Antioxidants and Malignancies

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A great deal of attention and hype has surrounded the role and usage of antioxidants in patients with cancer. This has been in the conventional research community, as well as with holistic practitioners and the lay public. This interest is very understandable; however, the details of the research suggest a very complex, sometimes contradictory and confusing picture.

The rationale behind the role of antioxidants in the prevention and treatment of malignancies is compelling. There is very substantial epidemiological research suggesting that populations of people with diets containing substantial amounts of foods rich in antioxidants, such as fruits and vegetables, have a lower incidence of malignancies (1). There is ample evidence showing that patients with malignancies have a higher incidence of reactive oxygen species (ROS), and a lower concentration of antioxidants (2,3,4), including having further decreasing levels as the spread of the malignancy increases (2). There is also a mechanistic rationale, as ROS leads to an increase in DNA mutations, as well as to immunosuppression (5,6,7).

This enthusiasm was tampered by the unexpected negative findings in the trials of Beta carotene supplementation, especially the CARET and ATBC trials (1). These were trials where patients, some from high risk populations (smokers and patients with asbestos exposure), were treated with combinations of alpha tocopherol, B-carotene, and vitamin A. Epidemiological data had suggested that there would be a protective effect regarding the development of lung cancer. Contrary to widely held expectations, the incidence of lung cancer was actually increased. The generally understood take home message was that the antioxidant hypothesis, that antioxidants will prevent the onset of cancer, was false. A closer look at the data reveals a much more complex picture, however. In the CARET trial, instead of the expected **antioxidant** effect, a **prooxidant effect was unexpectedly obtained** (8). It was also noted that the dosages used in the intervention, and the subsequent carotene blood levels obtained, were considerably higher than those obtained from a diet rich in carotenoid substances. A recent study suggested that much lower doses of 5 antioxidants (120 mg of ascorbic acid, 30 mg of vitamin E, 6 mg of beta carotene, 100 mg of selenium, and 20 mg of zinc) led to a decrease in cancer incidence in men (but not in women), who typically have a lower consumption of antioxidant rich foods than women (9). As an additional aside, B-carotene is one of numerous carotenoids. Supplementing B carotene alone, as opposed to mixed carotenoids, or other combinations using bioflavonoids commonly found in these foods could be expected to lead to different results. So it's not unreasonable to draw the conclusion that the incidence of lung cancer was increased because B carotene supplementation led to **increased** levels of ROS!

Integrative treatment regimens of antioxidants commonly employ a wide range of interacting antioxidants and detoxifying substances. These commonly include vitamins such as E succinate, ascorbic acid, mixed carotenoids and bioflavonoids, herbs, and substances such as n-acetyl cysteine (which acts as a precursor to glutathione, an internally produced antioxidant and detoxifying substance), green tea, and occasionally melatonin. These supplements are combined with dietary recommendations that emphasize antioxidant rich foods. They are considered a part of a multipronged integrative approach. This approach is totally different than the approach of supplementing one or two isolated vitamins, as was done in the ATBC and CARET trials. Nonetheless, it's also clear that we don't know the effect of these antioxidant/detoxification regimens. We don't know if they lead to the expected antioxidant effect or not. An important research question is the investigation of this issue.

In addition to the controversies regarding the use of antioxidants as a primary or secondary prevention strategy, significant concern has been raised regarding the concurrent use of antioxidants while patients are receiving chemotherapy or radiation therapy. This is because these treatments are partially effective due to the generation of ROS. The concern is that the use of concurrent antioxidants might block this therapeutic effect. There is also concern that the use

of substances which increase the production of glutathione might mitigate the effectiveness of chemotherapy. These issues are discussed in more detail below.

Antioxidants and Reactive Oxygen Species in Cancer Patients

Substances typically described as antioxidants can have other effects besides acting as antioxidants. Some, such as Vitamin C, can act as a prooxidant. A seminal paper by Chen, Levine and colleagues studied intravenous administration of Vitamin C given in doses greater than 10 grams. Intravenous administration of Vitamin C can achieve vastly higher levels than oral dosing. Studies show that levels of Vitamin C necessary to be cytotoxic can **only** be achieved through intravenous administration. It was found that intravenous ascorbate acted by production of the prooxidant hydrogen peroxide which was highly proapoptotic to lymphoma cells, without effecting normal cells at the concentrations achieved intravenously (10). Numerous studies have looked at a combination of Vitamin C and Vitamin K3 in promoting apoptosis through redox cycling and prooxidant effects (11,12,13). Vitamin E, especially Vitamin E succinate, has been shown to be proapoptotic (14,15). Numerous antioxidants, including Vitamins E and C, and n-acetyl cysteine, have been shown to have positive effects on immune functioning (16,17). Antioxidants have been shown to decrease chronic inflammation in patients with solid tumors (18,19).

Numerous studies have shown a depletion of antioxidants and an increased amount of ROS in patients with malignancies. Liu studied total antioxidant capacity (TAC) and DNA damage in patients with malignant pleural effusions, and found a decrease in TAC in the plasma and effusions of patients compared to controls (20). Patients with breast cancer were compared with those with benign fibroadenoma and found to have decreased amounts of antioxidants as well as increased lipid peroxidation (21). A similar situation was found in patients with colon cancer (22) and ovarian cancer (23). Different researchers have used employed comprehensive nutritional and supplement protocols, including antioxidants, in patients with malignancies. Mantovani et al have studied patients with advanced malignancies, in a cachexia/anorexia state (24,25) The patients were treated with a diet with high polyphenol content (400 mg), p.o. pharmaconutritional support enriched with *n* – 3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid) 2 cans (237 mL each) per day, medroxiprogesterone acetate 500 mg/d, antioxidant treatment with α-lipoic acid 300 mg/d plus carbocysteine lysine salt 2.7 g/d plus vitamin E 400 mg/d plus vitamin A 30,000 IU/d plus vitamin C 500 mg/d, and selective cyclooxygenase-2 inhibitor Celecoxib 200 mg/d. The treatment has been shown to be effective for clinical response, increase of lean body mass, decrease of reactive oxygen species and proinflammatory cytokines, and improvement of quality of life (25). This program demonstrates the interrelatedness of processes such as inflammation and production of ROS. It is also an excellent example of an integrated approach using multiple agents. Another multiagent program was utilized in patients with non metastatic breast cancer. They were treated with mega-doses of beta-carotene, vitamin C, niacin, selenium, coenzyme Q10, and zinc in addition to standard therapies and were compared with matched controls. Breast cancer-specific survival and disease-free survival times were not improved for the vitamin/mineral treated group over those for the controls (26). The clinical situations of the patients, the endpoints measured, as well as the programs themselves, are so different that it's impossible to draw any general conclusions. The Mantovani program is a valuable example, as it investigates numerous pertinent endpoints, both laboratory and clinical. It also addresses the understanding that an integrative approach to malignancies needs to address numerous aspects, in order to approach the complexity of malignancies.

The use of antioxidants in patients receiving chemotherapy or radiation therapy

Chemotherapy and radiation therapy are effective through varied mechanisms. The production of ROS is one of the ways that radiation therapy, and some chemotherapeutic agents (alkylating agents, platinum agents) work (27). It is not clear that this is the most important mechanism for their action. On the other hand, the production of ROS leads to many of the side effects associated with these treatments. As there is concern that antioxidants can neutralize ROS, and

therefore interfere with chemo/radiation therapy, considerable controversy has emerged over the issue if patients should refrain from using antioxidants while receiving chemotherapy or radiation therapy. The great majority of oncologists and radiation therapists will advise their patients against using antioxidants during these treatment phases, particularly in earlier stages of treatment, when these treatments have the most likelihood of benefit. This is probably a prudent recommendation, as the bottom line is that we don't know if there is any decreasing of the efficacy of chemotherapy and radiation therapy if antioxidants are used concurrently. However, the issue is very complex, and most of the literature does not support this position. In fact, many studies suggest that concurrent use of antioxidants not only decreases adverse reactions, but also might increase the efficacy of chemo/radiation therapy.

As noted above, antioxidants have actions beyond their effect on free radicals. Vitamin C, for instance, was shown to stabilize p53 and enhance, in a cell culture medium, the sensitivity of cervical cancer cells to cisplatinum (28). Numerous studies show that Vitamin C decreases the concentration of Glutathione (GSH) (29). GSH, as well as being an antioxidant, is a detoxifying agent. A high level of GSH is associated with resistance to multiple chemotherapeutic agents. This might be because the presence of GSH within the malignant cell protects the cell, as well as promoting the detoxification of the chemotherapeutic agent itself (30,31). Therefore, through the mechanism of Vitamin C depleting GSH, this might explain the enhanced efficacy of certain chemotherapeutic agents used in conjunction with Vitamin C, as has been shown in different studies (32, 33). Vitamin C, in conjunction with vitamin K3, has been shown to enhance cell killing, used alone and in conjunction with chemotherapy (10,11,12) With some chemotherapeutic agents, such as 5-FU, the production of ROS is not a significant contributor to their efficacy. Numerous studies showed enhanced efficacy when 5-FU is used in conjunction with different antioxidants (33,34,35). The issue of multidrug resistance is of great importance. Factors such as increased concentration of Glutathione and upregulation of glutathione peroxidase and transferase, as well as increased production of NFkB and AP-1 have been considered of central importance. In addition, the proteosome (ubiquitin) pathway, which is important for degradating intracellular proteins is involved. Various flavonoids, including especially curcumin, have been shown to have potential beneficial effects in these areas.

Curcumin was shown to increase sensitivity to doxorubicin (36), and act as a radiosensitizer in a prostate cancer cell line (37), by effecting NFkB,AP-1, GSH, and the ubiquitin pathways (38,39).

Various clinical studies have looked at this issue. Protection of hearing loss was looked at with patients receiving cisplatinum and a combination of Vitamins C, E and selenium. A partial protection was noted in patients who achieved the highest level of these nutrients (40). Another study noted protection against bone marrow suppression and nephrotoxicity in patients treated with cisplatinum who also received selenium, compared to controls (41). A non randomized study looked at patients with non small cell lung cancer who were treated with conventional approaches as well as a combination of antioxidants, trace elements, and fatty acids. A significant improvement was noted compared to historical controls, and patients were also noted to tolerate chemo/radiation therapy better (42). Obviously, one can only draw limited conclusions from a nonrandomized trial with historical controls, but we should note that this group of patients didn't receive antioxidants alone, but received a more comprehensive protocol, including substances like fatty acids likely to decrease inflammation. Two patients treated at the University of Kansas with advanced Stage III ovarian cancer were treated with cisplatinum/paclitaxel and various antioxidants given orally. They also received high doses of intravenous Vitamin C (60 g twice weekly) in conjunction with chemotherapy, and are reported to be completely free of disease 3 years later (43).

In addition to various vitamins and minerals, other substances, such as herbs, have significant antioxidant activity. Melatonin, the pineal hormone, has considerable antioxidant activity, as well as immunomodulating effects. Patients with metastatic non small cell lung cancer were treated with chemotherapy with or without melatonin (20mg/night). Those receiving melatonin had statistically improved survival (44). Patients with metastatic colorectal cancer who had failed 5-FU

regimens were treated with irinotecan with or without melatonin. The group receiving melatonin had improved responses (45). A group of 250 patients with different tumor types, who had a poor prognosis, were treated with conventional chemotherapy regimens with or without melatonin. Those treated with melatonin showed significantly superior responses. The 1-year survival rate and the objective tumour regression rate were significantly higher in patients concomitantly treated with MLT than in those who received chemotherapy (CT) alone (tumour response rate: 42/124 CT + MLT versus 19/126 CT only, $P < 0.001$; 1-year survival: 63/124 CT + MLT versus 29/126 CT only, $P < 0.001$). Moreover, the concomitant administration of MLT significantly reduced the frequency of thrombocytopenia, neurotoxicity, cardiotoxicity, stomatitis and asthenia (46).

Various review articles can be consulted regarding these issues (47,48,49). An entire issue of the journal Integrative Cancer Therapies (Vol 3, #4, 2004), devoted itself to these questions. All have concluded that no firm conclusion or recommendations can be made at the present time. They do, however, point out the potential importance and clinical relevance of these issues.

The Use of Anti-inflammatory Substances in Patients Receiving Chemotherapy and Radiation Therapy

Many naturally occurring products, such as herbs and foods, have significant antioxidant as well as anti-inflammatory properties. In contrast to the paucity of literature and theoretical concerns regarding the use of antioxidants such as those mentioned above, there is substantial supportive literature and an absence of compelling theoretical concern regarding concurrent use of anti-inflammatory substances during chemo/radiation therapy.

Mohammed et al, treated diffuse large cell lymphoma cells with genistein (an isoflavone from soy), CHOP, or CHOP and genistein. At 30 micro M, compared to CHOP alone, genistein with CHOP inhibited the growth significantly, induced G(2)-M arrest, increased Bax:Bcl-2 ratio, decreased NF-kappaB DNA binding, and induced apoptosis. Genistein also inhibited NF-kappaB DNA binding in vivo, whereas CHOP enhanced it (50). A murine model of lung carcinoma was studied comparing standard chemo/radiation therapy with or without genistein. Genistein statistically enhanced the benefit of the treatment regimen (51). Prostate cancer cells were treated with radiation therapy without or without curcumin, from the plant which produces the spice curry. “Compared to cells that were irradiated alone (SF(2)=0.635; D(0)=231 cGy), curcumin at 2 and 4 microM concentrations in combination with radiation showed significant enhancement to radiation-induced clonogenic inhibition (SF(2)=0.224: D(0)=97 cGy and SF(2)=0.080: D(0)=38 cGy) and apoptosis. It has been reported that curcumin inhibits TNF-alpha-induced NFkappaB activity that is essential for Bcl-2 protein induction. In PC-3 cells, radiation upregulated TNF-alpha protein leading to an increase in NFkappaB activity resulting in the induction of Bcl-2 protein. However, curcumin in combination with radiation treated showed inhibition of TNF-alpha-mediated NFkappaB activity resulting in bcl-2 protein downregulation. Bax protein levels remained constant in these cells after radiation or curcumin plus radiation treatments. However, the downregulation of Bcl-2 and no changes in Bax protein levels in curcumin plus radiation-treated PC-3 cells, together, altered the Bcl2 : Bax ratio and this caused the enhanced radiosensitization effect. In addition, significant activation of cytochrome c and caspase 9 and 3 were observed in curcumin plus radiation treatments. Together, these mechanisms strongly suggest that the natural compound curcumin is a potent radiosensitizer, **and it acts by overcoming the effects of radiation-induced prosurvival gene expression** in prostate cancer.” (52) This explanation highlights the reason why these natural agents appear to enhance the effect of chemo/radiation therapy. Chemo/radiation therapy appears to elicit a counter response in the organism of producing prosurvival mechanisms, such as increased production of NFkB and AP-1, which act to counteract the apoptotic effect of the treatments. Numerous natural substances inhibit signaling molecules and genes such as NFkB and AP-1 and block this escape mechanism. It’s to be noted that multiple drug resistance also uses this mechanism, and therefore these natural substances are likely to be beneficial in this scenario. In this context, Curcumin has been shown to have beneficial effects on Glutathione, another

important component related to multiple drug resistance (53). Various other substances, such as green tea (54), resveratrol from grape seeds (55), silymarin from milk thistle (56), ganoderma mushroom (57), and quercetin (58) show similar effects.

Conclusions and Summary

The production of ROS is a plausible mechanism to explain one aspect of the etiology and progression of cancer. Numerous epidemiological studies have shown that a diet high in a wide, varied range of antioxidants is protective against the development of malignancies, as well as against other illnesses. It's not clear if we can extrapolate from these epidemiological findings involving diet, to the use of antioxidant supplements, especially when these are used in high doses. Some landmark studies (ATBC and CARET), have shown that using high doses of one or two antioxidants can actually have a deleterious effect in specific patient populations. It's likely, however, that this occurred because these supplements led to a paradoxical **prooxidant** effect. Therefore, the question still remains that if we are able to produce an antioxidant effect, will there be a positive clinical effect.

Most integrative protocols recognize that the use of antioxidants will likely be more beneficial if used in the context of a well rounded dietary and supplement program. This program usually addresses numerous important pathophysiological processes, such as chronic inflammation, angiogenesis, inhibition of apoptosis, and dysfunctional immune function. Therefore, though it's important to explore the role of isolated antioxidant use, they are most likely to be of more benefit in the context of a balanced, multiagent program.

The use of antioxidants during chemo/radiation therapy is very controversial. Although it's generally recommended that antioxidants not be given concurrently with chemo/radiation therapy, the literature, which is complex and clearly inconclusive, is not necessarily supportive of this position. One exception to this is with the use of glutathione and substances such as n-acetyl cysteine. The present level of evidence advises against their use concurrently with chemotherapy, as they appear to promote resistance. Their use can be recommended, however, when chemo/radiation therapy is not being given. There are some antioxidants, specifically high dose melatonin, where clinical studies do support concurrent use with chemo/radiation therapy. A prudent approach to the use of antioxidants would be to withhold them when there is potential for significant benefit from chemo/radiation therapy. In more advanced situations, where there is increased ROS production, and the patient is likely depleted of antioxidants, and when the chemo/radiation therapy is likely to be less efficacious, consideration should be given to including antioxidants (in conjunction with a multiagent integrative protocol), particularly as adverse treatment reactions might be minimized. Glutathione and n-acetyl cysteine should not be used in either of these scenarios.

This review has limited itself primarily to vitamins, minerals, and trace elements. Many herbal substances have significant antioxidant activity. These substances, even more so than vitamins, have a very wide range of activities, including effects on inflammation, apoptosis, immune function, etc. In contrast to the controversial position regarding the vitamins, minerals, etc, these herbal substances have substantial literature supporting their concurrent use with chemo/radiation therapy.

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