

VITAMIN C AS A CANCER TREATMENT: STATE OF THE SCIENCE AND RECOMMENDATIONS FOR RESEARCH

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As incidences of cancer increase, the number of patients who seek complementary and alternative medicine (CAM) is also expected to increase. Recent surveys estimate the prevalence of CAM use in a major comprehensive cancer center at approximately 69%, excluding spiritual approaches and psychotherapy/support groups.¹ Across 13 countries, the prevalence of CAM use is estimated at 31.4% (range 7-64%).² In the US and Canada, herbal teas, plant extracts, vitamins, high-dose antioxidants, and mind-body techniques are the most frequently used approaches by adult and pediatric cancer patients.^{1,3,4}

The rise in the use of dietary supplements and herbal medications by patients makes it imperative to reevaluate the past findings of clinical studies. Among unconventional approaches, high-dose vitamin C is one of the most widely used and studied, yet controversial approaches. In a survey assessing treatment approaches for breast cancer, 161 of the 1,356 naturopathic physicians practicing in the US and Canada reported that the most common approaches were vitamin C (39%), coenzyme Q-10 (34%), and the Hoxsey formula (29%).

The most common general CAM therapies included dietary counseling (94%), botanical medicines (88%), antioxidants (84%), and supplemental nutrition (84%).⁷ High doses of vitamin C and other naturally occurring substances are used in orthomolecular medicine as described by the renowned chemist Linus Pauling. The primary aim of this approach is to establish an optimal molecular environment,⁸ yet the benefits remain unproven and the approach discouraged.⁹⁻¹³

Vitamin C is a water-soluble glucose derivative with antioxidant activity *in vitro* and *in vivo*. It functions as an essential cofactor for various enzymes in diverse metabolic pathways, and exerts many non-enzymatic actions, including antioxidant effects.¹⁴⁻¹⁶ Antioxidant supplements (ie, beta-carotene and vitamin C) increase the resistance of lymphocytes to oxidative damage; moreover, a negative correlation is observed for antioxidant concentrations in tissue and oxidized bases in DNA.¹⁷ Recent evidence indicates that an increased intake of vitamin C is associated with a reduced risk of chronic diseases such as cancer, cardiovascular disease, cataracts and other eye diseases, and neurodegenerative conditions probably through antioxidant mechanisms.¹⁸⁻²¹ Nevertheless, individuals who may benefit from the anti-cancer effect of dietary supplements are currently restricted to those who have nutrient deficiencies; therefore, vitamin C may not benefit those who have adequate diets and healthy lifestyles.

Several consensus conferences have evaluated the biological effect of vitamin C, and more than 500 published articles have examined the association of vitamin C and cancer.²²⁻²⁷ Preclinical and clinical data suggest that vitamin C has potential as an anti-cancer agent,²⁸⁻³¹ and a growing body of scientific evidence suggests that ascorbic acid has immune activating properties in clinical studies, as well as anticancer properties in cell culture and animal systems.³²⁻³⁵ Although more striking effects have been observed in the elderly, evidence suggests that antioxidant nutrients can modify cell-mediated immune responses in younger individuals. Thus, it may be essential to have an adequate intake of antioxidant nutrients from an early age to prevent the development of, or at least delay, the onset of several degenerative disorders.³⁵ Reviews documenting the pharmacology, toxicology, pharmacokinetics, immunomodulatory, and antioxidant effect of vitamin C provide further evidence of the potential role of vitamin C.^{36,37,40}

Interest in the anti-cancer activity of vitamin C continues to grow, and recently some authors have suggested that high doses of vitamin C given intravenously to cancer patients should be explored further.^{16,41-43} This paper summarizes the evidence for the anti-tumor activity of vitamin C and reviews the biological plausibility supporting the use of high dose vitamin C as a cancer treatment. The majority of this data was presented at a workshop that was held in Montreal in 1999.^{41,44} In this meeting, scientists and

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practitioners, experienced in the treatment, biology, and pharmacology of vitamin C, along with oncologists experienced in the evaluation of anti-cancer drugs and biological response modifiers (BRMs), as well as clinical trial methodologists discussed the state of the science and possible role of vitamin C as a cancer treatment. The objectives of the meeting were to 1) assess the evidence of megadoses of vitamin C alone or with other agents as a cancer treatment, 2) assess the biology, pharmacology, and toxicology, 3) determine the most rigorous and appropriate study design, inclusion criteria, and objective outcome measures, and 4) test the feasibility of collaboration among members of the conventional and unconventional community.

BACKGROUND

Vitamin C is a biological reducing agent and antioxidant essential for biologic and biochemical functions.^{16,45-47} This labile micronutrient^{48,50} is available in fruits and vegetables, tablets, and powder forms at varying doses. Absorption depends on binders and dose. Vitamin C excretion occurs at 100 mg/d for healthy men at steady-state.⁵¹ Therefore, the estimated average requirement (EAR) is 100 mg/d, and the recommended daily amount (RDA) is 120 mg/d. Biochemical, clinical, and epidemiological evidence of the role of vitamin C in chronic disease prevention has been reviewed extensively, and the totality of these data suggests that an intake of 90-100 mg vitamin C per day is required for optimum reduction of chronic disease risk in nonsmoking men and women.^{18,20,52} With 100 mg of pure vitamin C twice daily, bioavailability is near maximal. For the many individuals who do not consume the RDA for vitamin C from foods,⁵³ a 200 mg vitamin C supplement is appropriate with almost complete bioavailability.

More than three decades ago, surgical oncologist Ewan Cameron, MD, used high doses of vitamin C to treat advanced, untreatable cancer in Scotland. The treatment typically included continuous intravenous (IV) ascorbic acid of 10 grams daily, but doses as high as 45 g/day were used occasionally. In 1971, Dr Cameron conducted a Phase I-II study in patients with advanced, untreatable malignancies and evaluated fifty consecutive cases for minimal/no response, growth retardation, cytostasis, tumor regression, or tumor hemorrhage/necrosis.⁵⁴ Approximately 4% of patients had been previously treated with chemotherapy and considered unlikely to respond to standard treatment.⁵⁵ Beyond subjective improvement in well-being, reduced tumor progression was documented by objective measures (ie, reduced pain from bone metastases, reduced accumulation of malignant effusions, and obstructive jaundice). Minimal or no response was observed in 27 patients; stabilization of disease in 3 pre-terminal patients with progressive disease; tumor regression in 5 patients (ie, reversal of intestinal obstruction, disappearance of palpable mass and osteolytic metastases, and relief of obstructive jaundice); and tumor hemorrhage/necrosis in 4 patients similar to responses to tumor necrosis factor.⁵⁶ The overall clinical response was similar to reports for NCI sponsored trials of interleukin-2 (IL-2).^{42,57,58}

The first 50 cases were published in 1974.^{54,59} The clinical responses in Scotland suggested a biological basis for further

investigation in several cancers. Subsequently, two retrospective studies compared survival for patients treated with vitamin C with that of patients treated with conventional treatment and who were matched on gender, age, tumor diagnosis, and clinical stage. Both studies demonstrated significantly improved survival with vitamin C.^{60,61} Increased interest in vitamin C resulted in two randomized, double-blind controlled trials of high dose oral vitamin C that were conducted at the Mayo Clinic. The 1979 study included patients with a variety of advanced cancers⁶² and a 1985 trial included patients with advanced colon cancer.⁶³ Neither found vitamin C beneficial.

Evidence of tumor hemorrhage and necrosis was not observed in the Mayo trials for several possible reasons. First, tumor hemorrhage and necrosis are infrequent responses, and are only likely to occur with high doses of IV vitamin C. Thus, the Mayo trials may not have used an adequate dose. Second, the dietary intake of vitamin C in the US is much higher than in Scotland.⁶⁴ Thirdly, colon cancer is a cancer least likely to respond to a BRM because of the fact that antigen-presenting cells (APCs) seem to be defective in this type of tumor.^{65,66} Finally, all the patients in the Mayo trials had received prior cytotoxic therapy which might have mitigated the restorative effects of vitamin C. High-dose vitamin C as a biological treatment would require careful analysis of current data showing the effects of BRMs on immune function, the anti-tumoral and cytotoxic activity of vitamin C, and the clinical data and documented case reports of vitamin C treatment.

Since the Mayo Clinical Trials were published, rational guidelines for testing biological agents such as vitamin C have been developed, and new information has emerged.^{8,42,67,74}

PHARMACOLOGY, MECHANISMS OF ACTION, AND ADVERSE EVENTS

Vitamin C undergoes glomerular filtration and renal reabsorption.¹⁶ Ascorbate probably passes unchanged through glomeruli and undergoes concentration-dependent active tubular reabsorption by a vitamin C transport protein. When the transport protein reaches saturation, the remaining C is excreted in urine. Vitamin C is dialyzable and not bound to plasma proteins.⁷⁵ At steady-state, vitamin C doses of more than 500 mg have little impact on body stores of normal persons.⁵¹ The threshold dose for vitamin C excretion is 100 mg/d, and the threshold plasma concentration for excretion is approximately 55 to 60 $\mu\text{mol/L}$. (An extensive review of the pharmacological data is presented elsewhere.^{16,75-76})

Although data about the effect of high vitamin C concentrations in modifying or enhancing biochemical or molecular function in human tissues is limited, it seems that high doses are safe and lack deleterious toxic effects. High doses up to 2,000 mg are generally well tolerated, although doses above this range may result in nausea and diarrhea.^{21,77} High vitamin C intakes do not cause iron imbalance in healthy persons and have not been found to increase oxidative damage in humans. The uptake, renal tubular reabsorption, and storage of vitamin C itself are

strictly limited after high-dose intake, so that no excessive plasma and tissue concentrations of vitamin C are produced.⁷⁶

Patients who maintain therapeutic levels of nutrients and are well nourished are thought to manage disease better, yet supplementation with vitamins and minerals is typically not part of standard oncology treatment. Although the exact mechanism of cell growth-regulation by vitamin C and other antioxidants is not completely known, antioxidants are hypothesized to interfere with oxidative activity of chemotherapy and radiotherapy by blocking the apoptosis-mediated pathway of cytotoxic agents⁷⁰ and preventing apoptotic cell damage induced by oxidative stress or homocysteine thiolactone.^{30,81} Recent data suggest that vitamin C is an excellent nitrite scavenger and reduces endogenous formation of carcinogenic N-nitroso compounds, particularly in the stomach. Epidemiological studies on high-risk populations suggest that ascorbic acid protects against gastric cancer.²⁰ Furthermore, recent studies have suggested a novel mechanism of action of vitamin C to induce tumor-specific death by autophagy and that high doses of intravenous vitamin C are cytotoxic to malignant cells.^{43,85} In summary, current evidence suggests several mechanisms of action for vitamin C alone or with conventional chemotherapy or radiotherapy:

- Immune modulation.⁸⁰⁻⁸⁵
- Stimulation of collagen formation.^{45,97}
- Inhibition of enzyme hyaluronidase to prevent metastasis.⁹⁸
- Inhibition of cell division and growth^{97,99-103} through the production of hydrogen peroxide,^{104,105} lipid peroxidation,¹⁰⁶ alteration of the cell redox status,^{104,107-110} cell autophagy,⁸⁵ oxidative stress with DNase activation, and DNA destruction.¹¹¹⁻¹²¹
- Induction of apoptosis^{109,122-125} as seen in human myelogenous leukemia,¹²⁶ promyelocytic leukemia HL-60,¹²⁷ neuroectodermal and melanoma cells,¹²⁸ and control of mitotic activity.¹²⁹
- Protection against activation of apoptotic cascades in human leukemia cells (HL-60) exposed to hydrogen peroxide.¹³⁰
- Correction of ascorbate deficiency in cancer patients.⁹⁹
- Enhanced cytotoxicity of conventional chemotherapy,^{107,131-136} radiotherapy,^{137,138} and hyperthermia.^{137,139,140}
- Potentiation of chemotherapy and radiotherapy with vitamin K3,^{98, 136, 138, 140} inhibition of human mammary tumor growth in mice with cupric sulfate (orally or intraperitoneally),¹⁰¹ modulate and potentiation when combined with beta-carotene, d-alpha-tocopherol succinate, and 13-cis-retinoic acid of cytostatic agents (ie, cisplatin, decarbazine, tamoxifen, recombinant interferon- α 2b).¹³¹ Synergistic cytotoxicity against human oral squamous cell carcinoma (HSC-2, HSC-3), human promyelocytic leukemia (HL-60) cells, human gingival fibroblast HGF, human periodontal ligament fibroblast HPLF, and human pulp cell HPC.¹⁴¹
- Increased cisplatin-induced apoptosis. In vitro study of mouse embryo fibroblasts derived from knock-out animals for c-Abl or p53 genes and in human colon carcinoma cell

lines deficient in MLH1 (Mut L homologue-1 gene), modulation of MLH1, and p73 gene expression improved cellular susceptibility to apoptosis that was triggered by the DNA-damaging agent cisplatin. In ascorbate-supplemented cells, increased cisplatin-induced apoptosis was seen involving activation of the MLH1/c-Abl/p73 signaling cascade, suggesting a potential mechanism for the anti-carcinogenic and anti-cancer activities of vitamin C.¹⁴²

- Reduction of toxicity for select chemotherapy (ie, adriamycin, cisplatin, and idarubicin);¹⁴³⁻¹⁴⁵ prevention of adriamycin cardiotoxicity in mice,¹⁴⁶ and idarubicin genotoxicity and induction of secondary malignancies;^{141,147} complete responses and few side effects with radiotherapy for various cancers;¹³⁸ stabilization of left ventricular ejection fraction (LVEF) decline associated with high-dose chemotherapy or radiotherapy when combined with vitamin E and NAC (N-acetyl cysteine).¹⁴⁸ Reversal of cellular resistance to chemotherapeutic agents^{144,150} in MCF-7 breast¹⁵¹ and melanoma cells.¹⁵²
- Improved survival in small-cell lung cancer with conventional standard chemotherapy and radiotherapy when combined with vitamins, minerals, and fatty-acid antioxidants.¹⁵³
- Reduced recurrence rate in transitional cell bladder cancer with BCG when combined with vitamins and minerals.¹⁵⁴

Doses of IV vitamin C as high as 200 grams per day¹⁵⁵ are well tolerated by healthy individuals.^{21,76,154} The few reports of vitamin C toxicity (ie, diarrhea or abdominal bloating) have been related to oral doses of several grams, which may also create adverse consequences for patients with iron overload and renal failure.¹² Vitamin C can cause false-negative test results in detecting gastric occult blood and enhance iron absorption in the small intestine by 1.5- to 10-fold, depending on the iron status, test meal, and ascorbate dose.^{86,153,156} Fear of stone formation with C is unwarranted, however, as a 14-year cohort of 85,557 women with no history of stone formation found no increased risk of symptomatic kidney stones with high (1500 mg/d) vitamin C intake compared with low (250 mg/d or less) intake.¹⁵⁷ However, hemolysis has been reported in subjects with glucose-6-phosphate dehydrogenase deficiency who receive high doses of ascorbate (6 g) as a single oral or IV dose.¹⁵⁸

In a Phase I clinical trial at the University of Nebraska Medical Center, no toxicity or changes in complete blood counts were observed among patients with end-stage metastatic gastrointestinal cancer. Continuous IV vitamin C was administered for 24 hours at five doses ranging from 150, 300, 430, 570, to 710 mg/kg/day; these doses are equivalent to 10, 20, 30, 40, and 50 grams per day for a 70 kg person. The highest plasma concentration was 66.5 mg/dL, slightly higher than the threshold plasma concentration for excretion of 55 to 60 μ mol/L.¹⁵⁹

In vitro experiments have shown that vitamin C is preferentially toxic to tumor cells. This phenomenon by Benade et al was reported by Hoffer¹⁶⁰ and hypothesized to be due to the relative deficiency of catalase in tumor cells. The theory has been supported by others,¹⁶¹ and new data suggests novel mechanisms of cytotoxicity

ty as well.^{148,139,162} Vitamin C (VC) and vitamin K(3) (VK(3)) administered in a VC:VK(3) ratio of 100:1 exhibit synergistic antitumor activity and preferentially kill tumor cells by autschizis, a novel type of necrosis that is characterized by exaggerated membrane damage and progressive loss of organelle-free cytoplasm through a series of self-excisions. Vitamin treatment induces a G(1)/S block, diminishes DNA synthesis, increases hydrogen peroxide (H₂O₂) production, and decreases cellular thiol levels. These effects can be prevented by the addition of catalase to scavenge the H₂O₂. Recent experiments indicate that oral VC:VK(3) increases the life-span of tumor-bearing nude mice and significantly reduces the growth rate of solid tumors without any significant toxicity by reactivating DNase I and II and inducing autschizis.⁸⁵

Growth rate and mitotic index of hepatoma cells BEL-7402 treated with ascorbic acid (AA) 3 mM + sodium selenite (SS) 1.5 microM decreased remarkably in another in vitro experiment. This finding suggests that the combination of ascorbic acid and sodium selenite may induce the redifferentiation of hepatoma cells and may inhibit cell growth by virtue of enhancing the activities of antioxidative enzymes and reducing the formation of H₂O₂, and altering the cell redox status. The authors conclude that the combination of ascorbic acid and sodium selenite may be a potent anti-cancer treatment option for human hepatoma cells.¹⁰⁰

Plasma concentrations of 200 mg/dL or more are difficult to maintain and thus, methods to enhance tumor cell sensitivity to vitamin C are needed. Riordan and Riordan found the water and lipid soluble antioxidant, lipoic acid, recycles vitamin C and enhances anti-tumor toxicity in a dose response fashion in the hollow fiber tumor model. In addition, the concentrations of vitamin C greatly increased collagen production. Lipoic acid decreased the dose of vitamin C required to kill 50% of the tumor cells from 700 mg/dl to 120 mg/dl and enhances the toxicity of vitamin C.^{43,67,16}

CLINICAL EXPERIENCE WITH ORTHOMOLECULAR MEDICINE THAT INCLUDES VITAMIN C

A protocol for orthomolecular medicine includes multiple nutrients such as vitamin B-3 (niacin or niacinamide), vitamin C, pyridoxine, B complex preparations, vitamin E, and zinc.¹⁵⁹ Reports have been published from a cohort of approximately 1000 cancer patients who were treated with a doses of vitamin C up to 12 grams daily.^{67,68,164} In the first paper published by Hoffer and Pauling,¹⁶⁴ positive trends in survival were observed and supported by a comparison of patients who were treated between 1993 and 1997 and complied with the regimen (ie, used the regimen for at least 2 months) versus patients who did not comply (Tables 1 and 2).^{67,166} The treatment appeared to enhance the effectiveness of the conventional treatment.¹⁶⁶ It should be noted that the results of this study must be replicated because it may be that the patients who received vitamin C were highly motivated or that patients with more progressive disease were unable to continue vitamin C treatment due to the severity of their condition. In addition, the comparisons may reflect a selection bias rather than treatment effects; However, the results warrant further research.

RECOMMENDATIONS FOR RESEARCH FOR VITAMIN C

The evidence of the biological effects of vitamin C as a potential cancer treatment is extensive even though efficacy has not been supported in two clinical studies.^{162,63} Adequate, systematic evaluation of the literature and further research on the potential complex interaction with other drugs are necessary. Any trial of vitamin C must carefully consider the number of subjects, study design, detailed information on complex concurrent treatments, mode of disease evaluations, and cancer site as well as the unpredictable natural history of particular cancers (ie, nodular or follicular lymphoma). Determinations of optimum doses, schedule, and administration should be carefully evaluated by both pre-clinical data as well as clinical data from experienced practitioners. Because optimal therapy is limited for renal cell carcinoma, ovarian, and small cell lung cancer, these cancer sites may be appropriate for study. Appropriate investigations would include:

- Phase I trials to determine optimal dose and schedule as well as toxicity alone or with cytotoxic chemotherapy and minimum bioeffective dose, if the mechanism of action is known (ie, depleting growth factor or activating cytotoxic T cells).
- Phase II or III randomized trials with placebo controls as adjuvant treatment for advanced disease that is known to respond initially but recur shortly thereafter (ie, surgery for pancreas cancer, chemotherapy for small cell lung cancer). Adequate selection of endpoints measures should be carefully discussed with experienced practitioners and researchers. Randomized controlled trials (RCTs) should include surrogate markers such as cytotoxicity and selected immune parameters.¹⁶⁷⁻¹⁷⁰

Testing Antitumor Immunity: In vitro and in vivo studies demonstrate immunomodulatory effects of vitamin C,^{87,88,171,172} but most focus on phagocytic and natural killer cells (NK) or innate and non-specific immune responses. Information on the generation of antitumor immunity with vitamin C is scarce. Results of in vitro studies demonstrate that vitamin C exhibits selective toxicity toward malignant melanoma cells, tumor ascites cells as well as acute lymphoblastic leukemia, epidermoid carcinoma and fibrosarcoma, and others.^{141,162} Immunotherapy is

TABLE 1 Survival with Orthomolecular treatment for all patients treated through 1993 (n=495): compliers versus noncompliers (adapted from Hoffer, 2000)

	Proportion Surviving by Year				
	1	2	3	4	5
Compliant (n=441)	73%	56%	48%	44%	39%
Noncompliant (n=54)	28%	15%	15%	13%	11%

an attractive approach, but not without problems, such as the well known functional alterations in T cells in cancer patients.¹⁷³ A second problem is that antigen presenting cells (APCs) are known to be defective in tumor-bearing hosts,^{65,66,74} indicating that one potential immune defect responsible for tumor progression is the inability of the host to initiate an effective primary immune response. The recognition of the critical role of APCs in mounting an effective immune response and the possibility of defective APCs in cancer patients have brought significant attention to this field. Any clinical trial of an agent that elicits or improves antitumor response must assess the molecular and functional status of APCs and T cells pre- and post-therapy. An understanding of the biological effects of vitamin C on APCs and T cells is essential for translational research and the design of more rational immune interventions.

There is currently much interest in the use of BRMs such as interleukin-2, Polysaccharide K (PSK), 5,6-dimethylxanthenone-4-acetic acid (DMXAA), or OK-432 to treat certain types of cancer. The research approaches to study BRMs differ greatly from those used to screen and test cytotoxic drugs.^{109,71} Evidence suggests that cytokines could mediate the effects of vitamin C.¹⁰¹ In addition, a body of experimental work suggests that vitamin C alone or in combination with other vitamins might act as a chemo-modulator, potentiating the cytotoxic activity of various cytostatic agents and influencing the production of interleukins by modulation the expression of interleukin genes.⁸⁹ To determine the specific role of vitamin C in the treatment of cancer, it would be important to build on the existing research of IL-2 and other BRMs. A report indicates that IL-2 therapy induces a precipitous and profound reduction in circulating vitamin C levels in cancer patients.¹⁷⁶ This effect may have implications both for vitamin C therapy and for improving IL-2 therapy.

Testing Impact on Immune Function: Ascorbate affects cell mediated and humoral immune responses, including enhancement of neutrophil adhesion; chemotaxis and respiratory burst; regulation of antigen-induced lymphocyte proliferation and cytokine function; enhancement of delayed-type hypersensitivity reactions; and elevation of antibody, complement C1q, and interferon production.^{86,85} The clinical impact of nutrients on these immune system indices has not been evaluated completely. To

establish adequate RDA levels for nutrients, studies must assess the association between nutrient intake and immune indices. Pharmacologically large doses of ascorbate may be necessary to impact immune function, but studies are needed to determine the optimum value against viral and other immunosuppressive diseases.⁹¹ In vivo studies are needed to determine the impact of ascorbic acid and metal chelators such as desferrioxamine (DFO) and calcium trisodium diethylenetriaminepentaacetic acid (DTPA) on antiviral and immunomodulatory activity.¹⁷⁷

Testing Anti-tumor Activity of Vitamin C: Vitamin C may play a role in cell growth, but the mechanism of exogenous antioxidants for regulating cell growth is unknown. Contradictory finds from several studies suggest that doses up to 5,000mg of ascorbic acid neither induce mutagenic lesions nor have negative effects on NK cell activity, apoptosis, or cell cycle.¹¹⁹ Nevertheless, some authors hypothesize that vitamin C modulates cell signaling and/or activates transcription factors that inhibit cell growth, such as kappa enhancer binding transcription factor (NF-Kappa B).¹⁰¹ The apoptosis-inducing activity of ascorbate may result from pro-oxidant action rather than antioxidant activity, and the antitumor activity or direct cell-killing action is hypothesized to be related to chemical properties, specifically oxidation and degradation of products rather than the metabolism of ascorbic acid as a vitamin.¹¹¹

Testing Vitamin C combined with other Nutrients: Synergistic cytotoxic activity of vitamin C and vitamin K3 and E has been demonstrated in experimental studies.^{100,107,112,118,121,111,102} Some studies suggest that increased oxidative stress and subsequent membrane damage as well as DNA fragmentation are responsible for the enhanced cytotoxicity of combinations of vitamins.^{111,121} Others have proposed novel mechanisms such as autschizis. Analysis of sections of tumors taken from mice used in solid-tumor growth experiments indicate that vitamin combinations induce a novel type of cell death called autschizis with degradation of tumor cell DNA as one of the principal effectors of tumor cell death.^{118,178} The proposed mechanisms for these effects 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-beta and p21 genes. Furthermore, antioxidant vitamins individually or in combination enhance the growth-inhibitory effects of x-irradiation (radiosensitizer), chemotherapeutic agents (chemosensitizer), hyperthermia, and biological response modifiers on tumor cells, primarily in vitro. These vitamins, individually and in combination, also reduce the toxicity of several standard tumor therapeutic agents on normal cells. It has been suggested by various authors that multiple antioxidant vitamin supplements together with diet and lifestyle modifications may improve the efficacy of standard and experimental cancer therapies.^{119,179} Vitamin combinations (particularly C and K3) may be a novel adjuvant cancer therapy to standard cancer therapy with no supplementary risk for patients.^{102,152,178} Conversely, other researchers have found that a mixture of vitamins C and E, plus selenium did not reduce the frequency of chromosomal damage in peripheral blood lymphocytes in

TABLE 2 Survival with Orthomolecular treatment for all patients treated through 1997 (n=844): compliers versus noncompliers (adapted from Hoffer, 2000)

	Proportion Surviving by Year				
	1	2	3	4	5
Compliant (n=769)	72%	48%	37%	30%	23%
Noncompliant (n=75)	24%	12%	12%	8%	8%

patients treated with cisplatin.¹⁸⁰ Nevertheless, more research is needed to confirm these results.

CONCLUSION

The value of vitamin C as a cancer treatment, alone or in combination with other nutrients, will only be established with scientific studies to determine effectiveness, if any, and appropriate clinical indications and dosages. Phase I and II studies as well as Phase III investigations are necessary given the plausible evidence from case reports, basic research, and the limitations of prior Phase III research. The types of clinical studies and mechanism of action studies include the following:

- Phase I trials to determine optimal dose, schedule, administration (ie, continuous infusion versus bolus), toxicity as a single agent (oral versus IV) and with cytotoxic chemotherapy, and the biologically effective dose since the mechanism of action is unknown (ie, depleting growth factor or activating cytotoxic T cells).
- Phase II or III randomized trials, placebo controlled studies as adjuvant treatment for patients who have advanced or metastatic disease and are known to respond initially but recur shortly thereafter (ie, surgery for pancreatic cancer, chemotherapy for small cell lung cancer). These types of tumors and therapies will limit trials since clinically accepted standards for adjuvant chemotherapy are changing (ie, colorectal cancer). In addition, previous exposure to immunosuppressive therapy (chemotherapy or radiotherapy) should be considered carefully since the benefits of vitamin C therapy may be limited for patients with impaired immune systems. Mechanism of action studies should be conducted concurrently with clinical trials to confirm biological effect and evaluate BRM and/or anti-angiogenic activity, not cytotoxicity. Therefore, relevant markers must be identified such as serum or plasma levels of IL-10, which is produced by tumor cells and known to inhibit antigen presentation or anti-angiogenic agents (ie, vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and matrix metalloproteinase (MMP). In addition, human cancer and normal cells could be tested for cytotoxic T lymphocyte (CTL) generation and activation.
- Analysis of interaction with conventional therapies and other nutrients may be evaluated in subgroups populations in specific phase II/III clinical trials.

The appropriate patient population includes several possibilities, and clinical studies must be guided by case report documentation and opinions from experts in this field. The optimal tumor site for study and the mechanism of action are uncertain; however, studies should be conducted in patients with both advanced disease of a common type such as breast or lung and an uncommon type such as pancreatic or renal cancer. The most powerful approach would be to begin with the clinical observations and develop studies based on these observations. Clinical

case reports from Dr Abram Hoffer indicate promising sites for colon (with 5-FU), breast, renal cell, sarcoma, and lymphoma, ovarian and lung; however, each site has their own limitation. Nevertheless, recommendations for specific cancer sites for evaluating vitamin C are as follows:

- Colon and breast cancer will be heavily pretreated, and some patients will be receiving concurrent treatment; however these cancer sites represent major public health concerns and should be considered.
- Renal cell and lymphomas are compelling, but these patients are limited by extensive prior treatment, competing protocols, the waxing and waning profile of the disease, and the number of responses to prior treatment. For renal cancer, vitamin C treatment may be evaluated under the Orphan Drug Act.
- Sarcoma patients are harder to accrue, but clinical experience in the orthomolecular treatment is intriguing.
- Prostate patients would be easy to accrue, particularly those with high grade and Gleason scores, low tumor volume, and post radiotherapy with elevated or rising PSA indicative of future recurrence. In this setting, vitamin C may be tested in combination with chemotherapy.
- Small cell lung cancer patients who are post chemotherapy, but at high risk for recurrence and whose tumor volume is low may be an optimal population since vitamin C may be mediated by host effector mechanisms associated with immunity. Concurrent data derived from in vitro analysis of the effect of vitamin C in the Lewis Lung Carcinoma model may be appropriate.

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