

CA

A Cancer Journal for Clinicians

Use of Antioxidants During Chemotherapy and Radiotherapy Should Be Avoided

Gabriella M. D'Andrea
CA Cancer J Clin 2005;55;319-321

This information is current as of October 3, 2005

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://caonline.amcancersoc.org/cgi/content/full/55/5/319>

To subscribe to the print issue of *CA: A Cancer Journal for Clinicians*, go to (US individuals only): <http://caonline.amcancersoc.org/subscriptions/>

CA: A Cancer Journal for Clinicians is published six times per year for the American Cancer Society by Lippincott Williams & Wilkins. A bimonthly publication, it has been published continuously since November 1950. *CA* is owned, published, and trademarked by the American Cancer Society, 1599 Clifton Road, NE, Atlanta, Georgia 30329. (©American Cancer Society, Inc.) All rights reserved. Print ISSN: 0007-9235. Online ISSN: 1542-4863.



(CAM) refers to products and regimens that individuals may employ either to enhance wellness, relieve symptoms of disease and side effects of conventional treatments, or cure disease. CAM articles provide evidence-based information on promising complementary and alternative methods, and inform clinicians of methods that may harm patients.

Use of Antioxidants During Chemotherapy and Radiotherapy Should Be Avoided

Gabriella M. D'Andrea, MD

ABSTRACT Many patients being treated for cancer use dietary supplements, particularly antioxidants, in the hope of reducing the toxicity of chemotherapy and radiotherapy. Some researchers have claimed, furthermore, that antioxidants also increase the effectiveness of cytotoxic therapy and have explicitly recommended their use. However, mechanistic considerations suggest that antioxidants might reduce the effects of conventional cytotoxic therapies. Preclinical data are currently inconclusive and a limited number of clinical studies have not found any benefit. Clinicians should advise their patients against the use of antioxidant dietary supplements during chemotherapy or radiotherapy. Such caution should be seen as the standard approach for any unproven agent that may be harmful. (*CA Cancer J Clin* 2005;55:319–321.) © American Cancer Society, Inc., 2005.

Dr. D'Andrea is Assistant Clinical Member, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY.

This article is available online at <http://CAonline.AmCancerSoc.org>

INTRODUCTION

Practicing oncologists are commonly asked by their patients if there is anything they can do to reduce the toxic effects of chemotherapy and radiotherapy and, if possible, help fight their cancer. The topic of perhaps greatest interest is vitamins and other nutritional supplements. It is estimated from survey data that 50% of cancer patients use some kind of dietary supplementation.^{1,2} Patients often understand in a general sense that supplements "help protect the body," and the mechanism for protection against chemotherapy and radiotherapy toxicity is well understood. Radiotherapy and many chemotherapy agents act by producing free radicals; some vitamins and supplements, including vitamins C and E, are antioxidants and bind to free radicals, preventing oxidative damage.

Preclinical Evidence

There are considerable in vitro and animal data showing that vitamin C and other antioxidants can protect cells against radiation and chemotherapy.³⁻⁵ It seems likely that they would therefore reduce treatment-related toxicities and there are promising, although not unequivocal, data that this indeed is the case.⁶⁻¹⁰ However, it also follows that antioxidants might protect cancer cells, thereby reducing the oncologic effectiveness of cytotoxic therapy. This is the reason why most oncologists discourage patients from using antioxidants during treatment.

Proponents of antioxidant therapy believe that this policy is mistaken and expressly recommend that antioxidants should be taken during chemotherapy and radiotherapy. They claim that the protective effects of antioxidants are selective for normal cells, such that they can reduce toxicities without compromising oncologic efficacy. It is also sometimes claimed that antioxidants are directly cytotoxic and/or can actually increase the effectiveness of cytotoxic treatments. These claims are based on a variety of laboratory studies. For example, in vitro studies have reported that vitamins A, C, and E, as well as carotenoids, can enhance the effectiveness of chemotherapy and radiotherapy.¹¹⁻¹⁵ Yet some laboratory data suggest that

antioxidants might compromise the efficacy of cytotoxics. For example, the mechanism by which oxidized dehydroascorbic acid universally enters cells via glucose transporters and accumulates inside the cells in its reduced state (ascorbic acid) has been well described.¹⁶ Cancer cells have been shown to exhibit upregulation of these facilitative glucose transporters and hence take up more glucose and more vitamin C than their normal neighbors.¹⁷ This would suggest that the protective effect of vitamin C might be even greater for tumors than for normal cells. It has been empirically demonstrated that cancer cells can become resistant to oxidative injury by treatment with vitamin C.¹⁸ Similarly, although there are *in vitro* data suggesting a direct antitumor effect for vitamin C, some investigators have claimed that these effects depend on the culture medium used and hence are of questionable validity.¹⁹

Clinical Evidence

Even if the laboratory data were not conflicting and confusing, they would be insufficient to guide clinical practice. There is no need here to recount the reasons why it is inappropriate to administer an agent to a cancer patient on the basis of cell culture studies and why we require data from human clinical trials. But it is worth restating that the 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. Human trials therefore need to be large. There has been no attempt to mount the kind of trial needed to guide clinical practice, in which many hundreds of patients are randomized to receive chemotherapy or radiotherapy with or without antioxidants. Nonetheless, the clinical trial literature does provide some interesting data.

The antioxidant perhaps most widely used for treating cancer is vitamin C. The possibility that this compound may be useful in the treatment of cancer was first raised by Cameron and Campbell in 1974.²⁰ Subsequently, Pauling and Cameron published research suggesting a survival benefit from vitamin C.²¹ The use of historical controls and the methods of patient selection weaken the

level of evidence provided by this study. Subsequently, two randomized double-blind trials were conducted comparing placebo to vitamin C in patients with advanced cancers.^{22,23} Neither study was able to show any objective improvement in disease progression or survival over placebo. Indeed, there seems to be somewhat worse survival in the vitamin C group.

A study that more directly addresses the issue of antioxidant use concurrently with cytotoxics is that of Lesperance, et al.²⁴ In this trial, 90 patients with early stage breast cancer who were prescribed megadoses of combination vitamins, minerals, and other antioxidants concurrent with standard therapy were compared with 180 well-matched controls. Breast cancer-specific survival ($P = .16$) and disease-free survival ($P = 0.07$) showed a trend toward worse survival in antioxidant-treated patients. Although many confounding factors may explain these differences in survival, the data should concern any oncologist who has patients considering antioxidant therapy.

It should also be noted that several large prevention trials have reported clinical data showing no benefit for supplementation. In fact, there are reports that it may be detrimental. Two trials, the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (ATBCPS)²⁵ and the Beta-Carotene and Retinol Efficacy Trial (CARET),²⁶ demonstrated an increased relative risk for developing lung cancer in the high-risk cohort receiving beta carotene supplementation. A meta-analysis of 14 randomized trials of antioxidant supplementation for the prevention of gastrointestinal cancers found no evidence that antioxidant supplements are effective. A subgroup analysis of higher quality trials suggested a small increase in mortality among people taking antioxidants compared with those in the placebo group.²⁷ In the HOPE-TOO (Heart Outcomes Prevention Evaluation—The Ongoing Outcomes) trial, participants randomized to take either 400 IU of vitamin E daily or a placebo did not differ significantly with regard to incidence of or mortality from cancer overall or cancers that previous studies suggested might be prevented by vitamin E (prostate, lung, oral, colorectal, breast, and melanoma). However, people on vitamin E were more likely to develop heart failure.²⁸

In another recent study, vitamin E had no effect on the incidence of second primary head and neck tumors among survivors of Stage I or II head and neck cancer previously treated with radiotherapy.²⁹ Although these chemoprevention trials are not directly applicable to the question of antioxidant use during treatment for active cancer, they do demonstrate that even though there was a plausible mechanism for antioxidant effect, good laboratory data, and promising results from preliminary human studies, antioxidants were found to do more harm than good when tested in randomized trials.

Taken together with treatment studies, these trials illustrate the complexity and the contra-

dictory nature of existing data. Further study is necessary to clarify the role of antioxidants.

CONCLUSION

Pending the publication of suitable trials, clinicians must be guided by existing data in the context of a fundamental principle of medicine, "Primum non nocere." There are reasons to believe that taking antioxidants concurrently with chemotherapy or radiotherapy might be harmful; therefore, patients should be advised against it. Contrasting evidence from extensive human studies is needed before patients are advised to take antioxidants during cytotoxic therapy.

REFERENCES

- Burstein HJ, Gelber S, Guadagnoli E, Weeks JC. Use of alternative medicine by women with early-stage breast cancer. *N Engl J Med* 1999;340:1733-1739.
- VandeCreek L, Rogers E, Lester J. Use of alternative therapies among breast cancer outpatients compared with the general population. *Altern Ther Health Med* 1999;5:71-76.
- Witenberg B, Kalir HH, Raviv Z, et al. Inhibition by ascorbic acid of apoptosis induced by oxidative stress in HL-60 myeloid leukemia cells. *Biochem Pharmacol* 1999;57:823-832.
- Greggi Antunes LM, Darin JD, Bianchi MD. Protective effects of vitamin C against cisplatin-induced nephrotoxicity and lipid peroxidation in adult rats: a dose-dependent study. *Pharmacol Res* 2000;41:405-411.
- Sonneveld P. Effect of alpha-tocopherol on the cardiotoxicity of adriamycin in the rat. *Cancer Treat Rep* 1978;62:1033-1036.
- Pace A, Savarese A, Picardo M, et al. Neuroprotective effect of vitamin E supplementation in patients treated with cisplatin chemotherapy. *J Clin Oncol* 2003;21:927-931.
- Iarussi D, Auricchio U, Agretto A, et al. Protective effect of coenzyme Q10 on anthracyclines cardiotoxicity: control study in children with acute lymphoblastic leukemia and non-Hodgkin lymphoma. *Mol Aspects Med* 1994;15:207-212.
- Weijl NI, Elsendoorn TJ, Lentjes EG, et al. Supplementation with antioxidant micronutrients and chemotherapy-induced toxicity in cancer patients treated with cisplatin-based chemotherapy: a randomised, double-blind, placebo-controlled study. *Eur J Cancer* 2004;40:1713-1723.
- Legha SS, Wang YM, Mackay B, et al. Clinical and pharmacologic investigation of the effects of alpha-tocopherol on adriamycin cardiotoxicity. *Ann N Y Acad Sci* 1982;393:411-418.
- Mills EE. The modifying effect of beta-carotene on radiation and chemotherapy induced oral mucositis. *Br J Cancer* 1988;57:416-417.
- Teicher BA, Schwartz JL, Holden SA, et al. In vivo modulation of several anticancer agents by beta-carotene. *Cancer Chemother Pharmacol* 1994;34:235-241.
- Chinery R, Brockman JA, Peeler MO, et al. Antioxidants enhance the cytotoxicity of chemotherapeutic agents in colorectal cancer: a p53-independent induction of p21WAF1/CIP1 via C/EBPbeta. *Nat Med* 1997;3:1233-1241.
- Prasad KN, Sinha PK, Ramanujam M, Sakamoto A. Sodium ascorbate potentiates the growth inhibitory effect of certain agents on neuroblastoma cells in culture. *Proc Natl Acad Sci USA* 1979;76:829-832.
- Rutz HP, Little JB. Modification of radiosensitivity and recovery from X ray damage in vitro by retinoic acid. *Int J Radiat Oncol Biol Phys* 1989;16:1285-1288.
- Koch CJ, Biaglow JE. Toxicity, radiation sensitivity modification, and metabolic effects of dehydroascorbate and ascorbate in mammalian cells. *J Cell Physiol* 1978;94:299-306.
- Vera JC, Rivas CI, Fischberg J, Golde DW. Mammalian facilitative hexose transporters mediate the transport of dehydroascorbic acid. *Nature* 1993;364:79-82.
- Vera JC, Rivas CI, Velasquez FV, et al. Resolution of the facilitated transport of dehydroascorbic acid from its intracellular accumulation as ascorbic acid. *J Biol Chem* 1995;270:23706-23712.
- Guaiquil VH, Vera JC, Golde DW. Mechanism of vitamin C inhibition of cell death induced by oxidative stress in glutathione-depleted HL-60 cells. *J Biol Chem* 2001;276:40955-40961.
- Clement MV, Ramalingam J, Long LH, Halliwell B. The in vitro cytotoxicity of ascorbate depends on the culture medium used to perform the assay and involves hydrogen peroxide. *Antioxid Redox Signal* 2001;3:157-163.
- Cameron E, Campbell A. The orthomolecular treatment of cancer. II. Clinical trials of high dose ascorbic acid supplements in advanced human cancer. *Chem Biol Intract* 1974;9:285-315.
- Cameron E, Pauling L. Supplemental ascorbate in the supportive treatment of cancer: Prolongation of survival times in terminal human cancer. *Proc Natl Acad Sci U S A* 1976;73:3685-3689.
- Creagan ET, Moertel CG, O'Fallon JR, et al. Failure of high-dose vitamin C (ascorbic acid) therapy to benefit patients with advanced cancer. A controlled trial. *N Engl J Med* 1979;301:687-690.
- Moertel CG, Fleming TR, Creagan ET, et al. High-dose vitamin C versus placebo in the treatment of patients with advanced cancer who have had no prior chemotherapy. A randomized double-blind comparison. *N Engl J Med* 1985;312:137-141.
- Lesperance ML, Olivetto IA, Forde N, et al. Mega-dose vitamins and minerals in the treatment of non-metastatic breast cancer: an historical cohort study. *Breast Cancer Res Treat* 2002;76:137-143.
- Omenn GS, Goodman GE, Thornquist MD, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *N Engl J Med* 1996;334:1150-1155.
- Alpha-Tocopherol BCCPSG. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med* 1994;330:1029-1035.
- Bjelakovic G, Nikolova D, Simonetti RG, Glud C. Antioxidant supplements for prevention of gastrointestinal cancers: a systematic review and meta-analysis. *Lancet* 2004;364:1219-1228.
- The HOPE and HOPE-TOO Trial Investigators. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. *JAMA* 2005;293:1338-1347.
- Bairati I, Meyer F, Gélinas M, et al. A randomized trial of antioxidant vitamins to prevent second primary cancers in head and neck cancer patients. *J Natl Cancer Inst* 2005;97:481-488.