Exploiting intracellular iron and iron-rich compounds to effect tumor cell lysis

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Summary The regimen outlined in this brief paper focuses on therapeutically utilizing iron and iron compounds in transferrin receptor-rich tumor cells in ways that inhibit and lyse same.
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BACKGROUND
During the past 60 years a large body of laboratory and clinical data has accrued that demonstrates neoplastic cells require a great deal of iron to divide and thus tend to have high concentrations of this element. The oncolytic activity of many chemotherapeutic drugs, as well as that of radiotherapy, is potentiated or otherwise contingent on iron (1).

Recent developments and theory, when placed in sequence suggested by their effects (and/or anticipated effects) on neoplasia, yield a regimen that should readily lyse certain types of tumor.

One caveat is in order: The regimen that follows is oriented towards the eradication of malignancies that bear a large number of cell surface transferrin receptors. It is expected that this approach should produce less notable results in cancers that are transferrin receptor poor or whose (receptor) function is compromised.

FACILITATING ONCOLYSIS BY TARGETED MODULATION OF IRON

Hyperthermia therapy or thermoradiotherapy
Local if a well circumscribed tumor, wider scope or whole body if disseminated. The therapeutic objective is to increase tumor vascular permeability to ferritin, something hyperthermia and thermoradiotherapy was shown to do in animal studies carried out in Japan (2).

Iron loading
Here the goal is to the maximize intracellular iron levels of neoplastic cells. In the study cited in #1 (above), vascular permeability to ferritin occurred at one day following hyperthermia and three days following thermoradiotherapy. It follows that enhancing intracellular iron levels should be done in accordance with these findings.

Candidate forms of iron can include but is not limited to ferrous sulfate, ferrous citrate, ferrous gluconate, and iron-rich phthalocyanines, etc.

Supplemental ascorbate should be introduced to boost dietary absorption of iron (3,4).

Contraindicated: Use of drugs or ingestion of dietary substances that hinder or inhibit iron absorption, interfere with transport or utilization, e.g., plant phytates and tannins (wheat, tea, etc.), desferrioxamine, EDTA, manganese, zinc, ACE inhibitors, Levodopa, and tetracycline, etc.
Adjuvant/adjunctive measure: Use of exogenous insulin. Insulin could conceivably significantly boost uptake of iron by transferrin and/or possibly potentiate transferrin receptor function. This is suggested by both in vitro and in vivo studies (5,6). If chemotherapeutic drugs are utilized, insulin should increase their effectiveness while concomitantly reducing the dosages needed to achieve oncolysis. This is suggested by numerous published studies, as well as a wealth of case history data (7).

Pulsed electromagnetic field hyperthermia therapy

(Ferritin-mediated electromagnetic hyperthermia). The clinical objective: Expose iron-rich neoplastic cells to PEFHT, which will induce lethal thermal levels.

Adjuvants: Glucose (see below), quercitin hydrate [Normally tumors exposed to high temperatures develop thermoresistance via the production of heat shock proteins. Quercitin helps circumvent this process and thus leave the tumor susceptible to hyperthermia therapy. In cervical carcinoma cells, quercitin did not exert cytotoxic effects at normal body temperatures, but did potentiate hyperthermia-induced toxicity at 41 °C (8)].

In a paper published in Medical Hypotheses (9), the authors suggest that an alternating magnetic field no greater than ~100 KHz (kilohertz) should induce heating of intracellular ferritin sufficient to lyse tumor cells without adversely effecting normal tissues and cells. The iron core in ferritin is strongly paramagnetic and thus can be utilized to produce heat via the Brown and Neel effects (respectively). Since ferritin is often found at higher levels in neoplastic cells than normal ones, this makes achieving hyperthermia by way of an externally applied high frequency magnetic field very probable.

Japanese, German, and other researchers have published many papers indicating that intracellular hyperthermia sufficient to achieve cell lysis is possible employing magnetite cationic liposomes and other ‘magnetic fluids’ (10,11). The ferritin-mediated electromagnetic hyperthermia approach, while different from these, retains many features in common and should be explored in the laboratory and in well controlled clinical trials.

NOTE: Interestingly, there is published animal studies indicating that hyperthermia used in tandem with glucose administration enhances the tumor lysing impact of the former (12,13). Part of the reason this occurs may be related to the lowering of tumor microenvironment pH. Researchers at Jefferson Medical College found that i.v. and iv. plus oral glucose effectively lowered tumor extracellular pH in 17 nondiabetic cancer patients at Henan Tumor Hospital. They were looking into boosting tumor acidification as a potential thermosensitizer (14).

While dwelling on the merits of inducing electromagnetic intracellular heating using ‘magnetic fluids’ and/or ferritin (1999), it occurred to me that iron phthalocyanines (15) might be exploited to achieve sufficient intracellular hyperthermia to lyse tumor cells.

The phthalocyanines are being employed in photodynamic oncolytic therapy (research) with varying degrees of success. Since these compounds are selectively retained by tumors, resist photochemical and chemical breakdown, are essentially nontoxic, and can be synthesized readily with a neutron-activated nuclide (boron compounds) and as conjugates with epidermal growth factor (thus making tumor cell targeting more certain), they are very attractive to cancer researchers and research-oriented oncologists (16).

Setting aside the photodynamic uses aspect, it is the electromagnetic heating potential of the iron-rich phthalocyanines (PCs) which justifies their inclusion in the treatment protocols embodied in this paper.

Administration of the sesquiterpene lactone artemisinin or it’s analogs

Therapeutic goal: Lysis of remaining tumor cells by generation of free radicals brought about by the interaction of artemisinin or it’s analogs with iron. [Prior PEFHT treatment may increase artemisinin saturation of solid tumors by virtue of the fact that hyperthermia has been shown increase nonneurological vasodilation in cancerous tissue. This effect, modulated by nitric oxide (NO) whose formation is catalyzed by Fe2+ released by ferritin, is dependent on the ferritin content of neoplastic tissue (17). The iron loading phase of this regimen (step #2) helps assure the sufficient tumor Fe2+ is available for NO synthesis. (During hyperthermia therapy, cell-mediated immune responses are enhanced. These processes involve NO and subsequent free radical generation)]

NOTE: The use of antioxidants including ascorbate should cease, as use of same will scavenge very free radicals needed to achieve oncolysis. Treatment efficacy may be enhanced by concomitant or follow-up use of certain chemotherapeutic drugs and immunopotentiating/immunoaugmentative agents.

ARTESIMININ: BACKGROUND

Obtained from Artesmisia annua L. (Wormwood), artemisinin and its derivatives such as artesunate are employed to treat all forms of malaria. The latter, one of the most readily available and widely used analogs of artemisinin, has an endoperoxide bridge that reacts with iron (and especially heme) to form singlet oxygen as well as
free radicals. Following oral administration, artesunate is rapidly absorbed and reaches Cmax within 45–90 min. It is metabolized in the liver by hydrolysis to dihydroartemisinin. It has a very low level of toxicity.

**ARTEMISININ AS AN ONCOLYTIC AGENT**

On November 28, 1996 the United States Patent Office issued a patent to Henry C. Lai, and Narendra P. Singh (University of Washington, Seattle, Washington USA), for the use of ‘compounds having an endoperoxide moiety that is reactive with heme under conditions that enhance intracellular iron concentrations’. Among the compounds listed in this patent are artemisinin, dihydroartemisinin, arteether, arteether, artemunate, and artesunate salts (18).

The BACKGROUND section includes a citation of studies (mostly in vitro) indicating that various artemisinin derivatives were cytotoxic to specific tumor cell lines such as Erlich ascites tumor cells, while artemisinin ‘alone has been shown to be toxic to cancer cells in vitro at 20–180 µM range’ (…more effective for hepatoma and embryonic lung cells than against human gastric cancer cells) (19).

In the DETAILED DESCRIPTION section, four examples were furnished to indicate the oncolytic effects artemisinin and dihydroartemisinin:

(a) An in vitro study involving incubating Molt-4-lymphoblastoid cells and human lymphocytes to holotransferrin and dihydroartemisinin. A significant response (cell die off) was seen in the former, with much less in the latter (20).

(b) An in vivo study involving a 7-year-old canine (basset hound) with lymphosarcoma of the lymph nodes. Treatment with artemisinin (10 mgs/d) and ferrous sulfate (10 mgs/d per os) according to a specific schedule. Lymph nodes in multiple sites shrunken, many singificantly so. When treatment was stopped, all nodes increased in size. The animal survived 5 months post-treatment, then was euthanised (21).

(c) An in vivo study was carried out on a female canine retriever which had been operated on for hemangioepicytoma of the right thigh. Treatment with artemisinin (10 mgs/d) and ferrous sulfate (10 mgs/d per os) was begun on the animal one week post-op, and continued for 23 consecutive days. No tumor recurrence was observed during or at 3 months following treatment cessation (22).

(d) An in vivo study involving a 12-year-old female canine which had been diagnosed with a malignant mast cell tumor (grade 11) on the right thoracic wall. The animal underwent surgery, after which she was treated with ferrous sulfate (10 mgs/d per os) and artemisinin (10 mgs/d per os) for 7 days, followed by artemisinin alone (10 mgs/d per os) for the ensuing 10 days. The animal showed no evidence of tumor recurrence when examined 4 weeks following treatment. The pet’s owner reported no signs of recurrence at 4 months after therapy cessation (23).

Very recently, Lai and Singh reported observing very pronounced oncolytic effects in breast cancer cells treated with holotransferrin and dihydroartemisinin (Life Sciences Journal) (24).

**CONCLUDING REMARKS**

The regimen presented herein is consonant with many aspects of cancer cell biology, embraces components that have garnered at least a modicum of support from published studies, and structured to strategically take advantage of various biologic windows of opportunity to effect lysis in tumor cells (Especially those whose cell surface is rich in transferrin receptors).

**REFERENCES**


