ORIGINAL RESEARCH

ANTIOXIDANTS AND OTHER NUTRIENTS DO NOT INTERFERE WITH CHEMOTHERAPY OR RADIATION THERAPY AND CAN INCREASE KILL AND INCREASE SURVIVAL, PART 1

Charles B. Simone II, MD; Nicole L. Simone, MD; Victoria Simone, RN; Charles B. Simone, MD

Purpose • Some in the oncology community contend that patients undergoing chemotherapy and/or radiation therapy should not use food supplement antioxidants and other nutrients. Oncologists at an influential oncology institution contended that antioxidants interfere with radiation and some chemotherapies because those modalities kill by generating free radicals that are neutralized by antioxidants, and that folic acid interferes with methotrexate. This is despite the common use of amifostine and dexrazoxane, 2 prescription antioxidants, during chemotherapy and/or radiation therapy.

Design • To assess all evidence concerning antioxidant and other nutrients used concomitantly with chemotherapy and/or radiation therapy, the MEDLINE® and CANCERLIT® databases were searched from 1965 to November 2003 using the words *vitamins, antioxidants, chemotherapy,* and *radiation therapy*. Bibliographies of articles were searched. All studies reporting concomitant nutrient use with chemotherapy and/or radiation therapy (280 peer-reviewed articles including 62 in vitro and 218 in vivo) were indiscriminately included.

Results • Fifty human clinical randomized or observational trials have been conducted, involving 8,521 patients using beta-carotene; vitamins A, C, and E; selenium; cysteine; B vitamins; vitamin D_3; vitamin K_3; and glutathione as single agents or in combination.

Conclusions • Since the 1970s, 280 peer-reviewed in vitro and in vivo studies, including 50 human studies involving 8,521 patients, 5,081 of whom were given nutrients, have consistently shown that non-prescription antioxidants and other nutrients do not interfere with therapeutic modalities for cancer. Furthermore, they enhance the killing of therapeutic modalities for cancer, decrease their side effects, and protect normal tissue. In 15 human studies, 3,738 patients who took non-prescription antioxidants and other nutrients actually had increased survival. (*Altern Ther Health Med*. 2007;13(1):22-28.)

Charles B. Simone II, MD, and Nicole L. Simone, MD, are consulting physicians, Victoria Simone, RN, is a research nurse, and Charles B. Simone, MD, is a consulting physician and medical director, all at the Simone Protective Cancer Institute in Lawrenceville, NJ.

Editor's note: The following is part 1 of a 2-part article. Part 2 will appear in the March/April 2007 issue of Alternative Therapies in Health and Medicine.

Two of every 5 Americans will develop cancer, and the incidence of most cancers has increased annually since 1930.[1-5] In addition, since 1930, despite the use of radiation therapy, chemotherapy, immunotherapy, and improved surgical and diagnostic techniques, there has been limited improvement in cancer survival rates for most adult cancers.[1-5] Chemotherapy and radiation therapy, however, continue to have a large role in cancer treatment but produce great morbidity. Two prescription medicines, amifostine and dexrazoxane, both antioxidants, reduce cancer therapy side effects without interfering with antitumor killing. Amifostine (WR-2721) is an antioxidant analog of cysteamine that was discovered by the armed forces at Walter Reed Army Medical Center, Washington, DC, and became the first antioxidant agent to be approved by international regulatory agencies.[6] According to 29 studies, amifostine reduces side effects and increases response rates of chemotherapy and radiation therapy without interfering with their antitumor killing activity.[6-18] Twenty-one studies indicate that dexrazoxane (ICRF-187) protects the heart from adriamycin toxicity without interfering with the antitumor effect[19-22] by chelating iron that would otherwise form free radicals.[23-26]

Despite the common use of amifostine and dexrazoxane, and in direct opposition to clear scientific findings since the 1970s,

many patients have been told not to use food supplement antioxidants and other nutrients while undergoing chemotherapy and/or radiation therapy because there is an erroneous but seemingly logical belief that antioxidants interfere with radiation and some chemotherapies because those modalities kill by generating free radicals that are neutralized by antioxidants, and another erroneous belief that folic acid interferes with methotrexate.[27-32]

In an article that appeared on the front page of *The New York Times* on October 26, 1997, Larry Norton, MD, of Memorial Sloan Kettering Cancer Center, New York, was quoted as saying, "Research at [Memorial Sloan Kettering] showed that large doses of vitamin C could blunt the beneficial effects of chemotherapy for breast cancer. . . . It is also known that folic acid can negate the effects of methotrexate, a drug used to treat cancer."[27] The research referred to was finally published almost 2 years later and demonstrated only the mechanism by which cancer cells obtain vitamin C and that more vitamin C was found in mice cancer cells compared to normal mice cells.[29] However, the senior author of that paper stated in a news release on the day of publication (September 15, 1999), "It's possible that taking large amounts of vitamin C could interfere with the effects of chemotherapy or even radiation therapy."[30] So a single interview in *The New York Times* in 1997 that was not based on published scientific work and a single research paper involving mice, along with a press release by its author in 1999, led to the erroneous notion that vitamin C interferes with chemotherapy and radiation in humans. This notion soon applied to all antioxidants as physicians, patients, the media, the American Cancer Society,[31,32] and scores of websites took the same position without reviewing the scientific evidence.

This 2-part article presents the scientific data that antioxidants do not interfere with chemotherapy and/or radiation therapy. Furthermore, it is not folic acid that interferes with the action of methotrexate, but rather folinic acid, a prescription drug that is neither a vitamin nor an antioxidant.[33-35] This article reviews data about vitamin A, beta-carotene, and vitamin E. Part 2 will review data about antioxidant combinations, B vitamins, vitamins D_3 and K_3, and the glutathione-selenium complex.

METHODS

MEDLINE® and CANCERLIT® searches were done using key words: vitamins, antioxidants, chemotherapy, and radiation therapy. All studies reporting food supplement nutrients used concomitantly with chemotherapy and/or radiation therapy were indiscriminately included; however, in cases in which an author had published his or her findings in multiple sources, only the most recently published paper was used as it usually contained the greatest number of patients.

BACKGROUND

Radiation and certain chemotherapies produce cellular kill by generating free radicals; antioxidants neutralize free radicals and the oxidative reactions that are caused by free radicals (Table 1).

Other nutrients are included in this review. B vitamins enhance the immune system and protect normal cells from the harm of radiation and other destructive mechanisms. Glutathione peroxidase, a selenium-containing antioxidant enzyme complex, protects the cell from free-radical injury. Glutathione peroxidase is easier to measure than selenium and has the advantage of assessing only biologically active selenium. Vitamin A and retinoids have anti-cancer effects, repair normal cells, and modulate the growth and differentiation of malignant cells. Vitamin D_3 inhibits cancer cell proliferation and replication, induces differentiation of leukemia cells, inhibits the oncogene c-*myc*, and enhances the immune system. Vitamin K_3 (menadione) inhibits cell growth, cell proliferation, DNA synthesis, and the cell cycle. Vitamin K_3 acts on apoptosis through expression of c-*myc* and c-*fos* proto-oncogenes and lowers intracellular pools of reduced glutathione.

TABLE 1 Agents That Generate or Neutralize Free Radicals

Generate Free Radicals	Antioxidants (Neutralize Free Radicals)
Alkylating Agents	Amifostine
Alkyl sulfonate—busulfan	Carotenoids—beta-carotene, lutein, lycopene
Ethylenimine derivative—thiotepa	Coenzyme Q10
Metal salt—cisplatin, carboplatin	Dexrazoxane
Nitrogen nustard—chlorambucil, estramustine, cyclophosphamide, ifosfamide, melphalan	Glutathione-selenium complex
Nitrosourea—carmustine	N-acetyl cysteine
Triazine—dacarbazine	Selenium
	Vitamin C
Natural Products	Vitamin E
Antibiotic—bleomycin, dactinomycin, daunorubicin, doxorubicin (adriamycin), idarubicin, mithramycin, mitomycin, mitoxantrone	
Podophyllum derivative—etoposide, teniposide	
Other—procarbazine	
Radiation—all forms	

Effects of Chemotherapy and Radiation Therapy on Serum Nutrient Levels

Cancer patients suffer from caloric and nutritional malnutrition and have vitamin deficiencies, particularly of folic acid, vitamin C, pyridoxine, and other nutrients because of poor nutrition and treatment.[38] Chemotherapy and radiation therapy reduce serum levels of antioxidant vitamins and minerals due to lipid peroxidation and thus produce higher levels of oxidative stress.[36-66] Iron could be the intermediate cause of this oxidative stress.[20-23] Therefore, supplemental iron should not be recommended to cancer patients who have anemia unless it is an iron-deficiency anemia.

Early Studies

Five early studies showed that N-acetyl cysteine, an antioxidant, protects the heart from the cardiac toxicity of adriamycin without interfering with the tumor-killing capability of adriamycin.[67] Seven cellular studies,[68-70] 22 animal studies,[71-75] and human studies[76-78] have demonstrated that vitamins A, E, C, and K, as well as beta-carotene and selenium—as single agents or in combination—all protect against the toxicity of adriamycin and actually enhance its cancer-killing effects.

Cellular and Animal Studies

Fifty-one cellular[79-88] and 81 animal studies[89-110] using nutrients that include vitamins A, B_6, B_{12}, C, D, E, and K, beta-carotene, other retinoids, selenium, or cysteine as single agents or in combination given concomitantly with chemotherapy, radiation, or combinations of these modalities show the same effect—no interference, increased protection of normal tissues, increased tumor killing, and, in some studies, increased animal survival.

Observational Versus Randomized Clinical Studies

Compared to randomized studies, observational studies are less costly, can be done more quickly, and have a broader range of patients. Observational studies provide valid information and virtually the same results as randomized studies, a finding that differs from previous conclusions.[111,112] Furthermore, "Observational studies do not overestimate the magnitude of the effects of treatment compared with those in randomized trials on the same topic."[113(p1887)] In this 2-part article, we will summarize 50 human studies, 36 observational and 14 randomized, that reported concomitant nutrient use with chemotherapy and/or radiation therapy.

Review of Human Studies

Fifty human studies, involving 8,521 patients, have been conducted using single or multiple nutrients in combination with systemic treatment and/or radiation treatment and demonstrate that nutrients do not interfere with treatment. In fact, 47 of these 50 studies indicated that nutrients decrease side effects of treatment, and the other 3 studies showed no difference. In addition, many of the studies reported that nutrients produce higher response rates and higher survival rates when administered concomitantly with chemotherapy and/or radiation therapy. This part of the 2-part article reviews data about vitamin A, beta-carotene, and vitamin E.[114-130]

VITAMIN A (RETINYL PALMITATE)

In a randomized study of 100 postmenopausal patients with metastatic breast carcinoma undergoing chemotherapy (cyclophosphamide, 5-fluorouracil, bleomycin, adriamycin, mitomycin), patients were given daily doses of vitamin A (350,000-500,000 IU, according to body weight). Vitamin A—which many people erroneously believe is an antioxidant—significantly increased the complete response rate, duration of response, and projected survival.[114]

In an observational study of 275 patients with head and neck cancer, patients were treated with 5-fluorouracil and cobalt-60 radiation, as well as vitamin A. Vitamin A enhanced the cellular sensitivity to irradiation, increased treatment response rate, and lowered toxic side effects.[115]

In a randomized study of 153 patients with chronic myelogenous leukemia (CML), patients were randomized to receive pulse oral busulfan with or without the daily administration of oral vitamin A (50,000 IU). Patients receiving only busulfan had a shorter survival, with a 42% greater risk of death. In addition to increasing survival, vitamin A decreased side effects and increased treatment response rate.[116]

In an observational study of 40 patients with stage IIIB or stage IV non-small cell lung cancer, patients were treated with cisplatin (120 mg/m^2 divided into 5 days), vindesine (3 mg/m^2 on days 1 and 5), 5-flourouracil (500 mg/m^2 on days 1 and 5), beta-interferon (1 million IU 3 times a week), and retinyl palmitate (50,000 IU twice a day). Vitamin A produced fewer side effects, a higher response rate, and increased survival compared to historical controls.[117]

In an observational study, 23 patients with unresectable or recurrent advanced oral cavity cancer were treated with 5-flourouracil (1,000 mg/m^2) and cisplatin (20 mg/m^2) for 5 days. Vitamin A (15,000 IU twice a day) was also given throughout the treatment. Vitamin A decreased side effects, increased response rate, and slightly increased survival.[118]

In an observational study of 36 patients with stage IV breast cancer, patients were treated with cyclophosphamide, 5-flourouracil, 4-epidoxorubicin, vincristine, and prednisone every 3 weeks for 6 courses, followed by 2 courses of methotrexate, mitomycin-C, and mitoxantrone. Treatment continued with tamoxifen and vitamin A. Sixty-four percent of patients had a clinical response, 19% had stable disease, and side effects were minimal. Median overall survival was 32 months. These results compare favorably with historical controls.[119]

In an observational study of 22 patients with unresectable and/or metastatic pancreatic cancer, patients were treated with folinic acid (200 mg/m^2), 5-flourouracil (370 mg/m^2), epirubicin (60 mg/m^2), mitomycin-C (10 mg/m^2), interferon (1 million IU/m^2 3 times a week), and vitamin A (50,000 IU twice a day). Response rates and survival were similar to historical controls.[120]

In an observational study of 49 patients with metastatic breast cancer, 33 were treated with tamoxifen (30 mg/d), interferon (1 million IU 3 times a week), and vitamin A (15,000 IU twice a day). Sixteen patients were treated with tamoxifen (30 mg/d), interferon (3 million IU 3 times a week), and vitamin A (50,000 IU twice a day). There was no statistically significant difference in the response rate, response duration, or survival in the 2 groups treated with different dose levels of vitamin A and interferon. Compared to the Surveillance, Epidemiology, and End Results (SEER) Program data of the National Cancer Institute, however, these patients had a higher response rate and longer survival with fewer side effects.[121]

BETA-CAROTENE

In a randomized study of 20 patients with advanced squamous carcinoma of the mouth, patients were given 60 Gy cobalt radiation therapy in 30 fractions. The week before and after radiation, and also during the third and sixth weeks of radiation, patients were given synchronous injections of chemotherapy consisting of vincristine (2 mg), methotrexate (200 mg), and bleomycin (30 mg). Patients were randomized to receive supplemental beta-carotene (250 mg for days 1-21; 75 mg daily thereafter). No toxic side effects of beta-carotene were observed. Patients who received supplemental beta-carotene had less severe acute mucosal reactions.[122]

In an observational study of 15 patients treated with chemotherapy for various advanced cancers, patients were given chemotherapy/radiation therapy and beta-carotene. Beta-carotene decreased side effects and allowed for a longer than expected disease-free interval in all surviving patients.[123]

VITAMIN E (ALPHA-TOCOPHEROL)

In an observational study of 66 patients with transfusion-dependent myelodysplastic syndrome, patients received either high-dose 13-cis-retinoic acid only or high-dose 13-cis-retinoic acid with alpha-tocopherol. Patients who received alpha-tocopherol had decreased measures of skin and constitutional toxicities and were able to achieve longer treatment continuation with 13-cis-retinoic acid. As a result, fewer of these patients experienced progression to acute leukemia (28%) when compared to patients who received 13-cis-retinoic acid only (60%). A 2-fold increase in median survival also was observed in the group treated with vitamin E.[124]

In an observational study of 39 patients with head and neck, skin, or lung cancer, study participants were treated with high-dose 13-cis-retinoic acid (100 mg/m^2 orally per day) and alpha-tocopherol administered in escalating dose schedules of 800, 1200, 1600, and 2000 IU per day for each subsequent 4-week treatment cycle. Over a 3-month period, patients experienced fewer grade 2 and grade 3 toxicities from high-dose 13-cis-retinoic acid without altering its plasma concentration.[125]

In an observational study of 17 patients with myelodysplasia, patients were treated with all-trans-retinoic acid (45 mg/m^2 in 2 divided doses), granulocyte colony-stimulating factor (started at 1 microgram/kg per day), erythropoietin (5,000 IU per day starting on day 2), and vitamin E (400 IU per day). Vitamin E reduced the toxicity and increased the response rate without affecting the performance of all-trans-retinoic acid.[126]

In an observational study involving 1 patient, the patient developed a skin carcinoma in a chest wall scar from having a mastectomy and radiation therapy 17 years earlier. After surgical excision of the carcinoma, she was treated with radiation therapy to the site. She also was given a vasodilator (pentoxifylline 1,200 mg/d) and vitamin E (400 IU per day) in an attempt to reduce the new scar formation. The authors concluded that vitamin E decreased the side effects of radiation, and the skin condition began to improve by the fourth month.[127]

In an observational study of 21 patients with metastatic breast cancer, patients had endomyocardial biopsies and were given alpha-tocopherol orally at 2 g/m^2 daily starting 7 days before cyclophosphamide, adriamycin, and 5-fluorouracil administration. Vitamin E did not compromise the antitumor activity of the chemotherapy. Fifteen of 21 achieved an objective response—similar to the authors' previous experience. Vitamin E allowed for an additional 100 mg/m^2 of adriamycin to be given, but the authors stated that vitamin E did not protect the heart.[45]

In a randomized study of 12 patients with metatstatic breast cancer, patients were treated with doxorubicin as an intravenous bolus infusion (60 mg/m^2), and 6 were randomized to receive 200 mg alpha-tocopherol given intramuscularly 6 hours before infusion and 60 mg nifedipine given orally each day for 2 days before treatment. A higher response rate was achieved and cardiac toxicity was prevented in those who received vitamin E and nifedipine.[46]

In a randomized study of 20 patients with acute myelogenous leukemia, patients were given vitamin E daily and treated with induction chemotherapy (10 patients) and intensive chemotherapy followed by bone marrow transplantation (10 patients). Vitamin E increased treatment response rate and prevented mucositis—an inflammatory response of the oral cavity caused by radiation therapy—especially during induction therapy for acute myelogenous leukemia.[128]

In a randomized study of 18 patients with various cancers, patients received chemotherapy appropriate for their cancer site and were randomized to receive either placebo oil or topical vitamin E (400 IU/cc) to control mucositis. For the 16 patients with head and neck cancer, 5-fluorouracil (1,000 mg/m^2 as a continuous infusion for 5 days) and cisplatin (100 mg/m^2 on day 2) were given. For the patient with hepatocellular carcinoma, doxorubicin (45 mg/m^2 every 3 weeks) was given. The patient with acute myelogenous leukemia (AML) received Ara-C (100 mg/m^2/d for 7 days) and doxorubicin (45 mg/m^2 on days 1-3). Oral mucositis lesions were observed daily before and 5 days after the application of either vitamin E or placebo oil. Vitamin E prevented chemotherapy-induced mucositis. In fact, whereas only 1 of 9 patients receiving placebo achieved complete resolution of their oral lesion, 6 of 9 patients receiving vitamin E achieved complete resolution.[129]

In a randomized study of 16 patients with various cancers, all participants were treated with a regimen containing adriamycin appropriate for the cancer site. Seven were randomized to receive 1,800 IU tocopherol daily starting 24 hours before adriamycin administration and continuing for at least 1 week after adriamycin administration. Vitamin E did not interfere with chemotherapy but also did not protect against cardiac toxicity.[47]

Sixteen evaluable cancer patients in an observational study of 18 patients receiving adriamycin were given dl-alpha-tocopherol acetate (1,600 IU a day) to determine whether vitamin E would protect against alopecia (hair loss), which occurs in virtually all patients receiving adriamycin. Sixty-nine percent of patients given adriamycin and vitamin E did not have alopecia.

Furthermore, a correlation was found between the time vitamin E was taken and the degree of alopecia. Most patients who began taking tocopherol more than 72 hours before chemotherapy treatment did not have alopecia.[130]

SUMMARY

These studies show that vitamin A, beta-carotene, and vitamin E do not interfere with and actually can enhance the killing capabilities of therapeutic modalities for cancer, decrease their side effects, protect normal tissues, and, in some studies, prolong survival. Part 2 will review antioxidant combinations, B vitamins, vitamins D_3 and K_3, and the glutathione-selenium complex. A summary and discussion will then be presented.

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