

Artemisinin: From Malaria to Cancer Treatment

by Robert Jay Rowen, MD



Artemisinin, the key ingredient obtained from *Artemisia annua*, has a long history of use as an antimalarial remedy. *Artemisia annua*, or "sweet wormwood," is mentioned in the *Recipes For 52 Kinds Of Diseases* found in the Mawangdui Han Dynasty tomb, dating from 168 B.C. In that work, the herb is recommended for use for hemorrhoids. It is also mentioned in the *Zhou Hou Bei Ji Fang (Handbook of Prescriptions for Emergency Treatments)* written in 340 A.D. The major active principal was first isolated in 1972, and investigators at the Walter Reed Army Institute of Research located and crystallized the active component in 1984.¹

Artemisinin and two synthetic derivatives, artemether and sodium artesunate, were evaluated in the 1970s. A number of the tropical countries have conducted trials. In China in 1979, wherein 2,099 patients infected with *P. vivax* and *P. falciparum*, artemisinin had good therapeutic effects and improved or cured all patients. Furthermore, the treatment with artemisinin was without any obvious side effects. Artemisinin is also effective in cerebral malaria. Body temperature of patients normalized within 72 hours, and asexual parasites were eliminated within 72 hours. However, there was a relapse rate of 21%.²

In clinical trials in Vietnam, children aged one to 15 years were randomly selected to receive artemisinin suppositories or oral quinine. The results indicated that the suppositories rapidly cleared asexual *P. Falciparium* parasitemia in children and confirmed the problem recurrence rates.³

Artemisinin has been extensively researched for malaria and has been used on over a million patients, mostly in China and Vietnam. It is very helpful for drug-resistant malaria. Extensive review articles documenting the extensive testing that has been done are available.⁴⁻⁶

Various oral-dosage regimens have been adopted in treating over one million

patients. Early studies suggested that an optimum total dosage of 3 grams (about 50 mg/kg) was administered over a three-to-five-day period. In most cases, parasite and fever clearance times were in less than two days. Recurrence were much more common with tablets than with parenteral formulations. Because of the rapid clearance time of fever and parasites, the use of artemisinin was favored, and recurrences, which were common, were treated with artemisinin again or with another drug.⁷

About 12 years ago, Dr. Leo Galland and Dr. Herman Bueno worked together in New York City and began using artemisinin as a broad spectrum antiparasitic agent. According to Dr. Galland: "Artemisinin is a powerful oxidant. I have used it orally to treat small bowel bacterial overgrowth and Clostridial overgrowth, and (along with other herbal extracts, such as berberine, grapefruit seed extract, and oregano oil) as a treatment for intestinal parasites."

Very recently, news reports have trumpeted artemisinin as a leading treatment for malaria. Affected nations are calling for it to be accepted as the number one first-line treatment, but the US has blocked its acceptance as the primary treatment, alleging that yet more studies are needed.

For the past ten years, the Hoang medical family, with three generations of sophisticated physicians, have used artemisinin in combination with several other herbs to treat cancer and eliminate necrosis material from the body – for example, from wounds, from the intestines of people who have ulcerative colitis, and from those with Crohn's disease. The efficacy of the artemisinin compound is very impressive for the treatment of breast cancer and may possibly prevent it. This potential use of artemisinin is not only because of direct anti-cancer activity, but also due to its hormonal-balancing properties. Herein, doses of 300 mg twice per day were adequate with other herbs.⁸ According to Dr. Hoang: "The herb itself, *Artemisia*

annua, is one of the best things for PMS, cramping, excessive bleeding and all symptoms of hyperestrogenemia and hyperprolactinemia."

Artemisinin contains an internal peroxide group. Due to this group, reactive oxygen is already present in the molecule. This conclusion is verified by observations that derivatives of artemisinin lacking the peroxide moiety are devoid of antimalaria activity.⁹ Additional support for the oxygen-mediated toxicity of artemisinin is generated from other studies. The antimalarial activity of artemisinin *in vitro* against *P. falciparum* could be enhanced by increased oxygen tension. Drugs such as miconazole and doxorubicin, which are known to work via oxygen radical effects, enhance the activity of artesunate, a derivative of artemisinin. The effectiveness of artemisinin is reduced by catalase, dithiothreitol, and alpha tocopherol.¹⁰

Furthermore, Levander, et al. found that manipulation of the host antioxidant defense status could provide prophylactic or therapeutic enhancement for the control of malaria. In this study, mice were fed with diets deficient in vitamin E or with diets supplemented with cod liver oil, which would deplete antioxidants. Vitamin E deficiency enhanced the antimalarial action of artemisinin against *P. yoelii*, but selenium deficiency did not. A diet containing five percent cod liver oil had a very strong antimalarial action.¹¹

Artemisinin has been shown to work through oxygen- and carbon-based free radical mechanisms. Its structure includes an endoperoxide bridge. Peroxides generate free radicals in a Fenton-type reaction when exposed to unbound ferrous iron. Malaria, which grows in the erythrocytes, has the opportunity to accumulate much excess iron, which can spill into the unbound form. Electron microscopy has confirmed destruction of plasmodium membranes with morphology typical of free radical mechanisms.

With the knowledge of a high accumulation of iron in cancer cells, researchers Henry Lai and Narendra Singh of the University of Washington became interested in possible artemisinin activity against malignant cells. In 1995, they published a paper in *Cancer Letters* concerning the use of artemisinin against numerous cancer cell lines *in vitro*. This article has mobilized interest in artemisinin as an addition to anti-cancer treatments.¹²

There are a number of properties shared by cancer cells that favor the selective toxicity of artemisinin against cancer cell lines and against cancer *in vivo*. In addition to higher rates of iron flux via transferrin receptors than normal cells, cancers are particularly sensitive to oxygen radicals.¹³

A subsequent article appeared in *Life Science* in 2001 by Singh and Lai on the selective toxicity of artemisinin and holotransferrin towards human breast cancer cells.¹⁴ In this article, rapid and complete destruction of a radiation-resistant breast cancer cell line was achieved when the *in vitro* cell system was supported in iron uptake with holotransferrin. The cancer cell line was completely nonviable within eight hours of combined incubation with minimal effect on the normal cells.

Artemisinin becomes cytotoxic in the presence of ferrous iron. Since iron influx is naturally high in cancer cells, artemisinin and its analogs selectively kill cancer cells under conditions *in vivo*. Further, it is possible to increase or enhance iron flux in cancer cells using the conditions that increase intracellular iron concentrations. However, intact *in vivo* systems do not need holotransferrin; the living body provides all the necessary iron transport proteins.

A third paper, by Efferth et al., published in *Oncology* in 2001 stated that the antimalarial artesunate is also active against cancer.¹⁵ This article described dramatic cytotoxic activity against a wide variety of cancers, including drug-resistant cell lines. Artesunate (ART) is a semi-synthetic derivative of artemisinin and has been analyzed for its anti-cancer activity against 55 cell lines by the Developmental Therapeutics program of the National Cancer Institute, USA. ART was most active against leukemia and colon cancer cell lines (Mean growth inhibition 50% (GI 50), 1.11 microM and 2.13 microM, respectively). Non-small cell lung cancer cell lines showed the highest mean (GI50 26.62 microM) indicating the lowest sensitivity towards ART. Intermediate GI 50 values were

obtained for melanomas, breast, ovarian, prostate, CNS, and renal cancer cell lines. Most importantly, a comparison of ART's cytotoxicity with those standard cytostatic drugs showed that ART was active in molar ranges comparable to those of established anti-tumor drugs. Leukemia lines resistant to either doxorubicin, vincristine, methotrexate, or hydroxyurea were tested. Remarkably, none of these drug-resistant lines showed resistance to ART. The theorized reason for this is the absence of a tertiary amine in ART, present in virtually all other chemotherapy agents, which is required for cellular transport systems to usher the drug outside the cell.

Cancer Cells Are Deficient in Antioxidant Enzymes

Cancer cells are notoriously deficient in antioxidant enzymes. Both forms of superoxide dismutase – the manganese form in mitochondria and the copper zinc form in the cell cytoplasm – are generally low in cancer cells. Cancer cells are grossly deficient in catalase and glutathione peroxidase, both of which degrade hydrogen peroxide. It is these deficiencies in antioxidant enzymes that lead to the use of many of the common chemotherapeutics which are superoxide generators.¹⁶

The higher iron fluxes, especially associated with the reproductive phase of tumor cells, should render these cells even more susceptible to oxidative damage via hydrogen peroxide and superoxides. Normally, the profound catalase deficiency in cancer cells is credited with creating vulnerability to oxidants, in relationship to IV vitamin C or IV hydrogen peroxide. However, since all these protective antioxidant enzymes are most often deficient in transformed cells, the oxidant vulnerability should be enhanced dramatically, and further so, due to enhanced unbound iron during cell division.

Dr. Hugh Riordan has suggested that very high doses of IV vitamin C can kill cancer cells via conversion of vitamin C to hydrogen peroxide, and due to deficiency of catalase. For this procedure to work, very high levels of IV vitamin C are required to reach "kill concentrations." IV vitamin C may be one of the best-documented, alternative cancer treatments.¹⁷

Artemisinin may be a most effective method, and certainly one of the easiest, of delivering a knockout oxidative stress to cancer cells. Artemisinin is appealing for oral use in that the pharmacodynamics, dosage, and toxicity have been

well studied for use in relationship to the treatment of malaria. Artemisinin is relatively safe with few side effects even at high dosages (70 mg/kg per day) in short-term malaria use.

Artemisinin has two semisynthetic derivatives. Artesunate is a water-soluble derivative with no reported toxicity at usual levels. However, its serum half-life is relatively short. Artemether is a lipid soluble derivative, effective in cerebral malaria, and therefore may be more effective in brain cancers by better penetration of the blood-brain barrier. Artemether, however, has been reported to cause some neural toxicity in laboratory models in rather high doses. Artemether has an intermediate half-life and can cross the blood-brain barrier. The two semisynthetic derivatives are available overseas in both oral and injectable forms for artesunate and artemether.

As mentioned, Lai used holotransferrin, which is iron-loaded transferrin, to further sensitize tumor cell lines to the oxidizing properties of dihydroartemisinin, which is derived from the parent compound metabolically *in vivo*. A human leukemia cell culture, Molt-4-lymphblastoid cells, and normal human lymphocytes were used in this experiment.

A significant decrease in cell count was noted with artemisinin alone, with $p < .035$. Greater effects were noted when transferrin and dihydroartemisinin were used together. In combined treatment, considerable tumor cell death was observed at a concentration of dihydroartemisinin of 1 uM after eight hours of incubation. Furthermore, there is reason to believe that artemisinin can work at lower concentrations *in vivo* than *in vitro*, due to destruction of the artemisinin molecule *in vitro*.

Lai suggests that this procedure would be most effective for the treatment of aggressive cancers, in which large numbers of transferrin receptors are expressed on the cell surface. It may not be effective for T-cell leukemias, which have defective internalization of transferrin receptors, and therefore may not be susceptible to this treatment.¹²

Case Reports

1. Patient D.A., a 47-year-old mechanic who presented with a 4.5 cm, Non-Hodgkin's lymphoma on the right side of his head, with gaping incision from a recent biopsy, and tremendous inflammatory erythema. Artesunate, 60 mg, was administered IM for 14



consecutive days, and he switched diets to high-protein/vegetable (Kelley parasympathetic type) diet. At the end of two weeks, a depression appeared at the apex of the tumor. Four weeks later, the mass was completely gone; the skull surface was smooth; the incision had totally healed; and erythema virtually cleared. The patient is apparently cancer-free as of this writing six months later.

2. Patient V.M., an 83-year-old Toronto resident. Healthy most of her life, she now had a non-small cell lung carcinoma in the right lower lobe, considered nonresectable because of heart failure and circulatory problems. She received artemisinin, 500 mg, BID from Allergy Research Group and Carnivora, oral, via nebulizer, 5cc BID. In four months, the tumor shrunk to 1 x 2 cm, and her oncologist felt this represented scar tissue and declared the patient cancer-free. (Her heart condition improved considerably with CoQ10, 600 mg daily).

3. Patient D.E., a 47-year-old Alaska resident with stage 4 breast cancer and metastases to T1 with significant pain, vertebral collapse, and local neurological impairment. First seen May 2001, she received a series of insulin potentiation therapy (IPT) low-dose chemo-therapy, high-dose vitamin C infusions, supplements, dendritic cell vaccine, dietary management (Kelley sympathetic-type diet), and detoxification strategies. Most symptoms had cleared within four months (October 2001). In January 2002, she received artesunate IV (source: mainland China), plus oral artemisinin 300 mg BID (ARG and Wellcare Pharma) which has been continued. Six months later, she was happy to report she has no symptoms whatsoever and is living a normal life. Her local provider believes the regressed mass is now scar tissue.

4. Patient F.A., an 81-year-old Californian with multiple skin cancers including one active recurrent quarter-sized lesion that had been burned four times previously. Topical artemisinin (one capsule ARG artemisinin in 50% DMSO) applied twice daily caused the large lesion to fall off within five days and other smaller skin cancers to regress. His wife reported the same with her skin cancers.

5. L.L., is a West Coast woman in her 40s with breast cancer and extremely painful metastases all over her spine. She had received limited radiation therapy to reduce the pain in the thoracic spine prior to consulting me. She began artemisinin and a variety of complementary

strategies, including diet, detoxification, and Kelley-type proteolytic enzymes (from Allergy Research Group). Immediately, her energy exploded. Her pain level took a dive when she received treatment from an Edgar Cayce Foundation healer. Her comment after two weeks on artemisinin was, "Last week I thought I was dying, and today, for the first time in months, I believe I am going to live." Four months into therapy using oral supplements alone (no IV therapy), diet, and detoxification strategies, a PET scan, the most efficient and sensitive study for spread of cancer, did not show any activity anywhere in her spine, even in places that were present before and not radiated! Further, the scan did not confirm definite cancer activity anywhere else.

All patients who took oral artemisinin did so in the morning and evening on an empty stomach with either conjugated linoleic acid and/or omega-3 supplements and/or some full fat cultured organic dairy product to enhance absorption. Simultaneous iron in the stomach might neutralize its effectiveness.

Conclusion

Artemisinin has been used for about 30 years in Vietnam and China for cancer treatment. And the experience with artemisinin for this purpose is increasing. This history probably led to the recently cited cancer research with artemisinin.

The fact that artemisinin's direct antineoplastic effects closely resemble that of high-dose intravenous vitamin C is intriguing. The potential benefit of artemisinin in cancer treatment should be further explored because it is simple, safe, and well-understood. It also capitalizes on the multifold weakness in cancer cells to defend themselves against oxygen radicals. Enhancing the oxidant activity with other oxidation agents (such as carnivora, ultraviolet blood irradiation, H₂O₂, or higher oxygen tension itself) may add significant synergism. Adding artemisinin to low-dose chemotherapeutic regimens, inducing cytotoxicity via free radical mechanisms (such as doxorubicin), may safely add to the effectiveness of such treatment.

Dr. Singh, in a personal communication to me, has shared that he has been following a series of cancer patients with nearly universal improvement on artemisinin or its derivatives. He believes artemisinin prove to be the most powerful, yet extremely inexpensive and safe,

chemotherapeutic agent yet found, one that is also effective orally for home use. However, like myself, he and the Hoang family of physicians, believe artemisinin should only be used in a professional atmosphere together with complementary strategies employing detoxification, diet, immune support, spiritual work, etc. This use of complementary strategies and professional supervision cannot be emphasized enough, especially since long-term use of artemisinin and/or its derivatives has had little study. The Hoang family has shown me a 50%-60% long-term remission in over 400 cancer patients utilizing artemisinin together with a comprehensive cancer strategy and with no observed toxicity.

I gratefully acknowledge Drs. Lai and Singh in their pioneering work and their personal assistance in providing me with the information needed to work with artemisinin and its derivatives for the benefit of my patients.

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Notes

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