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Short Review

Orthomolecular Medicine, Micronutrients, High Dose Vitamin C, and Cancer: Why it Should be Revisited?

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Abstract

Orthomolecular Medicine is a form of alternative medicine, with a purpose to maintain human health through nutritional supplementation. The concept builds on the idea of an optimal nutritional environment in the body and that diseases reflect deficiencies in this environment. Treatment for disease involves attempts to correct the imbalances or deficiencies based on individual biochemistry by use of substances such as vitamins, minerals, within others. The approach is referred as megavitamin therapy, such as high dose intravenous vitamin C. The practice has evolved and uses doses of vitamins and minerals many times higher than the recommended dietary intake. Micronutrients, such as vitamins and minerals, play crucial roles in human nutrition, including the prevention and treatment of various diseases and conditions such as cancer. In Oncology, response rates, survival rates, toxicity profiles, compliance and cost-effectiveness as well as integrating psycho-social issues are related to the nutritional status of cancer patients. We need to work harder regarding the use of those micronutrients in this 21st Century for the benefit of our cancer patients.

Keywords: Cancer; Integrative Oncology; Micronutrients; Orthomolecular Medicine; Vitamin C

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Introduction

The Burden of Cancer in the United State is very high. An estimated 1,735,350 new cases of cancer will be diagnosed in the United States on 2018 and 609,640 people will die from the disease. The number of new cases of cancer is 439.2 per 100,000 men and women per year (based on 2011-2015 cases). The cancer mortality is 163.5 per 100,000 men and women per year (based on 2011-2015 deaths) [1]. All patients with cancer will undergo either one of the modalities of therapy such as surgery, radiation therapy or chemotherapy. More than 40% of oncology patients develop signs of malnutrition during treatment [2]. Malnourished patients incur in higher costs for their care. Their malnutrition have impacted responses to treatment, greater risk of drug toxicity, and increased rates of morbidity and mortality compared to patients with normal nutritional status.

In view of high risk potential for malnutrition and side effects from chemotherapeutic agents, those patients' benefits from nutritional supplements and vitamins, although some evidence states that it's controversial. Recently calorie-restricted dietary regimens and compounds such as vitamins, curcumin, green tea extracts and omega-3 fatty acids have attracted attention for their potential anticancer effects. While definitive conclusions cannot be drawn in this field, many patients adopt complementary anti-tumor therapies aiming to improve efficacy or reduce toxicity of chemotherapy, with uncertain benefits and the risk of additional toxicities or antagonistic interactions with standard therapies [3]. On the contrary, the role of specific interventions or supplements in patients with advanced malignancies is much more uncertain and actually a highly debated topic.

On the other hand, significant evidence sustained that IV Therapy with vitamins such as vitamin C, glutathione is beneficial for cancer patients [4-6]. In this review, will discuss the importance of this role in oncology and it should be revisited.

Orthomolecular Medicine and Micronutrients

Good nutrition is important for our health. The goal of orthomolecular medicine is to provide the best molecular habitat for the brain and other organs by changing/improving the intake of nutrients such as vitamins, minerals, trace elements and other naturally occurring substances. Orthomolecular is a term originally from the Greek word for "correct" (ortho) and "molecule", so it literally means the "right molecule". According to Linus Pauling, orthomolecular medicine involves the practice of preventing and treating disease by providing the body with optimal amounts of substances which are natural to the body [7].

The role of orthomolecular medicine is to restore the ideal and beneficial environment of the body by correcting molecular imbalances, and this approach is used in cancer, infections, depression and atherosclerosis, among others.

Micronutrients are often referred to as vitamins or minerals. They are required only in small amounts, but are important for production of enzymes, hormones and other substances that are needed for proper

growth and development. Even though only small amounts are needed, their deficiency has severe consequences. Important micronutrients are for example iodine, vitamin A, iron, folate and zinc [8].

Issues have been raised with micronutrients and metanalyses of 68 randomized trials with 232,606 participants (385 publications) have been done where they found that treatment with beta carotene, vitamin A, and vitamin E may increase mortality, whereas vitamin C and selenium had no significant effect on mortality, although potential roles of them on mortality need further study [9].

At oncology clinic we follow the principle of orthomolecular medicine that medicine and patients is individual- not only is every patient unique but also his or her nutrient requirements and the response to treatment. For every patient, we provide a balanced mix of micronutrients, in oral or high-dose intravenous form (high-dose vitamin and antioxidant infusions).

Complementary and Alternative Medicine in Cancer Patients

The use of Complementary and Alternative Medicine (CAM) in cancer patients is widespread and appears to be increasing. However, it is not clear whether patients use CAM as an 'alternative' to standard oncology care or as an adjunct to the conventional treatment they receive. Most patients use CAM to supplement the conventional treatments such as radiotherapy, chemotherapy, hormone therapy and surgery. Many professionals in general have expressed positive views when CAM is used 'complementarily' and not as an 'Alternative'. Results so far published have shown that CAM can contribute to improving the quality of life of cancer patients and their general well-being [10].

CAM therapies may be categorized in a variety of ways. NCCAM currently classifies CAM therapies into five categories: alternative medical systems, mind-body interventions, biologically based therapies, manipulative and body-based methods and energy therapies. Currently popular therapies within each of these categories are discussed below. Many of these approaches are unproven methods promoted as alternatives to mainstream cancer treatment. Patients should be advised to avoid questionable alternative therapies in a receptive, evidence-based atmosphere. Many unproven alternatives are promoted in a very appealing and convincing fashion. Brushing the topic aside categorically without open discussion may not dissuade patients' use. On the other hand, complementary therapies that help manage pain, nausea, fatigue, anxiety and other symptoms should be integrated into the patient's overall care. In some cases, patients feel that problems they perceive as important fail to receive sufficient attention. Complementary therapies improve patients' qualities of life, patient satisfaction and the physician-patient relationship [11].

Both nutrition and antioxidants play a big role in the prevention and treatment of cancer patients and studies have been performed in patients with gastrointestinal cancer, prostate cancer, breast cancer, non small lung cancer and small cell lung cancer [12-17].

Another study has been performed combining natural supplements with anti-cancer drugs in cancer cells and demonstrated synergistic effect as anti-proliferative agents. One of those is the combination of gefitinib with calcitriol or their synthetic analogs that resulted in a greater antiproliferative effect than with either of the agents alone in EGFR and HER2 positive breast cancer cells [18]. The mechanistic explanation for these results includes down regulation of MAPK signaling pathway, decrease of cells in G2/M phase and induction of apoptosis mediated by up regulation of BIM and activation of caspase 3.

In others they used vitamin such as riboflavin in laboratory models as anti-cancer and demonstrated that Irradiated Riboflavin (IR) has potential antitumoral effects against Human Leukemia cells (HL60), human Prostate Cancer cells (PC3), and mouse melanoma cells (B16F10) through a common mechanism that leads to apoptosis, but the group showed again that IR treatment leads to inhibition of Matrix Metalloproteinase-2 (MMP-2) activity and reduced expression of renal cancer aggressiveness markers caveolin-1, Low Molecular Weight Phosphotyrosine Protein Phosphatase (LMWPTP), and kinase insert domain receptor (a type III receptor tyrosine kinase) (VEGFR-2). Together, these results show the potential of IR for treating cancer [19]. This is why more human studies needs to be done in clinical trials based on those reports.

High Dose Vitamin C and Cancer

There is an excellent book by Gonzalez and Miranda-Massari that reviewed the use and role of high dose vitamin C in cancer patients [4]. Vitamin C breaks down to generate hydrogen peroxide, which can damage tissue and DNA. It has been demonstrated that DNA is susceptible to damage by Reactive Oxygen Species (ROS). 8-oxo-2'-deoxyguanosine (8-oxodG) is probably one of the most abundant DNA lesion formed during oxidative stress and this potentially mutagenic lesion causes G --> T transversions and is therefore an important candidate lesion for repair, particularly in mammalian cells. Several pathways exist for the removal, or repair, of this lesion from mammalian DNA. One alternative pathway in humans is the Nucleotide Excision Repair (NER), which could possibly remove the 8-oxodG lesion. Lunex ER, et al., proposed that redox-active components of the diet, such as vitamin C, may promote such repair, affecting NER specifically [20].

Another important mechanism is the enhanced enzymatic degradation of Hypoxia Indecible Factor (HIF) 1 alpha by ascorbic acid. Hypoxia-Inducible Factor (HIF) plays an important role in determining patterns of gene expression in cancer [21]. HIF is down-regulated in oxygenated cells by a series of Fe (II) and 2-oxoglutarate dependent dioxygenases that hydroxylate specific residues in the regulatory HIF-alpha subunits. Because these enzymes require ascorbate for activity *in vitro* we analyzed the effects of ascorbate on HIF in human cancer cell lines. Ascorbate at physiological concentrations (25 μM) strikingly suppressed HIF-1alpha protein levels and HIF transcriptional targets, particularly when the system was oncogenically activated in normoxic cells. Similar results were obtained with iron supplementation. These results indicate that both ascorbate and iron availability have major effects on HIF, and imply that the system is commonly regulated by limiting hydroxylase activity under normoxic tissue culture conditions.

An excellent review of a total of 23 trials involving 385 patients was done and one trial, in ovarian cancer, randomized patients to receive vitamin C or standard of care (chemotherapy) was a good representative sample [22]. That trial reported an 8.75 month increase in Progression-Free Survival (PFS) and an improved trend in Overall Survival (OS) in the vitamin C treated arm. Overall, vitamin C has

been shown to be safe in nearly all patient populations, alone and in combination with chemotherapies. The promising results support the need for randomized placebo-controlled trials such as the ongoing placebo-controlled trials of vitamin C and chemotherapy in prostate cancer.

Integrative Oncology

This is an interesting field that should be encouraged. Studies in integrative oncology have been shown to be clinically proven and cost effective but clinical trials should be motivated [23].

Conclusion

In conclusion, it has been demonstrated that integration of alternative medicine to oncology is effective for the cancer patients; we need to work with comprehensive protocols including IV and oral nutrients and botanicals for clinical research studies looking for response rates, survival rates, toxicity profiles, compliance and cost-effectiveness as well as integrating psycho-social studies too. We need to eliminate the taboo in this 21st century for the benefit of our cancer patients.

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