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The use of antioxidant therapies during chemotherapy

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Abstract

Objective. At the present time, many cancer patients combine some form of complementary and alternative medicine therapies with their conventional therapies. The most common choice of these therapies is the use of antioxidants.

Results. A review of four common antioxidants is undertaken, which includes vitamin E (mixed tocopherols and tocotrienols), β-carotene (natural mixed carotenoids), vitamin C (ascorbic acid), and vitamin A (retinol and retinoic acid). Antioxidants act as electron acceptors as well as therapeutic biologic response modifiers. Despite the fact that chemotherapy-induced formation of free radicals is well-demonstrated, chemotherapy-induced cytotoxicity in general does not seem to depend on formation of reactive oxygen species.

Conclusions. Currently, evidence is growing that antioxidants may provide some benefit when combined with certain types of chemotherapy. Because of the potential for positive benefits, a randomized controlled trial evaluating the safety and efficacy of adding antioxidants to chemotherapy in newly diagnosed ovarian cancer is underway at the University of Kansas Medical Center.

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Introduction

Oncologists attempt to improve survival rates for patients with malignancies with a wide variety of treatments including combination chemotherapy with or without radiation therapy. Despite these efforts, living with the diagnosis of cancer is usually an ongoing and difficult experience. Because of the pervasive feeling of sadness, fear, anxiety, and anger, and as a result of the potential for mortality, patients often turn to complementary and alternative therapies [1–6]. Yet, complementary and alternative therapies are not widely accepted by the oncologists who are directing the cancer therapeutic regimens.

The reason that cancer patients give for the use of complementary and alternative therapies varies. Patients describe a wish to improve their quality of life, improve immune system function, prolong their life, or relieve their symptoms [5,6]. Only approximately 40% of patients expect complementary and alternative therapies to cure their disease [6]. As these surveys emphasize, the high prevalence of use of these therapies represent an invisible phenomenon, and this phenomenon may be effecting evaluation of conventional therapies, since 2/3 of vitamin and mineral users were also receiving chemotherapy, radiation, and surgery [6].

Of the types of complementary and alternative therapies used by oncology patients during neoplastics cytoreductive treatments, antioxidants are a common choice. While it is accepted that antioxidants are useful in the reduction of adverse effects of chemotherapy, the prevailing opinion is that antioxidants reduce the effectiveness of chemotherapy and radiation therapy's neoplastic toxicity [7–11]. However, there is evidence that antioxidants may also be a choice for therapeutic intervention alongside chemotherapy with demonstrated benefit in tumor size reduction and/or increased longevity [8,11–21].

Despite the theoretical concern that antioxidant therapies interfere with chemotherapy and radiation by lowering ox-
idative damage, evidence supporting this mechanism is currently lacking [22]. In fact, antioxidants act as therapeutic biologic response modifiers and are able to directly induce apoptosis in already established neoplastic cells [7,21,23–25]. There is also supportive evidence that antioxidants enhance antitumor effects of chemotherapy in vitro and in vivo [12,18,20,21,24]. It is now recognized that chemotherapy kills tumor cells not by damaging essential biological functions but by initiating programmed cellular responses [21,25]. Correspondingly, mutations that interfere with apoptosis may produce tumor chemotherapy resistance [21,25].

Reactive oxidant species are essential for life, involved in cell signaling, used by phagocytes for bactericidal activity, and a component of mitochondrial respiration. However, reactive oxidant species result in oxidative stress in the cellular and extracellular environment and are implicated in the etiology and progression of many disease processes. Reactive oxidant species are held in check by an elaborate antioxidant defense system, but under conditions of organism stress, the antioxidant cellular defense system becomes depleted. In normal cellular milieu, reactive oxidant species are essential for life while in cases of antioxidant exhaustion they may become a detriment [21,26].

Administration of antineoplastic agents during cancer chemotherapy results in a much greater degree of oxidative stress than is induced by the cancer itself [21]. With chemotherapy, there is elevation of lipid peroxidation products, the reduction of free radical trapping capacity of blood plasma, and marked reduction of plasma levels of antioxidants such as vitamin E, vitamin C, and β-carotene. The high level of oxidative stress during chemotherapy may overcome the oxidative defenses of the cancer cell, which has specialized systems to reduce lipid peroxidation. Increasing lipid peroxidation reduces or halts cancer cell proliferation and interferes with the activity of chemotherapy. This has important implications because the antioxidant status of cancer patients may play an important role in response to chemotherapy, with individuals having an impaired status being relatively unresponsive to chemotherapy. However, supportive nutritional therapy with antioxidants during chemotherapy, which reduces the generation of lipid peroxides, may overcome the growth inhibiting effects of oxidative stress and maintain responsiveness to chemotherapeutic agents.

Common antioxidants used during cancer treatment include vitamin E (mixed tocopherols and tocotrienols), β-carotene (natural mixed carotenoids), vitamin C (ascorbic acid), and vitamin A (retinoic acid). Antioxidants work in concert with one another by a series of oxidation–reduction (redox) reaction to quench reactive oxidant species. Redox buffering systems of the common antioxidants are all related in a stepwise, sequential recycling process, which provides ongoing neutralization of free radicals [27–30]. If each of these nutrients is present in adequate amounts, they can all be restored to their active antioxidant forms after reacting with the active oxidant species. An understanding of these free radical defenses provides a scientific basis for the use of nutritional supplementation with antioxidants during chemotherapy.

Vitamin C—Ascorbic Acid

Ascorbic acid is an essential nutrient involved in many biochemical functions. The biochemical roles of vitamin C are related to its action as an electron donor or reducing agent. In vitro, ascorbate has pro-oxidant activity, but there is little evidence for such activity in vivo [31]. When neutrophils encounter bacteria, neutrophils are activated to produce oxidants, which leak out and oxidize vitamin C to dehydroascorbic acid. Dehydroascorbic acid is transported into the neutrophils and reduced back to vitamin C by a glutathione-dependent protein. This cycle quenches large amounts of extracellular oxidants with subsequent increases in intracellular vitamin C [9,31].

One of the most studied and, until recently, most controversial therapies is the use of high-dose ascorbic acid [9,13,16,17,32–34]. Recent work has increased the understanding of the activity of vitamin C. This work has shown that vitamin C in doses many times over the RDA is a potent immunomodulator and has been found to be preferentially cytotoxic to neoplastic cells [16–18,20,35]. Vitamin C enhances the activity of natural-killer cells in vivo [36] and also enhances both B- and T-cell activity [35]. At doses in the gram range, it has been demonstrated to increase survival time of patients with malignancies [13,16,17].

Gold and his group at Memorial Sloane Kettering demonstrated that vitamin C accumulates in some tumor cells via an increase in specialized cell surface transporters [9]. Gold hypothesized that because vitamin C accumulates in some tumor cells at a greater rate than normal cells, vitamin C and possibly other antioxidants should be avoided during cancer treatment. The basis of this argument is the fact that increases in antioxidants in the cellular environment during treatment with radiation and/or chemotherapy would interfere with reactive oxidant species generation and cytotoxicity by these therapies. However, increasing evidence points to other mechanisms by which chemotherapeutic cytotoxicity is achieved; evidence supports cytotoxic synergism between chemotherapy and/or radiation and antioxidants when used appropriately [16–18,20,21].

Gold et al. also described increases in ascorbic acid cell surface transporters in certain neoplastic cells [9]. These specialized glucose transporters take up oxidized ascorbic acid, dehydroascorbic acid, from the extracellular environment and transported intracellularly; dehydroascorbic acid in normal cells is rapidly reduced back to its reduced form ascorbic acid. The cytotoxic property of ascorbate is believed to be due to intracellular generation of toxic hydrogen peroxide produced by the oxidized form of ascorbic acid, dehydroascorbate [37–39]. In contrast to normal cells,
neoplastic cells are relatively deficient in catalase by a factor of 10- to 100-fold; catalase is the enzyme that rapidly breaks down hydrogen peroxide to water and oxygen [37]. Therefore, intracellular increase of ascorbate in neoplastic cells may be toxic rather than protective through the actions of hydrogen peroxide in contrast to normal cells.

Neoplastic cytotoxicity by ascorbic acid has been proposed to be based on several mechanisms. Murine studies indicate that when neoplastic transformation occurs after carcinogen exposure, vitamin C is able to decrease the number of neoplastic cells by 35–40% compared to controls [15]. This decrease appeared to occur by cytosis, apoptosis, and increased collagen synthesis, which acted to promote tumor regression [15]. It has also been demonstrated that tumor cells take up dehydroascorbic acid that has been oxidized in the tumor environment, most likely by superoxide-generating anion, which is directly cytotoxic [9].

Another critical feature of toxic activity of ascorbic acid on neoplastic cells was delineated [40]. The investigators manipulated the structure of ascorbate in vitro to maximize its cytotoxic effect on tumor cell growth and it was found that the cytotoxic activities were apparently not related to the metabolic or vitamin activities at the cellular level [40]. The cytotoxic activity was a result of direct cell killing by ascorbate.

In healthy adults, steady-state plasma vitamin C concentrations as a function of dose were evaluated; plasma saturation was found to reach 80% at a 200-mg oral dose and saturation was observed at 1000 mg/day [31]. This produced a plasma concentration of approximately 80 μmol/L. At steady-state in healthy adults, oral doses more than 500 mg have little impact on body stores [31]. Vitamin C undergoes glomerular filtration and concentration-dependent tubular reabsorption. When its transport protein reaches saturation in healthy young adults, the remaining vitamin C is not transported and is excreted in the urine [31]. However, episodes of increased oxidative stress elevate total body requirements for antioxidants, including vitamin C.

One of the limitations of high-dose oral ascorbic acid is irritation of the gastrointestinal tract, followed by diarrhea. To eliminate the potential for diarrhea and to attain plasma concentrations of greater than 200 mg/dL, ascorbic acid is administered intravenously [16,17]. In patients with malignancies, much larger doses are needed to attain neoplastic cytotoxicity with a plasma concentration greater than 200 mg/dL; this can be attained only by intravenous therapy [17]. Plasma concentrations greater than 200 mg/dL can result in cytotoxicity of tumor cells and very little negative effect on normal tissues. The longer the plasma level can be maintained above 200 mg/dL, the more effective will be the cytotoxic effect [16,17].

Cameron and Pauling published extensive evidence for prolonged life in terminal cancer patients taking both oral and intravenous ascorbic acid [31,41–43]. Investigators at the Mayo Clinic who used only oral high-dose ascorbic acid were unable to find a benefit in the treatment of cancer [32,34], while other investigators were able to find some added advantage when adding oral ascorbic acid in their treatment of cancer [33]. In the latter studies, neoplastic cytotoxic ascorbate plasma levels above 200 mg/dL were most likely not obtained with the oral regimens alone, but appropriate clinical trials are being designed to test this hypothesis. But most importantly, while there is preferential cytotoxicity to tumor cells, little toxicity to normal host cells has been demonstrated [13,16–18].

Vitamin C increased the activity of doxorubicin, cisplatin, and paclitaxel in one in vitro study [44]. However, the potential exists for increased resistance to doxorubicin in already resistant breast cancer cells [14,45]. Adverse effects that have been reported include hyperuricosuria, increased renal oxalate excretion, hemolysis in G-6-PD deficiency, rebound scurvy, hypoglycemia, vitamin B12 destruction, and infertility. G-6-PD deficiency with resulting hemolysis is the only probable concern for patients treated with large-dose ascorbic acid infusions, although the theoretical concern for oxalate stones does exist in those few patients that are oxalate formers [31].

Mixed carotenoids

A very important defense against the destructive reactive oxygen species is the dietary intake of β-carotene, which is provitamin A [46,47]. Comparatively little is known about the use of carotenoids as anti-cancer agents in vivo. The interest seems to stem from promising epidemiologic evidence associating dietary intake with lower incidences of many cancer types [14].

There is evidence to support the notion that carcinogenesis may be reversed in the preinvasive stage by β-carotene and that β-carotene may prevent its progress [48]. Mixed carotenoids have also been shown to regulate differentiation of various cells, protooncogenes, and oncoproteins [48]. Teicher et al. [48] suggest a role for carotenoid supplementation in conjunction with cytotoxic therapies in established malignant disease. However, other studies have found a negative correlation between the use of β-carotene and tumor regression or development [49,50]. These reported equivocal results are probably related to the use of a single antioxidant in the study design and its negative effect on redox buffering.

The use of synthetic β-carotene as a single agent rather than natural mixed carotenoids may actually promote cancer formation [12,14]. When taken alone in high doses, synthetic β-carotene suppresses uptake of the other carotenoids and acts as a pro-oxidant [12]. An important complement for patients is a whole foods diet, one that includes unprocessed fruits and vegetables to obtain a variety of carotenoids, of which there are over 1000 known types [12]. In addition, it is necessary to include modest amounts of natural, not synthetic, β-carotene [12,14]. Natural mixed carotenoids, in doses up to 20–40 mg/day, were found to be
without toxicity and to act synergistically with cisplatin [14]. These modest amounts have been shown to increase cell differentiation in vivo, which acts to promote apoptosis of neoplastic cells [12].

Vitamin E—Mixed tocopherols and tocotrienols

The name tocopherol for vitamin E was derived from the Greek term meaning "to bear offspring" because it was first recognized to be essential for reproduction in rats. There are various isomers of vitamin E, including the tocopherol and tocotrienol forms, with different isomers having different biological activities. Vitamin E is known to be an important free radical scavenger [29]. Human evidence indicates an inverse relationship between vitamin E levels and tumor incidence [51]. Binding proteins for vitamin E exist in plasma as well as in cells and have been identified in tumor cells as well [51]. Tocotrienols have a negative effect on growth and proliferation of some types of human cancer cells [52–54].

Vitamin E may play an important role in the genetics of dedifferentiated malignant cells by indirectly causing differentiation, most likely through the effects of adenylate cyclase [51]. This has been shown to result in an increase and release of transforming growth factor beta, which acts as a growth inhibitory signal for malignant cells [12]. Vitamin E has been shown to decrease the toxicity of chemotherapy without reducing its effectiveness [14]. At this time, no evidence exists for a reduction in the effectiveness of chemotherapy when combined with vitamin E in vivo.

Vitamin A (retinoic acid)

The fat-soluble vitamin A comes in various forms, but the majority of these are inactive in tissue cultures because of their poor aqueous solubility [12]. The vitamin A metabolite retinoic acid is a better choice for study because of its solubility and because it possesses all of the biological functions of vitamin A except for its role in vision. Retinoic acid and its derivatives can induce cell differentiation and growth inhibition in some cancer cell lines [55,56]. High doses are required, and patients may take these orally for a defined period of time without fear of normal tissue toxicity [12].

The precise mechanism of vitamin A actions on inhibition of cancer growth is unknown, however it seems to increase inhibitory levels of specific signaling pathways in neoplastic cells. Examples of vitamin A actions include inhibition of kinase C activity in cancer cells and reduction of expression of c-myc and H-ras oncogenes and other cellular genes in cell culture [12,14,54]. Vitamin A also induces cell differentiation in some tumors of epithelial origin and appears to work synergistically with chemotherapy agents [54].

Animal studies show an inhibition of transplanted tumor growth when high doses of vitamin A are administered; this is associated with the absence of toxicity to normal tissue [14,57,58]. However when added in treatment of late stage cancers in human trials, vitamin A combined with the biological response modifier interferon has had some reports of tissue toxicity although some promising benefits point to the use in earlier stage cancers [14,54,59]. Because benefits are demonstrated when combined with chemotherapy and there is no evidence for the reduction of effectiveness of chemotherapy when vitamin A is added in therapeutic doses, further trials are warranted [14].

It is apparent that high numbers of cancer patients are using antioxidants with or without the knowledge of their oncologist; as stated, this represents an invisible phenomenon. Currently, evidence is growing that antioxidants may provide some benefit when combined with certain types of chemotherapy. Because of the increased use and the mounting evidence for potential benefit, a randomized clinical trial is underway at the University of Kansas Medical Center addressing the safety and efficacy of antioxidants when added to chemotherapy.

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