



Should patients take or avoid antioxidant supplements during anticancer therapy? An evidence-based review

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1. INTRODUCTION

The debate over the usefulness of and contraindications against antioxidants during conventional anticancer therapy is currently based more on opinion than scientific fact. A search of the U.S. National Library of Medicine reveals no level 1 evidence (that is, prospective randomised clinical trials) that proves antioxidants to be either beneficial or detrimental to the outcome of anticancer treatment.

To be of benefit, an antioxidant therapy should increase the therapeutic gain. In other words, it should either improve tumour control or reduce normal-tissue toxicity. A therapy that equally reduces tumour control and normal-tissue toxicity has not produced a therapeutic gain and therefore is not clinically useful.

Speculation on clinical benefit has been extrapolated from a combination of interventional laboratory studies (usually based on cell cultures) and observational studies of cancer prevention. Opinion on clinical detriment is based on a number of conflicting laboratory studies and on the fundamental teaching of clinical oncologists that free radicals [or reactive oxygen species (ROS)] are the major weapons in cancer destruction and should never be suppressed for fear of reducing tumour control. Pundits on both sides of the debate make good points, but those points are based mainly on opinion rather than on fact.

Part of the controversy arises from a futile attempt to compare apples and oranges. Many biochemicals have either oxidant or antioxidant activity that varies under different metabolic conditions¹⁻⁴. The human population is heterogeneous in relation to levels of ROS and ability to moderate them⁵. An assumption has been made that antioxidant activity alone is responsible for any interventional benefit. That assumption is clearly naïve, because all of the antioxidants have many additional biochemical and pharmacologic effects⁶.

2. DEFINING THE GROUNDS FOR DISCUSSION

Any discussion of antioxidants needs to be very specific in defining both the intervening chemical and

the measured effect. For example, the carotenoids are generally regarded as antioxidants, but they also interact with cell membrane receptors to initiate differentiation⁷⁻¹⁰.

The efficacy of antioxidants in preventing cancer should be differentiated from the contribution of antioxidants during anticancer therapy. For example, epidemiologic studies indicate that lycopene can inhibit the development of prostate cancer¹¹⁻¹⁶, but laboratory experiments show that lycopene reduces the ability of radiation to destroy prostate cancer cells¹⁷. Synthetic beta-carotene can increase the risk of lung cancer in people who have previously smoked cigarettes, revealing a paradox between cancer promotion and prevention¹⁸⁻²³. On the other hand, another antioxidant, vitamin E, seems to promote destruction of cancer cells by radiation *in vitro* and to enhance the normal healing of tissue following completion of radiation therapy²⁴⁻⁴⁰.

The source of an antioxidant may affect its biologic activity. Synthetic and natural beta-carotenes manifest different biologic effects⁴¹. The differential response implies that the effects of the antioxidant are either highly dependent on the metabolic environment or are totally unrelated to antioxidant activity^{42,43}.

The present review focuses on the limited evidence available for combining antioxidants and anticancer therapy, with a view to providing the best current evidence for designing a randomised controlled clinical trial. Attention is directed toward dietary antioxidants, especially vitamins (rather than the multiple herbal derivatives touted for their antioxidant activity), and an evaluation is made regarding whether a role exists for pharmacologic intervention with micronutrients above the recommended supplement doses.

Non-vitamin antioxidants include sulphhydryl compounds (such as glutathione) and antioxidant enzymes, whose major effects are to quench free radicals and to reduce radiation damage to both normal and tumour tissue. The micronutrient selenium is an essential component of glutathione peroxidase, an enzyme that quenches ROS. Other non-vitamin antioxidants include melatonin, pycnogenols, and coen-

zyme Q10, all of which have pharmacologic properties that can inhibit cancer, but that are not necessarily related to their antioxidant activity. These antioxidants may also have a role in counteracting the long-term toxicity of conventional anticancer therapies⁴⁴⁻⁴⁹.

Observational surveys that report associations between antioxidant levels and outcome may provide leads and hypotheses, but they cannot replace the data obtained in prospective clinical trials⁵⁰⁻⁵². For example, people whose diets are rich in fruits and vegetables have a reduced chance of developing cancer and an increase in the concentration of beta-carotene in their blood^{22,53-61}. However, supplements of beta-carotene do not have an anticancer effect, and they actually increase cancer in smokers^{21,23,62-67}. Blood levels of beta-carotene may simply be a surrogate for the activity of an associated compound.

Despite the beneficial effect of fruit and vegetable consumption in reducing the free radical damage from environmental pollutants (including radiation) in human observational studies, supplements of vitamins C and E and beta-carotene generally do not reduce DNA damage from irradiation in many *in vitro* and animal studies⁶⁸⁻⁷³. In contrast, lycopene does reduce DNA damage from ROS¹⁷. Other studies have shown that levels of vitamin C below the recommended dietary allowance (RDA) are associated with increased free-radical damage to DNA and greater tissue sensitivity to radiotherapy; moderate vitamin C supplementation can reduce the free radical damage stemming from radiation treatment and can enhance cancer cell survival^{68,74}. Paradoxically, treatment with very high doses of vitamin C can inhibit cancer cell division and increase the sensitivity of tumours to radiotherapy⁴².

The effects of antioxidants are multi-factorial and highly dependent on initial conditions. Their actions are indeed a tangled web.

3. THE PARADOX OF DIETARY ANTIOXIDANTS

The effect of dietary antioxidants on tumours is dose-dependent. High doses inhibit the growth of cancer cells without affecting the growth of normal cells^{5,42,43,75}. Prasad and colleagues have defined "high dose" as more than the RDA, but not enough to cause toxicity. A "high dose" of vitamin C is up to 10 g daily; vitamin E, up to 1000 IU daily; vitamin A, up to 10,000 IU daily; and natural beta-carotene, up to 60 mg daily⁶.

Research by Prasad *et al.* has also defined the equivalent doses in tissue culture. The results from tissue cultures suggest that high doses of the dietary antioxidants vitamins A, C, and E, and D- α -tocopherol succinate and beta-carotene inhibit the growth of cancer cells without affecting the growth of normal cells, and actually enhance the effect of irradiating cancer

cells, while protecting normal cells^{3,7-10,26-28,31,37,38,40,76-87}. An additional critical factor is to ensure that the dose of the vitamin antioxidants is within the high-dose range and that the cells are exposed to the high dose of antioxidants for a prolonged treatment time before and after irradiation. In contrast, doses of vitamin antioxidants that are intermediate between the RDA and the high level reduce the efficacy of X-irradiation in destroying cancer cells⁸⁸⁻⁹².

This *in vitro* and animal tumour research suggests that these specific antioxidants can quench the toxic effects of free radicals on normal tissues and increase the cell kill in tumours by mechanisms unrelated to their antioxidant activity. Also, the efficacy of this combination of antioxidants is synergistic. The combination inhibits the growth of tumours by causing differentiation and apoptosis in cancer cells^{24,30,93-95}. That effect is reflected in the ability of the antioxidant combination to downregulate genes involved in proliferation of cancer cells. However, the issue is complicated by the fact that the growth-inhibitory doses vary between species and tumour types. In addition, the relative degree of uptake of dietary antioxidants is highly variable between tumour cells and normal cells and does not seem to define the therapeutic gain^{82,96-100}.

Laboratory experiments indicate that a mixture of dietary antioxidants is more effective in reducing the division of cancer cells than are individual antioxidants⁹¹. Because each dietary antioxidant has a different mode of action, a combination of dietary antioxidants should be considered for a clinical trial.

Another paradox is that, although total antioxidant status declines during cancer treatment, the serum levels of specific antioxidants may increase. A systematic review of patients with cancer who were receiving chemotherapy revealed no consistent pattern in serum changes of vitamins C and E and of selenium and beta-carotene¹⁰¹. Total antioxidant status is depleted before treatment, perhaps because cancer cells use antioxidant vitamins more efficiently than normal cells do, or perhaps simply because cancer patients become malnourished through reduced appetite. The initiation of anticancer therapy may further lower levels of antioxidants through poor diet, but levels of individual antioxidants may improve as the cancer burden is reduced¹⁰². Supplementation with individual antioxidants inconsistently affects serum levels. It is not known whether the standard RDA is sufficient for supplementation during anticancer therapy¹⁰³⁻¹⁰⁵.

4. ANTIOXIDANTS DURING CHEMOTHERAPY

Specific antioxidants have been proposed as anticancer agents. One of them, vitamin C, has been most publicised since Nobel laureate Linus Pauling postulated its anticancer activity when prescribed at high

doses (5 – 10 g daily)^{106,107}. Plausible data have been presented to suggest that vitamin C has no effect on cancer^{55,59,108–115}, that lower doses can stimulate tumour growth^{97,116}, and that both low and high doses can inhibit tumour cell formation and progression^{98,117–125}. Reasonable evidence exists that a deficiency of vitamin C in the diet is a factor in carcinogenesis and that replacement may prevent the development of some tumours, such as gastric and oesophageal cancers^{122,123,126–129}. In contrast, the evidence for a therapeutic role of vitamin C in treating established tumours is weak. At least two double-blind randomised controlled clinical trials have failed to find a significant effect of improved outcome^{130,131}.

Serious concerns have been raised about the potential of antioxidants to antagonise the activities of certain chemotherapy drugs, especially the alkylating agents¹³². Proponents of high-dose antioxidants during chemotherapy often cite amifostine (an antioxidant) as a conventional agent that is widely used to protect normal tissues from the toxicity of cisplatin. However, amifostine has specific pharmacologic properties that increase its therapeutic ratio toward normal tissue. Amifostine is a pro-drug that is dephosphorylated by alkaline phosphatase in tissues to a pharmacologically active free thiol metabolite that can reduce the toxic effects of cisplatin in conventional oncology^{133–135}. Amifostine's ability to differentially protect normal tissue is attributed to the higher capillary alkaline phosphatase activity, the higher pH, and the better vascularity of normal tissue relative to tumour tissue. The result is a more rapid generation of the active thiol metabolite and a higher rate constant for uptake. The higher concentration of free thiol in normal tissues is available for binding to, and thereby detoxifying, reactive metabolites of cisplatin. Even so, most oncologists exercise caution and do not use amifostine when treating highly curable cancers such as germ-cell tumours.

Mesna is also touted as an example of a pharmaceutical antioxidant that is acceptable for use in chemotherapy. However, that comparison ignores the important pharmacokinetic advantage that mesna confers in improving therapeutic gain. Mesna is rapidly metabolised *in vivo* to mesna disulfide, which undergoes rapid renal excretion. That compound's high antioxidant activity is concentrated in the renal pathway, where it reacts with acrolein, the highly oxidant metabolite of the alkylating agent iphosphamide, thereby limiting the renal and bladder toxicity of the chemotherapy without affecting tumour cytotoxicity¹³⁶.

The literature contains no clear evidence that individual dietary antioxidants at RDA doses reduce the toxicity from chemotherapy^{101,132}. On the other hand, studies have been inconsistent in evaluating various combinations of micronutrients, their doses, and their timing: appropriate controls have been lacking, and usually no validation of covert antioxidant supple-

mentation has occurred. The most promising studies propose that selenium (a component of glutathione peroxidase) is an effective antioxidant to prevent cisplatin-induced nephrotoxicity⁴⁷.

Laboratory experiments suggest that some antioxidants may potentiate the cytotoxicity of specific chemotherapy agents on some tumours^{137,138}. The cytotoxicity of some chemotherapy drugs—such as etoposide and cisplatin—may not depend solely on ROS production¹³⁹. However, many concerns have been raised over the potential pharmacokinetic and pharmacodynamic interactions between chemotherapy agents and higher-than-supplemental doses of dietary antioxidants¹³². In general, alkylating agents and anthracyclines create ROS that can react with nucleic acids to incapacitate the function of DNA and RNA^{140–143}. Thiols, such as cysteine, are endogenous antioxidants that neutralise ROS¹⁴⁴. Higher levels of free thiol groups can be associated with tumours that have a greater resistance to alkylating agents¹⁴⁵. On the other hand, some studies show that thiols and other endogenous antioxidants, such as superoxide dismutase, can potentiate the activity of some alkylating agents^{146–150}. Dietary antioxidants can quench free radicals generated from endogenous sources and chemotherapy agents alike¹⁵¹.

In summary, the interactions are complex and unpredictable, because various kinds of free radicals are produced, pharmacokinetics are variable, multidrug-resistant gene induction is highly conditional, and the distribution, metabolism, and excretion of metabolites of the chemotherapy agent may differ from those of the parent compound.

The potential for a reduction in the efficacy of certain categories of chemotherapy agents that owe their cytotoxic activity to the formation of ROS is clear. On the other hand, high doses of some antioxidants themselves have cytotoxic activity *in vitro* and may contribute to therapeutic gain. Only a randomised controlled trial will provide clinically useful answers¹³⁸.

Of more concern is the influence of high doses of antioxidants on the sensitive pharmacokinetics of chemotherapy drugs. Those drugs are often administered near their maximum tolerated dose, such that toxicity may occur following a small effect on their pharmacokinetics. Patients are cautioned about taking aspirin with high-dose methotrexate, because even a low dose can reduce excretion and cause major toxicity. Until we know more about the influence of antioxidants on the pharmacokinetics of specific chemotherapy drugs, the same advice should apply to higher-than-RDA doses of those antioxidants.

5. ANTIOXIDANTS DURING RADIOTHERAPY

The inference from laboratory experiments is that high doses of some specific dietary antioxidants selectively enhance the effect of irradiation on cancer

cells while protecting normal cells⁴². In contrast, *in vitro* experiments suggest that low doses of dietary antioxidants either have no effect on cell proliferation or may even stimulate the growth of cancer cells^{6,43}. Specific attention to the particular antioxidant is important, because high-dose vitamin E and retinoic acid enhance the effect of X-irradiation on tumour cells (by preventing the repair of potentially lethal damage in cancer cells more than in normal cells), and lycopene inhibits the effect^{3,17,32,33,89,152-155}. Laboratory studies have established that vitamins A, C, and E, and carotenoids can protect normal cells, but not cancer cells^{29,32,152,156-161}. In contrast, elevated levels of endogenous antioxidants, such as thiols and superoxide dismutase, enhance radioresistance¹⁶²⁻¹⁶⁵.

The situation with radiotherapy may be quite different from that with chemotherapy. Within milliseconds, radiotherapy produces extraordinary high levels of ROS inside the targeted volume. It seems implausible that such high levels of ROS could be significantly quenched by dietary antioxidants. On the other hand, high doses of micronutrient supplements could replenish the total antioxidant status, thereby reducing normal-tissue toxicity.

A rodent study showed that antioxidant vitamins reduce normal-tissue toxicity induced by radioimmunotherapy^{156,166}. Similarly, selenium and vitamin E reduced radiation-induced intestinal injury in rats³³. A randomised controlled study in patients with advanced squamous carcinoma of the mouth showed that beta-carotene reduced radiation- and chemotherapy-induced oral mucositis, with no significant effect on the tumour recurrence rate^{167,168}. Amifostine is often cited as evidence that antioxidants do not antagonise the efficacy of radiotherapy on tumour cells. However, the therapeutic gain in treating head-and-neck cancers is achieved because amifostine is concentrated and activated more efficiently by the parotid glands than by adjacent tumour cells, thereby preventing the side effect of xerostomia without compromising tumour control¹³⁵.

Evidence of synergy between antioxidants and radiotherapy from human studies is limited. Advocates of antioxidant treatment sometimes cite two phase II studies that demonstrated an increased response of carcinoma of the cervix and advanced squamous cell carcinoma of the skin to 13-*cis*-retinoic acid combined with interferon- α ^{81,169}. However, the protocol that was used contains a synthetic carotene in combination with interferon; that protocol bears no resemblance to the dietary antioxidants investigated in the laboratory.

Another study evaluated 18 nonrandomised patients with small-cell lung cancer who received vitamins, trace elements, and fatty acids¹⁷⁰. The conclusion was that patients receiving antioxidants showed improved tolerance to chemotherapy and radiation treatment and experienced prolonged sur-

vival as compared with historical controls. Unfortunately, although the results are promising, comparison with an historical control group introduces potential bias and cannot be considered a high level of evidence.

6. ANTIOXIDANTS FOLLOWING COMPLETION OF ANTICANCER THERAPIES: TREATMENT OF IATROGENIC COMPLICATIONS

Despite the uncertainties of combining high-dose antioxidants with conventional anticancer therapies, some progress has been made in evaluating antioxidants for reversal of the side effects of both chemotherapy and radiotherapy.

A randomised controlled trial that evaluated the efficacy of antioxidant supplementation on the neurotoxic effects of cisplatin therapy showed a significant reduction of neuropathy when vitamin E (300 mg daily) was administered during chemotherapy³⁴. A small single-arm study suggested that α -lipoic acid (600 mg intravenously per week for 4 weeks, followed by 1800 mg orally thrice daily for a maximum of 6 months) reduces docetaxel/cisplatin-induced polyneuropathy¹⁷¹. A case report suggested that a combination of pentoxifylline (PTX) and tocopherol (PTX 800 mg and vitamin E 1000 IU daily for 18 months) may produce regression of radiation-induced fibrosis³⁹. A small phase II study showed that childhood radiation therapy-induced uterine dysfunction was reversed by vitamin E and PTX, resulting in increased measured uterine blood perfusion and increased embryo implantation rate¹⁷². A recent randomised controlled trial that enrolled 24 women showed that 6 months of treatment with combined vitamin E and PTX can significantly reduce radiation-induced breast fibrosis¹⁷³. Synergism between PTX and vitamin E was likely, because treatment with each drug alone was ineffective. A randomised controlled trial of grape seed extract (containing proanthocyanidin antioxidants) has recently been completed at the Royal Marsden Hospital in the United Kingdom¹⁷⁴. That trial evaluated whether a 6-month course of grape seed antioxidant following radiotherapy prevents radiation-induced breast fibrosis. Results are pending.

Despite the controversies over advocating high doses of specific antioxidants, a balanced diet rich in fruits and vegetables (when tolerated) should be encouraged for all patients so as to reduce toxicity from nutritional deficiencies and to help prevent further cancer development during and following anticancer therapy^{59,175}.

7. CONCLUSIONS

Free-radical and antioxidant activity exist in humans within a complex physiologic and biochemical

framework that cannot be duplicated during *in vitro* experiments. Surveys of patients undergoing cancer treatment have shown that 25% – 85% use nutritional supplements containing antioxidants at doses higher than the RDA^{176,177}. Recently published meta-analyses indicate that both beta-carotene and high-dose vitamin E (>400 IU daily) can increase mortality in some patient populations^{178,179}. In light of plausible benefits and potential adverse interactions with conventional therapies, further clinical studies are warranted.

Antioxidant studies need to focus on cancer patients receiving conventional treatments within the context of a randomised controlled clinical trial^{180,181}. Laboratory and observational studies have produced a plausible hypothesis that specific combinations of antioxidant micronutrients, at doses greater than the RDA, may improve tumour control and reduce toxicity when administered with some conventional anticancer therapies¹⁰⁷.

The design of a clinical trial to evaluate the role of antioxidants in anticancer treatment should be very specific in selecting the interventional agents and should measure both the benefits and the toxicities. Mixtures of antioxidants can be synergistic, and so preclinical and phase I – II studies are needed to affirm optimal combinations. Factorial phase III trials may provide greater efficiency in testing a variety of combinations¹⁸².

In reality, the evaluation can never simply be “antioxidants”: instead, it must be the activity of specific agents with multiple biochemical effects, some of which may be antioxidant in certain circumstances. Important issues in designing a clinical trial include defining the appropriate patient population, establishing well defined end-points, and measuring the total antioxidant status as well as serum and tissue levels of the specific interventional agents^{5,100,183,184}. The study should measure short- and long-term tumour control and normal-tissue toxicities. The intervention must be designed to exceed the standard dietary antioxidant supplementation. It would not be ethically appropriate to malnourish patients during their standard anticancer treatment, given that we already know that depletion of antioxidants below accepted normal levels increases toxicity and is associated with the side effects of malnourishment¹⁰³.

A pilot study will be necessary to determine the variance of outcomes so that the appropriate number of trial participants can be calculated to avoid a beta error—namely, lacking sufficient patients to detect a statistical difference.

In short, what is required is a randomised, double-blind, placebo-controlled trial of a specific antioxidant intervention for a defined tumour type, realising that the results of the specific intervention cannot be generalised to alternative antioxidant combinations, any more than the effects of various categories of drugs can be so generalised.

A major challenge for the initiation of a clinical trial is deciding on the combination of antioxidants to evaluate and the doses to administer. A phase I study may be required to ascertain optimum doses. For a radiotherapy study, a combination of high doses of vitamin E, vitamin C, vitamin A, beta-carotene, and selenium (limited to 200 µg daily) seems reasonable. A phase III trial will require large numbers of patients to detect the likely small differences in outcome. The number of potential combinations of various antioxidants is vast, and their relative clinical efficacies are unknown. Clinical trials will definitely be limited in their ability to evaluate treatment combinations, and funding of the endeavour is unlikely to occur until phase II studies have defined the most effective combination of antioxidant agents. Knowledge of the molecular mechanisms of activity of the agents is essential, and methods are required for predicting their complementary and synergistic activity before the randomised controlled clinical trial is initiated.

Antioxidants may improve short-term toxicity, but could be followed by an increase in the long-term probability of recurrence. Clinically meaningful data should include long-term recurrence and survival rates. Ultimately, only phase III trials can determine the relative advantage of one combination over another; multi-arm and factorial designs may enable a more efficient mechanism for testing multiple regimens simultaneously.

Until we can obtain valid clinical facts, opinions will be based upon theory, superstition, and ignorance.

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