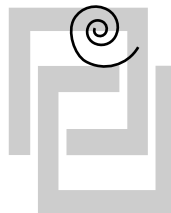


Dietary Supplements During Cancer Treatment

by Omer Kucuk, M.D., F.A.C.N., and Faith D. Ottery, M.D., Ph.D., F.A.C.N.



Many patients with cancer have nutritional deficiencies when they enter treatment due to poor diet and lifestyle factors or the metabolic effects of the cancer itself. These deficiencies can worsen during radiation therapy or chemotherapy because of the adverse effects these treatments have on the gastrointestinal tract and other organs. In addition, treatment-induced deficiencies of micronutrients (such as zinc; selenium; vitamins C, E, and A; and the carotenoids alpha-carotene, beta-carotene, cryptoxanthin, lutein, and lycopene), which have critical cellular functions, can cause significant morbidity and mortality and intensify the adverse side effects of chemotherapy and radiation.

Patients undergoing chemotherapy or radiation therapy who receive micronutrient supplementation usually do not develop these nutritional deficiencies and have less severe side effects from their treatment. Nutritional supplementation may also improve immune function, treatment outcome, and the patient's quality of life.

Because many micronutrients and phytochemicals are antioxidants, there is concern about whether they will inhibit the antitumor effect of radiation and chemotherapy. These compounds could theoretically have a tumor-protective effect, but there has been almost no clinical investigation of the problem, and very little data are available. Since dietary supplement and phytochemical use is common among cancer patients, there is a great need for clinical studies investigating the potential risks and benefits of using these compounds during chemotherapy and radiation therapy.

Epidemiological studies show an inverse relationship between cancer risk and the dietary intake of antioxidant micronutrients;¹ but placebo-controlled randomized clinical trials with these compounds have produced conflicting results. These conflicting results could be due to the fact that nutrients that are part of a healthy diet react synergistically with other nutrients that are ingested at the same time, and this synergy produces a number of positive effects that might not occur when a pharmacological dose of a single compound is taken during a clinical study. Dietary micronutrients are consumed in small quantities over a long period of time, whereas clinical trials typically administer a large quantity of a single micronutrient over a short period of time.

Many cancer patients have low antioxidant micronutrient levels at presentation. One reason for these nutritional deficiencies is the fact that cancer is a disease of aging and micronutrient deficiencies are common among older individuals. Monget and colleagues² found that the serum concentrations of most micronutrients were inversely associated with age and most elderly nursing home residents had low serum levels of vitamin C, zinc, and selenium.

Micronutrient deficiency may also be present in non-geriatric cancer patients. Donma and colleagues³ found reduced hair zinc levels in children with active cancer compared to healthy children and children with cancers in remission. Melichar and colleagues⁴ found an increased level of zinc excretion in the urine of cancer patients, which could be due to poor renal tubular

function. It may be that chemotherapeutic agents with renal tubular toxicity worsen the zinc deficiency in these patients.

MICRONUTRIENTS AND TOBACCO/ALCOHOL CONSUMPTION

Tobacco consumption is also a major risk factor for many human cancers and tobacco use has consistently been associated with increased oxidative stress and decreased serum antioxidant micronutrient levels.

Pamuk and colleagues⁵ reported on the relationship between current cigarette smoking and the serum concentrations of vitamins C, E, and A plus five carotenoids in 91 low-income, African-American women. Among smokers, serum concentrations of alpha-carotene, beta-carotene, cryptoxanthin, and lycopene averaged only 71 to 79 percent of the concentrations among non-smokers. Mean serum concentrations of vitamins C and E and lutein/zeaxanthin were only slightly lower among smokers than non-smokers. Among current smokers, mean serum concentrations of all five carotenoids decreased with increases in the amount smoked.

Ross and colleagues⁶ determined the concentrations of carotenoids, ascorbic acid, alpha-tocopherol, and gamma-tocopherol in the plasma of 50 male smokers and 50 age-matched men who had never smoked. Significantly less alpha-carotene, beta-carotene, cryptoxanthin, and ascorbic acid were found in the smokers' plasma than in the plasma of the men who had never smoked.

Pakrashi and Chatterjee⁷ measured the prostatic excretion of zinc in the ejaculates of 29 tobacco smokers, 25 tobacco chewers, and 30 nonusers of tobacco and found reduced levels of zinc in tobacco smokers compared to tobacco chewers and men who had never used tobacco.

Faruque and colleagues⁸ observed a lower dietary intake of vitamin C, carotenoids, and zinc and lower plasma level of vitamin C in 44 male students who smoked compared to 44 male nonsmoking students.

Alcohol consumption has also been associated with increased oxidative stress and decreased micronutrient levels and alcohol and tobacco in combination may result in even more severe micronutrient deficiencies than either one used alone.

Tsubono and colleagues⁹ examined the association between smoking, alcohol, and plasma levels of beta-carotene, alpha-carotene, lutein, lycopene, and zeaxanthin in 634 healthy men between the ages of 40 and 49. After controlling for age, serum cholesterol, serum triglycerides, body-mass index, green and yellow vegetables, and fruits, there was a significant inverse association between smoking and alcohol consumption and the plasma levels of beta-carotene and alpha-carotene. Only smoking reduced the level of lutein, and neither smoking nor alcohol significantly reduced the level of lycopene or zeaxanthin.

Brady and colleagues¹⁰ conducted a population-based study of 400 individuals and found an association between smoking and alcohol consumption and lower serum levels of alpha-carotene, beta-carotene, beta-cryptoxanthin, and lutein/zeaxanthin. Lower levels of serum lycopene were associated with older age.

Lecomte and colleagues¹¹ measured plasma carotenoid levels in 118 healthy men consuming low or moderate amounts of alcohol and 95 alcoholics. Beta-carotene, alpha-carotene, lutein/zeaxanthin, lycopene, and beta-cryptoxanthin levels were significantly lower in alcoholics, but 21 days after alcohol consumption was stopped, plasma levels of all the carotenoids increased.

Leo and colleagues¹² did not find a significant difference in the levels of carotenoids, retinol, and alpha-tocopherol found in the oropharyngeal mucosa of 11 chronic alcoholics with oropharyngeal cancer and 11 control subjects.

NUTRITIONAL STATUS AND MORBIDITY

Nutritional status is known to profoundly impact treatment morbidity, efficacy, and the eventual outcome of cancer patients.¹³⁻²⁰ For example, approximately 30 to 40 percent of patients with advanced-stage head and neck cancer have severe malnutrition, and an additional 20 to 30 percent have moderate malnutrition at the time of presentation.^{13,17} These patients frequently present with significant weight loss and chronic protein-calorie malnutrition, which may be exacerbated if tumor-induced dysphagia further reduces oral intake.^{13,17} Head and neck cancer patients with poor nutritional status are at increased risk for postoperative wound breakdown and infections, fistula formation, and flap loss.^{13,17}

Olmedilla and colleagues²¹ found that the plasma levels of carotenoids, retinol, and vitamin E were significantly lower in patients who had undergone a laryngectomy for laryngeal cancer than in healthy control subjects. After commercial enteral formula feeding, carotenoid levels further decreased and retinol and tocopherol levels increased, but all micronutrient levels remained lower than the corresponding levels in control subjects.²¹

Postoperative alterations of the upper aerodigestive tract may further compromise intake, increase metabolic demands, and compound nutritional deficiency.^{15,18} Since there are no known zinc stores in the human body, zinc deficiency develops quickly with malnutrition in these patients.²² Another potential contributor to zinc deficiency in head and neck cancer patients is alcohol use, which is common among patients who present with this disease. Alcohol intake is known to result in zinc deficiency.

Zinc deficiency causes a profound reduction in the activity of the thymic hormone thymulin. Prasad and colleagues²³ found decreased production of interleukin-2 and interferon-gamma by TH1 cells, reduced NK cell activity, and decreased recruitment of T cell precursors in zinc-deficient subjects.

Mocchegiani observed a significant increase or stabilization in the body weight of AIDS patients who received zinc supplements in addition to AZT. Zinc supplementation was also associated with an increase in CD4 cells and plasma thymulin and a decrease in the frequency of opportunistic infections.²⁴

Abdulla and colleagues²⁵ observed that plasma zinc was decreased and the copper/zinc ratio was significantly increased in patients with squamous cell carcinoma of the head and neck compared to healthy controls. The patients with a marked decrease in their plasma zinc

level died within 12 months. The authors suggested that plasma zinc and the copper/zinc ratio may be of value in predicting the prognosis of patients with head and neck cancer, but Garofalo and colleagues²⁶ found that these tests were not able to predict the prognosis of patients with squamous cell carcinoma of the head and neck.

THE NUTRITIONAL CONSEQUENCES OF RADIATION AND CHEMOTHERAPY

Both radiation therapy and chemotherapy have been associated with increased oxidative stress, which may further deplete tissue levels of antioxidant micronutrients, particularly in smokers and in the presence of inadequate dietary intake.

Faber and colleagues²⁷ measured lipid peroxidation, plasma glutathione and glutathione peroxidase activity, and plasma micronutrient levels in patients with cancer before and after doxorubicin-containing chemotherapy. The concentration level of lipid peroxidation products (measured as thiobarbituric acid reactant materials) in the plasma of cancer patients was higher than in controls, and the level increased still more after chemotherapy. These results indicate that the subjects had increased oxidative stress at presentation, which was further aggravated by doxorubicin treatment. Cancer patients had lower levels of glutathione, glutathione peroxidase, selenium, and zinc, but these were not further modified by chemotherapy.

Torii and colleagues²⁸ reported that doxorubicin treatment caused cardiomyopathy, increased lipid peroxidation, and lower alpha-tocopherol levels in the myocardium of spontaneously hypertensive rats.

The radiation of malignancies in the head and neck area results in a marked reduction in saliva flow and alterations in saliva composition within the first week of therapy, and impairs saliva flow throughout the duration of therapy. The decreased secretion of saliva may lead to symptoms such as oral pain and burning sensations, the loss of taste and appetite, and an increased incidence of oral disease. These symptoms can affect eating and increase the risk of inadequate nutritional intake.

Backstrom and colleagues²⁹ investigated the average nutritional intake of 24 patients treated for malignancies in the head and neck region who had dry mouth symptoms that had persisted for at least four months after the completion of radiation therapy. The average caloric intake was 1,925 calories in the irradiated patients with dry mouth symptoms and 2,219 calories in age- and sex-matched controls. The average intakes of vitamin A, beta-carotene, vitamin E, vitamin B6, folic acid, iron, and zinc were significantly lower in the irradiated patients than in controls.

EFFECTS OF MICRONUTRIENTS ON RADIATION AND CHEMOTHERAPY TOXICITY

Micronutrient use, including vitamin E, zinc, and selenium, has been shown to prevent or decrease treatment-induced toxicities.

Vitamin E. Many of the toxicities associated with chemotherapy and radiation therapy may be prevented with vitamin E supplementation. The protection afforded by vitamin E could be due to either its antioxidant

effect³⁰ or its immunomodulatory effects.³¹⁻³⁴ Vitamin E has effectively prevented chemotherapy-induced oral mucositis^{35,36} and may decrease doxorubicin cardiotoxicity without compromising the antitumor activity of the drugs.³⁷

Vitamin E selectively protects murine erythroid progenitor cells from chemotherapy toxicity³⁸ and prevents the severe toxicity caused by tumor necrosis factor.³⁹ It also has a selective antitumor effect against murine leukemia cells while protecting the murine bone marrow against the toxicity of doxorubicin.⁴⁰

Srinivasan and Weiss⁴¹ showed that alpha-tocopherol could protect mice against lethal radiation and enhance the effect of another radioprotective agent, WR-3689. Nattakom and colleagues⁴² observed complete resolution of the clinical and biochemical signs of severe hepatic dysfunction when they used vitamin E and glutamine to treat a 44-year-old woman who developed significant veno-occlusive disease after bone marrow transplantation.

In addition to its cardioprotective effect, alpha-tocopherol pretreatment prevented the development of doxorubicin-induced focal glomerulosclerosis and renal failure in an animal model.⁴³ Topical application of vitamin E was also very effective in promoting the healing of skin wounds caused by doxorubicin-induced skin necrosis.⁴⁴ In animals given an oral or topical vitamin E preparation prior to treatment with doxorubicin, dermal incision wounds healed much faster compared to control animals, suggesting that vitamin E may play an important role in postoperative wound healing, especially in doxorubicin-impaired wounds.⁴⁵

An oral preparation of Vitamin E was given concurrently with intravenous chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) in rats, and protected their intestinal membranes against chemotherapy-induced toxicity.⁴⁶ CMF-induced decreases in intestinal basolateral membrane levels of ATPases, alkaline phosphatase, 5'-nucleotidase and sulfhydryl groups, and increases in malondialdehyde levels were also restored to normal by the co-administration of vitamin E.

Vascular endothelial damage induced by intravenous cisplatin administration was prevented by vitamin E treatment in rats.⁴⁷ In the cisplatin plus vitamin E group, cisplatin-induced morphological changes in the endothelium were reversed and superoxide dismutase and Na/K-ATPase levels returned to normal.

Zinc. In a review article,⁴⁸ Sorenson said that copper, iron, manganese, and zinc complexes will protect lethally irradiated animals against radiation-induced immunosuppression, cell damage, and death. Srivastava and colleagues⁴⁹ have observed decreased platinum-induced nephrotoxicity and gastrointestinal toxicity in animals given a zinc-chelate of histidine before chemotherapy treatment.

Radiation therapy to the head and neck region frequently results in xerostomia and lack of taste. Abnormalities of taste have also been related to a deficiency of zinc in humans by several investigators.^{50,51} Decreased taste acuity (hypogeusia) has been observed in zinc-deficient subjects with liver disease, malabsorption syndrome, and chronic uremia, and after burns and

the administration of penicillamine. Chronically debilitated patients (such as cancer patients) also develop hypogeusia. Mahajan and colleagues⁵¹ conducted a double-blind study that revealed that zinc could improve taste acuity in subjects with chronic uremia.

Another neurosensory disorder, decreased dark adaptation, has also been connected to a deficiency of zinc.⁵² Warth and colleagues discovered that giving zinc to zinc-deficient sickle cell anemia patients with decreased dark adaptation will correct this abnormality.⁵² Decreased dark adaptation has recently been identified as the dose-limiting toxicity for fenretinide (4-

cysteamine were ineffective.⁵⁶ In vitro studies showed that benzylideneascorbate was a very effective antioxidant, scavenging both superoxide anions and hydroxyl radicals and preventing the auto-oxidation of linoleic acid.⁵⁶ Glutathione at biological concentrations decreased doxorubicin-dependent hepatic microsomal lipid peroxidation in rats, whereas acetylcystein had no effect.⁵⁷ This inhibition appears to be enzyme dependent and requires tocopherol. A similar mechanism has been observed in the microsomal membranes of the rat heart.⁵⁷

Geetha has reported the effects of doxorubicin on rat heart mitochondria^{58,59} and lysozymes.⁶⁰ Doxorubicin caused swelling, lipid peroxidation, and thiol depletion in vitro in rat mitochondria, and this effect was preventable by pretreating the animals with alpha-tocopherol.⁵⁸ In vivo chronic doxorubicin treatment decreased the activity of NADH-dehydrogenase, cytochrome-C-oxidase, and Na/K-ATPase in rat heart mitochondria, and this effect was prevented by the concurrent oral administration of alpha-tocopherol.⁵⁹ The in vivo effects of chronic doxorubicin treatment on rat heart lysosomes included a decrease in the activities of acid phosphatase, beta-D-glucuronidase, cathepsin D, and beta-D-galactosidase with a concomitant increase in microsomal lipid peroxide. These effects were also prevented when oral tocopherol was administered concurrently with doxorubicin.⁶⁰

Hida and colleagues⁶¹ showed that the stimulation of microsomal lipid peroxidation could be prevented in vitro by zinc, superoxide dismutase, alpha-tocopherol, and desferrioxamine; but glutathione, catalase, and selenium were not effective in preventing lipid peroxidation.

Miura and colleagues⁶² reported that doxorubicin inactivated the erythrocyte membrane enzymes Na/K-ATPase and Ca-ATPase during lipid peroxidation in vitro, and this effect was prevented by the administration of trolox (a water-soluble form of vitamin E) and butylated hydroxytoluene.

Nephrotoxicity. Cisplatin is a drug that is active against many cancers. Its dose is limited by severe nephrotoxicity and neurotoxicity, both of which can result in significant morbidity. Pre- and post-treatment hydration and mannitol-induced diuresis lowers the concentration of cisplatin in the kidneys and reduces its nephrotoxicity.

An alternative approach is the use of chemoprotectors. Selenium has been reported to reduce cisplatin-induced nephrotoxicity^{63,64} in addition to its known chemopreventive properties,⁶⁵ and sodium selenite protects rodents against cisplatin nephrotoxicity without reducing the drug's antitumor activity.⁶⁴

Vermeulen and colleagues⁶⁷ also concluded that sodium selenite protected rodents against cisplatin-induced nephrotoxicity without influencing the systemic availability of cisplatin. Reactions between cisplatin and the nucleophilic metabolites of selenite may be responsible for these protective effects.⁶⁶

Sadzuka and colleagues^{68,69} demonstrated that cisplatin-induced nephrotoxicity was closely associated with an increase in lipid peroxidation and a decrease in the activity of enzymes that protect against lipid peroxidation. Pretreatment with alpha-tocopherol and glutathione significantly decreased the amount of lipid

Antioxidant micronutrients can prevent the gastrointestinal toxicities of radiation and chemotherapy, doxorubicin-induced cardiotoxicity, and cisplatin-induced nephrotoxicity.

hydroxyphenylretinamide), a cancer chemopreventive retinoid compound currently under intensive clinical investigation. Clinical trials could be conducted with zinc and fenretinide to determine if the combination of the two substances can decrease fenretinide toxicity and enhance its chemopreventive activity at the same time.

PREVENTION OF TOXICITY

Antioxidant micronutrients can prevent the gastrointestinal toxicities of radiation and chemotherapy, doxorubicin-induced cardiotoxicity, and cisplatin-induced nephrotoxicity.

Oral and gastrointestinal toxicity. Antioxidant micronutrients prevent the gastrointestinal toxicities of radiation and chemotherapy. Mills reported that beta carotene decreases the oral mucositis that is induced by chemotherapy and radiation therapy,⁵³ and Klimberg and colleagues⁵⁴ observed a protective effect of glutamine on the small bowel mucosa of rats receiving abdominal radiation. Carroll and colleagues⁵⁵ found that a variety of antioxidant compounds and micronutrients (including ribose-cystein, amifostine, glutamine, vitamin E, and magnesium chloride/ATP) prevented radiation-induced small bowel and large bowel injury in rats.

Cardiotoxicity. Various micronutrients and micronutrient compounds have been used to prevent doxorubicin-induced cardiotoxicity. In an animal model, benzylideneascorbate protected against doxorubicin-induced cardiotoxicity but ascorbate, 6-palmitoylascorbate, and

peroxides produced in the kidney by the administration of cisplatin.⁷⁰

Sugihara and colleagues^{71,72} found that alpha-tocopherol prevented the lipid peroxidation and nephrotoxicity induced by cisplatin in rodents, and Bogin and colleagues⁷³ reported that pretreatment with a combination of cysteine and alpha-tocopherol is protective against the nephrotoxicity and biochemical changes induced by the administration of cisplatin in rats.

MICRONUTRIENTS AND THE ANTITUMOR VS TUMORIGENIC EFFECTS OF RADIATION AND CHEMOTHERAPY

The mechanism of action of radiation therapy and some chemotherapeutic agents involves the generation of toxic oxygen free radicals. Supplementing patients with antioxidant micronutrients during therapy may potentially interfere with the antitumor effects of the treatment. Fortunately, many of the antioxidants have been found to prevent treatment toxicity without reducing the efficacy of radiation or chemotherapy, and certain micronutrients have antitumor effects of their own, including inhibiting cancer cell proliferation and inducing malignant cells to differentiate and divide properly.

Vitamin E inhibits growth and causes morphological changes in several tumor cell lines in tissue culture.^{74,75} Animal studies and clinical trials have demonstrated the chemopreventive^{76,77} and antineoplastic activities^{78,79} of vitamin E, and a number of experimental studies suggest that vitamin E can enhance the growth inhibitory effect of various cancer treatment modalities such as radiation, chemotherapy, and hyperthermia.⁷⁴ At some doses, vitamin E enhanced the tumor killing properties of irradiation.⁸⁰

Prasad and colleagues⁸¹ observed the growth inhibitory effects of vitamin C alone, vitamin E alone, and combinations of vitamin C, vitamin E, beta-carotene, and 13-cis-retinoic acid on SK-30 melanoma cells in vitro. They also found that ascorbic acid, alone or in combination with beta-carotene, vitamin E, and 13-cis-retinoic acid, enhanced the growth-inhibitory effect of cisplatin, dacarbazine, tamoxifen, and interferon-alpha 2b.

Certain micronutrients have chemopreventive properties and may play a role in the prevention of radiation- and chemotherapy-induced cancers.

Krishnaswamy and colleagues⁸² produced a 57 percent complete remission rate for oral preneoplastic lesions in 150 subjects by administering a multivitamin capsule containing vitamin A, riboflavin, zinc, and selenium twice weekly for one year.

Satoh and colleagues⁸³ reported that increasing the level of pulmonary metallothionein by giving animals zinc or bismuth compounds could prevent the development of lung cancer in mice that received repeated injections of cisplatin and melphalan. Zinc aspartate administration potentiated the radioprotective effect of diltiazem in mice given lethal doses of radiation,⁸⁴ and the combination of zinc aspartate with amifostine, an antioxidant compound, conferred protection against the lethal effects of radiation and the development of radiation-induced lymphomas in mice.⁸⁵

The oral administration of vitamins A and E in

conjunction with FEMTX (fluorouracil, epirubicin, methotrexate) chemotherapy in patients with unresectable or metastatic gastric cancer did not appear to reduce the antitumor activity of the chemotherapeutic agents.⁸⁶ Glutathione administration protected rodents against both the renal and lethal toxicity of cisplatin, but did not interfere with the drug's antitumor activity.⁸⁷ Small clinical studies similarly found that glutathione had a protective effect against the renal toxicity of cisplatin^{88,89} with no reduction in its antitumor activity.⁸⁹

Di Re and colleagues⁹⁰ confirmed these results in a larger series of 40 patients with ovarian cancer who were treated with high-dose cisplatin and cyclophosphamide plus pre- and post-treatment glutathione. The glutathione had a significant protective effect against renal toxicity with no effect on antitumor activity.

Oral glutamine supplementation enhances the sensitivity of the tumor cells to methotrexate chemotherapy while protecting normal cells from methotrexate's adverse effects.

Rouse and colleagues⁹¹ hypothesized that intravenous glutamine would protect liver cells from oxidant injury by increasing their intracellular glutathione content, and thought that supplemental oral glutamine would increase the therapeutic index of methotrexate by improving host tolerance through changes in glutathione metabolism. Giving rats with implanted fibrosarcomas being treated with methotrexate a glutamine-rich diet decreased tumor glutathione and increased the antitumor effect of methotrexate, while maintaining or increasing host glutathione stores.⁹² Significantly decreased glutathione levels in tumor cells correlated with their susceptibility to methotrexate and tumor shrinkage in animals that received the combination of glutamine and methotrexate.

Unfortunately, zinc has been shown to interfere with the antitumor activity of cisplatin by increasing metallothionein synthesis, which in turn increases the amount of cisplatin that the body can eliminate.⁹³ C3H mice inoculated with bladder tumors (MBT-2) were given cisplatin and zinc sulfate, and reductions in both renal toxicity and the antitumor activity of cisplatin were observed.⁹³

COMBINING NUTRITIONAL AND PHARMACEUTICAL COMPOUNDS TO PREVENT TOXICITY

Certain pharmaceutical compounds have been used for the prevention and treatment of the toxicities caused by chemotherapy and radiation therapy. Thiosulfate, calcium channel blockers, bismuth, glycine, cimetidine, and probenecid⁶³ have been used to prevent the nephrotoxicity of cisplatin.

Floersheim⁸⁴ reported that mice were protected against lethal dose of radiation by diltiazem and other calcium channel blockers such as nifedipine and nimodipine, and that synergistic effects occurred when diltiazem was combined with zinc aspartate, dimethyl sulfoxide, and nifedipine. In another study, Floersheim and colleagues⁸⁵ found that small doses of zinc aspartate and amifostine also protected mice against lethal radiation.

George and colleagues⁹⁴ have shown that pretreat-

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Antioxidant Use During Radiation or Chemotherapy: A Summary

by Kathleen Mayer, M.S., R.D., and Maree Ferguson, Ph.D., R.D.

Use of antioxidants during cancer therapy is widely discussed, and at times debated, by clinicians, researchers, and patients. Many patients with cancer are using alternative nutritional methods alone or as a complement to standard therapies to treat their disease. Controversy exists in the literature regarding whether the use of antioxidants, such as vitamins A, C, E, beta-carotene, and selenium, inhibits or enhances the antitumor effects of radiation and chemotherapy.¹ Discussion centers around general use during therapy, dosing (meeting requirements versus pharmacologic doses), and timing of antioxidant use (prior, during, and after the specific antineoplastic intervention). An extensive review is available in the supplement but the general issues are summarized here.


Radiation and certain types of chemotherapy agents promote oxidation and free-radical production as part of their tumoricidal effect. Some researchers have suggested that pharmacologic doses of antioxidants may protect the tumor, thereby decreasing the effectiveness of the cancer therapy.² The impact of antioxidants on the effectiveness of cancer therapies depends on the type and dosage of the antioxidant and the therapeutic agent involved, as well as the tumor type.³ However, the evidence that antioxidants actually decrease the antitumor effects of cancer therapies is limited.^{3,4} Much of the available information is speculative or anecdotal.¹

Other researchers have indicated that antioxidants actually enhance radiation and chemotherapy by increasing tumor response to therapy and decreasing toxicities.^{5,6} These researchers have indicated that antioxidant administration, in both animal and human studies, did not reduce the efficacy of radiation or chemotherapy. Because the antioxidants protect healthy cells against free radical damage, there were actually fewer adverse events when antioxidants were provided.⁷ The specifics of dose and timing are important variables in study design and clinical intervention. Several studies have found that antioxidants can prevent some of the negative side effects resulting from treatment with antineoplastic agents.⁵ Antioxidant nutrients have been shown to prevent chemotherapy-induced oral mucositis and gastrointestinal toxicity, cisplatin-induced nephrotoxicity, and doxorubicin-induced cardiotoxicity without inhibiting the antitumor effects of these agents.⁸ Certain antioxidants, such as vitamin E, may also prevent chemotherapy toxicities due to immunomodulating properties.⁸ One study even demonstrated prolonged survival among patients who received antioxidants in combination with radiation and chemotherapy.⁹ No studies have examined the long-term effects of using antioxidants in combi-

nation with radiation and chemotherapy in humans.^{2,4}

The following information should be considered with respect to taking antioxidants during radiation or chemotherapy:

- Patients with cancer, especially those undergoing therapy, have reduced food intake. Many of these patients do not meet the recommended daily intake for many nutrients. Studies have shown that patients with cancer have lower levels of plasma antioxidants than patients without cancer.⁸ Therefore, patients with cancer may be deficient in several important nutrients, and vitamin and mineral requirements must be considered.
- No recommended minimum or maximum levels of antioxidants exist for patients with cancer during radiation and chemotherapy.
- Antioxidant dosing used in animal and clinical research studies are much higher (pharmacologic doses) than the levels found in foods or oral medical nutritional supplements.
- Critical questions in the area are under investigation.

A comprehensive review of this topic can be obtained by referring to the designated articles referenced.^{2,3,4,6,8,10} 

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ment with a combination of 5-hydroxy-L-tryptophan (5-HTP) and 2-aminoethyl isothiuronium bromide hydrobromide (AET) prior to total body irradiation protected mice against radiation-induced oligospermia and infertility.

Somani and colleagues⁹⁵ observed that mice given cisplatin had increases in their creatinine levels and decreases in the amount of glutathione in their kidneys. Both of these effects were prevented by giving the rats diethylthiocarbamate at the same time that cisplatin was administered.

The phosphorothioate amifostine has recently been approved for the prevention of cisplatin toxicity in humans. Its ability to prevent radiation toxicity and the toxicities of other chemotherapeutic agents is under investigation.

Phosphorothioates have toxicities of their own that limit their use, and it has been proposed that combining other agents with phosphorothioates may improve their efficacy and/or lower their toxicity.⁹⁶ Since zinc aspartate and the combination of zinc aspartate with amifostine protect normal tissue from radiation better than tumor tissue,⁹⁷⁻⁹⁹ further clinical studies should test low-dose amifostine and zinc combinations to see if they can prevent radiation toxicity so high-dose amifostine, with its associated side effects, can be avoided.

Hamers and colleagues¹⁰⁰ found that pretreatment with reduced glutathione protected rats against cisplatin-induced neuropathy without interfering with the drug's antitumor activity. Metallothionein induction by bismuth subnitrate has been reported to prevent cisplatin and doxorubicin toxicity,¹⁰¹ although Sadzuka and colleagues found no protective effect by bismuth subnitrate in their experiments.⁷⁰

Storm and colleagues¹⁰² found that mice were protected from the toxic cellular effects of radiation when they were fed a diet containing 2 percent squalene prior to and after receiving a lethal dose of whole body radiation. Irradiated mice fed squalene had significantly higher white cell and lymphocyte counts, better jejunal histology, and longer survival times than the control group.

CONCLUSIONS

Micronutrient supplementation may prevent the adverse effects of cancer chemotherapy and radiation therapy without interfering with their antitumor capabilities, resulting in an improved quality of life for cancer patients. Certain dietary supplements may enhance the antitumor effect of radiation and chemotherapy while protecting normal tissues from their adverse effects. However, caution should be exercised at this time regarding the concurrent use of antioxidant dietary supplements with chemotherapy and radiation because of the lack of data from well-designed randomized clinical trials about the effect of antioxidants on the potency of anticancer therapies. There is a great need for clinical trials that investigate the potential risks and benefits of supplementation with micronutrients and phytochemicals during cancer therapy. ☐

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