996 Jan;48(1):22-6.

Chemical stability of artesunate injection and proposal for its administration by intravenous infusion.

Batty KT[1], Ilett KF, Davis T, Davis ME.

Author information

[1]Department of Pharmacology, University of Western Australia, Nedlands.

Abstract

- Artesunate, the only artemisinin analogue that can be given intravenously, produces rapid parasite and fever clearance in falciparum malaria. A significant therapeutic problem is a high, late recrudescence rate, probably due to short half-lives of both artesunate and its active metabolite dihydroartemisinin relative to conventional dosing intervals. One method of extending the duration of action of artesunate could be to administer the drug by infusion rather than bolus injection, provided that it is chemically stable at ambient temperature. Artesunate was found to be stable in 0.9% w/v sodium chloride at 9 degrees C, 23 degrees C and 36.5 degrees C for 130, 10.6 and 1.6 h, respectively. Interpolating from an Arrhenius plot, artesunate should be stable for approximately 4 h at 30 degrees C, a temperature representative of ambient conditions in tropical countries. **Exposure to light did not affect the degradation rate.** Single compartment pharmacokinetic modelling was used to evaluate potential differences in artesunate and dihydroartemisinin plasma concentrations following administration of artesunate by intravenous bolus or infusion. A bolus injection of artesunate at a dose of 4 mg kg-1 gives a peak concentration of 5.3 mg L-1, falling to 0.005 mg L-1 at 5 h. The same dose infused over 4 h results in a peak concentration of 0.92 mg L-1, falling to 0.005 mg L-1 at 8 h. Simultaneous modelling of dihydroartemisinin showed that while its peak plasma concentration was reduced by 27% and the peak delayed by 2.5 h following artesunate administration by infusion, substantially higher concentrations were maintained compared with those predicted after bolus artesunate. These data indicate that artesunate can be administered as a high-dose intravenous infusion, thus avoiding high plasma concentrations. This strategy also has the potential to prolong the duration of antimalarial effect and reduce toxicity, and consequently improve clinical outcome in seriously ill patients

Protocol for Artesunate

- **D5W**
  - **100 mL bag**
- **Infuse directly prior to HDIVC (High Dose IVC)**
- **Infuse 60mg on the first occasion as a test dose**
- **120mg IV Artesunate on subsequent doses**
- **frequency: Once to twice weekly as directed;**
  - **Re-evaluate after 10-15 treatments.**
- **Short half life: oxidant within 20 min (not after 2 hours or less)**
- **Oxidative treatment**
  - **Compatible with IVC and other oxidants**

Uses include infections (especially viral) and oncology

Oral Artesunate

Artesunate

- 200 mg per day oral Artesunate

Artemesinin

- 300 mg three times per day x 3-5 days on 9-11 days off. (Pulsed dosage due to GI absorption issues).
  Best to take with food, preferably fat.

Liposomal Artemesinin (more effective than oil)

- 3 tsp daily 3 days on 4 days off.

Dosage: How high could you go?

Zhou X, Sun WJ, Wang WM, Chen K, Zheng JH, Lu MD, Li PH, Zheng ZQ . Artesunate inhibits the growth of gastric cancer cells through the mechanism of promoting oncosis both in vitro and in vivo. Anticancer Drugs. 2013 Oct;24(9):920-7. doi:10.1097/CAD.0b013e328364a109 Epub 2013.

This study aims to investigate the significance and mechanism of artesunate involved in suppressing the proliferation of gastric cancer in vitro and in vivo. In the in-vitro experiments, artesunate inhibited the growth of gastric cancer cell lines (SGC-7901, BGC-823, and AGS) with concentration-dependent activity, with no significant effect on GES-1 cells. BGC-823 cells treated with artesunate showed the typical morphologic features of oncosis rather than apoptosis. Meanwhile, we observed calcium overload, downregulation of vascular endothelial growth factor expression, and upregulation of calpain-2 expression in the artesunate-treated BGC-823 cells. In addition, the in-vivo study showed that artesunate produced a dose-dependent tumor regression in **nude mice**. **The antitumor activity of 240 mg/kg artesunate was similar to that of 10 mg/kg docetaxel.** Furthermore, compared with the control group, no significant difference was observed in the body weight of artesunate-treated nude mice other than docetaxel-treated nude mice. These observations show that artesunate has concentration-dependent inhibitory activities against gastric cancer in vitro and in vivo by promoting cell oncosis through an impact of calcium, vascular endothelial growth factor, and calpain-2 expression.

Toxicity

- Oral Toxicity

No toxicity in dogs using oral 45 mg/kg q6 hours x 3 weeks. Most common side effect was anorexia. Bioavailability wasn't high enough.

- Minimal AST, ALT elevations
- No neutropenia
- No anemia

- 556 mg/kg Artemether per day no toxicity in beagles
- No toxicity in monkeys which received 292 mg/kg (642 mg/pound) of Artemether over 1-3 months

Intravenous Vitamin C + Intravenous Artesunate:
Does the addition of Artesunate improve survival rates in Stage IV Breast Cancer?

Brenden Cochran, ND; Paul Anderson, ND;
Leanna Standish, PhD, ND

Introduction/Background

BIORC was established in 2009 in order to provide high quality integrative oncology care to patients in order to collect outcome data on each patient.

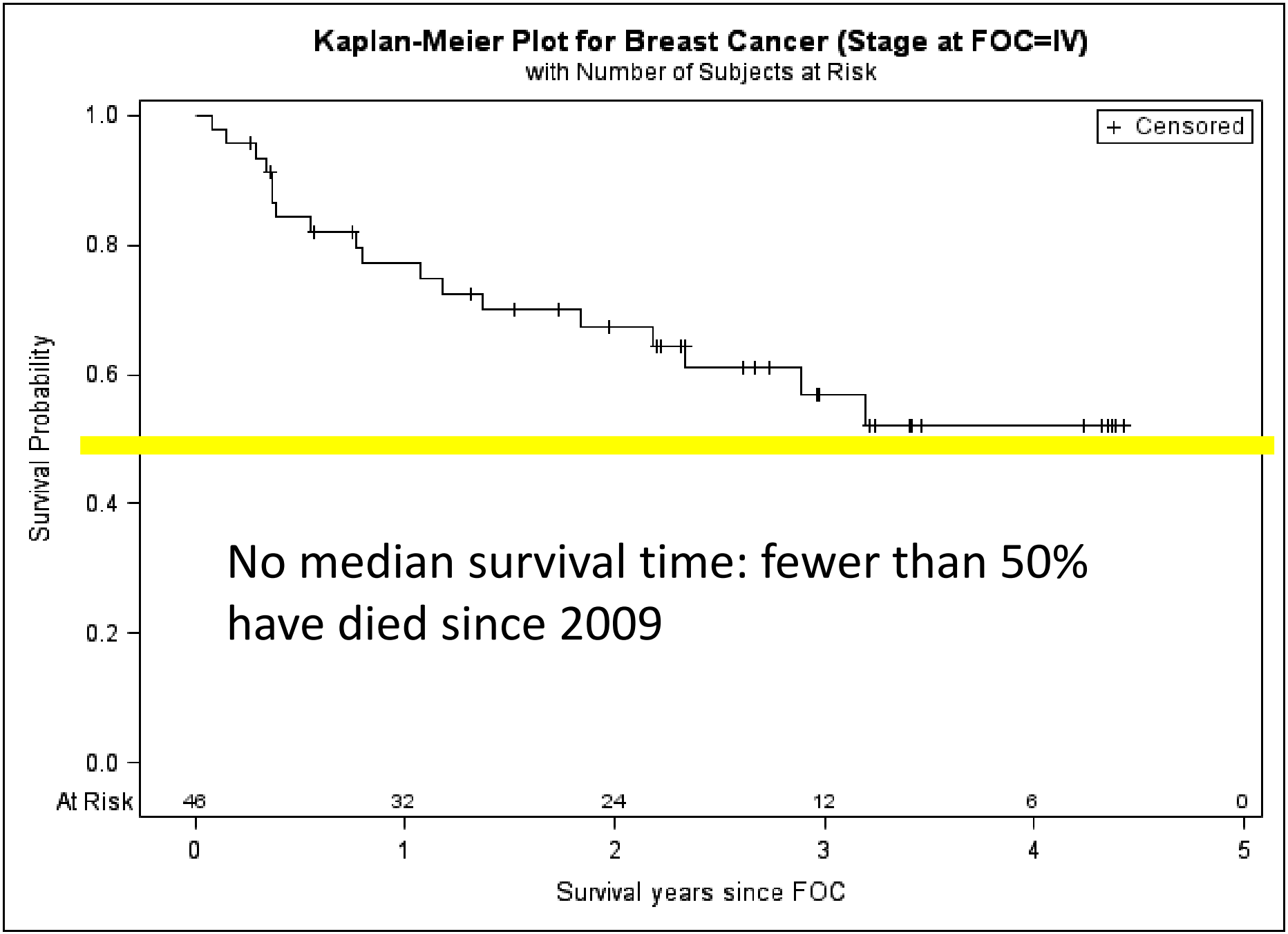
Most common types of cancer

Breast cancer
Lung cancer
Colon cancer
Pancreatic cancer
Brain cancer
Sarcoma
Merkel cell cancer

30.4% of BIORC patients are stage IV.

****95% of the IV study participants are stage IV**

N = 10 or more to warrant survival curves.


Kaplan-Meier Plot for Breast Cancer (Stage at FOC=IV)
with Number of Subjects at Risk
+ Censored
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
At Risk
46
32
24
12
6
0
0
1
2
3
4
5
Survival years since FOC
No median survival time: fewer than 50% have died since 2009

Introduction/Background

Based on preclinical and clinical data BIORC physicians added IV artemisinin (Artesunate) to the protocol for all stage IV breast cancer patients. Here we present survival outcomes for those stage IV patients who declined any BIORC IV therapy versus those who received the combination protocol of IVC + Artesunate.

Material and Methods

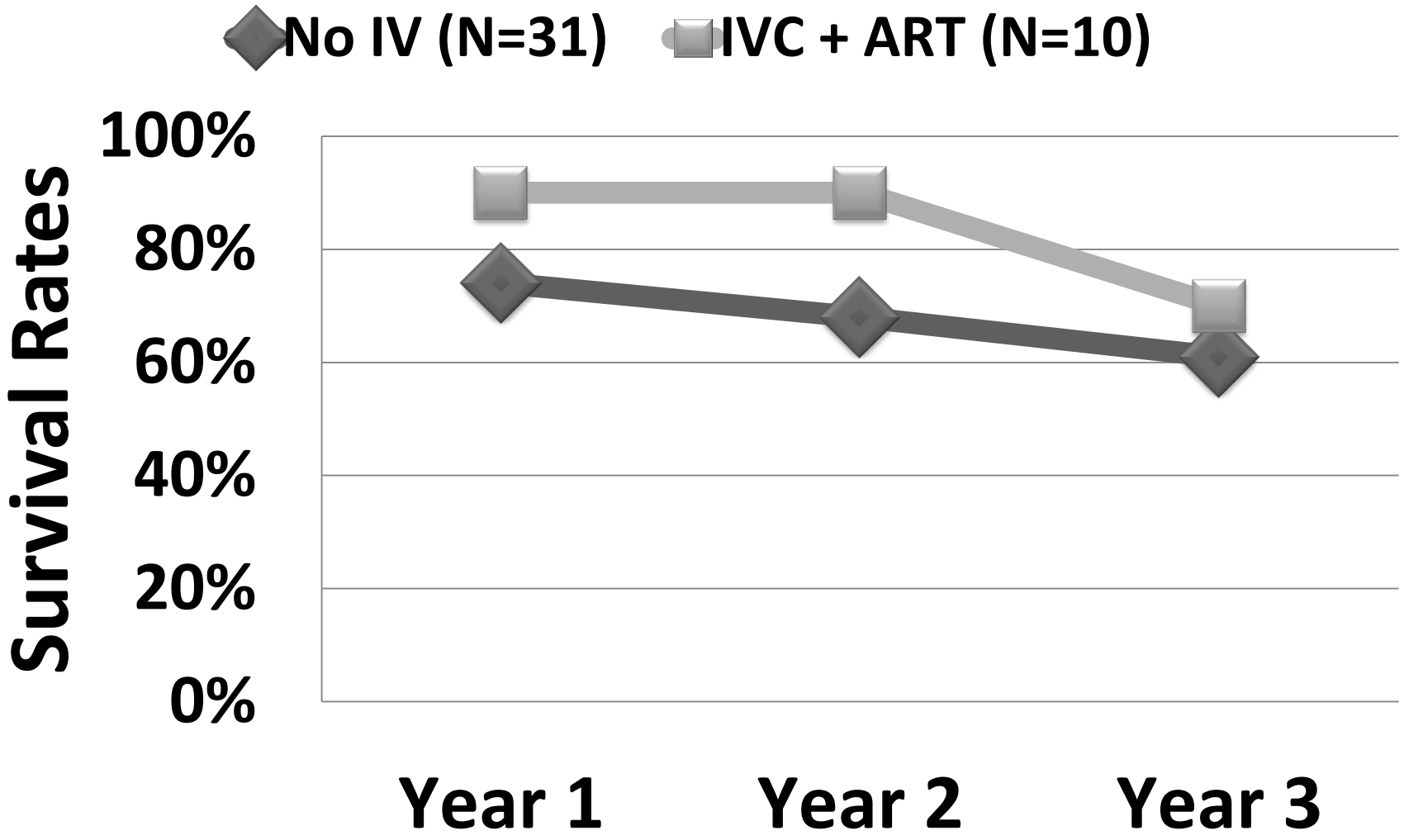
Survival data for the 41 stage IV breast cancer patients treated in BIORC between 2009 and 2013 were obtained using the National Death Index. We compared survival rates in patients who declined IV therapy and those that received IVC + ART. Adverse events were monitored and categorized using the NCI CTAE. Kaplan Meier's survival curves were used to calculate survival rates at 1, 2 and 3 years after starting BIORC treatment.

Results

Table 1. Relative survival rates in Stage IV breast cancer patients

Stage 4 IO BRCA (N=41)	Year 1	Year 2	Year 3
No IV (N=31)	23 (74%)	21 (68%)	19 (61%)
IVC + ART (N=10)	9 (90%)	9 (90%)	7 (70%)

Stage 4 IO BRCA (N=41)



These preliminary results suggest testable hypothesis that high dose IVC + IV ART improves survival in stage IV breast cancer patients. There were no adverse events associated with this treatment.

Conclusion

The addition of Artesunate to IV therapies such as high dose vitamin C during integrative oncology may improve survival rates. This suggests a novel treatment strategy of combination therapies with Artesunate and high dose vitamin C therapies. A controlled clinical trial will be required to further evaluate this novel and low toxicity therapy for metastatic breast cancer.

Studies currently underway

- **<u>Intravaginal Artesunate for the Treatment of HPV + High Grade Cervical Intraepithealial Neoplasia (CIN2/3)</u>**
  - Phase 1: Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
  - Looking at
    - 50 mg x 5 days Artesunate before resection
    - 200 mg x 5 days total Artesunate before resection
    - 200 mg x 10 days total Artesunate before resection (Week 0, Week 4)
    - 200 mg x 15 days total Artesunate before resection (Week 0, Week 4, Week 8)

  Estimated completion date: February 2019
- **<u>A Safety and Effectiveness Study of Pre-operative Artesunate in Stage II/III Colorectal Cancer</u>**

  Estimated completion date: December 2022

IND Protocol

IND Protocol: Intravenous Artesunate for

Treatment of Severe Malaria in the United States

IND Sponsor: Centers for Disease Control and Prevention (CDC)

CDC IRB #: 5032
IND #: 76,725

Revised December 19, 2016

Human Use

Phase I-II data for IV administration of artesunate from a WHO summary by Dr. Melba Gomes indicate the following:

- Phase I trial: 2-4 mg/kg IV artesunate resulted in a reversible decrease in reticulocyte counts [section 14 i of WHO summary].

- Phase II trial: Approximately 15 mg/kg IV artesunate was administered over 3 days. Reversible increases in liver function tests were seen. Bradycardia was seen in the artesunate group and also in the simultaneous quinine group. [section 14 ii of WHO summary].

- Phase II trial: Approximately 6 mg/kg IV artesunate to patients with cerebral malaria resulted in SGPT elevations and BUN elevations that persisted until Day 6, the last day of observation. [section 14 vi of WHO summary].

- Intrarectal (IR), intramuscular (IM), and IV administration for severe malaria: IR administration resulted in "no major adverse effects" in 30 patients, other than dizziness, nausea, vomiting, and abdominal pain, which are components of acute malaria infection; 5 patients had tenesmus or extruded their suppositories, and had to have them reinserted; tenesmus was also recorded in African patients. IM administration resulted in a

Artesunate References

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A Randomised, Double Blind, Placebo-Controlled Pilot Study of Oral Artesunate Therapy for Colorectal Cancer
Sanjeev Krishna, Senthil Genapathi, Irina Chis Ster, Mohamed Saeed, Matt Cowan, Caroline Finalyson, et al