

# Antioxidants and Cancer Therapy: Furthering the Debate

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The consideration of whether to use antioxidants concomitantly with chemotherapy and radiation therapy has evolved into a heated debate. This special theme issue brings together several contributors to this debate, whose perspectives enlarge our views of the questions at hand, pointing out several very relevant ideas. First, the early hypotheses of the role of antioxidants in carcinogenesis gave a simplified and often inaccurate picture of the physiological effects of specific antioxidants. Antioxidants can have protective effects that have nothing to do with oxidation; on the other hand, they can under some circumstances develop prooxidant properties and promote carcinogenesis. During treatment, however, their role is far from clear and may be either quite positive or potentially negative. A number of clinical studies have already demonstrated beneficial effects of antioxidants in ameliorating side effects of chemotherapy. More theoretical work on the chemistry of antioxidants and chemotherapy drugs suggests that antioxidants might improve therapeutic efficacy of antineoplastics by counteracting aldehydes that impede the passage of cells through the cell cycle. However, detailed clinical study also makes it clear that we are only at the very beginning of understanding the dynamics of antioxidants and oxidant damage in the body during conventional treatment. Nevertheless, research is under way on radioprotective and chemoprotective substances, some of them rooted in traditional medicine and others in our understanding of dietary antioxidants, that may eventually lead to antioxidant-based supplements that support tolerability and efficacy of treatment, without protecting tumors through interference from antineoplastic treatment.

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From great controversy can come great medicine. Great debates have sometimes spawned great breakthroughs in medical treatment, improving patient outcomes and saving lives. One such debate that has long loomed over the treatment of people with cancer is the use of antioxidant therapy concomitantly with chemotherapy or radiotherapy. There are 2 camps in this debate. One camp feels that the use of

antioxidants with cytotoxic or radiotherapy is problematic since antioxidants may interfere with the mechanism of action such therapies, causing diminished treatment effect and protection of tumor tissue. The other camp suggests that oxidation is a critical fuel for supporting malignant proliferation. Furthermore, oxidation may interfere with standard treatments, thereby diminishing overall therapeutic benefit. Thus, antioxidant supplementation may improve treatment efficacy. This camp also asserts, with several studies as its support, that antioxidants provide a host-protective effect from the toxicities of treatment. The articles in this special theme issue present fascinating perspectives and data that allow us to consider this controversy more fully. We will begin, however, by outlining the questions regarding antioxidant use more fully.

In the antisupplementation position, antioxidants are felt to be potentially harmful when included in a conventional drug protocol that causes oxidative damage for several reasons. First, even assuming that antioxidants might provide protection from the side effects of a treatment-related oxidant attack, their protective mechanisms may not distinguish between normal and malignant cells.<sup>1</sup> The degree of such “tumor protection” in the clinical setting is not yet defined and is still a matter of debate. Some physicians feel that any level of tumor protection, no matter how small, is unacceptable. Second, some antioxidants can alter the coagulation cascades and potentially place one at greater risk for hemorrhage.<sup>2</sup> Third, some classical antioxidants are known to cause toxicity on their own,<sup>3</sup> while the potential toxic effects of others in the cancer treatment setting remain uncertain due to lack of clinical trial data. Finally, radiotherapy as well as a significant number of conventional cytotoxic agents in use today rely on oxidative mechanisms for their effect,<sup>4</sup>

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and administration of reducing agents such as natural antioxidants might nullify such effects.

The prosupplementation group, on the other hand, feels that oxidation caused by the treatments just mentioned can potentially annihilate the very mechanism necessary for their therapeutic activity. Chemotherapeutics are effective only on metabolic cells, and most are cell-cycle specific. Reactive oxygen species (ROS) are the classical oxidation products resulting from cytotoxic and radiotherapeutic protocols (as well as natural processes), most notably, superoxide anions, aldehydes, and lipid peroxides. Excessive ROS may prevent apoptotic death from cytotoxic agents by interfering with the normal cell cycle.<sup>5</sup> The dangers here are 2-fold: cells not only survive but also can become resistant, over time, to cytotoxic treatments. Furthermore, cell kill may be reduced or shifted from apoptosis to necrosis.<sup>6</sup> The toxicity experienced by people undergoing chemo- or radiotherapeutic treatments can be so severe that dosage reductions or delays in treatment occur<sup>7</sup>; patients may be forced to abandon potentially helpful regimens prematurely,<sup>8</sup> or recovery from conventional treatment may be impaired, with significant long-term effects possible.<sup>9</sup> Patients who refuse conventional treatment altogether due to fears of side effects (including patients with recurrent disease whose fears rest on their prior adverse treatment effects) are, unfortunately, all too well known to most cancer clinicians, and perhaps especially to the integrative practitioners whom such patients often seek out.

We cannot, in this issue, decide which camp will prevail. The state of the research that exists regarding the important questions at hand prevents this. Numerous investigators have published on this debate, however, and it is worth considering a few specific articles that have raised interesting clinical possibilities and challenges before we proceed to discuss the contents of the current issue.

In 1999, Lamson and Brignall, for instance, reviewed the animal, human, and *in vitro* studies examining the effects of antioxidants combined with conventional treatments.<sup>10</sup> Examination of the data they located on human trials with the more strongly oxidative chemotherapy agents (cisplatin, the alkylating agents, and the antitumor antibiotics such as doxorubicin) reveals a set of studies on 5 antioxidants (vitamin A, selenium, melatonin, N-acetylcysteine, and glutathione) that varied in design and outcome measurements.<sup>11</sup> The outcomes can be summarized as toxicity and therapeutic efficacy. Among these studies were 17 reports of decreased toxicity, with 2 showing questionable toxicity decreases and 2 showing no difference from controls. There were 4 reports showing increased therapeutic efficacy:

1 showing a possible increase, and 6 showing no difference from controls. Similarly, 5 human trials with antioxidants and radiation showed decreased toxicity: 3 showed improved therapeutic efficacy and 3 no difference from controls. Data on animal studies (using a somewhat wider variety of antioxidants) were similar: notably, 16 animal trials showed decreases in toxicity and 16 increases in efficacy. Of particular interest was the fact that no studies showed increased toxicity or decreased therapeutic effect.

Despite these provocative data, many clinicians continue to raise questions about the use of antioxidants combined with conventional therapies. Rather than being simply a manifestation of some sort of bias, it is likely that such questions are an extension of the long-standing caution raised within the oncology community regarding chemotherapy and radiotherapy protectants and the more recent demands that the use of such protectants be supported by evidence-based studies. The American Society of Clinical Oncology (ASCO) has, in fact, issued clinical guidelines for the use of the conventional protectants that are now available—mesna, dexrazoxane, and amifostine—all based on clinical trials showing evidence of improvement of specific side effects, in light of a lack of evidence of adverse impact on outcome.<sup>12</sup>

Current controversies regarding amifostine exemplify some of the challenges that the use of antioxidants will face in becoming clinically accepted protectants. Since the 1970s, amifostine, a sulfhydryl compound with free radical scavenging properties (WR-2721, Ethylol, MedImmune Oncology, Inc), has been studied as a radioprotectant and later as a chemotherapy protectant.<sup>13</sup> Based on clinical trials, ASCO guidelines<sup>12</sup> suggest that it may be considered for the reduction of nephrotoxicity during cisplatin therapy and reduction of neutropenia during therapy with alkylating agents. Data regarding its use to prevent thrombocytopenia, neurotoxicity, and ototoxicity are considered insufficient to make any recommendation. In the 2002 edition of the guidelines, ASCO recommended retaining a guideline issued in 1999 suggesting that amifostine may be considered for reduction of xerostomia in head and neck radiation, although it found insufficient evidence for the reduction of mucositis.<sup>14</sup>

The latter 2 guidelines were discussed at length in the light of a study published in 2000 by Brizel et al in which 315 patients receiving radiation for head and neck squamous cell cancer were randomized to receive radiotherapy alone or with amifostine.<sup>15</sup> The amifostine group showed a significantly lower incidence of grade 2 and higher acute xerostomia. The patients were able to receive higher radiation doses, although no effect was found for mucositis. There was

evidence that amifostine significantly affected 2-year locoregional control (58% with and 63% without amifostine), disease-free survival (53% with and 57% without), or overall survival (71% with and 66% without).

Despite this seemingly convincing trial, controversy continues to swell about the continued clinical use of amifostine in radiotherapy. Andreasson and colleagues reviewed the literature on amifostine, pointing out with regard to the Brizel et al study that even this very large trial (unusually large for head and neck radiation, in fact) did not have the statistical power to detect a 5% to 10% decrease in local tumor control.<sup>16</sup> The controversy has gone so far as a head-to-head confrontation in the pages of *Lancet Oncology* between Brizel and Overgaard, another amifostine opponent.<sup>17</sup> The issue cannot be considered to be resolved because of continuing fears of a low level of tumor protection. Detecting such low levels with adequate statistical power would require clinical trials that are quite large, perhaps impractically so.

In this light, it is interesting to contemplate how far the natural antioxidants discussed in this issue have to go scientifically before one could expect conventional acceptance. Although clinical oncology has entered into the integrative realm (hence, the development and sustenance of this journal), monies are not readily available for the very large randomized trials that would be required. With that in mind, an examination of the articles in this issue is of genuine relevance for both the clinician and the researcher.

In this special issue, we present invited works from 6 distinguished academicians central to the field of antioxidants and the treatment of people with cancer. Homer Black offers relevant insights into the relationship of antioxidants and carcinogenesis.<sup>18</sup> The guiding principle of antioxidant research since the 1960s has been that oxidants can insult the integrity of biological systems and cause damage to the genome, the end result being carcinogenesis. Reduction of free radical damage to the genome would, in effect, lower the risk of carcinogenesis. In a fascinating historical overview, Black elucidates the hypotheses that have formed the basis of the decades-long investigation of antioxidants and carcinogenesis.

- First is the hypothesis of the benefits of caloric restriction, wherein for each calorie taken in, energy is produced in the form of adenosine triphosphate (ATP). During the production of ATP, oxygen is lost with a corresponding production of free radicals that can then damage DNA. By decreasing caloric intake, the gross amount of radical production can be decreased.
- The second hypothesis is that minimizing certain dietary components that are highly vulnerable to oxida-

tive attack, the polyunsaturated fatty acids (PUFAs), results in lower oxidative damage from the free radical by-products of such an attack. Black himself undertook a critical test of this hypothesis, demonstrating lower incidence of actinic keratoses in skin cancer patients assigned to a low-fat diet in a randomized trial.

- The third hypothesis is that the addition of 1 or more exogenous antioxidants will diminish overall free radical damage, resulting in a lower cancer rate.

Black's article takes us through the history of the investigation of the third hypothesis in detail. Both butylated hydroxytoluene (BHT) and  $\beta$ -carotene were investigated as potential anticarcinogenic supplements. This resulted in the discovery that BHT's anticarcinogenic effect was basically a physical effect of blocking transmission of ultraviolet radiation through the skin, rather than an antioxidant effect. Black examines the critical issues surrounding the use of  $\beta$ -carotene in cancer prevention and the revelation of its prooxidant activity. He does this through the merger of laboratory and epidemiological information from the studies he discusses. As he examines the diverse effects central to the  $\beta$ -carotene issue, Black explains how age,  $\beta$ -carotene dose, and interactions with other dietary factors acted in concert to produce the contradictory findings of first antioxidant and then prooxidant activity. A particularly interesting detail in this discussion is the finding that  $\beta$ -carotene displayed antioxidant effects in animals fed closed-formula diets, which are basically composed of whole grains, known to have antioxidant properties themselves. In this dietary setting, the prooxidant by-products that form when  $\beta$ -carotene interacts with free radicals appear to have been quenched by other antioxidants in the diet, resulting in an anticarcinogenic effect. When  $\beta$ -carotene was given with a semidefined diet, composed of refined corn starch, refined oils, casein, and vitamin supplements, the protective effect disappeared. It is hard to resist the speculation that similar effects might be occurring in antioxidant-supplemented human populations eating refined-food diets versus whole-foods diets!

Black concludes his article by explaining the nonoxidative effects that lie behind the anticarcinogenic activity of the low-PUFA diet, well known to integrative practitioners to affect prostaglandin synthesis. He urges a reconsideration of the original 3 hypotheses of antioxidant research, with special care in the consideration of supplementation, especially with single antioxidants. His caveats need to be taken with great seriousness.

Carmia Borek approaches the broad topic of antioxidant nutrition in human cancer from a more clinical perspective.<sup>19</sup> She begins with a general account of

diet and cancer prevention with antioxidant micronutrients and then presents a biological argument for the use of antioxidants in cancer therapy with both radiation and chemotherapy. Borek attempts to attack the issue of whether antioxidants would interfere with chemotherapeutics in general and states that most anticancer drugs do not rely on ROS for their activity. With regard to the entire range of cancer therapeutics, including the new molecular inhibitor drugs such as trastuzumab, this is probably the case. However, with regard to cytotoxics, Borek's information is in conflict with Kenneth Conklin's assertion that most of the widely used cytotoxic agents generate at least some level of oxidative stress. Because she feels that these agents do not work primarily through oxidative stress mechanisms, Borek argues that antioxidants would not cause interference with the anticancer activity of the drugs. She then examines many clinically relevant substances potentially useful for a variety of malignancies.

One common thread in Borek's article is that although it is unlikely that antioxidants protect cancerous cells from cytotoxic onslaught, there is compelling evidence that they protect normal cells. Most notable is her discussion of a recent randomized, placebo-controlled, double-blind study that tested the effects of supplementation with vitamin E, vitamin C, and selenium, 3 readily available, inexpensive, and well-known nutritive substances, in patients receiving cisplatin-based chemotherapy. The population that achieved the highest peak plasma level of the 3 nutrients had significantly less loss of high-tone hearing than those achieving lower levels, which suggests protection of normal hearing-related neurons in the face of a strong oxidizing agent. Borek points out that it is doubtful whether using antioxidants, even at recommended dietary allowance levels, would hinder therapy given the high dosages of radioactive and anticancer drugs that are known to deplete inherent antioxidants. The article closes by proposing leading questions for research in this area, including which antioxidants are most protective and whether isolated antioxidants, taken as supplements, are as protective as those acquired from food.

To begin to answer such questions, Ganesh Chandra Jagetia and his colleagues provide a comprehensive investigation into the utility of an indigenous foodstuff in their native country of India, namely, *Aegle marmelos*.<sup>20</sup> In this study, a hydroalcoholic extract from the fruit of *A marmelos* (AME), a tree commonly known as bael, is discussed as a valued source of Ayurvedic medicaments. Jagetia introduces his subject by discussing the clinical need for a radioprotective agent and, furthermore, the need for agents with little or no toxicity. Jagetia's investigation of the radioprotective

effect of AME in mice is scientifically rigorous and serves as an excellent model for discovery of effective therapeutic agents. In his discussion, Jagetia explores the parameters of a therapeutic window similar to that of other plant-based radioprotectors he has studied in the past and also examines the potential mechanisms by which AME exerts its multimodal therapeutic activity. These include the elevation of blood and liver reduced glutathione (GSH), the elevated activity of other antioxidant enzymes such as superoxide dismutase and catalase, and the concomitant reduction of lipid peroxidation. It should be pointed out that the elevation of blood- and visceral-based GSH is thought by some to be potentially problematic in terms of chemoresistance and cancer cell growth kinetics. It is well known that one mechanism of resistance to anthracyclines is a glutathione-escape mechanism, whereby the anthracycline, doxorubicin for instance, is conjugated to GSH and transported extracellularly via GS-doxorubicin pump, thereby decreasing the intracellular level of doxorubicin and limiting its cytotoxic effect; similar activity has been demonstrated for other cytotoxic agents such as cisplatin and irinotecan.<sup>21</sup> While this has not been confirmed through clinical testing, the concern and need for further study remains. Thus, while a substance that increases endogenous GSH levels may have a radioprotective effect, it may also confound therapy with cytotoxic drugs.

Jagetia also summarizes the entire process of discovering clinically relevant radioprotectors, including the concerns cited with tumor protection. Interestingly, AME was observed to have differential uptake in normal and tumor tissues, possibly due to the relatively poor vascularity of tumors, which could shunt uptake to normal tissue. AME, which is also cytotoxic to several tumor cell lines, may indeed be able to protect normal tissue while leaving malignant tissue more vulnerable to conventional treatment. If this is so, then the concerns surrounding GSH might be lessened in favor of a therapeutic benefit. More research on AME and other potential plant radioprotectors is clearly warranted.

An original observational study was submitted by Deborah Kennedy and coauthors working on a project initiated by Kara Kelley at Columbia University on 8-oxodeoxyguanosine (8-oxo-dG) in children receiving treatment for acute lymphoblastic leukemia (ALL).<sup>22</sup> Kennedy and colleagues begin by providing support for the use of 8-oxo-dG as a biomarker for oxidative stress, and they discuss the lack of good data on the effect of diet on the levels of this marker. Current treatment protocols for children with ALL, while effective, generally generate large numbers of oxidative by-products, including ones that can further

damage DNA. Kennedy's group observed newly diagnosed children and investigated 8-oxo-dG levels in 2 compartments: blood mononuclear cells and bone marrow. Notably, this is the first investigation examining oxidative damage directly in the marrow of children with ALL. The results were categorized in a clinically relevant manner by examining the variation in blood and marrow antioxidant level in relation to both disease status and oxidative damage. The interrelatedness of antioxidant status, dietary and supplemental intake of antioxidants, and levels of 8-oxo-dG is also described. The major finding was that levels of individual antioxidants varied according to disease status. Kennedy and colleagues determined that with initiation of therapy, there was a reduction in the level of 8-oxo-dG. With aggressive chemotherapy, the levels increased in the blood mononuclear cells but not in the cells derived from the marrow. Possible reasons for this phenomenon are discussed, most reasonably that the administration of chemotherapy to chemotherapy-naïve children with ALL decreased tumor bulk and that such tumor bulk contained significant levels of 8-oxo-dG. Those children with higher 8-oxo-dG levels overall had a higher risk of chemotherapy dose reduction, an interesting finding in light of the clinical studies described by Borek. Diet had a limited effect on 8-oxo-dG during interim maintenance and delayed intensification periods and no effect at diagnosis. Kennedy and colleagues suggest, however, that because dietary  $\beta$ -carotene and vitamin A were in fact correlated with low 8-oxo-dG levels, dietary counseling to increase fruit and vegetable intake once treatment has begun might be useful. They do not advocate simply giving an antioxidant supplement, citing an earlier study by van Poppel et al in which  $\beta$ -carotene did not lower levels of 8-oxo-dG in smokers, but carrot juice did.<sup>23</sup> Kennedy's study surely piques the curiosity of those who follow the relationship between antioxidant status and cancer and serves as a springboard for further investigation of this type.

Kenneth Conklin focuses on the generation of aldehydes as the central concern of oxidant stress for cancer therapy and offers cogent reasons to ameliorate such stress.<sup>24</sup> He begins with a succinct overview of oxidant-generated stress in general and then provides an account of how such stress is produced by cancer chemotherapeutics. His central theme is that the formation of ROS, in particular aldehydes, by cancer chemotherapeutics can actually diminish the cytotoxic activity of these treatments. Conklin sets the process in the context of the effects of oxidative stress on the cell cycle and the potential effects this has on treatment. For instance, most antineoplastic agents exhibit cell-cycle-specific activities and depend on the cell's progression through the cycle for their cytotoxic

activity. It is precisely the effects of ROS on progression through the cell cycle that cause concern in this model. As an example, Conklin discusses the cardiotoxicity brought about by anthracyclines. Anthracyclines act during the synthesis (S) phase of the cell cycle. Aldehyde activity may impede the cancer cell from entering this phase or may slow progression through it. Furthermore, aldehydes can inhibit the caspase system cancer cells use to initiate and undergo apoptosis.

The issues brought to light by Conklin serve as central themes for the responsible administration of antioxidants with chemotherapy. In this model, the antioxidant's ability to quench aldehydes would actually improve or accelerate the cytotoxic effects of the oxidative chemotherapies, thereby improving their efficacy. The antioxidant exposure to normal tissues would, according to the evidence presented by the other articles in this issue, aid in ameliorating side effects due to the activity of ROS on nearby normal cells. Conklin brings up an interesting possibility, however. By increasing antineoplastic activity with antioxidants, rapidly dividing cells (such as gastrointestinal cells) might actually be exposed to greater rates of cell death and worse side effects. This possibility is quite speculative at this point but certainly deserves consideration.

Conklin's account of the mechanisms by which anthracyclines interfere with energy production of the cell and the resultant cardiotoxicity should serve as a model for discovery of any cytotoxic agent's assault on normal biochemistry and physiology. Such discovery would not only yield a better understanding of how to administer the drugs but would also begin to elucidate other complementary treatments that may not only reduce side effects but also improve the primary effect of the drug itself.

Kedar Prasad provides a detailed account of the current state of his research regarding antioxidant use for people undergoing conventional cancer therapy.<sup>25</sup> He first discusses the general recommendations by oncologists regarding such use. In this section, although an advocate for the use of high doses of specific antioxidants with chemotherapy, he touches on a crucial point that was not discussed in the other articles featured in this issue: the use of micronutrient formulations instead of or in addition to antioxidants and the potential favorable effects this may have on the cancer itself. He explains that most oncologists do not recommend antioxidants, but some may actually recommend a multiple-vitamin preparation containing low dosages of antioxidants after the completion of therapy. Prasad suspects, however, that this may actually be deleterious since cancer cells, like normal cells, require such nutrients for growth and survival.

Prasad also questions the use of supplements that increase the levels of endogenous antioxidants (as opposed to the naturally occurring exogenous nutritive antioxidants) such as glutathione. It is well known that cancer cells can synthesize glutathione from precursors. However, it is less well known that glutathione can (1) increase resistance in some cancer cells as discussed above; (2) stimulate cell cycling to the S phase, which can actually have a 2-sided effect—beneficial in the sense discussed by Conklin above, but dangerous during chemotherapy intervals or during remission<sup>26</sup>; and (3) increase the metastatic potential for cancer cells.<sup>27</sup>

Prasad also makes the point that it is common for patients to consume vitamins and other nutritional agents without the knowledge of their oncologists. He reports that this may occur in 60% of patients and that this practice can be harmful. Furthermore, his concern is that not only are most of these patients receiving information from such sources as the Internet, but most also lack the scientific background to comprehend the information they receive. Internet sources or health food store books may actually deliver information on the mechanisms of the activity of nutritional agents, but most often, such information is outdated or presents only a partial accounting of the complex biophysiological activities displayed by the agents. It takes a great deal of scientific investigation, interpretation, and subsequent bridging of the science to the clinic to create an effective integrative protocol. This is what Prasad focuses on in this publication by outlining nutritional protocols divided into 2 categories: active cancer treatment protocols and maintenance protocols, with specific recommendations for each.

Prasad provides a keen argument for the use of specific nutritional agents at certain checkpoints in a long-term treatment plan. He also outlines the potential for certain agents to protect cancer cells from primary treatments. Nonetheless, Prasad concludes that the bulk of the information tips the scale in favor of using nutritionals with standard protocols and provides evidence for a more favorable patient outcome should they be employed. Prasad, like Borek, proposes that normal cells can be protected from the toxicities of therapies and goes on to suggest that it may be possible to both protect the patient and enhance the effects of standard treatments. Prasad's demonstration of this possibility favors the camp promoting the use of antioxidants and nutritional agents concomitantly with standard therapies.

In summary, these 6 presentations provide an addition to the information now in the literature and a valuable starting point for what promises to be a long and great debate on antioxidants and their impact on

standard treatments. This special issue is meant to recognize both potential value and risks inherent in the use of these agents and further elucidate their role in the complex physiology of our bodies. One of my additional hopes in publishing this issue is to identify and raise a misconception that many patients commonly have: just because something is natural does not mean it is always good to take. This notion becomes continually more relevant in daily clinical practice. As we have entered the electronic age, patients no longer have to learn to use microfiche and library coding systems to fish through medical literature; they do not even have to leave their homes. Rather, with access to the Internet and a credit card, anyone can order a bottle of nutrients promoted to be beneficial when taken with standard treatments. Such products are often produced with no quality control and no research to back them. At times, these may even be touted as providing a cure for cancer. It is certainly one goal of this journal, our staff, and our contributors to aggressively point out the dangers of this situation and provide the basis for integrative cancer therapies to be safely practiced in both the community and academic oncology setting.

The larger task for this issue is, however, to help move the field of integrative oncology further along the road to understanding whether antioxidants, supplemental or food based, truly have a contribution to make in improving tolerability and efficacy of cancer treatment regimens. The stakes in this question are high. Nontoxic agents that moderate treatment side effects without unduly protecting tumors have much to offer oncology, including (1) a lower need for dose reduction or treatment delays; (2) an improvement of overall well-being and quality of life that would translate into an improvement in psychological well-being and outlook on disease; (3) less oncology staff time needed to deal with side effects and patient complaints, which would improve interoffice logistical flow; (4) a lower need for pharmaceuticals; and (5) fewer adverse treatment-related sequelae, which translates as less suffering for patients.

How far has this special issue gone in resolving the great debate? Even with these excellent articles and more than 2 decades of personal clinical work on antioxidants, I feel the question is still open. Research on breast cancer chemotherapy patients at my clinic has indicated that survival is not impaired but improved when antioxidants are given alongside chemotherapy in the context of a comprehensive integrative intervention, although this study is only one of many that will need to be done.<sup>28</sup> If one were able to look into the future, my best guess would be that both camps will have partially prevailed. While I believe the benefits of antioxidant use for both diminishing toxicity and

enhancing efficacy will eventually be confirmed, I am also convinced there will be some select areas where concerns of interference and interaction will be borne out. Since the potential benefits are so significant, however, and the use of antioxidants so widespread, as long as the issue of tumor protection remains a clinical concern, this debate cannot be ignored.

So, do antioxidants interfere with treatment, providing tumor protection, or do they provide useful mitigation of toxicity while enhancing the efficacy of treatment? Provocative data exist on both sides of the question. It is my hope that the articles in this special issue of *Integrative Cancer Therapies* add considerably to the debate and, importantly, inspire further productive research to better assist us in answering questions in this important area.

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