

The Good, Bad, and Uncertain: Combining Antioxidants and Chemotherapy

In human oncology journals, debate is raging about whether or not cancer patients should receive antioxidants during radiation and chemotherapy treatment. The human literature is rife with articles like, “Use of antioxidants during chemotherapy and radiotherapy should be avoided”¹ as opposed to “Multiple dietary antioxidants enhance the efficacy of standard and experimental cancer therapies and decrease their toxicity.”² In 2004, an entire issue of *Integrative Cancer Therapies* focused on the topic, chock full of well-defended reasons why one should and should not combine the two. In the end, University of Illinois physician Keith I. Block, MD, the journal’s editor-in-chief, scientific director of the Institute for Integrative Cancer Research and Education, and medical director of the Block Center for Integrative Cancer Care at the University of Illinois, added the following comment: “Even with these excellent articles and more than 2 decades of personal clinical work on antioxidants, I feel the question is still open.”³

Typically, products designed to lessen side effects display strong antioxidant properties, whether they are dietary supplements, herbal mixtures, or vitamin combinations. Animals receiving these products may indeed feel better during treatment and be able to endure cytotoxic therapy longer. But, at what cost? No one knows for sure. For veterinary patients, the unanswered human questions multiply, due to variations in metabolism, treatment delivery, and reactions to medication or radiation therapy. Questions about supplementation should also take into account dietary micronutrient intake. Many pet foods manufacturers are now adding antioxidant herbs, fatty acids, and vitamins to foods. Will these products confer chemoprotective and radioprotective benefits to cancer patients without negatively impacting efficacy? Only clinical research on veterinary patients will answer this question definitively.

And yet, the stakes of not knowing the answer to this antioxidant conundrum are high. One author has argued that, “[T]he harmful effects of antioxidants might be important even if they were small: a reduction of only a few percentage points in the efficacy of chemotherapy might lead to hundreds or thousands of deaths every year.” Another adds, “The possibility remains that [antioxidants] could have deleterious effects by protecting cancer cells against apoptosis....In vitro and preclinical studies in animal models have suggested that maintaining sufficient levels of micronutrients could improve the anti-tumor activity of chemotherapeutic agents. However, these potential therapeutic benefits have

¹ D’Andrea GM. Use of antioxidants during chemotherapy and radiotherapy should be avoided. *CA, A Cancer Journal for Clinicians*. 2005;55(5):319-321.

² Prasad KN. Multiple dietary antioxidants enhance the efficacy of standard and experimental cancer therapies and decrease their toxicity. *Integrative Cancer Therapies*. 2004;3(4):310-322.

³ Block KI. Antioxidants and cancer therapy: furthering the debate. *Integrative Cancer Therapies*. 2004;3(4):342-348.

not been conclusively documented in cancer patients undergoing chemotherapy.”⁴ *In vitro* evidence does suggest that cancer cells take in more vitamin C than do normal neighboring cells; cancer cells also resist oxidative injury more successfully after treatment with vitamin C.⁵ Furthermore, there is general agreement that endogenous antioxidants such as glutathione and antioxidant enzyme-elevating agents may protect cancer cells against cytotoxic therapy.⁶

As a counterargument, a prolific pro-antioxidant researcher wrote, “The efficacy of standard therapy has reached a plateau for most solid tumors despite impressive progress in radiation therapy...and in chemotherapy.... Therefore, additional approaches must be developed to improve the efficacy of standard therapy and to reduce the risk of recurrence of the primary tumor and the development of a second new cancer among survivors. In addition, new approaches should be developed to improve the quality of life of those patients who become unresponsive to all standard and experimental cancer therapies.”⁷

Antioxidants combat the effects of both endogenously and exogenously produced pro-oxidants. In the body, free radicals and other reactive oxygen species (ROS) appear as a natural consequence of energy production in the organism. ROS include superoxides, hydrogen peroxide, and the hydroxyl radical. These cellular oxidants arise from oxygen and appear constantly, in part, as a result of mitochondrial release of electrons from the electron transport chain and the reduction of oxygen molecules to superoxides.⁸ Endogenous ROS participate in cell signaling and confer bacteriocidal activities to phagocytes. The burst of ROS formation also allows organisms to kill invading cancer cells.

Pro-oxidants can also appear in the body as a result of purposeful, exogenous administration; i.e., cancer treatment.⁹ This is why the effects of chemotherapeutics whose cytotoxicity depends either on ROS generation or free radical intermediates may be thwarted by antioxidants.¹⁰ Another issue to consider is that nucleophilic antioxidants such as glutathione (GSH), n-acetylcysteine (NAC), and alpha-lipoic acid (ALA) can compete with chemotherapy drugs that act by nucleophilic substitution reactions, such as most

⁴ Whiteside MA, Heimburger DC, and Johanning GL. Micronutrients and cancer therapy. *Nutrition Reviews*. 2004;62(4):142-147.

⁵ D’Andrea GM. Use of antioxidants during chemotherapy and radiotherapy should be avoided. *CA, A Cancer Journal for Clinicians*. 2005;55(5):319-321.

⁶ Prasad KN. Multiple dietary antioxidants enhance the efficacy of standard and experimental cancer therapies and decrease their toxicity. *Integrative Cancer Therapies*. 2004;3(4):310-322.

⁷ Prasad KN. Multiple dietary antioxidants enhance the efficacy of standard and experimental cancer therapies and decrease their toxicity. *Integrative Cancer Therapies*. 2004;3(4):310-322.

⁸ Salganik RI. The benefits and hazards of antioxidants: controlling apoptosis and other protective mechanisms in cancer patients and the human population. *Journal of the American College of Nutrition*. 2001;20(5):464S-472S.

⁹ Conklin KA. Dietary antioxidants during cancer chemotherapy: Impact on chemotherapeutic effectiveness and development of side effects. *Nutrition and Cancer*. 2000;37(1):1-18.

¹⁰ Conklin KA. Cancer chemotherapy and antioxidants. *J Nutr*. 2004;134:3201S-3204S.

alkylating compounds, thereby reducing their efficacy.¹¹ Lists of other interactions and concerns, based on pharmacologic properties and mechanisms of action appear throughout the literature.

Furthermore, certain categories of patients display own unique responses to antioxidants; the human population exhibits heterogeneity in endogenous ROS production. Thus, antioxidants in high ROS producers may help protect those individuals against degenerative diseases such as cancer, cataracts, and cardiovascular disease. In contrast, people and perhaps animals with low levels of ROS may become more prone to cancer by taking antioxidants, because their already deficient ROS generation becomes further suppressed, thereby numbing the rate of protective apoptosis.¹²

Advocates for high doses of dietary antioxidants cite pilot data in humans that show that high-dose multiple dietary antioxidants given adjunctively with radiation or chemotherapy actually enhance the effect of conventional cancer treatments, although the mechanism remains unknown.¹³ Based on these and other data, researchers have proposed nutritional protocols for both the active treatment phase and follow-up maintenance, consisting of varying doses of vitamins A, B, C, D, E, beta-carotene, and certain minerals, administered orally, twice daily. This contrasts with other research indicating that patients receiving megadoses of vitamin and mineral combinations fared worse in terms of survival.¹⁴

On the other end of the spectrum, low doses of individual antioxidants may stimulate cancer cell proliferation in certain instances.¹⁵ Kedar N. Prasad, PhD, at the Center for Vitamin and Cancer Research at the University of Colorado Health Sciences Center writes that “[I]t is likely that recommendation of low doses of multiple vitamins containing low doses of micronutrients including antioxidants after therapy may increase the risk of recurrence of the primary tumor among those who are in remission. On the other hand, more than 60% of cancer patients use vitamins, and the majority combines them with standard therapy, mostly without the knowledge of their oncologists. This practice may also be harmful because a multiple-vitamin preparation may contain antioxidants such as glutathione-elevating agents, including alpha-lipoic acid and n-acetylcysteine (NAC), and antioxidant enzyme-elevating agents such as excess

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¹² Salganik RI. The benefits and hazards of antioxidants: controlling apoptosis and other protective mechanisms in cancer patients and the human population. *Journal of the American College of Nutrition.* 2001;20(5):464S-472S.

¹³ Prasad KN. Multiple dietary antioxidants enhance the efficacy of standard and experimental cancer therapies and decrease their toxicity. *Integrative Cancer Therapies.* 2004;3(4):310-322.

¹⁴ Lesperance ML, Olivotto IA, Forde N, et al. Mega-dose of vitamins and minerals in the treatment of non-metastatic breast cancer: an historical cohort study. *Breast Cancer Res Treat.* 2002;76:137-143. Cited in: D’Andrea GM. Use of antioxidants during chemotherapy and radiotherapy should be avoided. *CA, A Cancer Journal for Clinicians.* 2005;55(5):319-321.

¹⁵ Prasad KN. Multiple dietary antioxidants enhance the efficacy of standard and experimental cancer therapies and decrease their toxicity. *Integrative Cancer Therapies.* 2004;3(4):310-322.

of selenium, which is a cofactor for glutathione peroxidase, or dietary antioxidants such as vitamin E or vitamin C, which, at low doses, may protect cancer cells against free radical damage produced by chemotherapeutic agents or x-irradiation. Neither oncologists nor patients are aware of these potential dangers of taking antioxidants without any scientific rationale.”¹⁶

What’s the best advice to give to clients on this issue? It may involve simply acknowledging the truth, that there are no clear answers. By honestly disclosing the potential risks and benefits of both pathways, clients can then make their own, informed determination as to which avenue they want to try.

¹⁶ Prasad KN. Multiple dietary antioxidants enhance the efficacy of standard and experimental cancer therapies and decrease their toxicity. *Integrative Cancer Therapies*. 2004;3(4):310-322.