PERSPECTIVE

Tocopherols and tocotrienols as anticancer treatment for lung cancer: future nutrition

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ABSTRACT

Nutrition has been known for ages to shield the immune system against several formulations that deregulate normal DNA repair mechanisms, and induce tumorigenesis. Vitamins and in specific Vit E and its members tocopherols (α-, β-, γ-, δ-) and tocotrienols (α-, β-, γ-, δ-) have demonstrated strong association with the prevention of cancer and inhibition of tumor, both *in vitro* and *in vivo*. Vitamin E has also demonstrated effective role against chemotherapy resistant cancer cell evolution and a protective role in acute interstitial disease. Several formulations of Vitamin E have been investigated conjugated with different carriers as nano-formulations and administered in different forms. Additionally, several tumorigenic pathways have been investigated separately in an effort to identify which member of Vitamin E inhibits efficiently every pathway. Vitamin E presented efficiency against specific subhistology types of lung cancer. Finally, in the current work up to date information regarding novel formulations with Vitamin E and inhibition pathways are going to be presented and commented.

KEY WORDS   Vitamin E; tocopherol; tocotrienol; lung cancer; nutrition; nanomedicine

Vitamin E has been known to play a key role in the prevention and inhibition of cancer (1-5). It has been investigated in many human cancers such as: (I) colon (6,7), (II) lung cancer (8,9), (III) prostate (10,11) and (IV) breast (12,13). It is a lipophilic antioxidant that consists of (α-, β-, γ-, δ-) tocopherol and (α-, β-, γ-, δ-) tocotrienol isomers. Tocopherols have direct antioxidant activity and indirect by activating the NF-E2 related factor-2-related antioxidant enzymes. A-tocopherol has been extensively studied because it is recognized in the liver by α-tocopherol transfer protein (αTTP) in humans (14). However, recent data

suggest that γ-tocopherol also interacts with αTTP (15). Because of these new data further investigation of γ-tocopherol demonstrated that this isomer has anti-inflammatory characteristics by inhibiting cyclooxygenase activity (COX-2) (16). This is explained because γ-tocopheryl quinone the final product of γ-tocopherol activates transcription factor 4, the co-activator of NF-E2-related factor-2, and the levels of glutathione a known cellular antioxidant (17). The major activities of γ-tocopheryl quinone can be summarized to the following: (I) increase cytotoxicity, (II) decrease mutagenesis and (III) induce endoplasmatic reticulum stress (18,19). These activities are not observed by α-tocopheryl quinone (18,19). Moreover, γ-Tocopherol can be nitrated to form the 5-nitro-γ-tocopherol, which traps reactive nitrogen species more effectively than α-tocopherol (20). It has been observed in previous studies that nitrogen dioxide can induce single-strand DNA break in V79 cells, however, this reaction was efficiently inhibited by γ-tocopherol (21). In the study by Wagner K.H. *et al.* (22) and Yu W. *et al.* (23) data were presented where the γ-tocopherol was superior to α-tocopherol, while in the study by Li GX. *et al.* (4)

δ-tocopherol was superior to both α- and γ- tocopherol. However, in the study by Lambert J.D. *et al.* (3) a comparison between γ- and δ- tocopherols did not present major differences in the antitumor activity in a lung cancer model. Further evaluation of the oxidative pathways was performed by Mukherjee S. *et al.* (24) in a half mustard gas-induced lung injury mouse model. In this study several different liposome formulations were investigated for their protective role against the mouse airways. In specific δ-tocopherol-liposome complex was instilled intra-trachealy after half sulfur mustard-gas administration and it was observed that protection was established by controlling the recruitment of eosinophils and neutrophils. Additionally, accumulation of red blood cells in the main bronchus, alveoli, veins and arterioles was blocked. Subsequently the platelet derived growth factor was inhibited and additionally septal, perivascular collagen and fibrin accumulation were efficiently blocked (24). However, it has to be noted that the protective effect is closely associated with the time of administration. The sooner the complex was administered (<1 hour), the sooner the inflammation cascade was blocked. Administration of the complex after 2hours of the gas inhalation did not have a major protective effect (24). However, these data have been presented for animals and not for humans. Another major problem between the several studies was the different laboratory assays and food databases that were used. Therefore there are controversial data presented. In the study by Slatore C.G. *et al.* (25) data are presented where there is no decreased risk of lung cancer if vitamin C, E and folate are used and it is proposed that supplements with these vitamins are not used. In addition, vitamin E was associated with a small increase of lung cancer. There are studies were an inverse relationship between lung cancer risk and α-tocopherol was presented (2). Moreover, few studies have investigated in the same study all isomers of vitamin E (1,2). It has been found that current smokers are more protected than non-smokers or former smokers. It has also proposed that vitamin E protects from emphysema which is an inflammatory condition observed in chronic obstructive pulmonary disease (2,26). In the study by Chen Z.L. *et al.* (26) data were presented where the vitamin E is involved in the mitochondrial pathway of cytochrome c-mediated caspase activation and blocks cytotoxic mechanisms to be further activated. In the study by Kim Y. *et al.* (27) a strong correlation was observed between α-tocopherol protection against squamous cell carcinoma. In addition, it was observed that the following pathways were inhibited: Jun N-terminal kinase (JNK), mitogen activated protein (MAP), urethane-induced extracellular signal-regulated kinase (ERK) and the ERK cascade member MAPK/ERK kinase MEK (28,29). In the study by Ji X. *et al.* (5) it was observed that δ-tocotrienol inhibited efficiently: (I) Notch-1, (II) Hes-1, (III) Survivin, (IV) matrix metalloproteinase-9 (MMP-9), (V) vascular endothelial

growth factor (VEGF), (VI) Bcl-XL and decrease in nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). Notch-1 pathway was majorly decreased through NF-kB downlegulation. In the study by Hahn T. *et al.* (30) the oncogene Human Epidermal Growth Factor Receptor 2 (*HER2/neu*) was inhibited with trastuzumab and alpha-tocopheryloxyacetic acid (α-TEA), a novel ether derivative of α-tocopherol. Although this study was performed in a breast cancer model, human epidermal growth factor receptor (HER) family members have been found in lung cancer cell lines and inhibited efficiently (31). In specific, in the study by Wu Y. *et al.* (31) the *HER2* and *HER3* oncogenes have been found to be inhibited by the novel antisense oligonucleotide: EZN-3920. The anticancer effect was enhanced when tyrosine kinase inhibitors such as: (I) gefinitib and (II) lapatinib were co-administered in HCC827 lung carcinoma cell lines (31). Further to the pathways and oncogenes vitamin E enhanced the anticancer effect of cytotoxic drugs by inhibiting the hypoxic adaptation. In the study by Kashiwagi K. *et al.* (32) the survival and invasion capacity of tumor cells under hypoxia was suppressed by 6-O-carboxypropyl-α-tocotrienol (T3E). The T3E inhibits the tyrosine kinase Src protein and induces Akt activation. Throughout this process reduction of plasminogen activator-1 (PAI-1) was observed by decrease of hypoxia-inducible factor-2α. Vitamin E analogs have been administered by alternative roots. Previously we have presented the liposome complex with vitamin E analogs that protect the airways by gas-mustard where the complex was administered intra-tracheal. In the study by Latimer P. *et al.* (33) the α-TEA was co-administered in an effort to enhance the antitumor effect of paclitaxel. Indeed tumor and metastasis were found to be reduced in the group where chemotherapy and α-TEA were co-administered. Further to the novel roots of administration several groups have investigated novel formulations of vitamin E analogs. In the study by Fu J.Y. *et al.* (34) encapsulation of tocotrienol-rich fraction (TRF) within vesicles bearing transferrin were investigated both *in vitro* and *in vivo*. It was observed that these vesicles were able to penetrate and diffuse within the tumor model, while not harming normal cells. This can be explained by the ability of transferrin were its receptors are expressed in tumor cells. In the study by Wang G. *et al.* (35) vitamin ETPGS-functionalized PLGA nanoparticles (TPNs) were investigated for controlled release paclitaxel. The results both *in vitro* and *in vivo* presented selective accumulation of the nanoparticles within the tumor and enhanced antitumor activity in A549 lung cancer xenografted nude mice. In the study by Gill K.K. *et al.* (36) Vitamin E-TPGS nanoparticles were co-encapsulated with paclitaxel and parthenolide in mixed micelles and delivered to A549 chemotherapy sensitive lung cancer cell line and A549-T24 chemotherapy resistant cell line. Paclitaxel and parthenolide were administered in both lines with and without being in a mixed micelle form. The results presented

enhanced cytotoxicity of the micelle nanoparticles in comparison to the normal drug formulations and increased antitumor activity of the micelle nanoparticles against the chemotherapy resistant cell line. We presented data regarding the tumor pathways and oncogenes that are inhibited by vitamin E isomers. In addition, novel roots of administration and formulations demonstrated promising results. Although vitamin E isomers have been investigated for more than two decades laboratory methods did not allow for all isomers to be properly evaluated in human trials. Moreover, vitamin E in a lung cancer tumor model has not yet fully explored. Current technology with nanoparticles demonstrated promising results as a method for enhancing chemotherapy formulations diffusion within tumors. The addition of vitamin E isomers to these nanocomplexes further enhance the antitumor activity of basic chemotherapy drugs in sensitive and resistant lung cancer cell lines. Further investigation of vitamin E as lung cancer treatment formulation is warranted.

Acknowledgements

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