Intravenous Vitamin C Therapy

A Natural Agent for Treating Cancer

Shari Lieberman, Ph.D., C.N.S, F.A.C.N.

According to the American Cancer Society, cancer rates continue to rise each year.[1] It has been estimated that the incidence of new cancers in the United States may be as high as 1.2 million cases per year. In addition, 600,000 deaths each year result from cancer.[2] Despite breakthroughs often announced by the media, there is presently no effective strategy to reduce the risk of recurrence of a primary tumor or the development of a second cancer induced by conventional treatment.

Conventional cancer therapy (radiation, chemotherapy, and surgery) has made very few breakthroughs in cancer treatment. These small breakthroughs include producing increased cure rates for specific tumors in Hodgkin's disease, teratocarcinoma, and childhood leukemia. Unfortunately, there are no major breakthroughs in the more common cancers, such as breast, prostate, lung, and colon.

Despite the strides that have been made, there is still risk of recurrence and development of new cancers and nonneoplastic disease—such as aplastic anemia; retardation of growth in children; and delayed necrosis in some organs such as brain, liver, bone, and muscle—without any good standard options for their prevention in conventional oncology. Serious side-effects and the potential for the damage of normal healthy tissues and organs is a continuing problem with chemotherapy and radiation therapy. Organ and tissue damage and other serious adverse effects often cause patients to disrupt and/or discontinue therapy.[2]

The question of whether or not to use antioxidants with chemotherapy and radiation therapy continues to be a cause of debate among most oncologists. Yet, they freely prescribe synthetic antioxidants, such as dexrazoxane and amifostine, to minimize chemotherapy and radiation side-effects. More than 30 years of human and animal research demonstrate that antioxidants reduce toxicity and increase tumor killing when given with chemotherapy and radiation.

Several studies have demonstrated that antioxidants enhance the growth inhibitory effect of chemotherapy and radiation, suggesting that mechanisms other than free-radical generation are responsible for the tumor-killing effects of these treatments.[2–9] However, Prasad, one of the foremost authorities on antioxidants and cancer, and other researchers have raised concerns about using low-dose antioxidants with chemotherapy and radiation.[2,8]

Prasad's in vitro and in vivo animal work and data from human studies demonstrate that, like normal cells, cancer cells require a certain amount of micronutrients for growth and survival. Low-dose, recommended daily intake (RDI) levels of supplemental antioxidants may support the growth of cancer cells while higher doses at multiples of at least 10 times these levels produce a tumor-killing action alone and in synergy with chemotherapy and radiation. Prasad has also shown that high-dose antioxidants work synergistically to decrease chemotherapy- and radiation-induced toxicity.[2]

A proposed rationale for this approach is that normal cells have intact membranes that control the amount of antioxidants going into cells tightly. This explains, in part, why high-dose antioxidants do not kill normal healthy cells but rather protect them against the deleterious effects of chemotherapy and radiation. Cancer cells, however, have leaky membranes, allowing large amounts of antioxidants to flood into cells at doses that are lethal to cancers.[7,10,11]

Cancer cells, in particular, are susceptible to high-dose ascorbate-induced peroxidation products (such as hydrogen peroxide) because of these cells' deficiencies in the antioxidant enzymes catalase and superoxide dismutase. Vitamin C accumulates in solid tumors at levels higher than those in surrounding normal tissue.[10,11] This article reviews the rationale, safety, and efficacy of high-dose intravenous (IV) vitamin C as a natural chemotherapeutic agent.

Overview of Vitamin C

Vitamin C (ascorbic acid) is most commonly known as an antioxidant. It regenerates vitamins E and A and prevents their oxidation. It prevents and blocks free-radical–induced damage that contributes to aging and to an entire spectrum of degenerative diseases, including certain types of cancer and cardiovascular disorders. Experimentally, both topical and oral use of vitamin C has been shown to protect the skin from free-radical damage induced by sunburn. Vitamin C plays a

role in immunity. The vitamin can stimulate the production of lymphocytes. Vitamin C also increases the motility of phagocytes and is required by the thymus gland to produce its immune complexes.

The adrenal gland uses vitamin C to synthesize adrenal hormones. It supports collagen and hyaluronic acid production and plays a role in carnitine synthesis. The vitamin also supports detoxification of numerous xenobiotics in the liver and blocks the formation of nitrosamine from sodium nitrite.

The RDI for vitamin C is 60 mg. However, human studies that examined many of the therapeutic and preventive roles of vitamin C supplementation used levels approximately 10 to many hundreds of times this dose without any serious adverse effects reported. Diarrhea appears to be the major reported side-effect with oral ingestion in the g dosage. To avoid this, patients are often given amounts of vitamin C to "bowel tolerance." That is, they are given an amount up until the point that diarrhea or loose stools are induced and then the amount is cut back until bowel movements are normalized.

In my own personal clinical experience (more than 20 years) and in the experience of other colleagues, it appears that bowel tolerance goes up when one is ill and goes down as health improves. I have found that 2000–5000 mg of vitamin C are tolerated by most people. Many clinicians and scientists consider the RDI an amount that is solely based on preventing scurvy. The science behind this recommendation is sorely lacking. Indeed, 60 mg of vitamin C is not an amount that would ensure any level of health beyond preventing scurvy.[12]

Metastatic lesions in the lung and liver of a man with primary renal-cell carcinoma disappeared in a matter of weeks.

Vitamin C Pharmacokinetics

There have been claims that, when vitamin C is ingested orally, one can achieve the same plasma levels associated with IV use. A study was conducted with 17 inpatients, using a depletion–repletion study design.[13] Subjects were hospitalized for 3–6 months and consumed a vitamin C–deficient diet until their plasma concentrations were less than 8 micromoles/L without any signs of scurvy.

Vitamin C plasma and urine concentrations were measured after administration of oral and intravenous doses of the vitamin at a dose range of 0.015–1.25 g, and plasma concentrations were calculated for a dose range of 1–100 g. Peak plasma vitamin C concentrations were higher after administration of IV doses than after administration of oral doses ($P < 0.001$), and the difference increased according to dose.

Vitamin C, given orally at a dose of 1.25 g, produced mean (± standard deviation) peak plasma concentrations of 134.8 ± 20.6 micromols/L compared to 885 ± 201.2 micromols/L with IV administration. For the maximum tolerated oral dose of 3 g, every 4 hours, pharmacokinetic modeling predicted peak plasma vitamin C concentrations of 220 micromols/L and 13,400 micromols/L for a 50-g IV dose. Peak predicted urine concentrations of vitamin C from IV administration were 140-fold higher than those from maximum oral doses.

Oral vitamin C produces plasma concentrations that are tightly controlled. Only IV administration of vitamin C produces high plasma and urine concentrations that may have antitumor activity. In this study, peak plasma vitamin C concentrations plateaued with increasing oral doses. However, peak plasma vitamin C concentrations increased with increasing IV doses. IV administration of vitamin C can result in plasma concentrations that are 70-fold higher than any concentrations achieved with oral doses.

Cytotoxicity of Vitamin C

Prior work has shown that vitamin C can produce cytotoxic levels of hydrogen peroxide at sufficient concentrations. As previously mentioned, tumor cells have leaky membranes that allow vitamin C to flood into cells[7] and cancer cells are generally catalase– and superoxide-dismutase–deficient, making them more sensitive to the killing effect of hydrogen peroxide.[11]

Vitamin C has enhanced the antitumor activity of doxorubicin, cisplatin, and paclitaxel in human breast-cancer cells in culture. Vitamin C also increased drug accumulation and reversed vincristine resistance of human non–small-cell lung carcinoma cells.[2] Pretreatment with antioxidants, such as vitamin C, beta-carotene, alpha–tocopherol succinate, and retinoic acid significantly enhanced the growth inhibitory effects of cisplatin, dacarbazine, tamoxifen, and several other anticancer agents on human melanoma and parotid carcinoma cells.[8]

Experiments with rodents demonstrated that vitamin C increases host survival times and inhibits tumor growth. Studies using high dose oral vitamin C along with other antioxidants adjuvantly with chemotherapy and radiation have shown decreased toxicity and increased tumor response, improved quality of life, and improved survival time.[2,7–11,13]

Intravenous Vitamin C as a Chemotherapeutic Agent

Riordan, who recently passed away, was a pioneer in IV vitamin C therapy. As a well-respected, published researcher and clinician, he coauthored several papers on the IV vitamin C protocol, application, use, pharmacokinetics, and cytotoxicity, as well as case studies.[10,11,13] In his more than 21 years of experience in using IV vitamin C in patients with cancer, he found that the best responses were obtained when maintaining a continuous high-plasma ascorbate level.

For these studies, patients were started on doses of 15-g infusions once or twice per week. It was observed that this dose improved patients' sense of well-being, reduced pain, and, in many cases, improved survival times beyond predictions of oncologists.

For a later case study, Riordan and his colleagues used 30 g of vitamin C, twice per week, and found that metastatic lesions in the lung and liver of a man with primary renal-cell carcinoma disappeared in a matter of weeks. Resolution of bone metastasis with primary breast cancer was reported using infusions of 100 g once or twice per week.

Samples of human serum from patients who received intravenous ascorbic acid (IAA) confirmed that vitamin C concentrations in vivo can reach levels that are cytotoxic to tumor cells in vitro. In a tumor-model study, it was found that ascorbic acid plasma concentrations of 400 mg/dL kills tumor cells effectively. This concentration in plasma can only be achieved with IAA administration.[10,11]

"It does not appear that high-dose antioxidants interfere with the effectiveness of chemotherapy when they are combined."

Additional Clinical Evidence

Ovarian cancer is one of the most lethal of all gynecologic cancers, accounting for more deaths than cervical and uterine cancers combined. Women with advanced-stage disease have dismal 5-year survival rates despite the use of new chemotherapeutic agents.

Drisko and colleagues published two excellent case studies of patients with late-stage ovarian cancer who responded remarkably to IAA.[14] This research was sponsored by the Cancer Treatment Research Foundation. Because of the positive results in the two case reports on ovarian cancer, a randomized controlled trial is now underway at the University of Kansas Medical Center to evaluate the safety and efficacy of antioxidants further when they are added to chemotherapy in patients newly diagnosed with cancer.

Two (2) patients with advanced epithelial ovarian cancer were studied. Drisko confirmed that the patients were given natural rather than synthetic supplements of vitamin E and beta-carotene (personal communication). Patient 1 had stage IIIC papillary serous adenocarcinoma and, after surgery, she received carboplatinum/paclitaxel therapy for 6 cycles. After her first cycle of chemotherapy, her CA-125 went to < 35 and her computed tomography (CT) scan was negative.

Consolidation paclitaxel therapy was given for 6/12 cycles. Prior to starting initial chemotherapy, she received the following oral supplements: 1200 international units (IU) of vitamin E; 300 mg of coenzyme Q10; 900 mg of vitamin C; 25,000 IU of beta-carotene; and 1000 IU of vitamin A daily.

Prior to receiving the paclitaxel, patient 1 received 60 g IAA twice weekly. Her dose was tailored from a starting dose of 15 g to achieve a pre- and postinfusion vitamin C concentration of 200 mg/dL. Patient 1 also received IAA twice weekly during consolidation therapy after which she continued it once per week. After 1 year, she received IAA every 10–14 days. Her CA-125 remains normal and there is no evidence of disease after more than 3 years from diagnosis as confirmed by several CT scans, a positron emission tomography scan, and a normal CA-125 value of 8.8.

Patient 2 was diagnosed with stage IIIC mixed papillary serous and seromucinous adenocarcinoma. She experienced a delay in initiation of chemotherapy because she had comorbid conditions and evidence of progression of disease after surgery.

Three (3) months after surgery this patient received 6 cycles of carboplatinum/paclitaxel therapy. She started the oral antioxidant regimen prior to receiving chemotherapy. Her CA-125 normalized but she still had evidence of disease in her pelvis. The patient refused consolidation therapy and, instead, opted for continuation of the oral antioxidants and initiation of IAA. Like patient 1, patient 2 started with 15-g IAA and this was increased to 60 g per infusion. The dose was adjusted to achieve a pre and post vitamin C infusion concentration of 200 mg/dL.

Patient 2 had daily 60-g IAA for 1 week and then graduated to IAA twice each week. She continues to receive these infusions 36 months postdiagnosis. Although this patient declined diagnostic imaging her physical examination has showed that her condition is normal and her CA-125 is 5. There appears to be no evidence of disease 3 years postdiagnosis.

These case studies were published in 2003 and these patients remain well today. Anecdotally, Drisko and her colleagues are seeing benefits when high-dose IAA is added to chemotherapy for treating cancer (personal communication). Drisko said: "It does not appear that high-dose antioxidants interfere with the effectiveness of chemotherapy when they are combined."

Performing IAA

It is important to conduct a full hematologic profile, a SMAC-20 profile, and a glucose 6-phosphate dehydrogenase (G6PD) test.[10] It has been reported that high-dose IAA is contraindicated in patients with renal insufficiency, who are on chronic hemodialysis, those who have unusual forms of iron overload, and those who are oxalate stone formers.

Two reports showed that 300 mg per day of oral magnesium oxide and 10 mg per day of vitamin B_6 inhibit oxalate stone formation in recurrent stone formers and can be given to prevent stones in these patients. Measuring G6PD deficiency is important because a rare hemolysis can occur in these patients as a result of increased formation of hydrogen peroxide.

Patients with large tumor loads should be carefully monitored for tumor lysis and appropriate medical management should be used if there is septic shock. However, this is a rare occurrence with IAA. To avoid localized pain from an infusion, the infusion rate should not exceed 1 g of ascorbic acid per minute and 0.9 percent NaCl should not be used.[10] Dextrose should never be used as a carrier solution because glucose may stimulate tumor growth by enhancing glycolysis.

In addition, because glucose and vitamin C are similar in structure, they can potentially compete for entrance into tumor

cells. Infusions of up to 25 g of vitamin C are best tolerated in Ringer's lactate. Higher amounts can be mixed in Ringer's lactate or sterile water. I and other colleagues have found that, for IAA, Ringer's lactate appears to be the best-tolerated carrier solution. An IV fluid osmolality of less than 1200 mOsm will be tolerated well by most patients.[10]

An equal volume of IV solution should be removed from the IV bag prior to adding the concentrated vitamin C solution (500 mg/mL). Most practitioners I know use a concentration of vitamin C based on their clinical experience. It is known that a concentration that is too high and/or an infusion that is too fast can cause sclerosis in the infused vein. Some practitioners I have spoken with say that they can do an IV push safely with as much as 10 g of vitamin C. However, most practitioners do not recommend doing this. Table 1, which shows recommended proportions of the vitamin and Ringer's lactate, is based on my personal observation and a consensus drawn from numerous licensed and experienced practitioners (M.D.s, D.O.s, R.N.s, and physician's assistants) who have used high-dose IAA to treat patients with cancer.

A similar amount of sterile water can be used if preferred. The amounts shown in Table 1 are for approximation purposes only. For example, there are many patients who can tolerate 60 g in 500 mL of Ringer's lactate. The most important point is to start patients with a lower dose of vitamin C (10–15 g) and build up over time and assess tolerance to adjust the fluid volume and osmolality.

The infusion rate should also be adjusted to patients' tolerance. It appears that achieving a transient plasma level of 400 mg/dL is possible with 50 g or higher IAA. The goal of the infusion is to raise plasma ascorbic acid concentrations for as long as possible.[10] Sicker patients may require amounts higher than 50–60 g of vitamin C to achieve these concentrations. However, if a patient is also taking 300 mg of lipoic acid b.i.d., transient plasma vitamin C concentrations can be as equally therapeutic as 200 mg/dL. Riordan, his colleagues, and other professionals recommended that IAA be given 2–3 times per week, for at least 1 year, after which a maintenance dose can be used, such as 60 g IAA, 2 times per month. Patients should take at least 5 g of vitamin C orally on noninfusion days.

Table 1. Solutions for IV Vitamin C

Ascorbic Acid (g)	Ringer's lactate (cc)[a]
10–15	250
30	500
60	750
75 and up	1000

[a]A similar amount of sterile water can be used.

Cancer cells are very susceptible to high-dose antioxidants, in particular, vitamin C.

Discussion

Patients with cancer are generally given standard treatment options despite the known lack of success. Discussing survival for a limit of 5 years is a very disheartening conversation for patients to have with any professional. In the conventional setting patients are still discouraged from taking high-dose antioxidants along with chemotherapy and radiation. This is what occurs despite the fact that there is an abundance of research showing that antioxidants work synergistically with these treatments and, even more importantly, can be used to prevent and treat most of the side-effects of these therapies.

Many oncologists recommend lower levels of antioxidant supplementation, which causes great concern. Low levels of antioxidants may help protect cancer cells rather than help destroy them. A patient getting antioxidants from foods, however, is taking in many antioxidants at the same time (e.g., polyphenols, lignans, phytochemicals, β-carotene) not merely vitamin C. There would be synergy among these antioxidants ingested. So, a patient would actually be taking in higher levels of particular phytochemicals (e.g., quercetin from apples or onions), some of which are many times more potent than vitamin C. A typical American diet is very low in antioxidants and would promote cancer. Adding just a low-potency RDI antioxidant supplement in this case, rather than instituting a dietary change, is really the issue of concern.

Conclusions

Cancer cells are very susceptible to high-dose antioxidants, in particular, vitamin C, because these cells have leaky membranes that allow high concentrations of ascorbic acid to flood into these cells. In addition, tumor cells are generally catalase– and superoxide-dismutase–deficient, making them more sensitive to the killing effect of hydrogen peroxide. The case studies presented in this paper offer compelling and supportive evidence that IAA may be a safe and effective chemotherapeutic agent.

It has been estimated that more than 80 percent of patients with cancer do not abandon conventional therapy but continue to use their conventional treatments along with alternative therapies.[14] Using IAA along with chemotherapy and/or radiation therapy may be the best possible integrative treatment that can finally bring both the alternative and conventional camps together, making it a potential win–win situation for patients. □

References

1. Online document at: www.cancer.org

2. Prasad KN. Multiple dietary antioxidants enhance the efficacy of standard and experimental cancer therapies and decrease their toxicity. Integrative Cancer Ther 2004;3:310–322.

3. Kienner FR. Observations on the dose and administration of ascorbic acid when employed beyond the range of a vitamin in human pathophysiology. J Applied Nutr 1971;23:61–88.

4. Fujimoto J, Mori T, Takai S. Amelioration of pulmonary toxicity of bleomycin by free radical scavengers. Gan To Kagaku Ryoho 1990;17:946–949.
5. Park CH, Amare M, Savin MA, Hoogstraten B. Growth suppression of human leukemic cells in vitro by L-ascorbic acid. Cancer Res 1980;40:1062–1065.
6. Kurbacher CM, Wagner U, Kolster B, et al. Ascorbic acid improves the antineoplastic activity of doxorubicin, cisplatin, and paclitaxel in human breast carcinoma cells in vitro. Cancer Lett 1996;103:183–189.
7. Lieberman S. Proactive cancer prevention and treatment: An interview with Charles B. Simone, M.M.S., M.D. Altern Complement Ther 2003;9:82–85.
8. Pathak AK, Bhutani M, Guleria R, et al. Chemotherapy alone versus chemotherapy plus high dose multiple antioxidants in patients with advanced non small cell lung cancer. J Am Coll Nutr 2005;24: 16–21.
9. Weijl NI, Cleton FJ, Osanto S. Free radicals and antioxidants in chemotherapy induced toxicity. Cancer Treat Rev 1997;23:209–240.
10. Riordan HD, Hunninghake RB, Riordan NH, et al. Intravenous ascorbic acid: Protocol for its application and use. Puerto Rico Health Sci J 2003;22:287–290.
11. Casciari JJ, Riordan NH, Schmidt TL, et al. Cytotoxicity of ascorbate, lipoic acid and other antioxidants in hollow fibre in vitro tumours. Br J Cancer 2001;84:1544–1550.
12. Lieberman S, Bruning N. The Real Vitamin & Mineral Book, 3rd ed. New York: Avery Penguin Putnam, 2003:151–162.
13. Padatty SJ, Sun H, Wang Y, et al. Vitamin C pharmacokinetics: Implications for oral and intravenous use. Ann Int Med 2004;140:533–537.
14. Drisko JA, Chapman J, Hunter VJ. The use of antioxidants with first-line chemotherapy in two cases of ovarian cancer. J Am Coll Nutr 2003;22:118–123.

Shari Lieberman, Ph.D., C.N.S., F.A.C.N., is a research scientist and industry consultant based in New York City and Pompano Beach, Florida. She is also the Founding Dean of New York Chiropractic College's (Seneca Falls, New York) M.S. Degree Program in Clinical Nutrition.

To order reprints of this article, write to or call: Karen Ballen, *ALTERNATIVE & COMPLEMENTARY THERAPIES*, Mary Ann Liebert, Inc., 2 Madison Avenue, Larchmont, NY 10538-1961, (914) 834-3100.