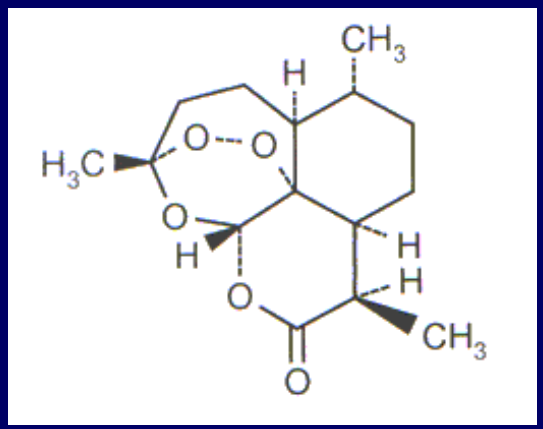
Artemisinin in Cancer Treatment

Dr. Narendra P. Singh

Department of Bioengineering
University of Washington

Seattle

What is Artemisinin?



- Artemisinin is a sesquiterpene lactone isolated from the plant *Artemesia annua* L. (has been used for the treatment of malaria).
- Dr. Zhenxing Wei was first to isolate artemisinin in 1970.
- The artemisinin molecule contains an endoperoxide bridge that reacts with a ferrous iron to form free radicals
- There are several analogs of artemisinin including artesunate and artemether.

How does Artemisinin work?

- Artemisinin causes the cancer cell to commit suicide.
- The artemisinin molecule contains an endoperoxide bridge that reacts with a ferrous iron atom to form free radicals
- Generation of free radicals leads to macromolecular damages and cell death.
- Cancer cells have a very high iron uptake and thus they are more susceptible.

Research on Artemisinin:
MOLT-4 (Leukemia Cell Line) Studies

- First study on artemisinin (1995) was done in cell culture (MOLT-4 lymphoblastoid leukemia cell line).
- Results show all MOLT-4 cells were killed in 8 hours by 200 micromolar of dihydroartemisinin.
- The drug is 100 times less toxic to human lymphocytes in culture.

Research on Artemisinin: Leukemia Cell Line

APOPTOSIS IN MOLT-4 LEUKEMIA CELLS	
(dihydro) Artemisinin (8 hours only)	
Control	0 %
200 μM	100 %
Hyperthermia (24 hr incubation)	
Control	3.26 %
44°C for 1 hr	5.01 %
Hydrogen Peroxide (24 hr incubation)	
Control	3.52 %
176 μM	40.09 %
Mitoxantrone (24 hr incubation)	
Control	3.51 %
0.5 μM	55.02 %
Novobiocin (24 hr incubation)	
Control	3.75 %
800 μM	22.68 %
Sodium Ascorbate (24 hr incubation)	
Control	3.47 %
2000 μM	62.59 %
X-ray (24 hr incubation)	
Control	3.2 %
100 rads	9.5 %

Research on Artemisinin: Trials in Dogs

- Dog trials were begun soon after encouraging results in MOLT-4 experiments (1994-1995).
- Dogs of different breeds (male and female) having various types of cancers (lymphosarcoma, breast adenocarcinoma, osteosarcoma, ETC) were treated.
- Results: Specific results varied with dogs, but generally positive. Tumor sizes were drastically reduced. No reoccurrence of cancer in 5 dogs operated and given artemisinin.

Research on Artemisinin: Human Breast Cancer Cells *in vitro*

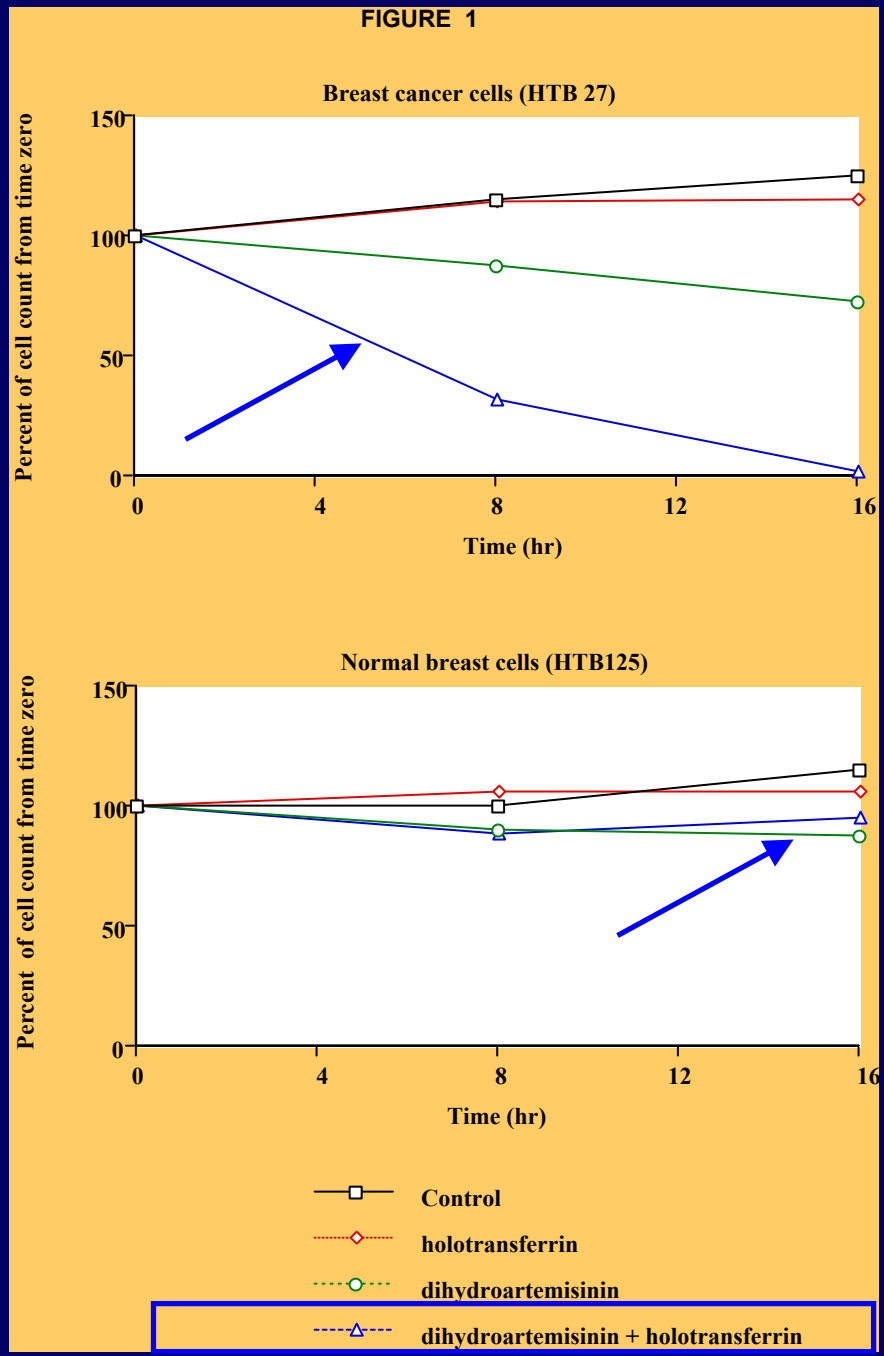
- Most recent research was published (2001) on a breast cancer cell line (HB 27) *in vitro*.
- Breast cancer cells treated with dihydroartemisinin and holotransferrin were almost completely eliminated (after 16 hrs of treatment cell count was only 2% of that at time zero).

Research on Artemisinin: Human Breast Cancer Cells *in vitro*

- A morphological examination of breast cancer cells treated with dihydroartemisinin and holotransferrin showed that they were undergoing apoptosis and necrosis.
- Drug had no effect on normal breast cells.

Research on Artemisinin:

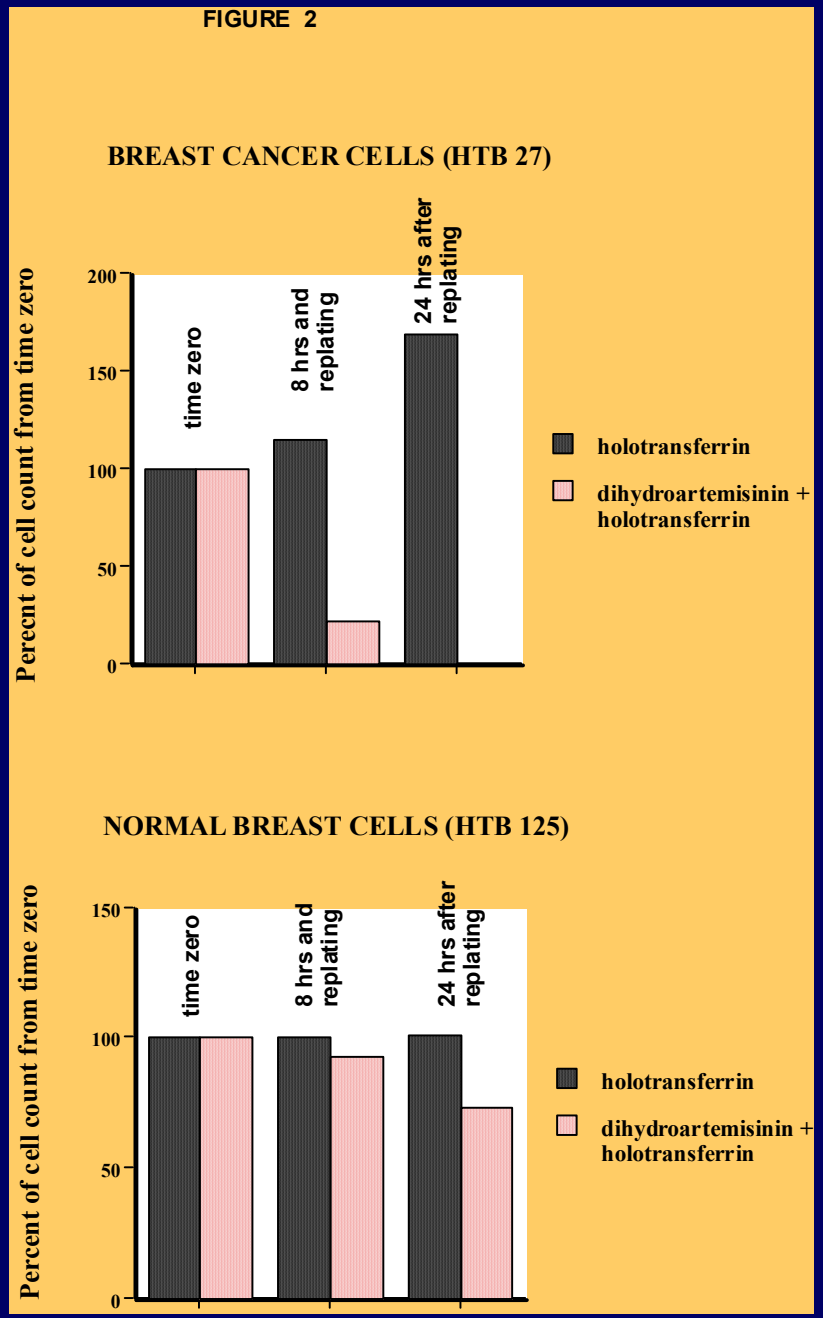
Breast Cancer Cells *in vitro* undergo rapid and almost complete cell death (98%) after treatment with dihydro-artemisinin and holotransferrin.



Research on Artemisinin:

Breast cancer cells were completely non-viable after 8 hours of treatment with holotransferrin and dihydroartemisinin, as proved by replating.

Normal breast cell counts slightly decreased with the same treatment, suggesting some damage to cells.



Case report:

Archive of Oncology, Volume 10 (In press)

Artesunate Treatment for Larynx Cancer in man

[1]Narendra P. Singh, [2]Krishna B. Verma, [1]Henry Lai

Artesunate injections and tablets were administered to the patient over a period of nine months. The tumor was significantly reduced (by approximately 70%) after two months of treatment. Treatment reduced the sufferings and prolonged the life of the patient

Principles of Artemisinin Therapy: How to kill cancer cells

- Starvation by depletion of nutrients
- Exercise by generating H_2O_2
- Drugs including vitamin C, vitamin D and artemisinin and analogs
- Alkaline pH in body

Benefits of Exercise

For killing of Cancer Cells:

- Generates Hydrogen Peroxide.
- Results in high concentrations of oxygen in the body.
- With the help of vitamin D, puts calcium in bones.
- Increases circulation allowing immune cells to reach cancer

General Benefits:

- Feeling of well-being (increased appetite)
- Increased excretory processes
- Raises Pain Threshold

Common Characteristics Observed among Cancer Patients (all of the following decrease calcium):

- Lack of sunshine in environment or aversion to going out in sun.
- Avoidance of physical activity or generally more sedentary lifestyle.
- Abnormal sleep habits (excessive sleeping, napping during the day etc.)
- Very limited consumption of/dislike of milk
- Eating late dinners and immediately retiring for the night

Conclusion

- **Artemisinin can be used to treat various types of cancer.**
- **Side effects are minimal and it can be taken orally.**

Frequently Asked Questions

- Q. How often and when should the drug be administered?
- A. Ideally, just once at bedtime as the immune system is at the lowest during the night and bacterial and cancer cells proliferate faster.
- Q. Is exercise essential?
- A. Yes. Importance-wise ranking: exercise, diet and drug.

Frequently Asked Questions

- Q. What is the half life of artemisinin
- A. Study in rats,
- artemisinin 3-4 hr
- artemether 12 hr
- artesunate 40 min (human)
- Blood levels are higher in females

Frequently Asked Questions

- Q. Does artemisinin cross blood brain barrier?
- A. Yes
- Q. What is peak plasma level time
- A Artemisinin and analogs are rapidly absorbed and peak in plasma within 1-2 hr

Frequently Asked Questions

- Q. Can Artemisinin be taken soon after or during radiation?
- A. No. Irradiated normal cells increase their transferrin receptors, allowing more uptake of iron and thus become sensitive to artemisinin. Artemisinin therapy can be started a minimum of two weeks after radiation (preferably more).

Frequently Asked Questions

- Q. Can artemisinin be given to smokers for the treatment of cancer?
- A. No, patients should have ceased smoking for at least two months before starting artemisinin. Research indicates that cells exposed to Benzo(a)Pyrene (primary carcinogen in cigarette smoke) have greater free iron content which makes even normal cells sensitive to killing by artemisinin.

Frequently Asked Questions

- Q. Do we need Holotransferrin?
- A. No we do not need Holotransferrin. Enough iron can be found in our daily diet.
- Q. What form of iron works with artemisinin?
- A. Artemisinin reacts with ferrous iron (Fe^{2+}). Transferrin carries ferric iron (Fe^{3+}) to the cell surface, the ferric iron is then converted to the ferrous form (Vitamin C can do this) and reacts with artemisinin.

Frequently Asked Questions

- Q. Should an iron supplement be taken along with artemisinin?
- A. No. This is not necessary. Iron is abundant in our diet in two forms: heme iron (found in animal products) and non-heme iron (found in plant products). Vitamin C helps in the absorption of non-heme iron, which is generally harder to absorb.

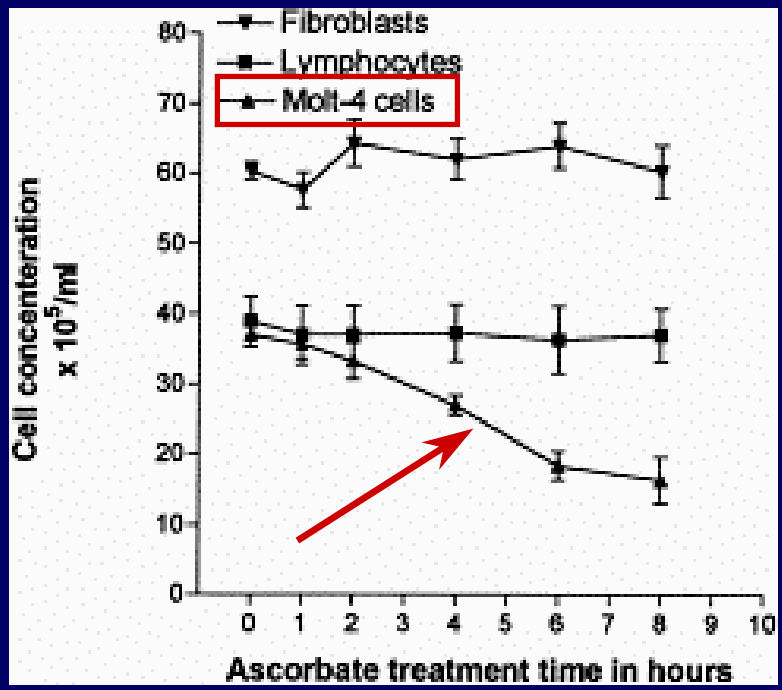
Frequently Asked Questions

- Q. Is a combination of Artemisinin derivatives better?
- A. A mixture of artemisinin, artesunate and artemether and is slightly better than individual components.

Frequently Asked Questions

- Q. How does Vitamin C affect the results?
- A. If taken after breakfast and after lunch, it enhances the iron absorption from the stomach. Iron is taken up more by cancer cells and thus Vitamin C makes cancer cells more susceptible for killing by artemisinin.

Frequently Asked Questions: Vitamin C



- Vitamin C also kills cancer cells in low doses without damaging normal cells.
- In Molt-4 cultures, a cell loss of approximately 40–50% was observed after 8 hours of treatment with Vitamin C (50 μM).

Frequently Asked Questions

- Q. How do other vitamins and antioxidants affect the results?
- A. Different studies show different results with vitamin E. Our own work shows glutathione enhances cancer cell growth and reduces the efficacy of artemisinin.

Frequently Asked Questions

- Q. What are toxic effects?
- A. In general, artemisinin and its analogs are relatively safe drugs with no obvious adverse reactions or noticeable side effects. Some patients complain of skin irritation and scratching in 1 to 2mg/kg/day doses.
- Anemia and weakness is reported by several patients on artemether but not by those on artesunate and artemisinin. Artemisinin does not have affinity to normal RBC unlike artemether

Frequently Asked Questions

- Q. How long the treatment should last?
- A. We have a very short experience, one pancreatic cancer patient is taking artesunate injections for last 22 months and a brain cancer patient taking artemisinin capsules for last 11 months. Artemisinin in low doses for a long duration may be safer anticancer treatment.

Frequently Asked Questions

- Q. Are there some on going clinical trial.
- A. No official clinical trial, but Dr. Joy Craddick MD (joyhealth@earthlink.net) and Dr. Dwight McKee MD (dmckeemd@aol.com) are conducting a clinical trial started 3 months ago on 30 cancer patients in Portland area. FDA approved a canine trial in DC area.