Editorial

The Use of Vitamin C and Other Antioxidants with Chemotherapy and Radiotherapy in Cancer Treatment

It is widely accepted that antioxidants play a very important role in the prevention of cancer. It is no great leap of logic, then, to surmise that they would likely play an important role in the treatment of cancer and the prevention of recurrence. This is certainly the experience of physicians, ourselves included, who have prescribed antioxidants for this purpose. More importantly, a substantial growing body of research supports this approach.

Curiously, in spite of compelling evidence that antioxidants have a promising role in the treatment of cancer, many oncologists have been led to believe that antioxidants are potentially harmful and advise their patients against taking supplemental natural antioxidants, especially if they are undergoing chemotherapy or radiation. To our knowledge, there is no substantial scientific evidence that supports this advice, while there is a growing body of substantial evidence that antioxidants may be valuable adjunctive treatments in this context. Since a majority of cancer patients take antioxidant supplements,[1,2] the question of whether antioxidants are helpful or harmful to take during chemotherapy or radiation is a very important one.

In this special issue of our journal, two recent reviews of research in the area of antioxidant use during chemotherapy are reported. The first, a review undertaken by Judith O. Stoute at my (Abram Hoffer's) invitation, is a compilation and summary of the medical literature related to the use of vitamin C, the most well-known of all the antioxidants, in the treatment of cancer. The second, a review undertaken by Dr. Hal Gunn and the research staff at the Centre for Integrated Healing (Vancouver, Canada), is a compilation and summary of all the randomized control trials (RCTs) to-date of the use of all naturally occurring antioxidants including vitamin E, ß-Carotene, selenium, melatonin, co-enzyme Q10, glutathione, n-acetylcysteine and multiple antioxidants in the context of chemotherapy or radiation in humans.

In both reviews, the weight of the current evidence strongly favours the use of naturally occurring antioxidants as a promising adjunct for cancer treatment. Overwhelmingly, the evidence points to antioxidants as a potentially important adjunct to decrease the side-effects of chemotherapy/radiation, increase the response to these treatments and improve survival. In the first review, Stoute found 24 positive studies, 12 positive reviews, one neutral study, one negative study, two negative reviews and four responses to the latter. The one negative 'study' was based on a substantial amount of conjecture based upon *in vitro* and animal studies. In the second review, Gunn found 22 positive RCTs, two neutral RCTs, and only one RCT that could be construed as 'evidence' of any negative effect what-so-ever. In this study, which is sometimes referenced as 'evidence' that antioxidants may be harmful, oral n-acetylcysteine (NAC) was given in conjunction with doxyrubicin therapy to assess whether NAC could prevent doxyrubicin induced cariotoxicity. The researchers found that, although there was a significant difference ($p<0.01$) between the NAC-treated and NAC-free groups in ejection fraction in favour of the NAC group, the rate of progression of cardiac injury in the two groups was identical. The authors were concerned that patients who received NAC had more diarrhea and slightly more hair loss, although they had somewhat less severe nausea. Since this is the only RCT in the review that found any negative effect of naturally occurring antioxidants in conjunction with chemotherapy or radiation, it was classified in the review as a 'negative' study.

As you will read in these reviews, the weight of the evidence clearly favours the use of antioxidants as a promising adjunct to chemotherapy and radiation. We have

asked oncologists/pharmacists we have encountered who believe that naturally occurring antioxidants should not be taken during chemotherapy or radiation to provide research evidence upon which this opinion is based. Over the years, we have been provided with three references. The first, the NAC study listed above, demonstrated that diarrhea and hair loss were worse in the NAC treated group, although severe nausea was better. The second, was an in-vivo study in mice that showed that tumour cells accumulate vitamin C.[3] One of the authors of this study speculated that, since radiation and some chemotherapy drugs kill cancer cells through oxidative mechanisms "that vitamin C (supplementation) might make cancer treatment less effective". This speculation was widely reported in the lay press in spite of the lack of evidence supporting those conclusions.

The third study referenced as evidence that naturally occurring antioxidants may be harmful to take during chemotherapy/radiation was a case-matched retrospective study by Lesperance et al,[4] which showed no statistically significant difference in recurrence or survival between a group of breast cancer patients who took vitamins and supplements and a case-matched control group (who may or may not have). However, the non-statistically significant 'trend' towards decreased disease-free survival ($p = 0.08$) and survival ($p = .19$) was considered a concern and was widely reported in the lay press in Canada as evidence that antioxidants may be harmful in the treatment of cancer. Although the results of this study should not be ignored, it is important that these results be placed into the context of all the available evidence on this subject. Retrospective case-matched studies are not an ideal method to study the effectiveness of a treatment since it is impossible to find controls that perfectly match the treatment group. In this particular study, the control group was much less likely to have lumpectomy without radiation than the treatment group (the number of patients in the control group that had lumpectomy without radiation should have been 28: it was actually 12). Since lumpectomy without radiation increases the risk of local recurrence (vs. lumpectomy with radiation), this may account for a proportion of the non-statistically significant difference in disease free survival between the two groups. In addition, both the T-stage and Tumour grade were not ideally matched, with the treatment group more likely to have more advanced tumour grade (the number of patients in the control group that had poorly differentiated tumour grade should have been 78: it was actually 64) and the treatment group more likely to have advanced stage (the number of patients in the control group that had stage T3 should have been 10: it was actually 8 and the number of patients in the control group that had stage T4 should have been 8: it was actually 6). These differences may account for a substantial proportion of both the non-statistically significant difference in survival and non-statistically significant difference in disease-free survival between the two groups. In other words, these non-statistically significant trends may simply reflect inherent differences between the groups.

From an evidence-based perspective, the important question is: What is the entire body of evidence for and against the use of antioxidants? The Lesperance study and the NAC study discussed above constitute the only clinical 'evidence' we have found that antioxidants may be harmful to take in the context of chemotherapy/radiation. On the other hand, there are 22 RCTs which provide a much higher standard of evidence that antioxidants are a very promising adjunct to chemotherapy or radiation, with the potential to reduce the side-effects of chemotherapy/radiation, increase response to con-

ventional treatment and increase survival.

It is our hope that this special issue of our journal will encourage an evidence-based dialogue about this important issue for the benefit our shared patients.

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