VITAMIN E SUCCINATE: THE PREFERRED FORM OF VITAMIN E TO COMBAT BREAST, PROSTATE AND OTHER CANCERS

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In Brief

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 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. As well, 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 antitumor 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 anti-cancer 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 be exerts its antitumor 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 Y. Zhang and fellow researchers demonstrated that VES suppressed the expression of androgen receptors, meaning that fewer androgen receptors are present on the cells 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, then 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 antiandrogen therapy ineffective as the disease becomes more advanced.

However, Zhang and fellow researchers 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 and fellow researchers 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 can also 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 anti-proliferative agent. (4)

Most recently Chung-Wai 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 and fellow researchers determined that VES lodges in a groove in the structure of the Bcl-xL protein, disabling 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 a 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 were also 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, primarily. (5)

In another study, K Israel and fellow researchers showed that VES also induces apoptosis in certain prostate cells that are 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 in 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 K 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 breast cancer section of this paper

Vitamin E Succinate and Breast Cancer

Vitamin E succinate has also been shown to induce programmed cell death (apoptosis) and inhibit proliferation of human breast cancer cells in numerous studies. In separate studies MP Malfa and fellow researchers and R. 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 R Schindler and fellow researchers demonstrated that certain flavonoids (naringin – from citrus fruits; rutin – a constituent of cranberries), vitamin E succinate, apigenin (found in 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 vitamin E succinate. Interestingly, the drug lovastatin showed an anti-angiogenesis effect that was 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 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). Thus, 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% of breast cancer patients, the ErbB2 receptor is overproduced, resulting in aggressive and uncontrolled growth of tumor cells.

It is well documented that women whose breast cells overexpress the erbB2 receptor (a member of the Epithelial Growth Factor Receptor Family) on their cell surface are at higher risk for breast cancer development. Additionally, their overexpression is associated with the estrogen receptor

negative form of the disease, which is known to be the most clinically aggressive form of this disease. (8,9)

Studies by XF Wang and fellow researchers demonstrated that vitamin E succinate was able to induce programmed cell death (apoptosis) in human breast cancer cells that exhibited high levels of erbB2 expression.

A study by W Yu and fellow researchers showed that vitamin E succinate could also induce apoptosis in human breast cancer cells that Fas- resistant. (10). Fas is an immunology protein that initiates programmed cell death. Apoptosis is important in cell-mediated immune response, autoimmune tolerance, and cancer control. Fas is a surface receptor that is expressed throughout the body. The Fas ligand is expressed mostly on activated T cells, natural killer cells, and microglia, but is sometimes found on other cells of the immune system. When a cell expressing Fas encounters another cell expressing Fas ligand, the receptor is stimulated in such a way as to transmit a message to secondary protein messengers within the cytoplasm (signal transduction) of the cell. In turn this activates a series of events that lead to cell death (apoptosis). Certain breast cancer cells are resistant to the apoptosis-inducing effects of Fas, such as MCF-7, MDA-MB-231 and MDA-MB-435 human breast cancer cells. (11) The study by T. Yu et al, showed that vitamin E succinate was able to convert Fas-resistant human breast cancer cells to Fas-sensitive phenotype, allowing apoptosis to proceed. These findings are important as they suggest another mechanism through which VES may prevent breast cancer development and/or inhibit the further growth and proliferation of existing breast cancer cells.

Other Mechanisms Through Which Vitamin E Succinate May Prevent Cancer

Reports from K Wu and fellow researchers indicate that vitamin E succinate also induces apoptosis of cancer cells by first stimulating production of transforming growth factor-B, which in turn, increases kinase activity of another protein messenger known as c-Jun N-terminal kinase (JNK), followed by phosphorylation of c-Jun, and finally activated c-Jun triggers apoptosis. K Wu et, al have shown this apoptosis pathway to exist in human gastric cancer cells, but it may also occur in many other cancer cells as well. (3) Other researchers have confirmed that vitamin E succinate induces apoptosis through stimulation of the c-Jun messenger system.(12,13) In addition, K Wu et al, report that vitamin E succinate also induces apoptosis of certain cancer cells by enhancing activity of the Fas-apoptosis system (sometimes called the Fas-death receptor, although other death receptors are also present on the cell surface), as described in the previous sections.(3).

Summary

In regards to vitamin E supplementation the current evidence suggest that health practitioners should strongly consider recommending supplements containing vitamin E succinate (alpha tocopherol succinate or alpha tocopheryl succinate), as part of a high potency multiple vitamin/mineral supplement or as a stand alone supplement, as part of a comprehensive program to reduce cancer risk. In this regard the evidence suggests that vitamin E succinate is superior to other available forms of vitamin E and related tocotrienols. Many experts suggest a daily dosage of 400 IU per day of vitamin E succinate for general health promotion and disease prevention. As an adjunct to cancer treatment some practitioners use a total daily dosage of 800-1600 IU (up to 2500 IU of vitamin E– Folkers and Lockwood, Molecular Aspects Of Medicine, 1984), in conjunction with high doses of other antioxidants and natural cancer-fighting herbs and phytonutrients. Preliminary human trials using these nutritional supplements have shown impressive results in reducing cancer progression, preventing metastasis and reducing side effects of chemotherapy and radiation. (14)

In the review presented by KN Prasad and fellow researchers (Center for Vitamins and Cancer Research, Department of Radiology, University of Colorado Health Sciences - 2003) the authors state, “Since it has been demonstrated that vitamin E succinate (alpha tocopheryl succinate) in combination with dietary micronutrients (retonoic acid, vitamin C and carotenoids) is more

effective in reducing the proliferation of tumor cells in culture than the individual agents and in enhancing the effect of some chemotherapeutic agents on these cells, we have recommended the use of alpha tocopheryl succinate in combination with dietary micronutrients as an adjunct to standard therapy in the treatment of cancer". These authors have provided an excellent review of the anti-cancer properties of vitamin E succinate for health practitioners who are interested in further reading on this subject. (15)

To sum up, abundant evidence indicates that vitamin E succinate possesses unique biological properties that enable it to inhibit or slow the replication of human cancer cells and/or induce apoptosis of many types of cancer cells, most notably prostate and breast cancer. In this regard vitamin E succinate has been shown to be superior to other forms of vitamin E. As cancer accounts for approximately 20% of all deaths in North America, this information should be of importance to health practitioners who routinely recommend multiple vitamins and/or vitamin E supplements to their patients for the purpose of reducing risk of degenerative disease, and/or who advise patients on evidence-based adjunctive nutritional therapies that may be helpful to prevent recurrences or metastasis of cancer in patients that have already been affected by this disease.

For more information on this or other related topics, visit Dr. Meschino's website at: http://www.renaisante.com/

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