Free Radicals: The Pros and Cons of Antioxidants

Rationale for Using High-Dose Multiple Dietary Antioxidants as an Adjunct to Radiation Therapy and Chemotherapy$^{1,2}$

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EXPANDED ABSTRACT

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Most oncologists do not recommend antioxidants to their patients during standard therapy, but some may recommend them at low doses after completion of therapy. However, about 60% of patients take antioxidants during standard therapy without the knowledge of their oncologists. Therefore, a rational strategy for the use of antioxidants and their derivatives in combination with standard therapy may be harmful, because endogenously made antioxidants (glutathione- and antioxidant enzyme–elevating agents) at any dose—or dietary antioxidants and their derivatives, such as vitamin A, including retinoic acid; vitamin C; vitamin E as d-α-tocopheryl succinate (α-TS)$^3$; and natural β-carotene at low doses—may protect cancer cells during therapy, and because low doses of individual dietary antioxidants may stimulate the proliferation of residual cancer cells. Appropriate therapy should be developed.

Dietary antioxidants at high doses induce differentiation, proliferation inhibition, and apoptosis, depending on the dose and type of antioxidants, treatment schedule, and type of tumor cells, without producing similar effects on most normal cells in vitro and in vivo (1–2). The growth-inhibiting effect of these agents on cancer cells may not involve antioxidant action but may involve changes in expression of genes and levels of proteins and translocation of certain proteins from one cellular compartment to another. A mixture of retinoic acid, α-TS, vitamin C, and carotenoids produces ~50% proliferation inhibition in human melanoma cells in culture at doses that do not reduce proliferation when used individually. Doubling only the dose of vitamin C in the mixture causes about 90% proliferation inhibition. In addition to dietary antioxidants and their derivatives, endogenously made antioxidants such as overexpression of mitochondrial manganese-superoxide dismutase (Mn-SOD) and the glutathione-elevating agent N-acetylcysteine (NAC) reduce the proliferation of cancer cells in culture.

Laboratory data (1–2) show that antioxidants protect cancer cells when dietary or endogenously made antioxidants are administered only one time, at low doses that do not affect the proliferation of cancer cells, shortly before therapeutic agents. For example, a single low dose of α-TS, d-α-tocopherol (α-T), vitamin C, or NAC administered shortly before irradiation reduces the effectiveness of x-irradiation in vitro and in vivo models. Overexpression of Mn-SOD enhances the radiosensitivity of tumor cells in culture.

Laboratory experiments (1–2) also show that growth-inhibiting doses of α-TS, vitamin C, and retinoic acid administered before and after irradiation enhance the effect of x-irradiation on cancer cells in culture and protect normal fibroblasts against some radiation damage. Vitamin A and β-carotene at high doses, administered daily before x-irradiation and during the entire observation period, produces a >90% cure rate in mice with transplanted breast adenocarcinoma; whereas treatment with radiation alone or antioxidant alone is ineffective. The administration of multiple dietary antioxidants (vitamins A, C, and E) reduces myelosuppression without protecting cancer cells in mice treated with radioimmunotherapy.

Several studies report that growth-inhibiting concentrations of vitamin C, α-TS, vitamin A (including retinoids), and carotenoids including β-carotene enhance the effect of chemotherapeutic agents on mouse and human cancer cells in culture. The extent of this enhancement depends on dose and form of the antioxidants; treatment schedule, dose and type of chemotherapeutic agents; and type of tumor cell. A mixture of retinoic acid, α-TS, vitamin C, and carotenoids at growth-inhibiting concentrations enhances the effect of some chemotherapeutic agents on human melanoma cells in culture. Vi-

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$^4$ Abbreviations used: α-T, d-α-tocopherol; α-TS, d-α-tocopheryl succinate; 5-FU, 5-fluorouracil; Mn-SOD, mitochondrial manganese-superoxide dismutase; NAC, N-acetylcysteine.
tamin A (retinyl palmitate) or synthetic β-carotene at high doses in combination with cyclophosphamide increases the cure rate from 0 to >90% in mice with transplanted adenocarcinoma of the breast. A water-soluble vitamin E analog (6-hydroxy-2,5,7,8 tetramethylchroman-2-carboxylic acid; Vitamin E), enhances the antitumor effect of 5-fluorouracil (5-FU) in athymic mice with human colorectal cancer. The synthetic retinoid (fenretinide) is effective against a human ovarian carcinoma xenograft and potentiated cisplatin activity. Treatment with dietary antioxidants reduces the toxicity of irradiation and chemotherapeutic agents in normal mice and in patients receiving therapy.

Some proposed mechanisms for the enhanced effect of x-irradiation and chemotherapeutic agents by dietary antioxidants and their derivatives include the following: a) high doses of dietary antioxidants before irradiation or chemotherapeutic agents initiate damage in cancer cells but not in normal cells, and cancer cells suffer additional damage during treatment with these agents through mechanisms other than free radicals; b) retinoic acid inhibits the repair of radiation damage in cancer cells, and therefore damage in cancer cells is further enhanced by the continued presence of retinoic acid after irradiation; c) α-TS–induced apoptosis in cancer cells is independent of p53 and p21, whereas 5-FU–induced apoptosis is mediated via p53 and p21, and therefore the combination of the two may be more effective than the individual agents; d) high expression of c-myc and H-ras oncogenes increases radioreistance of tumor cells, whereas high-dose α-TS reduces the expression of these oncogenes, and therefore α-TS administered before irradiation may enhance the sensitivity of these cells to radiation; and e) α-TS acts as an antiangiogenesis agent in vivo, whereas standard therapeutic agents do not, and therefore the combination of the two may be more effective than the individual agents.

Eighteen nonrandomized patients with small-cell lung cancer received multiple antioxidant treatment with chemotherapy and/or radiation. The median survival time was markedly enhanced and patients tolerated chemotherapy and irradiation well. Similar observations were made in several private-practice settings (3). A randomized pilot trial (Phase I–II) was conducted with high-dose multiple micronutrients, including dietary antioxidants and their derivatives—Sevak, a multivitamin preparation; 8 g of vitamin C as calcium ascorbate; 800 IU of vitamin E as α-TS; and 60 mg of natural β-carotene—administered orally, divided into 2 doses (half in the morning and half in the evening) to patients with Stage 0–III breast cancer undergoing radiation therapy. There were 25 patients in the radiation group and 22 patients in the combination group. A follow-up period of 22 mo during which no maintenance supplements were given showed that 1 patient in the radiation group developed a new cancer in the contralateral breast, and another in the same group developed lobular carcinoma in situ in the opposite breast. In the combination group, no new tumors developed (4). Another randomized trial with high-dose antioxidants (8 g of vitamin C as ascorbic acid, 800 IU of α-TS, and 60 mg of β-carotene, plus 800 μg of selenium) in combination with chemotherapeutic agents (cisplatin and paclitaxel) was carried out in patients with advanced non-small-cell carcinoma of the lung. This study of 34 chemotherapy patients and 31 combination-therapy patients reported beneficial effects on tumor response and tolerance to chemotherapeutic agents for a follow-up period of 1 y (5).

Based on the observed beneficial effects of multiple antioxidants in combination with standard therapy on 2 patients with ovarian cancer (6), Dr. Drisko began a new trial with multiple antioxidants on ovarian cancers. These studies suggest that well-designed trials with multiple antioxidants and their derivatives as an adjunct to standard therapy are needed urgently. In addition, how multiple antioxidants at low and high doses affect gene expression in normal and cancer cells should be evaluated, because very little is known regarding this issue.

LITERATURE CITED