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THE EMERGING LOW-DOSE THERAPY FOR ADVANCED CANCERS

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□ Generally minute doses of drugs have been prescribed in biotherapies, homeopathy, immunization and vaccinations for centuries. Now the use of low doses of drugs is on the rise to combat serious diseases such as advanced cancers around the world. This new therapeutic approach to address solid tumors and other advanced diseases is a departure from the conventional use of maximum dose protocol. A small dose of the prescribed drug is frequently administered in a continuous fashion, at regular intervals, either as a standard treatment or as a maintenance therapy for a long time. However, this new treatment method lacks any standard for drug quantization, dose fractionation, repetition frequency and duration of a treatment course for an individual patient. This paper reviews literature about metronomic therapy and discusses hormesis: both phenomena occur in low dose ranges. Better mathematical models, computer simulations, process optimization and clinical trials are warranted to fully exploit the potential of low dose metronomic therapy to cure chronic and complicated diseases. New protocols to standardize metronomic dosimetry will answer the age old questions related to hormesis and homeopathy. It appears that this new low-dose metronomic therapy will have far reaching effects in curing chronic diseases throughout the world.

Keywords: metronomic, homeopathy, apoptosis, hormesis, low-dose

BACKGROUND INTRODUCTION

The chronic diseases are now considered the major causes of physical disabilities and deaths worldwide. According to a World Health Organization (WHO) report, the chronic maladies around the world account for 59% of deaths and 46% for global burden of diseases annually (WHO 2008). The annual cost of treatment for chronic diseases was $277 billion and lost productivity reached over one trillion dollars in the USA alone during 2003. The incidences of chronic degenerative diseases affect every strata of population around the globe. The rise in cancer incidences has reached an epidemic level in the developing world. Most developing countries lack finances, infrastructure and expertise either to diagnose or to treat the advanced degenerative diseases affecting their growing populations (Bosanquet and Sikora 2004; Chirikos 2002; Tassinari *et al.* 2006). Hence there is an urgent demand to explore alter-

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native therapies and methodologies to address the health problems at all levels across the world.

Cancer is a hydra-headed chronic malady which produces pathological changes in a biological system. Such pathological changes are initiated at cellular levels. There are over two hundred types of cells in an average human body. Coincidently, there are about two hundred known types of cancers among human diseases repertory. A cancerous process may take at least a decade to grow to a detectable size. The typical predisposing cancer symptoms include melancholia and depression. A physician would be reluctant to administer any chemical drug or radiation therapy to a pre-cancerous patient simply because of the severe side effects associated with conventional Maximum Tolerable Dose (MTD) protocol. Furthermore, the above described symptoms may also be found in other common chronic diseases which do not require prescription of high chemo or radiation doses. However, conventional treatment approach toward chronic diseases may change if minimum-dose therapy protocol is adopted in routine clinical practice at an earlier disease stage.

A normal living cell inside a healthy body is able to tolerate a hundredfold potent drug dose compared to a single cell placed in a Petri dish. An injured cell inside a healthy body tries to repair and heal itself. An incurable cell is most likely to commit suicide during subsequent cell division processes. This altruistic behavior among living healthy cells is to protect the rest of the body from growing unwanted mutated cells. But at the same time, any living organism cannot evolve and adapt without controlled cellular mutations and differentiations. Hundreds of cancer laden mutations take place per day in a healthy normal size human body(Cameron and Moulder 1998).

These mutations are essential for the growth of our biological system. A healthy body cleanses itself of those mutated cells which fail to adapt to the new temporal-spatial conditions. If unnecessary stimulations repeatedly assault a normal cell for a long time and the body fails to adjust with necessary changes then hyperplasia takes place. A resilient healthy cell would take on average two to three years before it can develop into a hyperplastic state. Normally, a healthy system has sufficient time to recover from such mutations within hours.

Hyperplasia is not detectable with any of our existing diagnostic tools. If the unwanted stimulatory process continues for an additional two to three years, then the cell develops into dysplasia. Still it is considered a precancerous stage, which is not detectable through any existing means. It will take further two to three years for a dysplastic cell to develop into an in-situ cancer.

Our current biomedical and biochemical diagnostic tools can detect a cancerous mass only when it reaches an advanced stage. The conventional non-invasive diagnostic tools to detect cancer consist of ionizing

and non-ionizing radiations such as x-ray, Magnetic Resonance Imaging (MRI) and Ultra Sound (US). These diagnostic modalities use tiny particles/signals/waves which can cross through the living organism and produce images for analysis. However, these tools fail to detect small size tumors (Curry III *et al.* 1990).

The typical resolution of an x-ray image is about 3 millimeters (mm) in diameter. This x-ray resolving power grows worse in larger structures such as in the thoracic and pelvic regions where a minimum detectable size increases to 7 mm in diameter. A typical cancer cell has a diameter of about 10 micron (μm). It is estimated that there can be millions of cancer cells in a 3 mm tumor mass.

Oncologists have revised the classification of chronic diseases in an effort to address them at an earlier stage (Rost 2008). This modified early chronic disease treatment approach will only become possible after new technologies and low-dose protocols are applied. Today, researchers are investigating the application of nanotechnology for early diagnosis, drug processing and delivery of medicine to cure chronic diseases and advanced cancers in the near future.

The eradication of disease with relatively few side effects is the prime objective of every physician. Frustrated with conventional MTD outcomes, now physicians are increasingly resorting to the frequent repetition of low-dose chemotherapy administered regularly for a longer time. This methodology is described in the medical literature as Low Dose Metronomic Therapy (LDMT). It is expected that low-dose strategy may also produce better outcomes in patients suffering with chronic diseases. Such diseases, if left uncured at an earlier stage, are likely to progress into malignancies with the passage of time. Man *et al.* 2002 had reported the effectiveness and safety of the chemotherapeutic drug, cyclophosphamide at low doses, used on human orthotopic breast or ectopic colon cancer xenografts in nude or SCID mice. They conjectured that other drugs at low doses are likely to produce similar beneficial effects with less toxicity. After finding encouraging results in experimental animals, Kerbel *et al.* 2002, wrote an editorial about moving low-dose therapy from laboratory to clinical trials. Since then scores of research papers have reported encouraging results produced by LDMT as an anti-angiogenetic therapy in breast cancer patients alone (Colleoni *et al.* 2005; Colleoni 2006; duManoir *et al.* 2006; Mancuso *et al.* 2006).

Recently, Kamat *et al.* 2007 have studied the effects of low-dose chemotherapeutic drugs on ovarian cell lines in mouse model. They used about 60% of MTD of paclitaxel in HeyA8 cells, 50% of the MTD in SKOV3ipl cells, 6% of the MTD in HUVEC endothelial cell lines and 2.5% of the MTD in MUEC endothelial cell lines. The docetaxel dose in LDMT study was 35% and 32% of the MTD in HeyA8 and SKOV3ipl cell lines respectively. The use of docetaxel in endothelial cell line was only

2% for HUVEC and 6% for MUEC respectively. They have reported excellent clinical results and insignificant toxicity with LDMT in their experiment (Kamat *et al.* 2007).

The low-dose chemotherapeutic research for cancer patients began in 1972. All major pharmaceutical companies were involved in research and development of anti-angiogenetic drugs by 2002 (Brower, 2003). The strategy in anti-angiogenetic therapy is to attack the cancer-feeding endothelial vasculatures as well as the solid tumor itself. Gasparini has conducted scientific debate on the strategy, drug development and clinical indications for anti-angiogenetic agents and their scheduling (Gasparini, 1997, 2001).

Those physicians who seek the best care for their patients habitually keep themselves abreast of new findings. Such physicians in cancer care are gradually gearing toward this new low-dose methodology. By evaluating the positive early findings of anti-angiogenesis model, Miller has projected significant beneficial impacts to treat breast cancer with low dose therapy in routine clinical practice (Miller, 2004). Benefits related to low-dose chemo as a maintenance therapy for a long period of time has been reported in clinical practice (Munoz *et al.*, 2005). There have been reports of superior results with smaller doses in advance metastatic breast cancers, too (Munoz *et al.* 2006). A description about angiogenesis can be found in reference (Folkman, 2003).

Low-dose chemotherapy has been documented as an efficacious modality in ovarian cancers (Kamat *et al.* 2007; Garcia *et al.* 2008). Franchi *et al.* 2007 have reported that repetition of low-dose cancer drugs continuously for some time has low toxicity. They observed low toxicity associated with metronomic therapy in those patients suffering with advanced cancer who refused the aggressive standard therapies (Franchi *et al.* 2007). They urged an evaluation of the low-dose system and questioned the benefits of existing high-dose strategy over it. After critical analysis, Baruchel and Stempak, 2006, have concluded that low-dose metronomic chemotherapy is a clinical reality in the making.

Low-dose therapy acts as a double-edge sword against cancer: it attacks both the tumor-feeding endothelial vasculatures and the solid tumor. Shimizu and Oku, 2004, have reported that metronomic therapy spans over different phases of diseases which exist in precancerous states in human organism.

LESS IS MORE BUT HOW MUCH LESS?

Specific research in cancer has discovered the promising beneficial effects of micronutrients found in spices, herbs, conventional drugs and common foods. However, the correct dose, either as chemopreventive or therapeutic, has remained elusive to the scientific community. Scientists have found in various cancer research studies that small doses of

chemotherapy administered for a long period of time showed promising results in mouse models (Hanahan *et al.* 2000; Kamen *et al.* 2000; Kamen, 2005; Kamen, *et al.* 2006; Piccart-Gebhart, 2003). Young *et al.* 2006, have reported that low dose combination therapies proved beneficial in various advanced solid tumors with minimal toxicity to patients. Unfortunately, there is no "minimum-dose" standard defined for chemical drugs or ionizing radiation in medical literature. This is due mainly to the multiphase dose response in living organisms. One such example is arsenic trioxide (As_2O_3), now a standard chemotherapeutic drug used to treat Acute Promyelocytic Leukemia (APL). Interestingly, the drug is now being tested to treat other solid tumors. Arsenic Trioxide, like many other drugs, produces multiphase effects in cancer patients (Liu *et al.* 2006). Bertolini *et al.* 2003, have reported that As_2O_3 produces opposite effects on circulating endothelial progenitor cells when used at concentrations of MTD and LDMT.

Earlier, Bocci *et al.* 2002, pointed out that low-dose As_2O_3 has different narrow windows of actions in varied concentrations for human endothelial cells. Arsenic trioxide can either promote or inhibit angiogenesis, based on the amount of the dose (Soucy *et al.* 2003, Snow *et al.* 2005). We do know there exists a narrow window for each drug to produce specific reactions in a particular living organism. In that cancer cells are not an integral part of the natural organization of a living system, they respond differently to different stimulus, such as heat or specific doses of a drug. Below a specific dose, the cancer cells cease to respond. Such a study has been conducted by Walchli, *et al.* 2006 in which they have found normal primary lymphocytes responded to highly diluted homeopathic remedies, whereas, cancerous lymphocytes did not respond to such dilutions at all.

NANO PARTICLES

Drug-induced effects on living organisms can be further enhanced by modifying the drug manufacturing methods. New manufacturing processes can improve the bioavailability of active ingredients, even at lower drug concentrations. Such techniques can also enhance the biological effects, even with smaller doses. These novel strategies are likely to introduce new challenges to low-dose therapies. One such drug manufacturing process is based on nano technology. The nano particles are distributed over a wide area, which improves their surface chemistry for optimal reactions—proving to be much greater compared to bulk-scale chemicals. Fukai *et al.* 2006 have reported that As_2O_3 at nano-molar concentrations, as opposed to micro-molar, is sufficient to produce significant therapeutic effects in APL cells, provided other natural sources of arsenic, such as found in seafood, are restricted for a few days (Fukai *et al.* 2006). It is interesting to note that such dose-dependent multiphase bio-

logical reactions are not limited to particular chemical drugs. Dose-dependent dual effects have also been found in common herbal medicine (Barajas-Farias *et al.*, 2006, Jimenez-Medina *et al.*, 2006).

The resolution of a correct chemical concentration of a drug in low-dose chemotherapy is a challenge to both researchers and clinicians. Lam *et al.* 2006 have called on the scientific community to develop tangible scientific methodologies for metronomic therapy. They fear that mere simple empiricism may give rise to skepticism (Lam *et al.* 2006). The issue of dose strength becomes more complicated when combination drugs are used in cancer treatment. Yap *et al.* 2005 have showed that complementing various cancer drugs in small doses can produce optimal treatment results in mice, modeled after prostate cancer. Cancer researchers have also found that a combination of chemotherapy bolus dose and low oral-dose treatment makes the best strategy to combat cancer on a long-term basis in a human melanoma grown subdermally in nude mouse model (Shaked *et al.* 2005a).

Maraveyas *et al.* 2005 have questioned if any rationale dose strength can be designed for small-dose therapy. Drug quantization for low-dose therapy is the core problem because a multitude of biological reactions, such as stimulation, feedback, compensation, apoptosis, etc., have very narrow windows specific to individual constitution and the chemical concentration of a particular drug in the low-dose region. The search for optimal low-dose drug standardization is an ongoing unsettled issue in the medical community (Adjei, 2006).

ANTI-ANGIOGENESIS

An alternative approach to treat cancer is to attack the endothelial vasculature, which supplies nutrients to a tumor. This approach also requires smaller drug doses, compared to conventional MTD protocol. Shaked *et al.* 2005b have proposed the optimal dose associated with angiogenetic activity. The anti-angiogenetic therapy is claimed to be safe. It does not seem plausible that anti-angiogenetic therapy is absolutely free of any side effects. This strategy has its own shortcomings, due mainly to a time-dose fractionation schedule and the amount of dose of a particular drug appropriate to an individual patient. Chemotherapeutic drugs produce coagulation as an unwanted side effect in an antiangiogentic therapy. Ma *et al.* 2005 have expected that the use of low-dose chemotherapy would reduce the incidence of adverse clotting effects. Rozados *et al.* 2004 have claimed that low dose chemotherapy produced regression in rat tumors without any toxicity. But De Pas *et al.* 2005 have recommended an extensive study to ascertain the long-term real effects in metronomic therapy. Emmenegger *et al.* 2004 produced a detailed comparison of toxic effects between LDMT and MTD for Cyclophosphamide on highly sensitive tissues.

BEYOND HORMESIS

Hormesis is defined as the low-dose stimulatory and high-dose inhibitory processes observed in biological systems. An extensive literature database comprising hormesis is available in research journals and on the Web. As of June 10, 2008, the PubMed database search, containing the name “hormesis” returned 572 papers in medical journals. The word ”metronomic” in the same database yielded only 210 published articles. Like metronomic therapy, hormesis occurs in low-dose radiation energies and chemical concentrations.

Unlike hormesis, low-dose metronomic therapy is a new concept with claims of better effects, few to no side effects, and inexpensive. It is expected to radically change the practice of medicine related to chronic diseases in the future. Both metronomic therapy and hormesis take place in the low-dose chemical regions. Hormesis is generally considered a biphasic biological phenomenon that can result from stimulatory, compensatory, feedback or simple cellular repair processes (Calabrese, 2004). On the other hand, a different set of diseases requires a different mode of cellular reactions to heal a sick body. For example, an immune-stimulating process may be needed to heal an infection or cancer. On the other hand, immune boosting is usually discouraged in auto-immune diseases such as rheumatism. A cellular compensatory process may be deemed necessary to repair endocrinal systems.

It has been observed that a living organism develops resistance through different reactive mechanisms after being exposed to subtoxic doses of radiation and chemicals (Macklis and Beresford, 1991, Davies *et al.* 2006). Evolution of such a biological robustness in a living system is possible at different levels, i.e., DNA to organ levels. Minute amount of viruses can stimulate the DNA, which in turn affects the cell, organ and subsequently the entire body. Biological reactions induced with subtoxic doses are the multiphase stimulatory processes which result from interaction between the body's cellular systems and the energy supplied by a drug interaction or radiation exposure. The exact dose of a particular chemical to induce a specific kind of reaction in a particular biological system has not yet been quantified in scientific literature. It appears that diseases involving sluggish biological reactions are most likely to benefit from the biological reactive phenomenon such as hormesis. However, classification of such diseases, the health status of an individual, the amount of drug, its possible mode of administration and the expected stimulatory processes and their possible outcomes must be spelled out in concrete research settings.

On the other hand, hormetic effects induced by common foods are undisputedly recognized as health benefits in the scientific community (Mattson and Cheng, 2006). Hormetic benefits have also been realized in

subjects under stress, annoyance and noise (Rylander, 2004). Such beneficial effects are due to cellular compensatory responses to external stimulus. Again, the nature of cellular reaction depends on the amount of dose, time of administration, biological status of the organism and the previous levels of exposure to same or similar stimulants.

Hormetic benefits induced in one cell can also produce useful effects in bystander cells. Similarly, stimulation of one system can produce certain effects in another connected system in an integrated environment such as the human body. For example, any improvement in the respiratory system can enhance the cardiovascular efficiency by virtue of elevated oxygen uptake in the alveoli. This can lead to an efficient production and utilization of energy at the (w)holistic level. In a nutshell, bio-effects, such as hormesis, deserve due attentions as their unique integrated dynamical effects on living organisms can help heal the chronic diseases with less toxicity to the ailing body. Cuttler 2007 has rightly questioned the common sense for ignoring the role of low-dose effects on living organism. But realization of such a new approach to heal the sick in an established conventional medical practice is an uphill battle.

Biological effects based on nonlinear dose-response models, such as in hormesis, have been under severe criticism by various groups for a variety of reasons. Such a stereotypical attitude toward hormesis has so far made it unlikely to form the foundation of low-dose therapy in its present form (Thayer *et al.* 2005, Mushak, 2007). However, such an attitude is likely to change in the era of emerging metronomic therapy. The low-dose issue poses a great challenge to define the drug-dose decision for clinical practice, especially in metronomic therapy (Thayer *et al.* 2005, Lutz *et al.* 2005). Some of the information about cell stress and hormesis at molecular levels is well known but their concrete utilization in routine clinical practice has thus far been elusive (Agutter, 2007).

It appears there is an overlap of dose response between hormesis phenomenon and metronomic therapy in that both occur in the low-dose regions, as defined by the MTD standards. Standardization of drug-dose protocol for metronomic therapy will greatly pave the way toward recognizing the beneficial effects of hormesis in a biological system. A team of researchers have tried to scientifically elaborate hormesis with reference to dose-response phenomenon (Calabrese and Blain, 2005; Calabrese *et al.* 2007). There are many unanswered questions, such as time-dose fractionations, when it comes to applications of hormesis in routine clinical practice. Calabrese 2007 has expressed a great deal of frustration at the absence of such a clear-cut dose demarcation and lack of quantitative models in hormesis.

Calabrese and Baldwin 1998 have proposed hormesis as a possible biomedical hypothesis in a rigorous fashion. Cancer can also be initiated due to continued stimulatory processes, which generate multiple muta-

tions in single or multiple cells. Kinoshita *et al.* 2006 have discussed the implications of hormesis in carcinogenesis. This murky area needs crystal clear analytical foundations to develop a drug dose-based effective therapy for routine clinical practice. Stumpf 2006 has correctly pointed out it is not a linear issue. Doses differ quantitatively and qualitatively in their actions on a living organism. There is no lack of enthusiasm to utilize the hormetic phenomenon in clinical practice. Yun *et al.* 2005 have hypothesized to utilize the compensatory response of cells to treat chronic diseases. All the objectives require a comprehensive planning framework at pharmaceutical, biological, therapeutic and clinical levels.

CONCLUSION

The research database concerning continuous administration of low-dose chemotherapy reveals compelling evidence of its effectiveness and superior clinical results in cancer patients.

The use of low-dose chemotherapy for advanced cancers is on the rise. The main reasons, among others, for the new strategy are its reported effectiveness, alleged little to no toxicity and relative economic benefits (Bocci *et al.* 2005). The biological responses at low doses are known to the scientific community in the form of hormesis, homeopathy, immunization and vaccination practices. The drug concentrations in homeopathy can be extremely small, which sometimes lead beyond the possibility of finding a single drug atom or molecule in an entire bottle. Furthermore, there is no established drug standardization metric for its dilutions in homeopathy (Satti, 2005). However, homeopathic drugs are intended to produce reactions in a sick person. Such a reaction can be initiated with extremely small amounts. Hormesis, on the other hand, is a biological reaction that can also be initiated in a normal healthy system (Chen *et al.* 2006). A potent dose of a drug is required to produce any reaction in a healthy system. The dose can be more potent than the drug dose used in homeopathy. The normal amount of drug dose used in metronomic therapy must be sufficiently potent to kill an unwanted cancer cells. However, such drug-dose concentration is much less than the MTD. It appears that the dose concentration levels in hormesis and LDMT are comparable or overlap considering their similar actions at cellular levels.

The current trend of using low-dose therapy in advanced cancers is likely to steadily rise in the future because of its effectiveness, low toxicity and affordability. But the issues of time-dose fractionation are still greatly unresolved. A great deal of scientific literature is available about low dose effects, commonly known as hormesis. There is a need to develop new models, conduct simulations and run clinical trials to fully exploit the low-dose potential against chronic diseases, especially cancer.

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