

Should Supplemental Antioxidant Administration Be Avoided During Chemotherapy and Radiation Therapy?

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Despite nearly two decades of research investigating the use of dietary antioxidant supplementation during conventional chemotherapy and radiation therapy, controversy remains about the efficacy and safety of this complementary treatment. Several randomized clinical trials have demonstrated that the concurrent administration of antioxidants with chemotherapy or radiation therapy reduces treatment-related side effects. Some data indicate that antioxidants may protect tumor cells as well as healthy cells from oxidative damage generated by radiation therapy and some chemotherapeutic agents. However, other data suggest that antioxidants can protect normal tissues from chemotherapy- or radiation-induced damage without decreasing tumor control. We review some of the data regarding the putative benefits and potential risks of antioxidant supplementation concurrent with cytotoxic therapy. On the basis of our review of the published randomized clinical trials, we conclude that the use of supplemental antioxidants during chemotherapy and radiation therapy should be discouraged because of the possibility of tumor protection and reduced survival.

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Physicians must abide by the dictum *primum non nocere*, that is, “first, do no harm.” This tenet is central to the practice of medicine and serves as the foundation for medical treatments and therapeutic recommendations. At the earliest indication that a specific therapy may be harmful to a patient, a physician is obligated to assess the evidence about whether the putative benefit outweighs the potential harm. In the absence of good evidence of benefit, it is contrary to the principle of *primum non nocere* to advise patients to continue a potentially harmful intervention.

What, then, should physicians tell their patients about the use of supplemental antioxidants during chemotherapy and radiation therapy? Several clinical studies (1–6) have reported modest decreases in treatment-related side effects when supplemental antioxidants—either dietary or pharmaceutical—are administered concurrently with cytotoxic regimens. However, concern has been expressed (7,8) that the action of supplemental antioxidants might not be restricted to reducing the oxidative damage to normal tissues generated by radiation therapy and certain chemotherapeutic agents. Theoretically, antioxidants can exert their effects on all tissues to some degree, thereby protecting tumor cells as well as healthy ones. Experimental and clinical studies (5,6,9–16) lend support to this hypothesis, with some clinical data also suggesting that cancer patients who use antioxidant supplements during radiation or chemotherapy have worse survival than those who do not (5,6,14,17). Here, we present the available data on the use of supplemental antioxidants during chemotherapy or radiation therapy and highlight the reasons why this combined treatment approach should be avoided until it is shown to be safe.

Effects of Oncological Treatment and Mechanisms of Action of Antioxidants

The principal therapeutic effect of radiation occurs indirectly via the ionization of water molecules in the cytoplasm to reactive oxygen species, for example, superoxide and hydroxyl radicals.

These free radicals react with nuclear DNA, thereby creating structural bonds that are potentially fatal to cells. Some of this radiation damage can be repaired, leaving a cell that remains viable and that can proliferate. It takes only a millisecond for the free radical–DNA reaction to occur, and a normal cell that is not killed outright can repair the damage in as few as 6 hours (18). Antioxidants are compounds that can counteract free radicals and prevent them from causing tissue and organ damage (19). They function through a variety of mechanisms: as preventative agents that suppress the formation of free radicals, as radical scavenging agents that inhibit chain initiation and/or propagation, as repair and *de novo* enzymes that repair and reconstitute cell membranes, and as adaptation agents that generate appropriate antioxidant enzymes and transfer them to the necessary site of action (20). Antioxidants—whether produced endogenously (eg, α -lipoic acid, ubiquinone) or consumed in the diet (eg, α -tocopherol, ascorbic acid)—must be present in the cell during the free radical–DNA

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Table 1. Mechanisms of action of dietary antioxidants in cancer cells

| Observed effect | Potential mechanisms |
|----------------------------------|--|
| Decreased carcinogen formation | Cytochrome P450 modulation to 1) prevent carcinogen activation and 2) increase expression of phase 2 conjugating enzymes to facilitate carcinogen excretion |
| Decreased levels of DNA mutation | Decreased DNA oxidation |
| Decreased cell proliferation | Blocking growth-related signal transduction: 1) inhibition of protein kinase C and 2) inhibition of activator protein-1-dependent transcriptional activity; increased apoptosis; increased G ₁ arrest |
| Decreased metastasis | Decreased cell migration; increased DNA repair |

reaction, and at a sufficient concentration, to be effective in blocking free radical-mediated DNA damage. Although antioxidants, by definition, scavenge free radicals, it is important to recognize that most also act via other mechanisms to affect cell proliferation, apoptosis, angiogenesis, and other processes relevant to tumor growth and metastasis (21) (Table 1).

Although antioxidants may play a role in the primary prevention of cancer in part by reducing the oxidative modification of DNA (22), the same action might be expected to be counterproductive against radiation therapy and chemotherapeutic agents that act solely via the production of reactive oxygen species and induction of apoptosis (19). These agents include the anthracyclines (eg, doxorubicin), platinum-containing complexes (eg, cisplatin, carboplatin), alkylating agents (eg, cyclophosphamide, ifosfamide), and cytotoxic antibiotics (eg, bleomycin, mitomycin-C). Dietary antioxidants comprise a variety of chemical classes, including carotenoids, polyphenols, tocopherols, and triterpenes, and they display an array of biologic activities. Thus, it is not possible to make broad generalizations about whether or how they might interact with oncological treatments. Nonetheless, these nutrients are defined by their shared capacity for quenching reactive oxygen and nitrogen species even though their *in vivo* potency and selectivity can vary substantially by class, bioavailability, dose, and duration, as well as by route of administration (19). For example, the most readily bioavailable form of the antioxidant lycopene is in cooked rather than raw foods, and ascorbic acid acts as an antioxidant when taken orally but as a prooxidant when administered intravenously at high doses (19,23). Individual variations (eg, polymorphisms) in the expression of antioxidant enzymes such as superoxide dismutase and catalase further complicate potential interactions between oncological treatments and the antioxidant defense network. For example, some polymorphisms in the gene encoding glutathione-S-transferase, an antioxidant enzyme, can decrease the antioxidant activity of the enzyme (24,25).

In discussions of antioxidant supplementation, one must distinguish between high-dose antioxidant supplementation and supportive dietary antioxidant supplementation (ie, low-dose dietary intakes to support normal function through the intake of the essential vitamins C and E and the other antioxidants found in plant foods). In addition, it is important to recognize that when specifying

doses of an antioxidant, the matrix and mix of isomeric compounds can differ markedly between foods and supplements. Laboratory evidence indicates that the effect of dietary antioxidants on tumors is dose dependent. In the absence of radiotherapy or chemotherapy, high doses of dietary antioxidants often inhibit the growth of cancer cells without affecting the growth of normal cells (26–28). However, data from some studies indicate that antioxidant supplementation at doses that are intermediate to dietary intakes (relatively low doses) and high supplemental doses may reduce the efficacy of x-irradiation against cancer cells (10,12) or stimulate tumor cell growth (29). Interpretation of these experimental data is difficult because the doses that inhibit tumor cell growth vary between species and tumor types and the distribution of antioxidants varies between tumor cells and normal cells (29,31–36).

The above-mentioned variables (eg, high-dose vs relatively low-dose antioxidant supplementation, variations in antioxidant classes) may substantially define the efficacy and safety profiles of specific antioxidant supplements as therapy for cancer patients receiving selected chemotherapy agents or radiation therapy. Recommendations about the use of specific antioxidant supplements during radiation or chemotherapy can be established only after further clinical studies have evaluated these and other variables (eg, tumor and normal tissue protective effects at different antioxidant dose levels and mixtures of antioxidants).

Radiation Therapy and Antioxidants

We attempted to identify all published randomized clinical trials that have investigated the possible radiomodifying effects (ie, increasing or decreasing radiosensitivity) of concurrent administration of supplemental antioxidants on normal tissues and tumors by searching the Medline database with the following key words: radiation therapy, cancer, tumor control, side effects, toxicity, vitamins, and antioxidants (see Table 2).

Bairati et al. (5,37) reported that among 540 head and neck cancer patients who were randomly assigned to receive either α -tocopherol with or without β -carotene vs placebo concurrent with their radiation therapy, those who received both antioxidants had a statistically significant 38% reduction in severe, acute side effects. However, this benefit appeared to be offset by reductions of 29% and 56% in the local tumor control rates for α -tocopherol and α -tocopherol plus β -carotene, respectively. It is interesting to note that in a recently reported subgroup analysis of these patients (38), the interactions between antioxidant supplementation and cigarette smoking during radiation therapy were associated with an increase in both disease recurrence (hazard ratio [HR] = 2.41, 95% confidence interval [CI] = 1.25 to 4.64) and cancer-specific mortality (HR = 3.38, 95% CI = 1.11 to 10.34). There was no increase in either of these outcome measures for the nonsmokers. The most concerning data are presented in a subsequent publication by Bairati et al. (17) on the same cohort of patients. In this article, they demonstrate that the patients who received antioxidants had statistically significant poorer overall survival.

Relatively few randomized controlled trials of antioxidants and radiation therapy, such as those carried out by Bairati et al. (5,17,37), are available. Because of the reasonably large sample size

Table 2. Randomized trials investigating the concurrent use of antioxidants during radiation therapy*

| First author (reference) | Cancer type or site | No. of patients | Concurrent treatment | Antioxidant details | Results |
|---|---------------------|-----------------|---|---|---|
| Dietary antioxidants Bairati (5,17,37) and Meyer (38) | Head and neck | 540 | Radiation: patients randomly assigned to placebo vs vitamin E and β -carotene | α -tocopherol (400 IU/d, po) and β -carotene (30 mg/d, po) or placebo administered during radiation therapy and for 3 y thereafter. β -Carotene was discontinued after 156 patients had enrolled because of ethical concerns raised by other trials. | Antioxidant arm vs placebo arm: Severe, acute side effects: OR = 0.38, 95% CI = 0.20 to 0.74 (Quality of life was not improved by the supplementation.) Rate of local recurrence of the head and neck tumor: HR = 1.37, 95% CI = 0.93 to 2.02 Rate of disease recurrence in patients who smoked tobacco and took antioxidant supplements during radiation therapy: HR = 2.41, 95% CI = 1.25 to 4.64 (52-mo median follow-up) Rate of second primary cancers during the supplementation period: HR = 2.88, 95% CI = 1.56 to 5.31 Rate of second primary cancers after supplementation was discontinued: HR = 0.41, 95% CI = 0.16 to 1.03 Rate of having a recurrence or second primary cancer during the supplementation period: HR = 1.86, 95% CI = 1.27 to 2.72 Rate of having a recurrence or second primary cancer after supplementation was discontinued: HR = 0.71, 95% CI = 0.33 to 1.53 The proportion of participants free of second primary cancer overall after 8 y of follow-up was similar in both arms (6.5-y median follow-up) All-cause mortality: HR = 1.38, 95% CI = 1.03 to 1.85 Cause-specific mortality rates tended to be higher in the supplement arm than in the placebo arm Cause-specific mortality in patients who smoked tobacco and took supplements during radiation therapy: HR = 2.26, 95% CI = 1.29 to 3.97 All-cause mortality in patients who smoked tobacco and took supplements during radiation therapy: HR = 3.38, 95% CI = 1.11 to 10.34 |
| Ferreira (6) | Head and neck | 54 | Radiation (50–70 Gy): patients randomly assigned to placebo vs vitamin E | Vitamin E (400 mg) or placebo (500 mg primrose oil [contains 13 IU vitamin E]) dissolved in an oil-based rinse given immediately before (5 min) and 8–12 h after each radiation treatment | Antioxidant arm vs placebo arm: Symptomatic mucositis events (%): 21.6 vs 33.5, $P = .038$ Pain and decreased oral intake by the end of radiation (RTOG and EORTC grades 2–3; %): 11 vs 54, $P < .001$; OS2 (%): 32 vs 63; median OS (mo): 8.5 vs 12.5, $P = .13$ Stage 3 and 4 patients (%): 86 vs 62, $P = .086$ |
| Misirlioglu (39) | Non-small cell lung | 66 | Radiation therapy (60 Gy): patients randomly assigned to vitamin E and pentoxifylline vs radiation alone (no placebo control) | Pentoxifylline (400 mg, po, TID); α -tocopherol (300 mg, po, BID) | Antioxidant arm vs control arm: OS1 (%): 55 vs 40; OS2 (%): 30 vs 14; median OS (mo): 18 vs 10, $P = .0175$ PFS1 (%): 48 vs 24; PFS2 (%): 23 vs 18; median PFS (mo): 12 vs 8, $P = .0223$ No discussion of differences in normal tissue toxicities |

(Table continues)

Table 2 (continued).

| First author (reference) | Cancer type or site | No. of patients | Concurrent treatment | Antioxidant details | Results |
|--------------------------------|--|-----------------|--|--|---|
| Nondietary antioxidants | | | | | |
| Kwon (40) | Non-small cell lung | 47 | Radiation therapy (65–70 Gy): patients randomly assigned to pentoxifylline vs radiation alone (no placebo control) | Pentoxifylline (400 mg, po, TID) beginning 1 d before the start of XRT and continuing until the last day of XRT | Antioxidant arm vs control arm: OS1 (%): 60 vs 35; $P = .08$ OS2 (%): 18 vs 12; $P = .08$ All-site relapse rate: 13/27 (48%) vs 10/20 (50%), $P = .9$ LRF: 8/27 (29.6%) vs 5/20 (25%), $P = NS$ Normal tissue protection: no difference in any toxic effects (dysphagia, odynophagia, pulmonary fibrosis, and pneumonitis), $P = NS$ |
| Lissoni (41) | Glioblastoma multiforme | 30 | Radiation therapy (60 Gy): patients randomly assigned to concurrent melatonin vs radiation alone (no placebo control) | Melatonin (20 mg, po, at night). Continued after radiation therapy course (until disease progression) | Antioxidant arm vs control arm: OS1: 6/14 (43%) vs 1/16 (6%), $P < .02$ |
| Berk (42) | Brain metastases | 126 | Randomized phase II trial of radiation therapy (30 Gy, whole brain) plus melatonin (AM or PM dosing) compared with an RTOG historical control (and the RTOG 0118 control arm: XRT with or without thalidomide) for radiation alone for brain metastases (30 Gy, whole brain) | Melatonin (20 mg, po); patients randomly assigned to 8–9 AM or 8–9 PM dosing. All patients took the melatonin during radiation therapy and continued for 6 mo or until progression of their disease | Antioxidant AM arm, antioxidant PM arm, control arm: Median survival (mo): 3.4, 2.8, 4.1; $P = NS$ (actual P value not reported) Deterioration of mini mental status examination scores by 3 mo after radiation (%): 48, 51, <20 (historical control) (no P value discussed) |
| Sasse (43) | Multiple sites (head and neck, pelvic, thoracic) | 1451 | Meta-analysis of 14 randomized controlled trials of radiotherapy (with or without chemotherapy) vs radiotherapy plus amifostine (with or without chemotherapy) | Various doses (150–340 mg/m ²), routes of administration (IV and SC), and schedules (daily and twice weekly, before radiation therapy) of concurrent amifostine. No studies were placebo controlled. | Antioxidant arm vs control arm†: Rate of developing mucositis: OR = 0.37, 95% CI = 0.29 to 0.48, $P < .001$ Rate of developing esophagitis: OR = 0.38, 95% CI = 0.26 to 0.54, $P < .001$ Rate of developing acute xerostomia: OR = 0.24, 95% CI = 0.15 to 0.36, $P < .001$ Rate of developing late xerostomia: OR = 0.33, 95% CI = 0.21 to 0.51, $P < .001$ Rate of developing dysphagia: OR = 0.26, 95% CI = 0.07 to 0.92, $P = .04$ Rate of developing acute pneumonitis: OR = 0.15, 95% CI = 0.07 to 0.31, $P < .001$ Rate of developing cystitis: OR = 0.17, 95% CI = 0.09 to 0.32, $P < .001$ There was no difference in overall response rate between the groups. However, complete response rate was superior for patients using amifostine (OR = 1.81, 95% CI = 1.10 to 2.96, $P = .02$) |
| Mell (44) | Non-small cell lung | 552 | Meta-analysis of seven randomized controlled trials of radiotherapy (with or without chemotherapy) vs radiotherapy plus amifostine (with or without chemotherapy); 55–69.6 Gy | Various daily doses (200–740 mg/m ²), routes (SC and IV), and schedules (daily, 2 per wk, or 4 per wk) of concurrent amifostine. Only one of the seven trials was placebo controlled. | Antioxidant arm vs control arm‡: Overall response: RR = 1.07, $P = .17$ Complete response: RR = 1.21, $P = .33$ Partial response: RR = 0.99, $P = .95$ Evidence of cytoprotection: no evidence of cytoprotection in three of the seven trials |

(Table continues)

Table 2 (continued).

| First author (reference) | Cancer type or site | No. of patients | Concurrent treatment | Antioxidant details | Results |
|--------------------------|---------------------|-----------------|--|--|---|
| Buentzel (45) | Head and neck | 132 | Radiation therapy (60–70 Gy) with chemotherapy (carboplatin); patients randomly assigned to amifostine or placebo control (mannitol) | Amifostine (given on days with carboplatin, days 1–5 and 21–25: 300 mg/m ² IV, daily, approximately 60 min before radiation; given on days without carboplatin, days 6–20 and 26–30 and 35: 200 mg/m ² IV, daily, approximately 30 min before radiation) | Antioxidant arm vs control arm: Grade ≥ 2 , acute xerostomia (%): 39 vs 34, $P = .715$ Grade ≥ 3 acute mucositis (%): 39 vs 22, $P = .055$ Grade ≥ 2 late xerostomia (%): 39 vs 24, $P = .235$ Locoregional failure at 1 y (%): 38 vs 27, $P = .218$ Ratio of locoregional control rates (amifostine/placebo): 0.84 (95% CI = 0.64 to 1.10) PFS1 (%): 64 vs 72, $P = .5$ OS1 (%): 75 vs 77, $P = .7$ |

* po = orally; OR = odds ratio; CI = confidence interval; HR = hazard ratio; RTOG = Radiation Therapy Oncology Group; EORTC = European Organization for Research and Treatment of Cancer; OS = overall survival; TID = three times per day; BID = two times per day; OS1 = overall survival at 1 year; OS2 = overall survival at 2 years; PFS = progression-free survival; PFS1 = progression-free survival at 1 year; PFS2 = progression-free survival at 2 years; XRT = radiation therapy; LRF = local regional failure; NS = not statistically significant; IV = intravenous injection; SC = subcutaneous injection; RR = relative risk.

† Comments: 1) logistic support for the meta-analysis was provided by Schering–Plough; 2) 7 of the 14 included studies were documented to have pharmaceutical sponsorship; 3) seven trials did not state their sponsorship.

‡ Comments: 1) six of the nine authors received honoraria from Medimmune or Schering–Plough; 2) the meta-analysis included unpublished data (and/or data from personal communications regarding ambiguities in the published data) from five of the seven included trials.

($n = 540$ patients), the use of a placebo-controlled design, and standard prescribed doses of commonly used dietary antioxidants, this study is the most important randomized clinical trial, to date, on the use of a supplemental antioxidant and radiation therapy. When reviewing the available literature on clinical data, a higher level of evidence is usually assigned to randomized controlled trials than to observational studies because this rigorous study design reduces bias through balancing the confounding properties of the comparator groups (46).

Several other studies have provided evidence that antioxidants can decrease the effectiveness of radiation therapy. For example, Ferreira et al. (6) randomly assigned 54 head and neck cancer patients who were undergoing radiation therapy to receive an oil-based oral rinse that contained either vitamin E or placebo before and after each daily dose of radiation. Although the vitamin E supplementation was associated with a 36% reduction in symptomatic mucositis, the authors also reported a decrease in 2-year overall survival (32% with supplemental vitamin E vs 63% with placebo; $P = .13$). This concerning decrease in overall survival, albeit not statistically significant, may have been confounded by the greater percentage of patients with stage 3 and 4 tumors found in the vitamin E group. In another study, Lesperance et al. (14) investigated a historical cohort of 90 patients with nonmetastatic breast cancer who received conventional treatment (eg, surgery, chemotherapy, radiation therapy, and hormonal therapy) either alone or in combination with high doses of β -carotene, vitamin C, niacin, selenium, coenzyme Q10, and/or zinc. Breast cancer–specific survival (ie, patients censored only at death from breast cancer) and disease-free survival were shorter in the nutrient-supplemented group than in the nonsupplemented group, but the differences were not statistically significant (hazard ratio of breast cancer death = 1.75, 95% CI = 0.83 to 2.69, and hazard ratio of relapse =

1.55, 95% CI = 0.94 to 2.54, respectively). Despite the substantial limitations of these studies (6,14), it is troubling that both reported results suggesting poorer survival with concurrent administration of antioxidants and cytotoxic therapy, even though these results are at odds with other studies. For example, two randomized trials—Misirlioglu et al. (39), testing pentoxifylline and α -tocopherol in patients with non–small cell lung cancer, and Lissoni et al. (41), testing melatonin in patients with brain glioblastomas—found that radiotherapy combined with α -tocopherol or melatonin supplementation increased survival. However, this suggestion of radiosensitization of tumors was not confirmed by Berk et al. (42) in a randomized trial of radiation therapy and high-dose melatonin in brain metastases.

Despite concerns (8) about current recommendations supporting the use of antioxidant supplementation during oncological treatments, some antioxidants, such as amifostine (WR-2721), a thiol-containing antioxidant that has been approved by the Food and Drug Administration to increase the radioresistance of salivary gland tissues, show promise as cotherapies. Although some preclinical studies (47–50) have shown that amifostine increases the radioresistance of tumors, neither the randomized clinical trials (51–57) nor the meta-analyses (44,45) of this agent have provided conclusive evidence of increased radioresistance of tumors. This selective effect—of increasing radioresistance of normal tissues only—has been attributed to the preferential uptake of the active (ie, dephosphorylated) form of amifostine (WR-1065) into normal cells vs cancer cells (58,59). It is not possible to know definitively, with the available data, whether amifostine increases radioresistance of tumors because the randomized clinical studies of amifostine have had brief follow-up, used variable doses and regimens, and based their sample sizes on estimates of the primary endpoints of toxicity (ie, mucositis and xerostomia) rather than on local tumor control. In a meta-analysis of amifostine studies, Mell et al. (44)

stated that their "...results suggest that any effect of amifostine on reducing overall response [to radiation therapy], if it exists, is no larger than a 3% relative risk reduction. Assuming an expected overall response rate of 65%, this would correspond to a maximal risk difference no worse than approximately 2% (i.e., two fewer responses per 100 patients treated)." These authors further state that "These findings, therefore do not support the hypothesis that amifostine has a clinically important tumor protective effect in these patients." Although many patients may accept the potential benefits of experiencing fewer treatment-related toxic effects (eg, xerostomia, mucositis) over the small risk of diminished tumor control (eg, 2 of 100 patients may fail treatment as a result of the tumor-protective effects of an adjunctive antioxidant), these possible concerns should be discussed with the patient before initiating amifostine.

Chemotherapy and Antioxidants

We also conducted a systematic search of the Medline database for all published randomized clinical trials of antioxidants and chemotherapy using the following key words: vitamins, antioxidants, chemotherapy, cancer, tumor control, side effects, and toxicity. We identified 16 randomized clinical trials that studied the concurrent use of antioxidant supplements and chemotherapy; 6 of those trials included a placebo control (Table 3). Although no decrements in tumor response rates or survival rates were observed in the studies that reported response data (71,72), none of those studies were powered to evaluate these endpoints. For example, Pathak et al. (64) examined whether the concurrent administration of a high-dose antioxidant mixture containing vitamins C and E and β -carotene with paclitaxel and cisplatin improved tumor response and survival in 136 patients with advanced non-small cell lung cancer and observed no survival or tumor response benefits with the antioxidants. However, the authors' conclusion that the antioxidant supplementation was safe is not warranted because the study was not sufficiently powered to evaluate a reduction in survival or tumor response. In a systematic review of the randomized trials of antioxidants and chemotherapy, Ladas et al. (76) found such a wide range of cancer diagnoses, chemotherapy regimens, and antioxidant supplementation that they could not draw definitive conclusions about the safety and efficacy of the antioxidant interventions.

Although several studies [reviewed by Mills et al. (77)] have suggested that melatonin supplementation may improve the survival of chemotherapy-treated patients with some solid tumors, it is not clear that this effect is mediated exclusively by the antioxidant action of this hormone. For example, in a randomized clinical trial of cisplatin plus etoposide and melatonin, Lissoni et al. (66) observed improved tumor response rates in 100 patients with metastatic non-small-cell lung cancer. The same group of investigators (67) also observed similar results with melatonin in a study of 250 patients with various metastatic solid tumors who received several different chemotherapy regimens. These intriguing results should now be independently confirmed in larger trials.

Future Directions

Numerous literature reviews (7,8,76,78–86) have focused on the topic of whether supplemental antioxidants administered during

chemotherapy or radiation therapy can protect normal tissues without adversely influencing tumor control. As noted above, variations in study design, intervention protocol, eligibility criteria, statistical power, timing of the observation or intervention, malignancy type, and anticancer regimens limit the ability of the authors of these reviews to make definitive conclusions regarding the risk of decreased tumor control as a consequence of administering supplemental antioxidants during chemotherapy and/or radiation therapy.

It is with this in mind that we find it surprising that a recent review (85,86) definitively concludes that antioxidants (and other supplemental nutrients), when given concurrently with chemotherapy and/or radiation therapy, 1) do not interfere with chemotherapy and/or radiation therapy, 2) enhance the cytotoxic effects of chemotherapy and radiation therapy, 3) protect normal tissues, and 4) increase patient survival. In the concluding sentence of this review, the authors recommend that "Antioxidant and other nutrient food supplements are safe and can help to enhance cancer patient care" (86). Such a recommendation merits close examination of the evidence because it is at odds with other authoritative reviews on this topic (7,76,78,80,84). Of the 52 clinical studies Simone et al. (85,86) reviewed, 36 were observational, a study design that is limited by selection bias and unknown confounders. Of the 16 randomized controlled trials they reviewed, 10 included fewer than 50 patients, a sample size too small to inspire confidence in findings of equivalent survival. Indeed, if antioxidant supplements interfered completely with an agent associated with an absolute increase in survival of 5%, a suitably powered trial would require approximately 2000 patients. The six remaining reports reviewed by Simone et al. (85,86) were randomized trials with at least 50 patients, and, of these, only one (89) tested an antioxidant. In this trial ($n = 50$), glutathione improved response rates and decreased neurotoxicity in advanced gastric cancer patients who received cisplatin. This is an interesting result, but it must be confirmed in a larger study.

Importantly, many reports (39–41,60–72,79) provide a basis for continuing research on the potential for dietary and pharmaceutical antioxidants to enhance the effects of some cytotoxic regimens and/or decrease toxicity without interfering with oncological actions. However, a more sophisticated recognition of the complexity and diversity of antioxidants is required when designing new studies. The profile of antioxidant (ie, radical scavenging) and other (eg, on cell signaling and gene expression) actions of these compounds, as well as their differential bioavailability, distribution, metabolism, potency, and dynamic interrelationships, must be understood. In designing new trials of adjunctive treatments with antioxidants, consideration must be given to the specific chemotherapeutic agents and radiation therapy regimens and to the evaluation of appropriate intermediary biomarkers and clinical outcomes, including short- and long-term tumor control (84). A challenge to these considerations is the absence of any consistent pattern of serum status of vitamins C and E, β -carotene, or selenium in patients with cancer receiving chemotherapy (76). It is noteworthy that although the initiation of anticancer therapies may lower plasma antioxidant concentrations by altering dietary intakes, an increase in plasma antioxidant levels has been associated with a reduction in the cancer burden (90). It is important to consider results of research that

Table 3. Randomized trials investigating the concurrent use of antioxidants with chemotherapy*

| First author (reference) | Cancer site or type | No. of patients | Concurrent treatment | Antioxidant details | Results |
|--------------------------------|---|-----------------|---|--|--|
| Dietary antioxidants | | | | | |
| Mills (60) | Advanced squamous carcinoma of the mouth | 20 | Bleomycin, vincristine, leucovorin, methotrexate, and radiation | β -Carotene (250 mg for first 21 d, 75 mg/d for duration of cancer therapy; po) | No statistically significant difference in rate of remission for antioxidant patients vs no antioxidants Patients who received antioxidants had a decrease in grade 3 or 4 mucositis ($P < .025$) |
| Weitzman (61) | Variety (lung, breast, lymphoma, sarcoma, gastric) | 16 | Chemotherapy agents: not specified; radiation therapy | DL- α -tocopherol (1800 IU, route not specified) | No statistically significant findings |
| Wagdi (62) | Mixed | 25 | Mixed chemotherapy and/or radiation therapy | Mixed antioxidant regimen included vitamin C (1 g, route not specified) and vitamin E (600 mg, route not specified) and N-acetylcysteine | No statistically significant findings |
| Wadleigh (63) | Solid tumors, leukemia | 18 | Cisplatin, doxorubicin, cytarabine, and 5-fluorouracil | Vitamin E oil (400 mg, topical) or placebo oil | Resolution of mucositis was shorter in antioxidant patients vs placebo control patients ($P = .025$) |
| Pathak (64) | Stage 3–4 non-small cell lung | 136 | Paclitaxel and carboplatin | Antioxidant mixture (oral): vitamin C, 6100 mg; vitamin E (DL- α tocopherol succinate): 1050 mg; synthetic β -carotene: 60 mg | No statistically significant differences in tumor response rates or overall survival No statistically significant differences in toxicity rates |
| Nondietary antioxidants | | | | | |
| Falsaperla (65) | Hormone refractory prostate | 48 | Vinorelbine and estramustine | Ellagic acid (180 mg, po) | No statistically significant differences in progression-free survival Decreased neutropenia in antioxidant patients vs no antioxidants ($P < .05$) |
| Lissoni (66) | Metastatic non-small cell lung | 100 | Cisplatin and etoposide | Melatonin (20 mg, po) | Increased stable disease rate in antioxidant patients vs no antioxidants ($P < .01$) Increased tumor regression rate in antioxidant patients vs no antioxidants ($P < .05$) Decreased neurotoxicity ($P < .01$), thrombocytopenia ($P < .01$), weight loss >10% ($P < .001$), and asthenia ($P < .005$) in antioxidant patients vs no antioxidants |
| Lissoni (67) | Metastatic solid tumors (non-small cell lung, breast, colorectal, gastric, pancreatic, head and neck) | 250 | Non-small cell lung: cisplatin, etoposide, and gemcitabine; breast: doxorubicin, mitoxantrone, and paclitaxel; gastrointestinal (colorectal, gastric, pancreatic): 5-fluorouracil and folinic acid; head and neck: 5-fluorouracil and cisplatin | Melatonin (20 mg, po) | Complete response rate higher in antioxidant patients vs no antioxidants ($P < .02$) Increased partial response rate in antioxidant patients vs no antioxidants ($P < .01$) Increased tumor regression rate (complete response and partial response) in antioxidant patients vs no antioxidants ($P < .001$) Increased 1-y survival in antioxidant patients vs no antioxidants ($P < .001$) Increased overall survival in antioxidant patients vs no antioxidants ($P < .05$) Decreased neurotoxicity ($P < .05$), thrombocytopenia ($P < .05$), weight, myelosuppression ($P < .001$), asthenia ($P < .001$), cardiotoxicity ($P < .001$), and stomatitis ($P < .05$) in antioxidant patients vs no antioxidants |

(Table continues)

Table 3 (continued).

| First author (reference) | Cancer site or type | No. of patients | Concurrent treatment | Antioxidant details | Results |
|--------------------------|--|-----------------|---|--|--|
| Cerea (68) | Metastatic colorectal cancer | 30 | Irinotecan | Melatonin (20 mg, po) | No statistically significant difference in complete response or partial response Increased number of antioxidant patients had stable disease compared with no antioxidants ($P < .05$) No statistically significant differences in toxicity rates |
| Cascinu (69) | Advanced colorectal carcinoma | 52 | Oxaliplatin, leucovorin, and 5-fluorouracil | Glutathione (1500 mg/m ² , IV) or placebo (saline) administered 15 min before oxaliplatin | No statistically significant difference in response After eight cycles, decreased neuropathy in glutathione vs placebo ($P = .003$) After 12 cycles, decreased neuropathy in antioxidant patients vs placebo control patients ($P = .004$) |
| Schmidinger (70) | Head and neck cancer, non-small cell lung cancer | 20 | Cisplatin, 5-fluorouracil, and etoposide | Glutathione (5 g, IV) or placebo (electrolyte infusion) before administration of cisplatin | No statistically significant difference in response or overall survival Statistically significant decrease in hematologic toxicity in antioxidant patients vs placebo control patients No statistically significant difference in nonhematologic toxicity |
| Smyth (71) | Ovarian | 151 | Cisplatin | Glutathione (3 g/m ² every 3 wk, intravenous) or placebo (saline) | No statistically significant effect on response to treatment Improved creatinine clearance in antioxidant patients vs placebo control patients ($P = .006$) More patients received the recommended number of cycles in antioxidant patients vs placebo control patients ($P = .04$) |
| Cascinu (72) | Advanced gastric | 50 | Cisplatin, fluorouracil, 4-epidoxorubicin, and leucovorin | Glutathione (1.5 g/m ² , IV) or placebo (saline) | No statistically significant difference in response rate After 15 wk, decreased neuropathy in glutathione vs placebo ($P < .001$) |
| Parnis (73) | Advanced ovarian | 12 | Group 1: cisplatin × 2 days, group 2: cisplatin × 3 days, group 3: cisplatin × 4 days | Glutathione (1.5 g/m ² , IV) or placebo | Trial stopped after second dose escalation due to increased ototoxicity observed in first eight patients |
| Fujimoto (74) | Gastric | 207 | Mitomycin-C, 5-fluorouracil, and phenobarbital | Glutathione (30 mg/kg, IV) administered with phenobarbital | Increased serum 5-fluorouracil levels in antioxidant patients vs no antioxidants ($P < .01$) No statistically significant difference in overall survival No statistically significant difference in survival for patients with stage 1 or 2 Antioxidant patients with stage 3 or 4 had a statistically significantly higher survival rates compared with no antioxidants ($P < .025$ at 3 y; $P < .025$ at 4 y; $P < .025$ at 5 y) No statistically significant differences in toxicity |
| Colombo (75) | Relapsed ovarian | 33 | Cisplatin | Glutathione (2.5 g, IV) | No statistically significant differences in response or survival in antioxidant patients vs no antioxidants A trend toward decreased neurotoxicity in antioxidant patients vs no antioxidants Higher dose intensity in antioxidant patients vs no antioxidants |

* po = orally; IV = intravenous injection.

addresses the efficacy and safety of complementary therapy with high-dose antioxidant treatments in the context of the ongoing need for all patients to meet established dietary requirements for the essential vitamins C and E and the intake of carotenoids, flavonoids, and related antioxidant phytochemicals (91).

When a Potential for Harm Exists, *Primum non nocere*

Despite two decades of research on the concurrent use of antioxidants and chemotherapy or radiotherapy, the data remain insufficient to provide a clear guide for clinical practice. Much of the evidence to date regarding the effects of antioxidants on tumor control was derived from experimental research that has little relevance to patients, from observational studies that were confounded by known and unknown factors, and from clinical trials that lacked careful controls, adequate power, or accurate measures of tumor control. Further research is required to address these limitations and to more carefully consider the complexity of high-dose antioxidant interventions, including dose–response relationships, treatment timing and duration, and dynamic interrelationships with other antioxidants as well as with specific oncological therapies. New clinical investigations must identify appropriate patient populations, develop rational antioxidant doses and combinations, and establish well-defined intermediary biomarkers and clinical endpoints. Despite some intriguing studies (39,41,63,66–75) that have suggested the benefit of adjunctive antioxidant treatments in cancer patients, the totality of the available evidence is equivocal at best and leaves us with serious concerns about the potential for harm.

Our view on the use of complementary antioxidant therapy with chemotherapy or radiation therapy can be summarized in the following two points. First, data from a limited number of randomized controlled trials have shown that high-dose antioxidant supplementation during radiotherapy decreases local tumor control and shortens the survival of cancer patients. Although the potential for harm from this adjunctive therapy may be limited to a few antioxidants, the uncertainty about what doses and which compounds are clearly safe demands that high doses of any antioxidant should be avoided during radiation therapy unless clear evidence is available that the benefits outweigh the potential risk. Second, limited data and theoretical understanding regarding the mechanisms of action of dietary antioxidants suggest that at high doses, some of these compounds, alone or in combination, may enhance the effects of some cytotoxic regimens and/or decrease their toxicity without reducing oncological efficacy. As such, continuing research on the use of concurrent supplemental antioxidants with chemotherapy and/or radiation therapy is warranted.

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