PROVIDING INTEGRATIVE ENERGY IN CANCER: METABOLICALLY TARGETED THERAPY

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ABSTRACT

Cellular metabolism provides the energy for genes and proteins to be made, which subsequently influences the metabolic rate of a cell. Metabolic dysfunction is at the heart of a multitude of clinical conditions, including cancer. This paper will focus on cancer as an example of how to use integrative energy to combat metabolic dysfunction. This approach may be viewed as a metabolically targeted therapy (MTT). One example of MTT is palladium lipoic acid complex (PdLA). PdLA is composed of the transition element palladium covalently bound to the antioxidant alpha-lipoic acid, which enhances its solubility. PdLA is the active ingredient in a dietary supplement called Poly MVA. PdLA has the ability to donate electrons to the mitochondria of the cell, and this appears to be the key to its physiological effectiveness. The aims of this paper are to: explore metabolically targeted therapies; to introduce the unique PdLA supplement Poly MVA; and to provide data to support using PdLA supplements to target metabolic dysfunction.

INTRODUCTION

The genomics field has allowed major clinical advances. It began with the discovery of DNA over 60 years ago, and moved to the forefront with the completion of the Human Genome Project in 2001. Dr. Francis Collins, the Director of the National Institute of Health Human Genome Project, summed up his view regarding this major accomplishment with the following: *"For me, as a physician, the true payoff from the HGP will be the ability to better diagnose, treat and prevent disease, and most of those benefits to humanity still lie ahead."*(Collins, 2001) The expression, regulation and suppression of genes have led to this field in medicine focusing on genetics. Therapies are now designed based on the presence, absence, or identification of a particular mutation, in a specific gene. However, genomic evidence ("nature") may not necessarily translate

into a disease state. Frequently, environmental triggers ("nurturing") are necessary to initiate the etiology of the condition (i.e. stress, carcinogens, viruses, etc.). In addition, a number of genes must be translated into a protein, in some cases an aberrant protein, in order to perpetuate a disease state. This field is referred to as proteomics, and is just as important to medicine. Collectively attacking these key molecules in cancer (and in short order, other diseases) are referred to as Molecularly Targeted Therapy.

However, this definition can not narrowly end at the gene and protein level. Interactions within a cell are just as important as systemic interactions throughout the body. Cellular metabolism provides the energy for genes and proteins to be made. Likewise, certain genes and proteins affect the metabolic rate of a cell. Metabolic dysfunction is at the heart of a multitude of clinical conditions. This paper will focus on cancer as an example of how to use integrative energy to combat metabolic dysfunction. This approach may be viewed as a Metabolically Targeted Therapy (MTT).

Cancer is the leading causes of death in the United States. According to the American Cancer Society (ACS, 2008) approximately 11 million people, with a history of cancer, were alive in 2006. Unfortunately, more than 1.4 million new cases of cancer will be diagnosed this year, only adding to those staggering numbers. However, with all the treatment advances, the ACS still estimates that well over half a million people will die this year from cancer.

METABOLIC DYSFUNCTION IN CANCER

Metabolic dysfunction in cancer cells is related to neoplastic hypoxia. There are three categories of hypoxia associated with neoplastic disease:

- Perfusion hypoxia – increased anaplasia results in irregular angiogenesis and subsequent poor tissue perfusion.
- Diffusion hypoxia – with rapid mitotic rates vascular supplies are unable to keep up with demand.

- Anemic hypoxia – as the hematocrit decreases the oxygen content of the blood is reduced, therefore the amount of oxygen delivered to the tissues is also reduced. This type of hypoxia is usually a side effect of treatment. (Weinmann et al., 2004)

Consequently, varying degrees of hypoxia are associated with neoplastic disease. It is well documented that the level of hypoxia correlates to the degree of anaplasia (Miles, 2008; Pauwels and Mariani, 2007). Since the malignancy is becoming less specialized, it can proliferate more quickly, allowing the vascular perfusions to lag further behind, as well as, facilitate further compensatory blood vessel malformations. In effect, this exacerbates the hypoxic condition.

How do cancer cells respond to a hypoxic environment? Hypoxia switches on a gene called hypoxia inducible factor (HIF-1), which triggers a series of physiologic adaptations in cancer cells. These adaptations enable the cells to derive their energy from anaerobic metabolism (glycolysis). In a normoxic state HIF-1 is catalytically destroyed by an enzyme called Von Hippel-Lindau (VHL) protein. In a hypoxic state HIF-1 levels begin to rise, and HIF-1α forms a dimer with HIF-1β (a non-hypoxia related molecule), and this activates HIF-1.

So, the role of HIF-1 is to allow physiologic and metabolic adaptation to a neoplastic environment, but how does it do this? HIF-1 induces both a compensatory response and an adaptive response by upregulating a number of genes. In terms of a compensatory response HIF-1 upregulates vascular endothelial growth factor (VEGF) in order to improve vascularization by stimulating angiogenesis and erythropoietin (EPO) in order to increase blood cell specialization. In order to help cells adapt to the neoplastic environment HIF-1 upregulates genes that favor anaerobic metabolism, such as glucose transporter 1 (GLUT 1) and glycolytic enzymes, which both facilitate anaerobic respiration. HIF-1 also upregulates carbonic anhydrase 9 (CA9). Carbonic anhydrase (CA) is responsible for converting carbon dioxide to carbonic acid for transport out of the cell, CA 9 is an altered form of CA that actually hinders this process, thus resulting in a pH disruption within the cell which is advantageous to cancer cells. (Bacon and Harris, 2004; Escuin et al., 2004; Paul et al., 2004).

Thus it can be seen that metabolic dysfunction enables tumors cells to grow out of control, however MTT may enable us to use metabolic dysfunction to our advantage.

TAKING ADVANTAGE OF METABOLIC DYSFUNCTION

There is evidence to suggest that providing an alternative energy source to the mitochondria, the primary site of aerobic metabolism, in a hypoxic neoplastic state induces localized free radical generation and selectively destroys cancer cells (Gogvadze et al., 2008). In contrast, normal cells, which are well oxygenated, are supplemented by this extra energy source and thrive.

Palladium Lipoic Acid Complex

PdLA is a potent redox molecule composed of the element palladium bound to the antioxidant lipoic acid. PdLA exists as a dietary supplement called Poly MVA. This name was coined since it is composed of minerals, vitamins, and amino acids (MVA). In addition to the PdLA complex, the proprietary formulation contains thiamine, riboflavin, cyanocobalamin, formyl-methionine, and acetyl-cysteine.

There is no free lipoic acid or palladium in PdLA, they are covalently bound. Dr Merrill Garnett, the man behind PdLA, linked lipoic acid and palladium in order to increase its solubility, as well as create a polymer structure. Redox polymers more efficiently accept and donate charge, compared to single molecules. This allows the PdLA complex to serve as an energy source. (Garnett, 1995)

What exactly does this mean at the cellular level? When glucose enters a cell it is broken down under anaerobic conditions into pyruvate. Pyruvate subsequently enters the mitochondria, via complex I, and is quickly oxidized to acetyl-CoA, as can be seen in Figure 1. Lipoic acid and thiamine, two vital ingredients in the PdLA complex, are essential cofactors in the conversion of pyruvate to acetyl-CoA. Therefore, lipoic acid and thiamine help the PdLA complex to directly target the mitochondria. In the subsequent aerobic respiration steps, acetyl-CoA is then channeled into the Krebs/Citric Acid cycle to create the reduced forms of nicotinamide adenine

dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$). NADH and $FADH_2$ serve as high energy intermediates and donate their electrons to the electron transport chain to drive the phosphorylation of adenosine triphosphate (ATP), the cell's primary energy source.

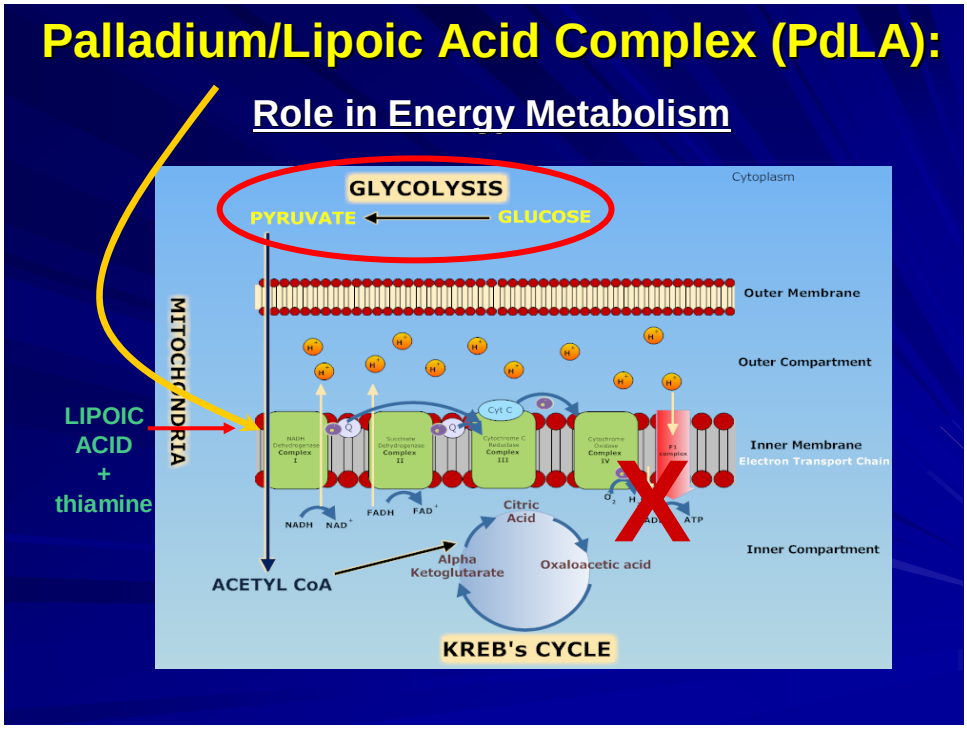

Figure 1. PdLA provides energy directly to the mitochondria of the cell.

Since the PdLA complex also serves as a high energy transferring molecule at the mitochondria, it will facilitate aerobic metabolism. Its role as a metabolically targeted therapy will vary based on the state of a cell: a healthy, richly oxygenated cell will benefit; while a neoplastic, hypoxic cell will be metabolically taxed. This taxed neoplastic cell may now be more vulnerable to destruction via radiation and chemotherapeutic intervention, rendering the PdLA formulation as an integrative therapy. However, this PdLA-induced metabolic manipulation alone may generate cell death via apoptosis and necrosis.

Palladium Lipoic Acid Complex and Cellular Energy

Recently, a study was conducted to evaluate the effect of PdLA on the decline of mitochondrial enzyme activity and respiratory chain complexes in aged rat's hearts. PdLA was

orally administered (0.05mL/kg daily- equivalent human dose of ½ tsp.) to aged rats (approximately 2 ½ years old) for a total of 30 days. Biochemical assays revealed that treatment with PdLA led to statistically significant increases in the metabolic efficiency of Krebs cycle enzymes – including malate dehydrogenase (MDH), succinate dehydrogenase (SDH), isocitrate dehydrogenase (ICD), and alpha-ketoglutaric acid dehydrogenase (αKGD) – and significantly enhanced complex I and II activity in the electron transport chain, thus increasing the metabolic rate of the mitochondria. Furthermore, previous studies have demonstrated by increasing the cellular energy demand (workload) on aged, rat-heart mitochondria, via supplementation, the mitochondrial morphology was more indicative of younger tissue compared to that of untreated control animals. (Sudheesh et al., 2009)

Another study that has produced exciting and extremely promising results was a clinical observation, by a leading veterinary oncologist, of five post-chemotherapy canines in remission from lymphoma. These fatigued dogs were each administered 2 drops/10 pounds (0.022mL/kg – equivalent human dose of ¼ tsp.) of a PdLA supplement for 2 weeks. Urine was collected prior to starting the supplement and after the two testing week period. The samples were sent to Genova Laboratory, Inc. for a "Cellular Energy Profile". Results of this study showed that treatment with PdLA supplement led to an increase in 41 out of 45 Krebs cycle markers, thus indicating that treatment enhanced cellular energy. Taken together, these results show that PdLA is able to direct energy to the mitochondria.

Palladium Lipoic Acid Complex and Cancer

We now know that PdLA provides an additional energy source to normal cells, but what about cancer cells? As we established earlier, hypoxia caused by a neoplastic environment causes metabolic dysfunction, is it possible that this metabolic dysfunction could be used to our advantage? Could a MTT like PdLA trick the mitochondria in cancer cells to induce apoptosis?

To determine whether this might be possible we contracted the services of KGK Synergize, Inc. They looked at nine different cells lines: human skin melanoma (SKMel-5), human liver hepatocellular carcinoma (Hep G2), human lung malignant melanoma (Malme-3M),

human mammary gland ductal carcinoma (MDA-MB 435), human prostate left supraclavicular lymph node carcinoma (LNCaP), human colon colorectal adenocarcinoma (HT-29), human brain glioblastoma astrocytoma (U87), glioblastoma (H-80), and canine osteosarcoma (D-17). Within 48 hours most of the lines demonstrated a dose-dependent cell death. Any variations in its effectiveness appeared to be due to the particular cell line used, its doubling time and its degree of anaplasia. These findings corresponded to our metabolic laboratory findings on effectiveness.

One of these lines was from a chemotherapy and radiotherapy resistant brain tumor isolated from a patient. To our astonishment, when we exposed these cells to very low doses of PdLA the cells started to shrink, become pyknotic, and die. It is important to emphasize that the cells become pyknotic and shrink, they do not swell up and explode, which occurs in necrosis. This suggests that cell death is being triggered by a cellular metabolic attack via apoptosis (programmed cell death). Higher dosages appear to be necessary to induce necrotic cell death.

Our pre-clinical experiments have demonstrated that the excess electrons sent to the mitochondria by PdLA have less oxygen to accept them in metabolically dysfunctional cancer cells, and that this results in a local generation of free radicals at the inner mitochondrial membrane. This activates apoptosis by facilitating the release of cytochrome C from the mitochondria, allowing the formation of an apoptotic complex in the cytoplasm. This complex, results in the subsequent activation of the caspase cascade of enzymes that destroy the malignant cells. (Fig. 2) Given that healthy cells are richly oxygenated, PdLA is nontoxic to them and they actually benefit from the energy boost.

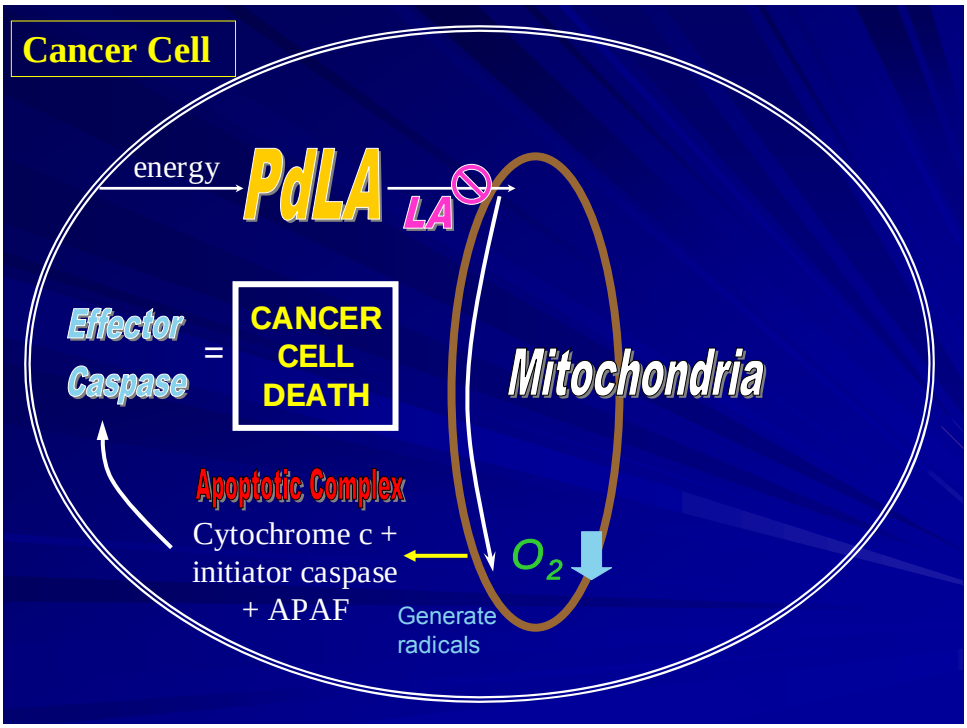

Figure 2. The mechanism by which PdLA induces cell death in cancer cells.

Some of the most exciting work carried out on the use of PdLA to treat cancer is that of a large scale study in dogs conducted at California Veterinary Specialists by Dr Gregory Ogilvie. The animals received the PdLA supplement Poly-MVA as part of their chemotherapy/radiation and/or surgical protocol at a dosage of 1 ml/5 pounds body weight orally twice daily – a comparatively similar dose to that used in human clinical studies. Results of the study showed that PdLA was most effective in the treatment of solid tumors, such as soft tissue sarcoma, hemangiosarcoma, mast cell, transition cell carcinoma, lung, anal sac carcinoma, renal carcinoma, squamous cell carcinoma, fibrosarcoma, melanoma, menigioma, neuroblastoma, and mammary adenocarcinoma. One of the best responders in this open-labeled study was osteosarcoma.

Canine osteosarcoma is frequently looked at in comparative oncology programs since it has a direct correlation to the etiology of the human disease. While in canines the “standard of care” is limb amputation followed by chemotherapy, in human patients, limb–sparing surgery following tumor excision is performed (Ogilvie and Moore, 2006). In this study, Dr Ogilvie

assigned the dogs to receive one of three treatment modalities: amputation with poly-MVA, amputation with chemotherapy, and amputation with chemotherapy and poly MVA. These results were compared with the historical controls of amputation alone. The results are shown in Figure 3.

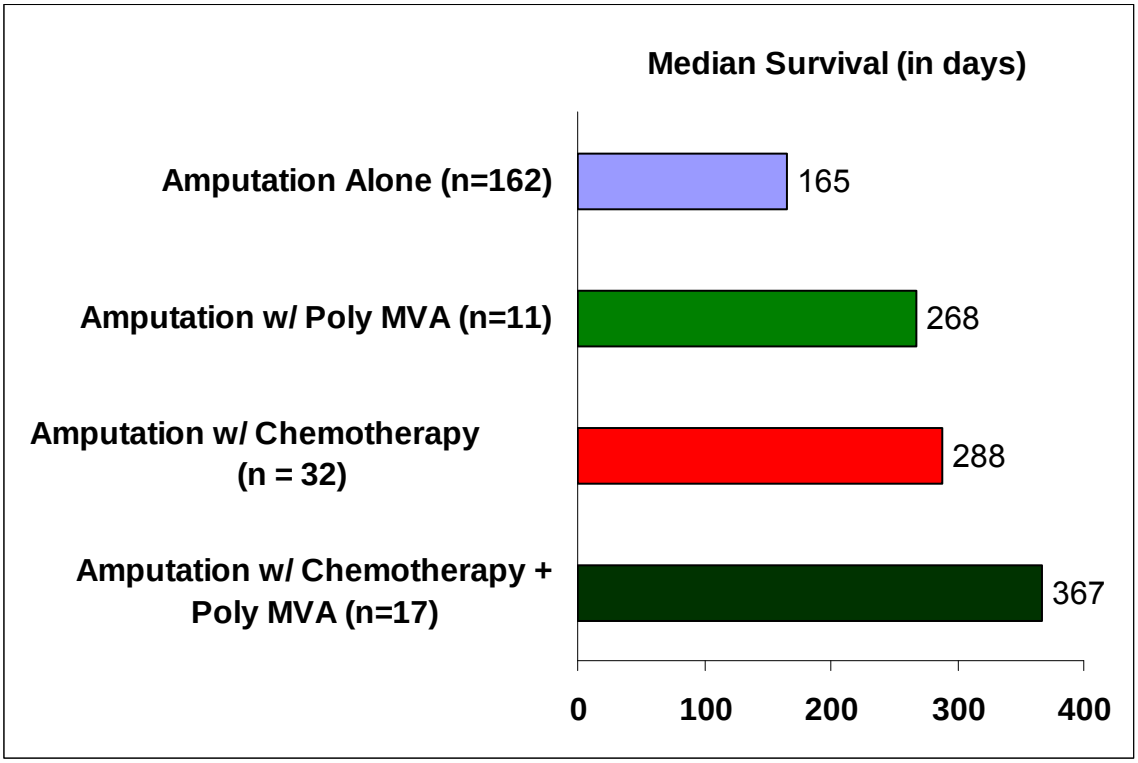

Figure 3. Results of Dr Ogilvie's study of the use of Poly-MVA in the treatment of canine osteosarcoma.

So, we can see that the PdLA supplement Poly-MVA increased survival by 103 days (62%) compared to surgery alone, and when used in combination with chemotherapy it increased survival by 79 days, or almost 30%. Furthermore, there was no significant difference between the mean survival of those animals treated with amputation/Poly MVA and amputation/chemotherapy (the chemotherapeutic regimen = carboplatin + doxorubicin). What was extremely exciting in these finding is that these animals not only had an increase in their survival rate, but their quality of life and additional objective clinical parameters improved (weight, anemia, liver and kidney panels). Additionally, 86% of the animal owners responded that they observed an improved quality of life in their pet (Ogilvie, 2009 in preparation).

Data on PdLA's benefits are not limited to animal clinical studies. An observational study of stage IV cancer patients began in January 2004 under the direction of Dr. James Forsythe. Over 212 stage IV patients were in this cohort, with prostate, breast and lung cancer being the best responders. The typical oral dosage used was 40 mL or 8 teaspoons per day.

There is currently a human clinical study of PdLA called the Dose Escalation Safety Study in Normal Individuals (DESSTINI) Trial, in which normal, healthy people are taking PdLA supplement at a major research university. Thus far two of the three tiers of the study have been completed (2 & 4 tsp. per day). There were no serious adverse events in patients. (A study of patients receiving 8 tsp per day is ongoing.) The most common adverse effects were gastrointestinal; in all cases these symptoms resolved. The DESSTINI Trial is the first phase of a formal protocol exploring the use of PdLA as integrative therapy, along with chemotherapy and radiotherapy, for the treatment of brain cancer.

CONCLUSION

In summary, PdLA appears to be a selective metabolic modulator. Since it is a potent redox molecule, it has the ability to provide an alternative energy source to cells. While this is of benefit to normal cells, it is detrimental to cancer cells, acting as a Metabolically Targeted Therapy. Studies also suggest that PdLA can improve the patient's quality of life. Furthermore, unlike many treatment modalities PdLA does not cause any severe adverse effects.

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