

Micronutrients and Cancer Therapy

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The effect of micronutrient supplementation on the effectiveness of cancer chemotherapeutic agents is reviewed, and the efficacy of antioxidants, folic acid, and other vitamins and minerals is discussed. Although some micronutrients show promise in enhancing the cytotoxicity of anticancer agents in vitro, caution should be exercised in recommending micronutrient supplementation for cancer patients receiving chemotherapeutic drugs. To date, few well-controlled clinical trials have been conducted to evaluate the efficacy of micronutrients in promoting the sensitivity of tumors to chemotherapeutic agents.

Key words: cisplatin, micronutrients, drug resistance

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Introduction

Cancer patients are susceptible to disease-related abnormalities in micronutrient metabolism. Federico et al.¹ showed that serum concentrations of selenium and zinc were significantly lower in cancer patients than in control patients, whereas serum copper concentrations were elevated in cancer patients compared with control patients. These differences in serum selenium, zinc, and copper concentrations were noted prior to patients receiving any form of therapy. In a case series study of patients with lung cancer, 64% of the patients evaluated had serum vitamin C levels that were below the threshold typically associated with the development of scurvy.² Investigators previously showed that surgically resected lung cancer tissues contained higher levels of vitamin C com-

pared with the normal adjacent tissue.³ Early studies reported low folic acid levels in cancer patients, especially in those with advanced cancer,^{4–6} and these results have been verified in many,^{7–9} but not all¹⁰ recent studies. Alterations in iron metabolism have also been reported.¹¹

Nearly 60 years ago, folic acid was reported to have a growth-enhancing effect on childhood lymphoblastic leukemia;¹² these early observations were confirmed in animal models.^{13,14} Some studies, however, suggest that encouraging adequate nutrition by micronutrient supplementation may preserve a patient's response to standard cancer therapies. For example, a study evaluating the effect of selenium and zinc supplementation in malnourished patients with gastrointestinal and esophageal cancer who were receiving chemotherapy determined that 70% of supplemented patients did not show worsening of nutritional status, whereas 80% of unsupplemented patients demonstrated a worsening of their nutritional status.¹ This study suggests that selenium and zinc supplementation may improve the clinical course of cancer patients receiving chemotherapy, since poor nutritional status has been linked with a poor prognosis in cancer patients. A cross-sectional study evaluating supplemental vitamin intake in patients with non-small cell lung cancer determined that supplemental vitamin use was associated with greater long-term survival (41 months in supplement users versus 11 months in those not using supplements).¹⁵ In the following paragraphs, we will review some of the latest information on the effects of nutritional supplementation on the efficacy and toxicity of commonly used chemotherapeutic drugs.

Antioxidants

The question of whether antioxidants (which influence metabolism in both normal and cancer cells) are beneficial or harmful to patients receiving cancer therapies has not been answered with certainty, since virtually all that is known in this area is from in vitro studies. In studies discussed below, some investigators have written in support of supplementing cancer patients with micronutrients that include antioxidants. A number of clinicians tend to caution against the use of high-dose antioxidants

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during chemotherapy, however, because of data suggesting that antioxidants may protect cancer cells against the oxidative damage that is induced with chemotherapy.

Jha et al.¹⁶ suggest that antioxidant vitamins, including vitamin E, selectively inhibit growth of cancer cells but not normal cells, perhaps by accumulating in the cancer cell and initiating events that lead to cell death, growth inhibition, or differentiation. They reported that γ -irradiation decreased mitotic accumulation in both human tumor cells and normal fibroblasts. When cancer cells were treated with vitamin E for 24 hours before, during, and after irradiation, however, investigators observed further decreased mitotic accumulation in human tumor cells but not in normal cells.¹⁶ More recent data reported by this group suggest vitamin E treatment induces chromosomal damage in cancer cells but not in normal cells.¹⁷

Potential mechanisms to account for the effects of antioxidant vitamins were reviewed;¹⁸ they include inhibition of protein kinase C activity, prostaglandin E1-stimulated adenylate cyclase activity, expression of c-myc, H-ras, and a transcription factor (E2F), and induction of transforming growth factor- β and p21 genes. This article summarizes primarily *in vitro* studies, which indicate that antioxidant vitamins individually or in combination enhance the growth-inhibiting effects of γ -irradiation, chemotherapeutic agents, hyperthermia, and biologic response modifiers on tumor cells. Other studies by this group found that a mixture of antioxidant vitamins (vitamins C and E, β -carotene, and retinoic acid) markedly inhibited the growth of human melanoma cells in culture, but that the individual vitamins at the same concentrations did not inhibit growth in these cells.¹⁹ They also noted that beneficial effects on cancer cell growth are observed only when relatively high concentrations of vitamin supplements are used, and that low doses may actually stimulate the growth of cancer cells *in vitro*.²⁰

This group and others also demonstrated that vitamins and cancer chemotherapeutic agents combined are much more effective at blocking cell growth than the chemotherapeutic agent alone. Vitamin C combined with 5-fluorouracil, γ -irradiation, bleomycin, or sodium butyrate had a greater growth-inhibiting effect on murine neuroblastoma cells than any agent alone. Likewise, vitamin E combined with bleomycin, 5-fluorouracil, adriamycin, or cisplatin inhibited the growth of murine neuroblastoma cells in culture to a greater extent than any agent alone. Other studies showed a synergistic effect of chemotherapeutic agents with vitamins C, E, A, or β -carotene in enhancing the effect of the agents on growth inhibition of cancer cells.¹⁸

Another argument for using antioxidants during cancer chemotherapy is that they may enhance the cytotoxic

effects of chemotherapy by blocking reactive oxidant species (ROS).²¹ ROS slow the rapid cell proliferation required for optimal action of many chemotherapeutic agents. The mechanism is believed to be the prolongation of the G₁ phase of the cell cycle by oxidative stress. A prolonged G₁ phase would slow proliferation and, because anticancer drugs are only cytotoxic when tumor cells are proliferating rapidly, antioxidants would counteract the inhibitory effect of oxidative stress on cell proliferation. Conklin proposed that growth-inhibitory peroxidative stress induced by cancer itself, and to an even greater extent by antineoplastic agents used for cancer chemotherapy, can be overcome by antioxidants in cancer cells, primarily vitamin E in the cell membrane.²¹ In this case, individuals with poor antioxidant status would be expected to be less responsive to chemotherapy. *In vitro* and preclinical evidence suggests that dietary antioxidant supplements may enhance the response to chemotherapy and protect against chemotherapy-induced mutagenesis and toxic side effects.²¹ However, very few clinical studies have been designed to address the question of whether or not antioxidants enhance the cytotoxic effects of chemotherapeutic agents toward tumor cells in cancer patients.

Several other studies illustrate how antioxidant status might have an impact on the efficacy of chemotherapy. In a recent study, the influence of high-dose chemotherapy and parenteral nutrition on plasma antioxidant concentrations was evaluated.²² Although the sample size was small, high-dose chemotherapy administration resulted in an acute and significant decrease in plasma glutathione concentration that persisted for more than 14 days. However, the plasma glutathione peroxidase activity increased over time after high-dose chemotherapy; this was attributed to the increased need for peroxide detoxification of ROS induced by chemotherapy. Similarly, plasma α - and γ -tocopherol concentrations declined progressively and were lowest 14 days after chemotherapy. The authors concluded that parenteral nutrition formulations do not maintain plasma concentrations of essential antioxidants after bone marrow transplantation, and suggested antioxidant supplementation of these formulations.

In another investigation of a vitamin not traditionally associated with antioxidant action, 1,25-dihydroxyvitamin D₃ (the hormonal form of vitamin D) was assessed for combined cytotoxic action with doxorubicin in MCF-7 human breast cancer cells.²³ Doxorubicin is a chemotherapeutic agent used in the treatment of breast cancer (Table 1). The quinone moiety of doxorubicin is converted to a free radical in the cancer cell; in the presence of oxygen, this free radical forms superoxide anions, which have the potential to form OH radicals, ROS that are very cytotoxic to cancer cells. Because

Table 1. Commonly Used Chemotherapeutic Drugs

Alkylating Drugs	Antimetabolites	Topoisomerase Inhibitors	Antimicrotubule Drugs	Miscellaneous Drugs
Cyclophosphamide	Methotrexate	Etoposide	Vincristine	Bleomycin
Ifosfamide	5-Fluorouracil	Camptothecin	Vinblastine	Suramin
Melphalen	LY231514	Irinotecan	Vinorelbine	L-Asparaginase
Chlorambucil	Cytarabine	Topotecan	Paclitaxel	Amifostine
Cisplatin	Gemcitabine	Doxorubicin	Docetaxel	
Carboplatin	6-Mercaptopurine	Daunorubicin		
Procarbazine	Capecitabine			
Mitomycin C				

1,25-dihydroxyvitamin D₃ promotes the cytotoxic effect of tumor necrosis factor (TNF) in breast and renal cancer cells, and because superoxide mediates both TNF- and doxorubicin-induced cytotoxicity, the authors studied the effect of 1,25-dihydroxyvitamin D₃ on cell damage and death resulting from exposure to doxorubicin. They reported that treatment of breast cancer cells with 1,25-dihydroxyvitamin D₃ increased their susceptibility to the cytotoxic action of doxorubicin. A key finding was that the thiol antioxidant *N*-acetylcysteine had only a small protective effect against doxorubicin on its own, but the protective effect of *N*-acetylcysteine was markedly increased in the presence of 1,25-dihydroxyvitamin D₃. This suggests that ROS are involved in the interaction between 1,25-dihydroxyvitamin D₃ and doxorubicin. Because the cellular activity of Cu/Zn superoxide dismutase was decreased by 1,25-dihydroxyvitamin D₃, and because superoxide dismutase plays a key role in generation of ROS, the authors concluded that its blockage might be the mechanism by which 1,25-dihydroxyvitamin D₃ enhances doxorubicin cytotoxicity.

Notwithstanding the above results of various studies, other studies have demonstrated that antioxidant supplements may have the undesired effect of protecting cancer cells against apoptosis. Zeisel suggested that antioxidants may interfere with apoptosis, which is a process necessary for killing cancer cells.²⁴ Increased intake of antioxidants could therefore potentially inhibit apoptosis and block the killing of cancer cells by chemotherapy or radiotherapy. Salganik suggested that because ROS play a pivotal role in triggering apoptosis, antioxidants might inhibit apoptosis induction by chemotherapeutic agents by depleting ROS.²⁵ Studies demonstrated that the antioxidant α -tocopherol inhibits ROS generation and blocks apoptotic death of breast cancer cells induced by cisplatin.²⁵ This group also reported that ROS and apoptotic death of brain tumor cells was increased, and brain tumor volume was decreased, in transgenic mice depleted of antioxidants.²⁶ There is also some indication that antioxidants might inhibit the efficacy of chemotherapeutic drugs in patients.²⁷

In summary, *in vitro* studies to date suggest that

antioxidants have the potential to play an important role in enhancing the susceptibility of cancer cells to the cytotoxic action of chemotherapeutic drugs and other cancer therapies. There is a paucity of clinical studies to back up these *in vitro* results, however, and it has been proposed that if antioxidants act to repair cancer therapy-induced oxidative damage to cancer cells, then the potential exists for antioxidant vitamins to interfere with cancer therapy.^{27,28}

Folic Acid

As discussed above, Farber et al.¹² initially described the tumor growth-enhancing effect of folic acid in children with acute leukemia. These findings suggested that supplementing cancer patients with folic acid might not be prudent. Backus et al.²⁹ examined *in vitro* the effect of folic acid depletion on the sensitivity of colon cancer and head and neck squamous cell carcinoma cells, adapted over a period of 5 to 6 months to low-folate culture medium, to various anti-folate drugs. The investigators determined that folate depletion enhanced the sensitivity of the cell lines to the anti-folate drugs tested. However, the cell lines were adapted over months to low-folate conditions before treating them with the anti-folate drugs. This may be analogous to a cancer patient who becomes chronically depleted of folate before being treated with chemotherapeutic drugs. These results are supported by a recent study in *Apc*^{Min/+} mice that showed that folate depletion enhanced the efficacy of 5-fluorouracil against intestinal tumors.³⁰

There are studies, however, that suggest reducing folate levels may detrimentally affect chemotherapy efficacy. Mice bearing P388 lymphocytic leukemia tumors were significantly more sensitive to 5-FU, cytosine arabinoside, 6-mercaptopurine, and methotrexate when these drugs were given simultaneously with or subsequent to a large dose of folic acid.³¹ A study using C3H mammary-adenocarcinoma-bearing mice demonstrated that mice suffered a 3000-fold greater adverse toxicity rate, measured by lethality, to treatment with lometrexol (an antipurine antifolate agent) when they were fed a

low-folate diet. In mice fed the low-folate diet, lometrexol caused little, if any, inhibition of tumor growth. Supplementing the diet with folic acid not only improved the anti-tumor activity of lometrexol but also allowed the investigators to use doses of lometrexol that were significantly higher than those that had initially caused such profound toxicity.³² Another study using C3H mammary-adenocarcinoma-bearing mice on a folate-depleted diet demonstrated that tumor growth inhibition could be improved by 60% in comparison with control animals on a folate-replete diet when 5-FU was administered 1 hour after leucovorin (5-formyltetrahydrofolate). 5-FU treatment without leucovorin in the mice fed a folate-depleted diet was less effective than in control animals.³³ The general results of these animal studies have been confirmed in a phase I trial involving cancer patients supplemented with folic acid and given lometrexol.³⁴ Folic acid supplementation reduced the toxicity of the drug, which allowed the investigators to increase the dose of lometrexol used.

These studies involving folate modulation of anti-folate drug efficacy and toxicity have been extended to include cyclophosphamide, an alkylating agent.³⁵ Using the MADB 106 rat mammary tumor xenograft model, the investigators demonstrated that the anti-tumor activity of cyclophosphamide could be increased almost 50% in both animals fed a folate-replete diet and animals fed a folate-supplemented diet when compared with animals fed a low-folate diet. In addition, cyclophosphamide toxicity was greatly reduced in the animals fed the folate-replete diet, and there was an even greater reduction in toxicity when the animals were supplemented with folate. A more recent study by the same group, however, did not confirm these initial findings.³⁶

We recently showed that non-small cell lung cancer cells and ovarian cancer cells become intrinsically more resistant to cisplatin upon acute folate depletion (unpublished data, Whiteside, MA, University of Alabama at Birmingham, 2003). Interestingly, some cell lines were not susceptible to developing resistance to cisplatin upon acute folate depletion. Other cell lines, however, developed resistance in response to folate depletion in a dose-response or threshold-response manner. For example, some cells gradually developed more resistance to cisplatin as the level of folate was reduced from 100 ng/mL to 50 ng/mL and finally to 1 ng/mL, whereas other cells attained full resistance to cisplatin at 50 ng/mL with no further increase at 1 ng/mL. The differences in our results compared with those of Backus et al.²⁹ may be explained by the fact that our study evaluated the effect of acute folate depletion on chemotherapy sensitivity, whereas Backus et al. treated cells that had been adapted to chronic folate depletion over a period of months.

In summary, folate levels are known to affect the efficacy and toxicity of various chemotherapeutic agents in vitro and in animal models. The results are inconsistent and may be due to the type of drug used and/or to the model system chosen for the study. Few clinical studies have been done in this area.

Other Vitamins and Micronutrients

Micronutrients, including vitamins other than folate and the antioxidant vitamins, have not been extensively evaluated for their potential to modulate the efficacy of cancer therapy. However, many micronutrients have been assessed from the standpoint of how they affect chromosomal stability or generation of oxidative lesions in normal and cancer cells. For example, bone marrow cells of niacin-deficient rats treated with the chemotherapy drug etoposide, which induces DNA single- and double-strand breaks, had greater DNA damage than cells from rats fed a diet with adequate niacin.³⁷ Niacin is a dietary precursor of NAD, and NAD is in turn a substrate for poly (ADP-ribose) polymerase (PARP). Because PARP binds to and is activated by DNA single- and double-strand breaks, the increased damage due to niacin deficiency was attributed to inhibition of PARP activity.

Using an in vivo assay system, Caffrey and Frenkel demonstrated that the selenium compounds selenite and selenomethionine, administered near the time of cisplatin treatment, prevented the induction of cisplatin resistance.³⁸ A review of other studies relating micronutrient deficiency with DNA strand breaks and oxidative damage to DNA concluded that enhancement of micronutrient intake could have a significant positive effect on cancer risk.³⁹

Summary and Conclusions

Antioxidants have shown promise as agents that can enhance the cytotoxicity of anticancer agents in vitro, possibly by blocking generation of ROS and/or other mechanisms, but few investigations have evaluated their efficacy in cancer patients undergoing chemotherapy. The possibility remains that they could have deleterious effects by protecting cancer cells against apoptosis. Folate status is known to affect sensitivity to chemotherapeutic agents. Results are inconsistent, however, and some studies have shown enhanced sensitivity to chemotherapeutic agents with folate depletion, whereas others have shown that folate depletion promotes development of resistance to chemotherapeutic agents.

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 ther-

apeutic benefits have not been conclusively documented in cancer patients undergoing chemotherapy. A recent study reported that breast cancer-specific survival and disease-free survival times were shorter for breast cancer patients prescribed mega-doses of β -carotene, vitamin C, niacin, selenium, coenzyme Q10, and zinc in addition to standard therapies, relative to matched controls.⁴⁰ Until controlled studies of this type provide conclusive evidence that micronutrients are either beneficial or harmful to cancer patients, it is necessary to exercise caution in recommending micronutrient supplementation for these patients. Very few clinical trials have evaluated the efficacy of micronutrients in promoting the sensitivity of tumors to chemotherapeutic agents, and this is an area of future research that may improve the health and well being of cancer patients.

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