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

The commentary by Lawenda et al. (1) concerning the use of antioxidants during cancer therapy caught our attention because they included our clinical trial (2) among others in their discussion of chemotherapy and antioxidants. In the initial part of the commentary, including the abstract and the introduction, the authors state that “use of supplemental antioxidants during chemotherapy and radiation therapy should be discouraged because of the possibility of tumor protection and reduced survival.” However, as we navigated through the commentary, it became apparent to us that this conclusion is probably premature and represents a gaping void between the data presented and interpretation thereof.

For example, none of the 16 clinical trials on antioxidants and chemotherapy reviewed by the authors reported decrements in tumor response rates or survival. It is difficult to interpret the data across the studies because most of them had a small sample size and were heterogeneous in the dose, type, schedule, number, mechanism of action, and combination of antioxidants. Although from a statistical point of view the results of these trials cannot be taken as evidence of lack of interference of antioxidants with chemotherapy, they also cannot be taken as evidence that antioxidants interfere with the efficacy of chemotherapeutic agents and thus should be discouraged, as suggested by Lawenda et al.

Fourteen of these trials used a single antioxidant. There are suggestions from preclinical studies that some antioxidants when used alone produce varying degrees of tumor regression (3). Mixtures of three or four antioxidants, on the other hand, have consistently been shown to selectively enhance the growth inhibitory effects of standard anticancer therapies in cancer cells (3). We have also reported that a mixture of three antioxidants statistically significantly enhanced paclitaxel and carboplatin–induced apoptosis in a human lung squamous cancer cell line (4). Consistent with these observations, our clinical trial showed a trend toward better response rates and survival in the antioxidant arm (2). We agree with Lawenda et al. that in view of limited power of the study, we could not have concluded that the addition of antioxidants to chemotherapy was safe. In fact, we discussed the limitations of our study, including the small sample size, and underscored the need for large-scale adequately powered trials (2). Thus, we agree with an earlier comment about our trial by one of the coauthors of this commentary that “The study is not perfect but leads the way for better clinical trials” (5).

Regarding the use of antioxidants during radiotherapy, the conclusion of Lawenda et al. is largely influenced by a single trial (6). This trial has already been contested on its design and conclusions (7). Moreover, this trial examined the effect of specific antioxidants in a specific type of tumor, whereas Lawenda et al. extrapolated the results to all antioxidants and all tumors, which seems inappropriate.

Instead of discouraging further scientific investigation, the data presented in the trials reviewed by Lawenda et al. underscore the need to explore these highly cost-effective agents further. We agree with Lawenda et al. that a definitive trial incorporating a more sophisticated recognition of the complexity and diversity of antioxidants is required. Nevertheless, small-scale trials such as ours are crucial to obtain the proof of concept before we embark on a large-scale pivotal trial.

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References


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DOI: 10.1093/jnci/djn279
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Response

We appreciate the comments from Pathak and Bhutani and share their perspective, as noted in our Commentary (1), that an adjunctive role for dietary antioxidant supplements holds substantial promise for clinical application in oncology. However, we feel that therapeutic guidelines for using dietary antioxidant supplements in current trials such as ours are crucial to obtain the proof of concept before we embark on a large-scale pivotal trial.
practice must be based on the recognition of their potential benefits and risks. The evidence on complementary antioxidant treatments is inadequate and equivocal with regard to benefits, and the most robust studies available indicate a likelihood of harm (2,3). Because most of the studies that suggest the safety of antioxidant supplements were inadequately designed or underpowered to detect a detrimental effect on tumor control or survival, we concluded with our advice to physicians: primum non nocere. Nonetheless, work by Pathak and Bhutani (4,5) and others, including our own investigations (6), has demonstrated the critical need to expand both basic and clinical investigations in this area. Indeed, these studies should directly inform the design and conduct of new trials in cancer patients. This new work needs to focus on the complex interactions between antioxidants and radiation and/or chemotherapy, including their individual and combined molecular mechanisms of action. However, until we can better define the efficacy and safety of these combination treatments, we should advise our patients to avoid high-dose antioxidant supplements during cytotoxic therapies for cancer.

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DOI: 10.1093/jnci/djn280
Published by Oxford University Press 2008.

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