PHARMACOLOGY

A Pilot Clinical Study of Continuous Intravenous Ascorbate in Terminal Cancer Patients

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Case studies suggest that vitamin C, given intravenously at doses of 10-100 grams/day can improve patient well being and in some cases, reduce tumor size. While ascorbate is generally considered safe, clinical data on high intravenous doses is limited. Twenty-four late stage terminal cancer patients were given continuous infusions of 150 to 710 mg/kg/day for up to eight weeks. Blood chemistry and blood count profiles were obtained at roughly one-week intervals while patient health, adverse events and tumor progression were monitored. The majority of patients were vitamin C deficient prior to treatment. Intravenous infusions increased plasma ascorbate concentrations to a mean of 1.1 mM. The most common adverse events reported were nausea, edema, and dry mouth or skin; and these were generally minor. Two Grade 3 adverse events 'possibly related' to the agent were reported: one patient with a history of renal calculi developed a kidney stone after thirteen days of treatment and another patient experienced hypokalemia after six weeks of treatment. White blood cell counts were stable while hemoglobin and hematocrit levels dropped slightly during treatment, consistent with trends observed prior to therapy. Blood creatinine, BUN, glucose, and uric acid concentrations decreased or remained stable during therapy, suggesting that ascorbate infusions did not adversely affect renal function. One patient had stable disease and continued the treatment for forty-eight weeks. These data suggest that intravenous vitamin C therapy for cancer is relatively safe, provided the patient does not have a history of kidney stone formation.

Key words: Ascorbic acid, Cancer, Clinical trial, Pharmacokinetics

Vitamin C (ascorbic acid, ascorbate) is a water-soluble redox agent that plays roles in collagen and carnitine synthesis and may be important in maintaining proper immune cell function (1). Pre-clinical data suggests that, at sufficient concentrations, ascorbate is toxic to tumor cells (2-4), enhances the efficacy of chemotherapy and radiation (5), and protects normal tissues from oxidative damage associated with these modalities (6). In two clinical studies conducted by Pauling and Cameron in the mid 1970's, advanced cancer patients given intravenous infusions of 10 g/day ascorbate for ten days, followed by longer term oral uptake at the same dose, showed increased survival when compared to 'historical' controls. Japanese case studies using similar doses of ascorbate found that supplementation increased survival times in a similar fashion (7). Two controlled double-blind studies at the Mayo Clinic, however, showed no benefit of orally administered (10 g/day) vitamin C in patients with advanced colon or rectal cancer (8,9).

Since plasma ascorbate concentrations were not measured in these clinical studies, we do not know if the protocols achieved ascorbate concentrations necessary to produce the effects observed in pre-clinical studies. For example, ascorbate is preferentially toxic to tumor cells at millimolar concentrations (2,4,10-12). Since ascorbate is not well absorbed at high doses when administered orally (13), the Mayo Clinic regimen was unlikely to produce plasma concentrations sufficient to reach a cytotoxic effect. With intravenous administration, however, plasma ascorbate concentrations sufficient to kill tumor cells can be attained (14). Moreover, several clinical case studies detail benefits ranging from improved quality of life to complete remission in cancer patients

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given intravenous ascorbate at doses between thirty and one-hundred-fifteen grams per day two to three times weekly (15-18). While intravenous doses of this magnitude are reportedly safe and some of us (HDR, NHR) have treated hundreds of patients with intravenous ascorbate without seeing any side effects, a regimen of this sort has not yet been tested in a controlled clinical study.

The purpose of the present study was to assess the safety of administering high dose intravenous to terminal cancer patients. Infusions of up to 710 mg/kg/day (roughly fifty grams per day in a seventy kilogram human) were administered continuously to terminal cancer patients for up to eight weeks. Blood cell counts, blood chemistry parameters, progression of disease, and adverse events were monitored in these patients.

Materials and Methods

Patient Eligibility Requirements. All patient treatment and evaluation was conducted at the Eppley Institute for Research in Cancer and Allied Diseases at the University of Nebraska Medical Center (Omaha, NE). Patients nineteen years of age or greater with a tissue diagnosis of metastatic cancer for which there is no effective available therapy (defined as any therapy with demonstrable chance for cure or prolongation of survival) were considered candidates for the trial. Prior therapy was permitted, provided four weeks had elapsed, or six weeks in the case of mitomycin-C or nitroso urease, between the last dose of therapy and entry into the trial. Patients with serious active medical problems (such as infection, heart disease, diabetes, and hypertension) requiring active medical management were excluded, as were patients who were not fully recovered from surgery (at least four weeks). Patients who were pregnant or mentally incompetent were excluded, as were patients with brain metastases.

Therapy Plan. Pharmaceutical grade sodium ascorbate (Ortho-CS 250, Merit Pharmaceuticals, Los Angeles, CA) was diluted in lactated Ringer's solution as necessary to provide the target dose at an infusion rate of 20 ml/hr (or 10 ml/hr for lower doses). This diluted solution was administered by continuous infusion using a Travenol Infusor (Pharmacie Deltac, St. Paul, MN) with a Cad-5400 or Sabrateck 6060 infusion pump. The ascorbate solution was changed daily and the infusion system was flushed with 100 mL normal saline daily to prevent buildup of crystals in the access line. The first three patients were given a vitamin C dose of 150 mg/kg/day. Doses for subsequent patients, with three patients per dose unless otherwise indicated, were increased to 300, 430, 570 or 710 mg/kg/day. These doses correspond to roughly 10, 20, 30, 40, and 50 grams per day for a 70 kg person. Each patient was treated over an eight-week period, unless an adverse event or progression of disease required that the treatment be stopped. In one case, a patient elected to continue therapy for forty eight weeks. Adverse events were assessed by the attending physician using the NCI Common Toxicity Criterion and were attributed to the agent according to the grades "not related", "possibly related" or "probably related". Therapy was stopped for any patient who experienced a grade three or four adverse event. In cases where such an event was observed among the initial three patients at a given dose (this occurred at 290 and 430 mg/kg/day), three additional patients were treated at that dose. The trial was to have been stopped if two or more grade three or four adverse events at least "possibly" related to the agent occurred at the same dose.

Blood Chemistry and Plasma Ascorbate Measurements. Samples for routine blood chemistry were collected one week prior to therapy and at roughly weekly intervals during treatment. White blood cell counts, hemoglobin and hematocrit, red blood cell counts and blood chemistry parameters related to renal function (creatinine, BUN, uric acid, and glucose) were determined using standard procedures at the Eppley Institute for Research in Cancer and Allied Diseases at the University of Nebraska Medical Center (Omaha, NE). Plasma vitamin C concentrations were measured as a function of time for twenty-two of the twenty-four patients in the trial. Serum was collected for this purpose roughly one week prior to therapy, daily for the first four days of therapy, and weekly for the first four weeks of therapy. Samples stabilized with 3% metaphosphoric acid (4.5 ml acid to 3 ml serum), frozen at –70 °C, coded, and shipped to the Bio Center Laboratory (Wichita, KS) for analysis. Vitamin C concentrations in the plasma samples were determined by measuring the reduction of 2,6 dichlorophenolindophenol (19).

Evaluation Criterion. Radiographic images (thoracic radiographs, CT scan) of measurable disease were performed at eight weeks of treatment to assess progression of disease. A complete response was defined as total resolution of all measurable disease sites for a minimum of four weeks. A partial response was defined as a fifty percent or greater decrease in the size (defined as the sum of the products of the perpendicular dimensions) of all measurable lesions for a minimum of four weeks without the appearance of new lesions. Stable disease was defined as no more than a fifty percent decrease and no less than a twenty five percent increase in the size of all measurable lesions and no development of new disease over eight weeks. Progressive disease was defined as a twenty-five percent or greater increase in the size of all measurable lesions compared to the measurements at the time of maximum regression.

Results

This study consisted of twenty-four late state, terminal cancer patients with poor prognosis for whom no effective therapy was available. Most of these patients had colon or rectal primary tumors (19 out of 24), and nearly all of them (22 out of 24) had metastatic disease. In all cases, the patients had received one or more prior regimens of chemotherapy, with their tumors proving refractory to these treatments. Table 1 summarizes the type of cancer, dose

Table 1: Summary of Patients given Intravenous Ascorbate

Primary	Mets	Dose	Ascorbate	Result	Adverse
Colon	Liver, Lung	150 mg/kg/day - 8 weeks	1.920 mg/dL	Progression	G1: Nausea, Dry Mouth & Skin, Constipation
Colon	Chest, Ab	150 mg/kg/day - 7 weeks	0.4à14 mg/dL	Progression	G1: Dry Mouth & Skin, Constipation
Colon	Liver	150 mg/kg/day - 4 weeks	1.4à19 mg/dL	Progression	G1: Edema
Liver	Adenophathy	290 mg/kg/day - 8 weeks	0.5à69 mg/dL	Progression	G1: Fatigue
Colon	Liver	290 mg/kg/day - 13 days	0.8à35 mg/dL	Progression	G1: Dry Mouth G3: Kidney Stone (possibly related)
Colon	Liver	290 mg/kg/day - 6 weeks	0.8à20 mg/dL	Progression	G1: Fever, Anorexia G3: Anemia (not related)
Appendix, carcinomatosis		290 mg/kg/day - 7 weeks	0.0à11 mg/dL	Progression	None
Colon	Liver	290 mg/kg/day - 8 weeks	0.4à11 mg/dL	Progression	G1: Nausea, Dry Mouth
Colon	Omentum	290 mg/kg/day - 8 weeks	0.0à9.0 mg/dL	Progression	G1: Nausea, Fever, Dry Mouth, High Blood Pressure
Colon		290 mg/kg/day - 8 weeks	0.0à5.1 mg/dL	Progression	G1: Nausea, Pain, Fever G2: Hypoglycemia
Rectal	Liver, Lung	430 mg/kg/day - 3 weeks	0.0à25 mg/dL	Progression	G1: Nausea, Edema G2: Hypokalemia G4: Cardiac Arrest (not related)
Colon	Liver	430 mg/kg/day - 8 weeks	0.0à31' mg/dL	Stable Disease	G1: Nausea
Colon	Lung	430 mg/kg/day - 7 weeks	16à 15 mg/dL	Progression	G1: Edema, Dry Mouth G2: Pain
Colon	Liver	430 mg/kg/day - 3 weeks	0.0à16 mg/dL	Progression	G1: Nausea, Edema
Pancreatic		430 mg/kg/day - 8 weeks	0.0à6.0 mg/dL	Progression	G1: Edema
Colon	Liver	430 mg/kg/day - 8 weeks	0.0à17 mg/dL	Progression	None
Colon	Liver, Lung	570 mg/kg/day - 8 weeks	0.0à8.4 mg/dL	Progression	G1: Pain, Fatigue
Pancreatic	Liver	570 mg/kg/day - 7 weeks	0.0à22 mg/dL	Progression	G1: Diarrhea, Edema, Fatigue, High BP G3: Hypokalemia (possibly related)
Colon	Lung	570 mg/kg/day - 8 weeks	0.0à20 mg/dL	Progression	G1: Edema, High Blood Pressure G2: Fever
Colon	Liver	710 mg/kg/day - 8 weeks	8.9à17 mg/dL	Progression	G1: Nausea
Colon	Liver, Lung	710 mg/kg/day - 8 weeks	No data available	Progression	G1: Pain, Fatigue
Esophagus	Liver	710 mg/kg/day - 10 days	No data available	Progression	G2: Nausea
Cholangio	Liver	710 mg/kg/day - 2 days	1.7à42 mg/dL	Progression	G1: Fatigue G2: Nausea
Colon	Liver, Lung	710 mg/kg/day - 8 weeks	4.4à25 mg/dL	Progression	G1: Sleeplessness, Dry Throat, Fatigue G2: Edema, Hypokalemia

and duration of ascorbate therapy, plasma ascorbate levels (before and during treatment), adverse events, and results for each study participant. One patient had stable disease while the others showed progressive disease during the treatment. Among those with progressive disease, eleven completed the eight weeks of therapy. Two were removed from the study due to Grade Three of Four adverse events and two elected to stop treatment due to problems with venous catheter occlusion. The remainders were removed from the trial before the eight-week time period expired due to progressive disease. Overall, eighteen of the patients received the treatment for at least six weeks.

One subject, a man with colon cancer and liver metastasis who was treated with 430 mg/kg/day ascorbate (subject #12 in Table 1), showed stable disease (no increase in size of pre-existing lesions and no new lesions) and elected to continue ascorbate therapy at his own expense for an additional forty-eight weeks. This subject was relatively healthy in that, unlike most other subjects, his blood chemistry and blood count parameters were all within normal ranges at the onset of treatment and remained normal during the study. Moreover, his plasma ascorbate levels increased steadily during the eight week study period, reaching a maximum value of 1.7 mM. In all the other subjects, the plasma ascorbate concentration went up initially and then remained constant. Of course, the relative good health and different ascorbate absorption in this subject may be coincidental and we are not aware of any aspect of this patient's cancer that might set it apart as being particularly amenable to ascorbate therapy.

Most adverse events experienced by the patients were minor (Grade 1 or Grade 2) and of the sort one would expect for late stage cancer patients regardless of their therapeutic regimen. The most common side effects were nausea (11 subjects), dry skin or mouth (7 subjects), edema (7 subjects), and fatigue (6 subjects). A total of four Grade 3 or Grade 4 adverse events were observed during the study, with only two of these being considered even "possibly" related to the ascorbate treatment. Since we did not observe two such "possibly related" events at any single dose, we are unable to estimate a maximum tolerated dosage. One patient (subject #5 in Table 1) developed a kidney stone after thirteen days of treatment at 290 mg/kg/day ascorbate. Prior to formation of the stone, the only adverse event he experienced during the treatment was a dry mouth. Acute renal distress is usually accompanied by increases in blood glucose, creatinine, urea, and BUN levels; however, this subject's blood creatinine, glucose and BUN levels remained stable (at 0.8, 74, and 14 mg/dL, respectively) during treatment while his blood uric acid concentration decreased (from 4.8 to 2.3 mg/dL). This subject had a prior history of kidney stones, and the rapidity of onset (13 days) suggests a pre-existing condition. However, a role for ascorbate in causing this adverse event could not be totally ruled out. A second subject, a female with colon cancer and liver metastases (subject #18) experienced a Grade 3 decrease in blood potassium level while being treated with 570 mg/kg/day ascorbate. She had pre-existing fatigue and abdominal pain, and complained of diarrhea, edema, and fatigue during the treatment. Her blood potassium levels were monitored on days 28, 35, and 42 of therapy, with concentrations of 3.0, 2.9, and 2.5 being obtained. This incidence of hypokalemia was graded "possibly related" to the ascorbate therapy, though it was probably induced by gastrointestinal potassium loss, a common problem in patients with diarrhea.

Two Grade 3 or 4 adverse events occurred during the study that were considered by the attending physician to be unrelated to ascorbate therapy (subjects #9 and #11). One subject (# 9) experienced a single incidence of Grade 3 anemia (hemoglobin at 7.6 g/dL) after six weeks of treatment at 290 mg/kg/day. Her previous hemoglobin level was 8.1 g/dL (after five weeks), and her hemoglobin level increased without intervention or cessation of treatment to 8.9 g/dL the following week. Chronic pain and recurrent anemia were reported as pre-existing conditions, and this subject's blood parameters as a whole were low but stable prior to and during treatment. Chronic pain and recurrent anemia were reported as pre-existing conditions. Her anemia was considered unrelated to ascorbate therapy. Another subject (#11) suffering from rectal cancer with both liver and lung metastases underwent cardiac arrest (a Grade 4 event) while being treated with 430 mg/kg/day ascorbate. This occurred three weeks into therapy and within a few days after she was given a diuretic by her family physician. She was admitted to the hospital, where she was also found to be hypokalemic (Grade 2). In all likelihood, severe hypokalemia brought on by a combination of nausea, vomiting, and the diuretic induced the heart attack. She was removed from the study and died two months later.

Most of the parameters measured in the standard blood count and chemistry profile either remained stable during therapy or changed modestly in accordance with trends observed prior to treatment. Average values of blood chemistry and count parameters before and during therapy, along with the incidence of clinically abnormal values, are summarized in Table 2. Hemoglobin, hematocrit, red cell counts, and lymphocyte counts were below normal before vitamin C therapy for a majority of the subjects. These parameters decreased slightly (or, in the case of red cell count, remained stable) during vitamin C therapy, reflective of trends observed prior to treatment. White blood cell

Table 2: Mean blood chemistry and count parameters (with standard deviations) for 24 patients along with the number of subjects with parameter values outside the normal range before, during (average of all values during treatment), and at the end (average for last two weeks of treatment) of therapy. Normal values were taken from the BioCenter Laboratory, Wichita, KS.

		Mean Parameter Value			Number of Abnormal Values					
	Normal	(Average for 24 Subjects)			Before		During		End	
Parameter	Range	Before	During	End	Hi	Lo	Hi	Lo	Hi	Lo
BUN (mg/dL)	5 – 26	13 ± 5	11 ± 4†	11 ± 5†	1	0	0	2	0	2
Creatinine (mg/dL)	0.5 – 1.5	0.9 ± 0.2	0.8 ± 0.2†	0.8 ± 0.2†	0	0	0	2	0	2
Uric Acid (mg/dL)	2.2 – 8.7	5.0 ± 1.2	2.5 ± 1.0†	2.8 ± 1.5†	1	0	0	10	0	9
Glucose (mg/dL)	65 – 110	112 ± 38	98 ± 22	99 ± 19	8	0	5	0	8	0
Hemoglobin (g/dL)	14 – 17	12 ± 2	11 ± 2†	11± 2†	0	20	0	22	0	23
Hematocrit (%)	39 – 55	35 ± 5	33 ± 5†	33 ± 4†	0	17	0	20	0	23
RBC (10^6/μL)	4.3 – 5.9	4.0 ± 0.5	3.9 ± 0.6	4.1 ± 0.7	0	18	0	19	1	19
WBC (10^3/μL)	4.6 – 11	8.2 ± 4.0	8.5 ± 2.6	8.7 ± 2.9	3	2	5	0	4	2
Neutrophils (%)	45 – 75	68 ± 8	72 ± 7†	73 ± 7†‡	1	0	8	0	10	0
Bands (%)	0 – 5	4.0 ± 3.9	3.5 ± 2.5	3.0 ± 2.6	5	0	4	0	2	0
Lymphocytes (%)	20 – 45	17 ± 8	15 ± 6†	15 ± 6†	0	18	0	18	0	19
Monocytes (%)	0 – 10	8.3 ± 3.1	7.8 ± 2.3	7.5 ± 2.9	7	0	5	0	4	0
Platelets (10^3/μL)	140 - 440	250 ± 90	260 ± 90	280 ± 90†‡	0	0	0	0	3	1

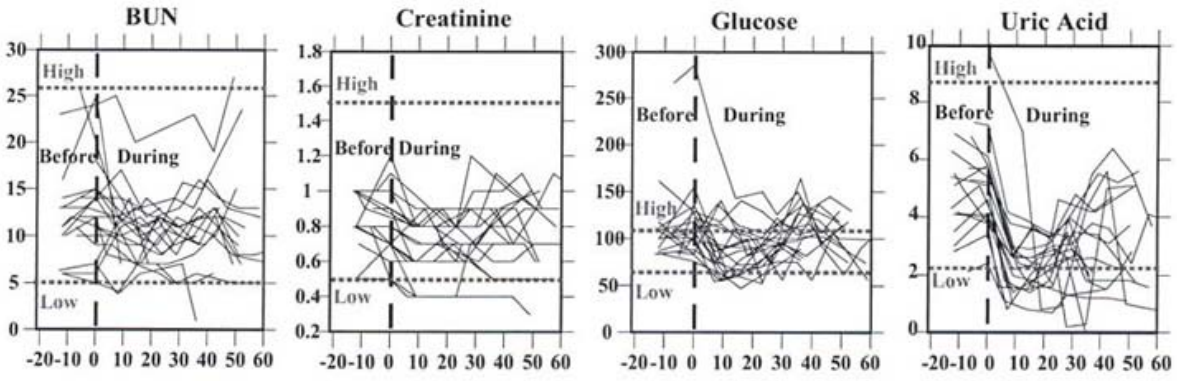
"†" denotes $p<0.05$ for comparison with pre-treatment values.
"‡" denotes $p<0.05$ for comparison with during treatment values.

counts remained stable during treatment, with neutrophil percentages increasing and lymphocyte percentages decreasing. Platelet counts increased only at the end of treatment. Overall, there appears to be a minimal effect of vitamin C on blood cell count parameters.

Blood chemistry parameters that serve as indicators of renal function (BUN, creatinine, uric acid, and glucose) remained relatively stable or, in the case of uric acid, decreased during therapy, as shown in Figure 1. This is significant, since the values of these parameters would have been expected to rise during treatment if ascorbate was having an acute detrimental effect on renal function. Only four subjects experienced BUN increases during therapy and only two experienced creatinine increases. The uric acid decreases reported here are unlikely to indicate a risk, since acute renal distress would involve elevated uric acid levels. In regard to uric acid, it should be pointed out that vitamin C can interfere with the standard colorimetric uric acid assay, though excess ascorbate oxidase is usually added during the assays to prevent this. For the particular assay kit used in this study (Vitros Chemistry Products), a serum ascorbate concentration of 100 mg/dL (~ 5 mM) creates a positive bias of 17%. Although this serum ascorbate concentration was not achieved in the present study, it is possible that actual plasma uric acid levels are somewhat lower than those reported herein.

Plasma ascorbate levels were measured in twenty-two

Figure 1. BUN, creatinine, uric acid and glucose levels in patients as a function of time from the onset of therapy (days). Normal range limits are indicated by horizontal dotted lines, while the onset of treatment is indicated by a vertical dashed line. Data from the twenty patients with the longest treatment times were selected for each graph.



of the twenty-four subjects in this study. Prior to therapy, the mean plasma ascorbate level in these subjects was 0.1 ± 0.2 mM. Considering the normal range to be between 0.11 and 0.03 mM, three subjects had above normal levels, five subjects had normal levels, and fourteen subjects were ascorbate deficient, with ten of them having no detectable vitamin C in their blood. In all but one case, plasma ascorbate levels reached steady state within two days of ascorbate therapy. The one exception occurred in the one subject who showed stable rather than progressive disease. The mean plasma ascorbate concentration (all subjects) during therapy was 1.1 ± 0.9 mM, significantly greater than the pre-treatment mean. Average plasma ascorbate concentrations during treatment ranged from 0.28 to 3.8 mM, suggesting that ascorbate absorption pharmacokinetics varied greatly among subjects. This variation highlights the necessity of monitoring plasma ascorbate concentrations in future studies examining the potential correlation between ascorbate concentration and efficacy. We should also note that the colorimetric assay employed to measure plasma ascorbate has a relatively low sensitivity. We saw no consistent relationship between plasma ascorbate concentration and ascorbate dosage. Since tissue and urine vitamin C concentrations were not measured in this study, we cannot determine whether additional ascorbate administered at higher doses was excreted in the urine or absorbed and metabolized by tissue.

Discussion

The purpose of this study was to assess the safety of administering high doses or intravenous ascorbate, up to 710 mg/kg/day for up to 8 weeks, to terminal cancer patients. The results of this study lead us to conclude the following: plasma ascorbate concentrations on the order of 1 mM were attained using intravenous infusion; the adverse events associated with this treatment were few and for the most part, minor; ascorbate therapy did not cause acute renal distress, provided the patient did not have a prior history of kidney problems and the effect of intravenous ascorbate therapy on blood count and chemistry parameters were, in most cases, minimal. Based on these results, we believe that further clinical studies with high dose intravenous ascorbate infusions are warranted.

Health concerns related to vitamin C utilization primarily focus on compromised renal function and the formation of renal calculi (13). In the present study, one patient developed a kidney stone after thirteen days of treatment. This patient had a history of oxalate stones, and the relatively short time after the onset of therapy at which the stone was detected suggests a pre-existing condition. In patients who did not have a history of kidney stones, unexpected renal calculi did not develop, consistent with other studies using lower doses (8,13,20). Moreover, blood chemistry parameters associated with kidney function (creatinine, BUN, uric acid, glucose) decreased instead of increasing as they would under conditions of renal compromise. This is interesting in light of reports by Levine and coworkers (13) that urine uric acid and oxalate levels were elevated in their study using oral doses of ascorbate. Overall, the preponderance of evidence in this study suggests that high doses of vitamin C do not compromise renal function in patients who do not have a prior history of kidney disease.

The relatively minor side effects of nausea, dryness, and edema reported in this study were consistent with observations by others (13,21). The only two adverse events of Grade 3 or more that were considered even possibly related to the treatments were the aforementioned kidney stone and a case of hypokalemia. The cause of the latter is unknown, though it may be related to diarrhea. Potassium levels should be monitored regularly in future studies. Speculation concerning the effects of vitamin C on white blood cells has covered the entire range from reported benefits, such as protection from oxidative damage (22), increased T-cell numbers (23), and increases T-cell activity (24), to claims that ascorbate is toxic to lymphocytes in vitro (25). Patient lymphocyte counts in our study were by and large unaffected by ascorbate administration; they decreased gradually during treatment, in accordance with trends observed immediately prior to therapy. This suggests toxicity reported in vitro might not be relevant in vivo.

Over sixty percent of the cancer patients in this study were deficient in vitamin C prior to intravenous ascorbate therapy, consistent with reports in the literature (26,27). Ascorbate infusions increased plasma ascorbate concentrations to millimolar levels, concentrations in excess of those needed to saturate neutrophils and lymphocytes (13), and approaching those reported necessary for virucidal activity against the HIV virus (25) and toxicity against tumor cells (11). The issue of determining what plasma concentration is necessary for anti-tumor efficacy is complicated by two factors. On the one hand, experiments conducted in our laboratory with three dimensional tumor models indicate that the vitamin C dose required to kill solid tumors may be much higher than that necessary to kill tumor cells in monolayer cultures (14). On the other hand, the known accumulation of ascorbate in tumors (29) suggests that doses higher than those attained in plasma may be reached there. In guinea pigs given subcutaneous injections of ascorbate, intra-

tumor ascorbate concentrations in excess of 2 mM were obtained, with these concentrations leading to decreased tumor growth in vivo (30).

More research is needed to understand how ascorbate distributes throughout the body and what concentrations can be attained in solid tumors. Plasma ascorbate measurements in this study failed to detect any systematic increases in concentration with dose. Similar qualitative trends have been reported by Levine and coworkers (13); in particular, these investigators found that plasma ascorbate concentrations in seven healthy adults given oral supplements reached a plateau level of roughly 1.5 mg/dl at an oral dose of 1 g/day, after which further increases in dose led to increased urinary excretion without significant increases in plasma concentration. This report suggests that higher doses would be of limited utility in healthy adults. However, the situation in cancer patients may be considerably different. Cancer patients often have below normal plasma vitamin C levels, and tumors are known to accumulate vitamin C at high levels relative to surrounding tissues (29). Mechanistic aspects pertaining this issue have been published elsewhere (31). It has also been observed that urinary excretion in leukemia patients following acute loading of ascorbic acid was significantly less than that in normal subjects (6). Preliminary experiments in our laboratory (unpublished) indicated that plasma ascorbate concentrations in cancer patients after one-hour infusions of 15g intravenous ascorbate were significantly lower than those attained in healthy adults given the same infusion. It seems likely in light of these observations that cancer patients may have an increased tissue demand for vitamin C relative to normal subjects.

Considering the short duration of this study, the relatively poor health of the patients involved, and their experience with prior chemotherapy, efficacy was not an expected result in this trial. It was thus surprising that one patient in the study had stabilized disease during therapy. Patients who have undergone prior chemotherapy may benefit less from vitamin C therapy (8,33) and cancers of colon or rectal origin may be less responsive to vitamin C therapy (9). We are planning future clinical trials with cohorts of cancer patients, such as those with renal carcinoma who have not had prior chemotherapy, who may stand a better chance of being aided by vitamin C (16,17). We are also examining the use of other supplements and additives, such as lipoic acid (14), that may boost immune system or modulate the cellular oxidation-reduction state in a way that decreases the vitamin C dose required for tumor cell cytotoxicity.

In conclusion, the results in this study suggest that intravenous vitamin C therapy for cancer is relatively safe.

Resumen

Informes de casos publicados sugieren que la vitamina C, administrada por vía intravenosa en dosis de 10 a 100 gramos puede mejorar la condición de salud de pacientes que padecen de cáncer y en algunos casos reducir el tamaño del tumor. Aunque el ascorbato es generalmente considerado como seguro, los datos clínicos sobre altas dosis administradas por vía intravenosa son muy limitados. Se les administraron infusiones continuas de vitamina C en dosis de 150 to 710 mg/kg/día por hasta ocho semanas a 24 pacientes con cáncer avanzado en etapa Terminal. Se obtuvieron muestras de sangre para análisis de laboratorio semanalmente, mientras se le daba seguimiento a la condición del paciente incluyendo efectos adversos y progreso del tumor. La mayoría de los pacientes tenían niveles deficientes de vitamina C antes de la terapia. Las infusiones intravenosas aumentaron la concentración de ascorbato en plasma a un promedio de 1.1 mM. Los efectos adversos mas comúnmente informados incluyeron nausea, edema, resequedad de la boca o piel y estos fueron de una magnitud modesta.

Se informaron dos efectos adversos de grado 3 (posiblemente relacionados al agente): un paciente con historial de cálculos renales tuvo recurrencia de un cálculo y otro paciente experimentó hipocalemia luego de seis semanas de tratamiento. Los conteos de células blancas se mantuvieron estables mientras que los niveles de hemoglobina y hematocrito disminuyeron levemente durante el tratamiento, en forma consistente con los patrones observados previos a la terapia. Las concentraciones de creatinina sérica, la urea nitrogenada en sangre y el acido úrico disminuyeron o se mantuvieron estables durante la terapia, sugiriendo que las infusiones de ascorbato no afectó adversamente la función renal. Un paciente se mantuvo estable en su condición por 48 semanas. Estos datos sugieren que la terapia intravenosa con vitamina C para cáncer es relativamente segura siempre y cuando el paciente no tenga un historial de formación de cálculos renales.

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References

1. Penn ND, Purkins L, Kelleher J, Heatley RV, Mascie-Taylor BH and Belfield PW. The effect of dietary supplementation with vitamins A, C and E on cell- mediated immune function in elderly long-stay patients: a randomized controlled trial. Age Ageing 1991;20:169-74.
2. Benade L, Howard T and Burk D. Synergistic killing of Ehrlich ascites carcinoma cells by ascorbate and 3-amino-1,2,4,-triazole. Oncology 1969;23:33-43.
3. Gonzalez MJ, Mora EM, Miranda-Massari JR. et al. Inhibition of Human Breast Carcinoma Cell Proliferation by Ascorbate and Copper. PR Health Sci J. 2002;21:21-3.
4. Chen Q, Espey MG, Krishna MC, Mitchell JB, Corpe CP, Buettner GR, Shacter E, Levine M. Pharmacologic ascorbic acid concentrations selectively kill cancer cells: action as a pro-drug to deliver hydrogen peroxide to tissues. Proc Natl Acad Sci U S A. 2005;102:13604-9.
5. Kurbacher CM, Wagner U, Kolster B, Andreotti PE, Krebs D, and Bruckner HW. Ascorbic acid (vitamin C) improves the antineoplastic activity of doxorubicin, cisplatin, and paclitaxel in human breast carcinoma cells in vitro. Cancer Lett 1996;103:183-9.
6. Fujita K, Shinpo K, Yamada K, Sato T, Niimi H., Shamoto M, Nagatsu T, Takeuchi T and Umezawa H. Reduction of adriamycin toxicity by ascorbate in mice and guinea pigs. Cancer Res 1982;42:309-16.
7. Murata A, Morishige F, and Yamaguchi H. Prolongation of survival times of terminal cancer patients by administration of large doses of ascorbate. Int J Vitam Nutr Res 1982;23:103s-13s.
8. Creagan ET, Moertel CG, O'Fallon JR, Schutt AJ, O'Connell MJ, Rubin J and Frytak S. Failure of high-dose vitamin C (ascorbic acid) therapy to benefit patients with advanced cancer. A controlled trial. N Engl J Med 1979:301:687-90.
9. Moertel CG, Fleming TR, Creagan ET, Rubin J, O'Connell MJ, and Ames MM. High-dose vitamin C versus placebo in the treatment of patients with advanced cancer who have had no prior chemotherapy. A randomized double- blind comparison. N Engl J Med 1985;312:137-41.
10. Koch CJ and Biaglow JE. Toxicity, radiation sensitivity modification, and metabolic effects of dehydroascorbate and ascorbate in mammalian cells. J Cell Physiol 1978;94:299-306.
11. Riordan NH, Riordan, HD, Meng X, Li Y and Jackson JA. Intravenous ascorbate as a tumor cytotoxic chemotherapeutic agent. Med Hypotheses 1995;44(3), 207-13.
12. Chen Q, Espey MG, Krishna MC, Mitchell JB, Corpe CP, Buettner GR, Shacter E and Levine M. Pharmacologic ascorbic acid concentrations selectively kill cancer cells: action as a pro-drug to deliver hydrogen peroxide to tissues. Proc Natl Acad Sci U S A. 2005;102:13604-9.
13. Levine M, Conry-Cantilena C, Wang Y, Welch RW, Washko PW, Dhariwal KR, Park JB, Lazarev A, Graumlich JF, King J and Cantilena LR. Vitamin C pharmacokietics in healthy volunteers: evidence for a recommended dietary allowance. Proc Natl Acad Sci USA 1996;93:3704-9.
14. Casciari JJ, Riordan NH, Schmidt TS, Meng XL, Jackson JA and Riordan HD. Cytotoxicity of ascorbate, lipoic acid, and other antioxidants in hollow fiber in vitro tumors. Br J Cancer 2001;84:1544-50.
15. Jackson JA, Riordan HD, Hunninghake RE and Riordan N. High dose intravenous vitamin C and long time survival of a patient with cancer of the head of the pancreas. J Orthomolec Med 1995;10:87-8.
16. Riordan HD, Jackson JA, Riordan NH and Schultz M. High-dose intravenous vitamin C in the treatment of a patient with renal cell carcinoma of the kidney. J Orthomolec Med 1998;13:72-3.
17. Riordan HR, Jackson. JA and Schultz M. Case study: high-dose intravenous vitamin C in the treatment of a patient with adenocarcinoma of the kidney. J. Orthomolec Med 1990;5:5-7.
18. Riordan HD, Riordan NH, Jackson JA, Casciari JJ, Gonzalez MJ, Miranda-Massari JR, Mora EM, Rosario N and Rivera A. Intravenous vitamin C as a chemotherapy agent a report on clinical cases. PR Health Sci J. 2004;23:119-120.
19. Henry RJ, Cannon DC and Winkleman JW. Determination of Ascorbic Acid. Clinical Chemistry: Principles and Techniques. New York: Harper & Row, 1974:1393-8.
20. Sauberlich HE. Pharmacology of vitamin C. Ann Rev Nutr 1994;14:371-91.
21. Cameron E. and Campbell A. The orthomolecular treatment of cancer. II. Clinical trial of high-dose ascorbic acid supplements in advanced human cancer. Chem Biol Interact 1974;9:285-315.
22. Ames BN, Shigenaga MK and Hagen TM. Oxidants, antioxidants, and the degenerative diseases of aging. Proc Natl Acad Sci USA 1993;90:7915-22.
23. Bendich A. Physiological role of antioxidants in the immune system. J Dairy Sci. 1993;76:2789-94.
24. Kennes B, Dumont I, Brohee D, Hubert C, and Neve P. Effect of vitamin C supplements on cell-mediated immunity in old people. Gerontology 1983; 29:305-10.
25. Eylar E, Baez I, Navas J, and Mercado C. Sustained levels of ascorbic acid are toxic and immunosuppressive for human T cells [see comments]. P R Health Sci J. 1996;15:21-6.
26. Anthony HM and Schorah CJ. Severe hypovitaminosis C in lung-cancer patients: the utilization of vitamin C in surgical repair and lymphocyte-related host resistance. Br J Cancer 1982;46: 354-67.
27. Marcus SL, Dutcher JP and Paietta E. Severe hypovitaminosis C occuring as the result of adoptive immunotherapy with high-dose interleukin-2 and lymphokine-activated killer cells. Cancer Res 1987;47:4208-12.
28. Harakeh S, Jariwalla RJ and Pauling L. Suppression of human immunodeficiency virus replication by ascorbate in chronically and acutely infected cells. Proc Natl Acad Sci U S A 1990;87:7245-9.
29. Agus DB, Vera JC and Golde DW. Stromal cell oxidation: a mechanism by which tumors obtain vitamin C. Cancer Research 1999;59:4555-8.
30. Casciari JJ and Riordan HD. Efficacy of high dose sodium ascorbate against tumors in vitro and in vivo (abstract). J Nutrition 2001;131:3153s.
31. Gonzalez MJ, Miranda-Massari JR, Mora EM, Guzman A, Riordan NH, Riordan HD, Casciari JJ, Jackson JJ, Roman-Franco A. Orthomolecular Oncology Review: Vitamin C and cancer 25 years later. Integrative Cancer Therapies 2005;4:32-44.
32. Hoffman FA. Micronutrient requirements of cancer patients. Cancer 1985;55:295s-300s
33. Pauling L. Vitamin C therapy of advanced cancer [letter]. N Engl J Med 1980;302:694-5.