Dynamic Chiropractic

VITAMINS / SUPPLEMENTS

Vitamin E Succinate, Part 1

THE PREFERRED FORM OF VITAMIN E TO HELP PATIENTS COMBAT BREAST, PROSTATE AND OTHER CANCERS

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An abundance of research has proven that vitamin E succinate is the most effective form of vitamin E in inducing differentiation, growth inhibition and programmed cell death (apoptosis) in cancer cells. A number of high-profile, university-based researchers now suggest using this form of vitamin E (alone or in combination with other supplements) to enhance the efficacy of medical cancer treatments (in conjunction with some chemotherapy drugs, ionizing radiation, hyperthermia and biological modifiers) and as a means to decrease the all-too-common adverse side effects of standard cancer treatment.

As vitamin E succinate has been shown to possess unique and markedly superior biological properties to prevent and combat cancer when compared with other forms of vitamin E (alpha-tocopherol, alpha-tocopherol acetate and nicotinate, gamma-tocopherol, as well as tocotrienols), health practitioners should strongly consider recommending a high-potency multiple vitamin supplement that contains this form of vitamin E (e.g., 400 IU vitamin E succinate) for health-promotion purposes. Higher doses of vitamin E succinate appear to be appropriate as part of adjunctive nutritional management in select cancer patients. This article reviews the research pertaining to the anti-cancer properties of vitamin E succinate for the purpose of educating health practitioners about this important and clinically relevant subject.

Introduction

Recent studies suggest that vitamin E succinate (VES) is the most potent anti-tumor analogue of vitamin E.[1] Although many individuals rely on vitamin E supplementation for its antioxidant properties, vitamin E taken in the form of vitamin E succinate provides additional anticancer benefits according to numerous in vitro and in vivo studies.[2,3]

More specifically, vitamin E succinate has been shown to induce programmed cell death (apoptosis) of human prostate cancer cells, human breast cancer cells and other human cancer cells, including leukemia cells and gastric cancer cells. Of note is the fact that VES has been shown to exert its anti-tumor influences on cancer cells but is nontoxic to normal cells. These impressive findings have spurred on researchers to determine the mechanism(s) of action through which VES combats cancer development, inhibits growth of cancer cells and induces apoptosis of certain cancer cells.[3]

Vitamin E Succinate and Prostate Cancer

A number of studies have shown that VES inhibits the growth and/or induces apoptosis of various forms of human prostate cancer cells. Researchers have identified various physiological effects through which VES induces these desirable outcomes.

The study by Zhang and fellow researchers demonstrated that VES suppressed the expression of

androgen receptors, meaning that fewer androgen receptors are present on the cell's surface in the presence of VES. This is of great clinical significance because the androgen receptor (receptors for testosterone, dihydrotestosterone and other androgen hormones) is required for the development of both the normal prostate gland and prostate cancer. In the early stages of prostate cancer, most cancer cells are androgen-dependent and highly sensitive to anti-androgens (drugs such as hydroxyflutamide). As such, most prostate cancer cells grow and proliferate in response to testosterone and other androgens binding to their androgen receptors. Thus, if VES prevents prostate cancer cells from expressing androgen receptors, these cells are less likely to flourish in the presence of testosterone and other androgens present in the male body.

Traditionally, the treatment of prostate cancer has included androgen ablation (e.g., castration to reduce circulating levels of testosterone from the testes, and/or anti-androgen drugs to reduce stimulation of androgen receptors by circulating testosterone and other androgen hormones). Interestingly, prostate cancer usually recurs after a few years of androgen-ablative treatment and most cancer cells become androgen-independent, rendering anti-androgen therapy ineffective as the disease becomes more advanced.

However, Zhang, et al., were able to show that the combination of VES and hydroxyflutamide provided significantly greater growth inhibition of androgen-dependent prostate cancer cells (LNCaP) than did hydroxyflutamide on its own, which only mildly inhibited growth of LNCaP cells when administered without VES.

The LNCaP cell line is derived from lymph node prostate cancer metastasis and is one of the best *in vitro* models for human prostate cancer studies, as it represents a hormone refractory prostate carcinoma and its growth is responsive to testosterone and other androgens. In addition, LNCaP cells express a functional mutant androgen receptor and produce PSA, which is a sensitive and specific tumor marker for prostate cancer screening and assessment.

Zhang, et al., also showed that VES decreases intracellular and secreted levels of prostate-specific antigen (PSA) in LNCaP cells, which was cultured either in normal serum or in androgen-stimulated conditions.

Other researchers have shown that VES also can induce programmed cell death (apoptosis) of human prostate cancer cells, in addition to its ability to down-regulate expression of androgen receptors. For example, it has been suggested that VES could inhibit the proliferation of prostate cancer cells by arresting DNA synthesis or by stimulating transforming growth factor beta (TGF-B), which is an intracellular antiproliferative agent.[4]

Most recently, Shiau and fellow researchers showed that VES induced programmed cell death of LNCaP prostate cancer cells by blocking the action of specific cellular proteins that are required for cell proliferation by cancer cells. More specifically, these researchers showed that VES blocked the action of a cellular protein known as Bcl-xL, which is found at abnormally high levels in cancer cells. Shiau, et al., determined that VES lodges in a groove in the structure of the Bcl-xL protein and disables it (disrupting the binding of Bak BH3 peptide to Bcl-xL and Bcl-2, which otherwise affect gene regulation in such a way as to encourage cell replication).

By disabling the Bcl-xL protein, VES essentially sets into motion a chain of events that triggers programmed cell death of prostate cancer cells (via caspase-dependent apoptosis). Of note is the fact that other forms of vitamin E are unable to perform this task. Only vitamin E succinate has been shown to appreciably induce programmed cell death of various types of cancer cells, most noteworthy, prostate, breast and gastric cancer cells. These researchers also were clear to point out that VES does not damage the function of healthy cells, but rather is able to selectively induce

apoptosis of cancer cells.[5]

In another study, Israel and fellow researchers showed that VES also induces apoptosis in certain prostate cells highly resistant to apoptosis. Certain cancer cells are known to resist programmed cell death triggered by stimulation of their Fas-receptors. When stimulated by a ligand (binding agent), usually from certain immune cells, the Fas-receptor stimulates the release of secondary messengers within the cell that trigger programmed cell death. As such, this is one way in which immune cells are designed to identify and kill cancer cells. However, some cancer cells are Fas-resistant in that they do not undergo apoptosis upon stimulation of their Fas-receptors. This has been shown to be the case with certain human prostate cancer cells. The study by Israel, et al., showed that vitamin E succinate could enhance the Fas-apoptosis pathway and lead to increased programmed cell death of various types of human prostate cancer cells, but did not affect normal prostate cells.[6] A further explanation of the Fas-apoptosis system is provided in the following section.

Vitamin E Succinate and Breast Cancer

Vitamin E succinate also has been shown to induce programmed cell death (apoptosis) and inhibit proliferation of human breast cancer cells in numerous studies. In separate studies Malafa, et al., and Schindler and fellow researchers demonstrated that VES inhibited the growth of certain breast cancer cells and induced apoptosis in other types of human breast cancer cells (MDA-MB-231 cells).[1,7]

These researchers showed that one way that VES induces apoptosis and growth inhibition is by inhibiting the release of vascular endothelial growth factor-A (VEGF).[1,7] VEGF is a protein required for angiogenesis (formation of new blood vessels) by tumor cells. The development and progression of solid tumors require rapid and persistent growth of new blood vessels to supply the growing tumor with nutrients and oxygen. Interestingly, increased vascular proliferation has been shown to correlate with a higher incidence of metastases and a worse prognosis. As mentioned, tumor neoangiogenesis is induced by angiogenesis-promoting growth factors (e.g., VEGF) produced by the tumor or nonmalignant tumor stromal cells (supporting connective tissue network cells in the vicinity of the tumor). The VEGF gene encodes differently spliced mRNAs from which pre-VEGF proteins are transcribed. These proteins are secreted directly from the cells after signal sequence cleavage in the rough endoplasmatic reticulum and glycosylation in the Golgi apparatus. Thus, VEGF is not stored in cells and synthesis correlates with release. VEGF expression is regulated by transcription factors as well as by mechanisms that control mRNA stability.

Earlier studies showed that the soy isoflavone genistein inhibited angiogenesis, VEGF expression and release by various human breast cancer cells which may partly account for the reduced incidence of breast cancer in populations consuming soy products as a main dietary staple. Of note is the fact that Schindler and fellow researchers demonstrated that certain flavonoids (naringin from citrus fruits; rutin - a constituent of cranberries), VES, apigenin (from apple skins, citrus fruits, celery roots) and genistein, were all among naturally occurring agents shown to inhibit release of VEGF and inhibit angiogenesis of human breast cancer cells. However, it should be noted that alpha-tocopherol and gamma-tocopherol (other popular forms of vitamin E) did not show significant anti-angiogenesis effects compared to that exhibited by VES. Interestingly, the drug lovastatin showed an anti-angiogenesis effect slightly inferior to that of VES, narigin and rutin, and slightly greater than apigenin and genistein.[7]

Other researchers have shown that VES induces apoptosis of human breast cancer cells by

affecting cell membrane receptors such as certain members of the epithelial growth factor family. In healthy tissue, protein receptors transmit a signal to the cell to grow when a smaller protein, called a growth factor or ligand, binds to the receptor. Ligand binding induces a change in the shape of the receptor which causes receptors next to each other to connect. This change in shape and the resulting connection between two receptors on the outside of a cell acts like a domino falling over and starts a chain reaction throughout the cell that causes the cell to grow. Thus, all that is needed to signal a cell to grow is a connection between two receptors. Such a connection between receptors can occur spontaneously (without the growth factor binding to a receptor) if there are a lot of receptors on the surface of the cell, such that they frequently bump into each other (auto stimulation).

Cells that have abnormally high levels of receptors can grow without receiving signals from external growth factors (such as hormones). Indeed, the most common abnormality in human cancers involves receptor overproduction. Such overproduction has been reported in breast, prostate, ovarian, bladder and lung cancers. One particular family of receptors called the epidermal growth factor receptors (EGF/ErbB1-4) has been implicated more than any other. In approximately 30 percent of breast cancer patients, the ErbB2 receptor is overproduced, resulting in aggressive and uncontrolled growth of tumor cells.

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