



IVC Protocol

IVC Protocol Vitamin C Research: The Riordan IVC Protocol for Adjunctive Cancer Care Intravenous Ascorbate as a Chemotherapeutic and Biological Response Modifying Agent

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INTRODUCTION

Vitamin C (ascorbate, ascorbic acid) is a major water-soluble antioxidant that also increases extracellular collagen production and is important for proper immune cell functioning (Hoffman, 1985; Cameron, et al., 1979). It also plays key roles in L-carnitine synthesis, cholesterol metabolism, cytochrome P-450 activity, and neurotransmitter synthesis (Geeraert, 2012). The Riordan intravenous vitamin C (IVC) protocol involves the slow infusion of vitamin C at doses on the order of 0.1 to 1.0 grams ascorbate per kilogram body mass (Riordan, et al., 2003). IVC use has increased recently among integrative and orthomolecular medicine practitioners: a survey of roughly 300 practitioners conducted between 2006 and 2008 indicated that roughly ten thousand patients received IVC, at an average dose of 0.5 g/kg, without significant ill effects (Padayatty, et al., 2010). While IVC may have a variety of possible applications, such as combating infections (Padayatty, et al., 2010), treating rheumatoid arthritis (Mikirova, et al., 2012), it has generated the most interest for its potential use in adjunctive cancer care.



vitamin C (Hoffman, 1985; Riordan, et al., 2005), replenishment may improve immune system function and enhance patient health and well-being (Henson, et al., 1991). Cameron and Pauling observed fourfold survival times in terminal cancer patients treated with intravenous ascorbate infusions followed by oral supplementation (Cameron & Pauling, 1976). However, two randomized clinical trials with oral ascorbate alone conducted by the Mayo clinic showed no benefit (Creagan, et al., 1979; Moertel, et al., 1985). Most research from that point on focused on intravenous ascorbate. The rationales for using intravenous ascorbate infusions (IVC) to treat cancer, which are discussed in detail below, can be summarized as follows:

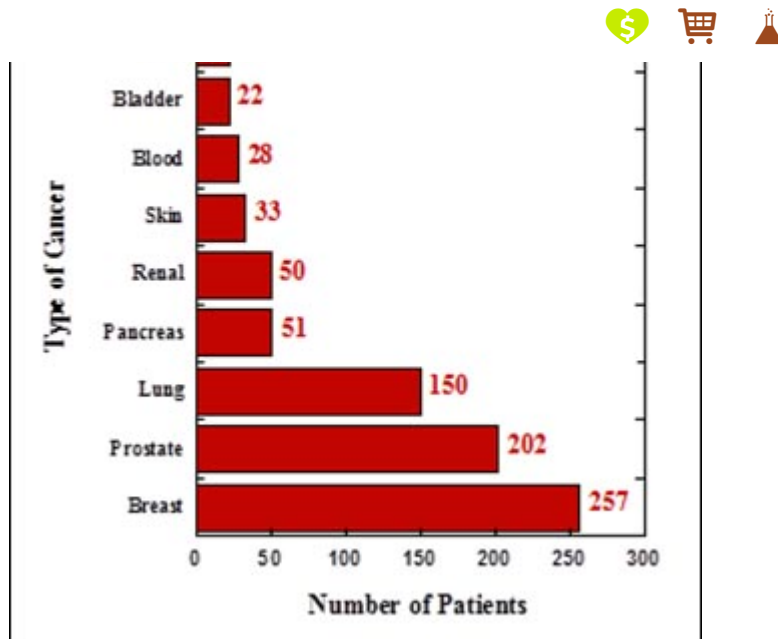
Plasma ascorbate concentrations in the millimolar range can be safely achieved with IVC infusions.

At millimolar concentrations, ascorbate is preferentially toxic to cancer cells in vitro and is able to inhibit angiogenesis in vitro and in vivo.

Vitamin C can accumulate in tumors, with significant tumor growth inhibition seen (in guinea pigs) at intra-tumor concentrations of 1 mM or higher.

Published case studies report anti-cancer efficacy, improved patient well-being, and decreases in markers of inflammation and tumor growth.

Phase I clinical studies indicate that IVC can be administered safely with relatively few adverse effects.



The Riordan clinic has treated hundreds of cancer patients (Figure 1) using the Riordan protocol. At the same time, Riordan Clinic Research Institute (RCRI) has been researching the potential of intravenous vitamin C therapy for over thirty years. Our efforts have included in vitro studies, animal studies, pharmacokinetic analyses, and clinical trials. The Riordan IVC protocol, along with the research results (by the RCRI and others) that have motivated its use, is described below.

SCIENTIFIC BACKGROUND

Pharmacokinetics

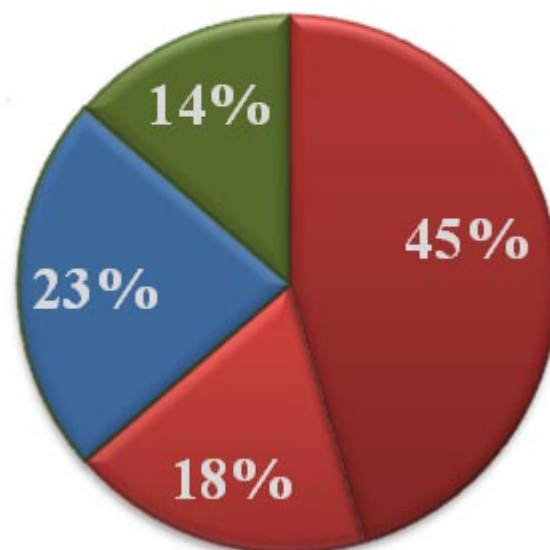
Vitamin C is water-soluble, and is limited in how well it can be absorbed when given orally. While ascorbate tends to accumulate in adrenal glands, the brain, and in some white blood cell types, plasma levels stay relatively low (Hornig, 1975; Keith & Pelletier, 1974; Ginter, et al., 1979; Kuether, et al., 1988). Data by Levine and coworkers indicate that plasma levels in healthy adults stayed below



C, with ten of those having zero detectable ascorbate in their plasma (Riordan, et al., 2005). This is shown in Figure 2. In a study of cancer patients in hospice care, Mayland and coworkers found that thirty percent of the subjects were deficiency in vitamin C (Mayland, et al., 2005). Deficiency (below 10 μM) was correlated with elevated CRP (c-reactive protein, an inflammation marker) levels and shorter survival times. Given the role of vitamin C in collagen production, immune system functioning, and antioxidant protection, it is not surprising that subjects depleted of ascorbate would fare poorly in mounting defenses against cancer. This also suggests that supplementation to replenish vitamin C stores might serve as adjunctive therapy for these patients.

Figure 2: Distribution of pre-treatment plasma ascorbate levels in terminal cancer patients: Depleted ($< 10 \mu\text{M}$), Low (10 to 30 μM), Normal (20 to 100 μM), and High ($> 100 \mu\text{M}$) (Riordan, et al., 2005).

■ Zero ■ Low ■ Norm ■ High





peak concentrations over 10 mM can be attained (Casciari, et al., 2001; Padayatty, et al., 2004) without significant adverse effects to the recipient. Figure 3 shows plasma ascorbate concentrations attained via IVC infusion at the Riordan Clinic, while Figure 4 shows pharmacokinetic data for two subjects given eighty minute IVC infusions. These peak plasma concentrations are two orders of magnitude above what is observed with oral supplementation. This suggests that IVC may be more effective than oral supplementation in restoring depleted ascorbate stores in cancer patients. Physicians at the Riordan Clinic have observed that (a) peak plasma concentrations attained after IVC infusions tend to be lower in cancer patients than in healthy volunteers, suggesting their depleted tissues act as a “sink” for the vitamin; and (b) in cancer patients given multiple IVC treatments, baseline plasma ascorbate concentrations tend to increase to normal levels slowly over time as reserves are restored with adequate IVC dosing.

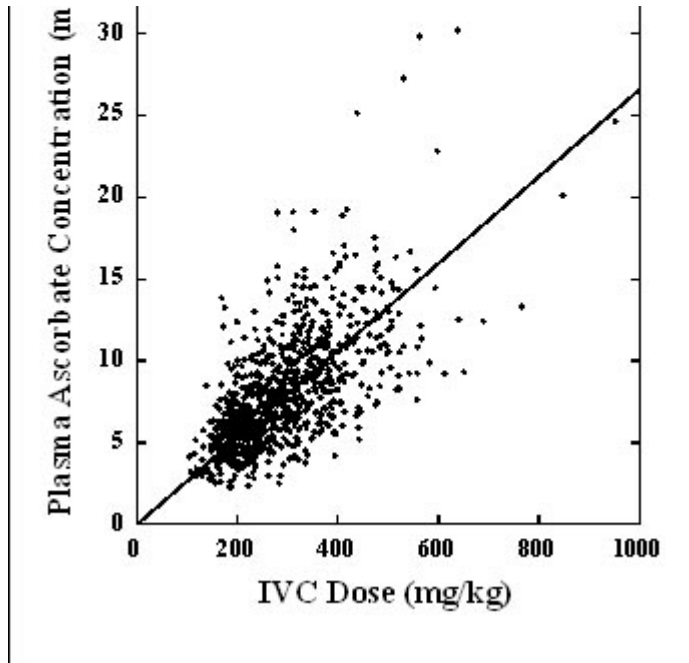


Figure 3: Peak plasma ascorbate concentrations (mM) versus IVC dose (mg/kg) for 900 subjects given treatments at the Riordan Clinic.

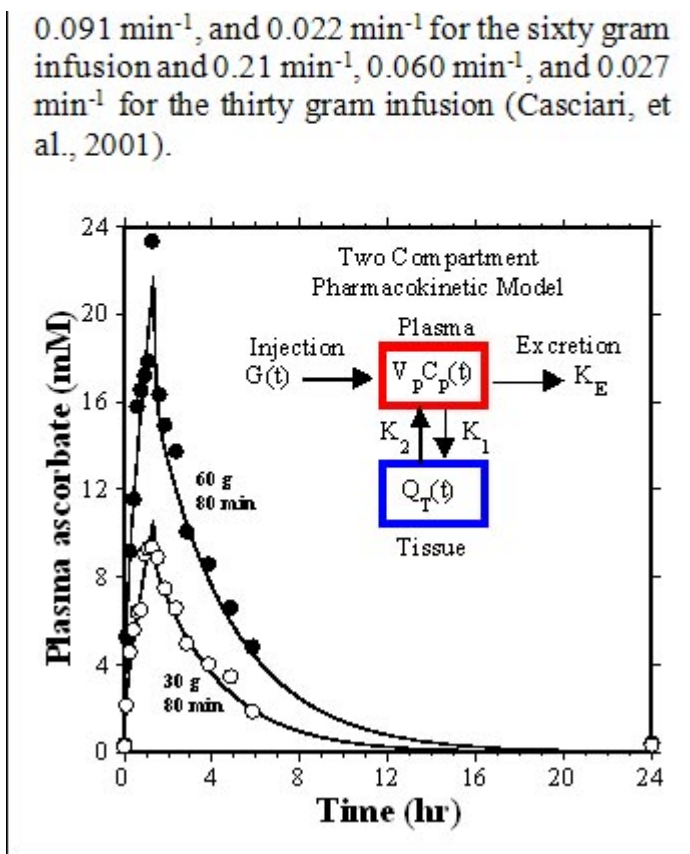


Figure 4: Vitamin C concentrations in plasma during and after an 80 min intravenous infusion of sixty (solid circles) or thirty (open circles) grams. The curves represents fits of the data to the two compartment pharmacokinetic model pictured in the figure inset, with K1, K2, and KE values of 0.31 min⁻¹, 0.091 min⁻¹, and 0.022 min⁻¹ for the sixty gram infusion and 0.21 min⁻¹, 0.060 min⁻¹, and 0.027 min⁻¹ for the thirty gram infusion (Casciari, et al., 2001).

In addition to providing ascorbate replenishment, IVC may allow oncologists to exploit some interesting anti-cancer properties, including high dose IVC’s ability to induce tumor cell apoptosis, inhibit angiogenesis, and reduce inflammation. In vitro and in vivo data supporting these potential mechanisms of action, discussed below, suggest that they may be relevant at ascorbate



1 hr. infusion would yield a peak plasma concentration of roughly 18 mM and an integral average of roughly 2.6 mM, a reasonable target for producing anti-cancer effects.

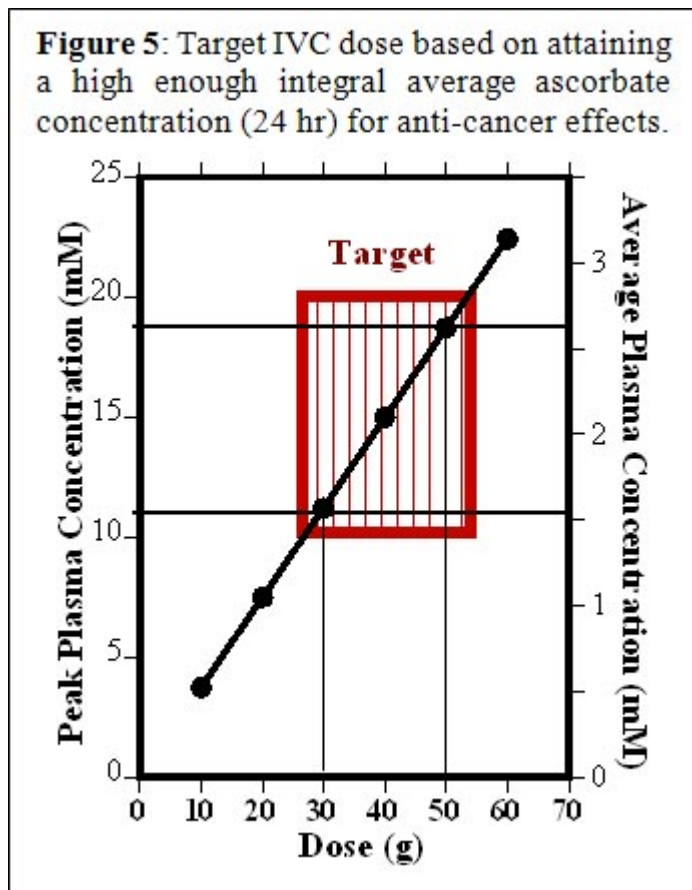


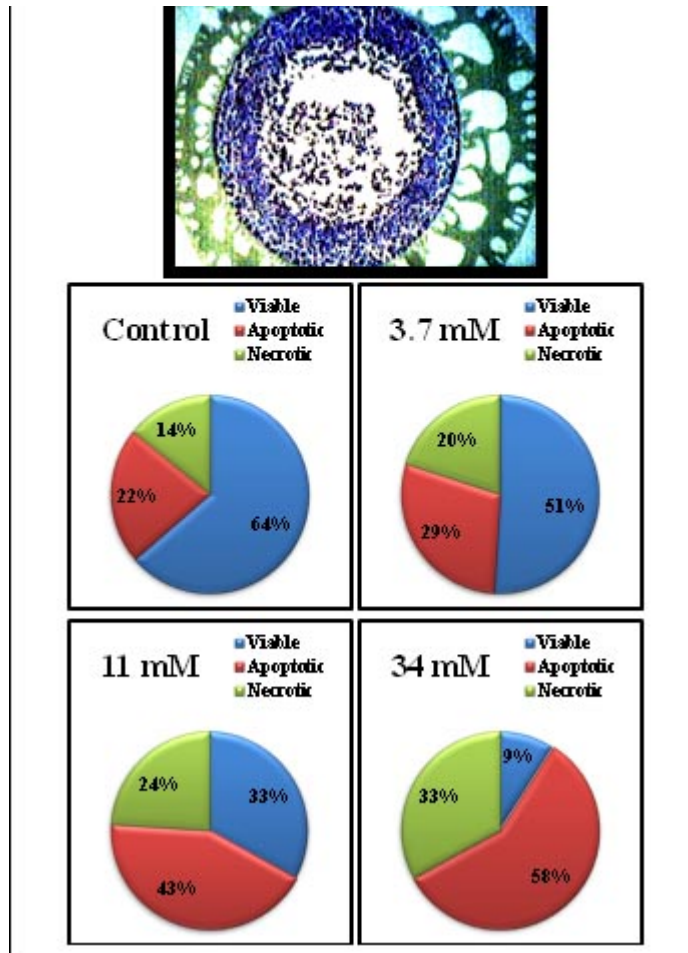
Figure 5: Target IVC dose based on attaining a high enough integral average ascorbate concentration (24 hr) for anti-cancer effects.

Peroxide-based Cytotoxicity

Vitamin C, at normal physiological concentrations (0.1 mM), is a major water-soluble antioxidant (Geeraert, 2012). At concentrations on the order of 1 mM, however, continuous perfusion of ascorbate at doses that trigger “redox cycling” can cause a build-up of hydrogen peroxide, which is preferentially toxic toward tumor cells (Benade, et



Dual staining annexin V and propidium iodide flow cytometry showed as significant increase in apoptosis, along with decreased surviving fractions, at ascorbate concentrations in the 1 mM to 10 mM range. Ascorbate concentrations required for toxicity in the HFST model (LC50 = 20 mM), with only two days incubation, were much higher than those typically observed in cell monolayers. The cytotoxic threshold could be reduced significantly (LC50 = 4 mM) by using ascorbate in combination with alpha-lipoic acid. Other reports suggest that ascorbate cytotoxicity against cancer cells can be increased by using it in combination with menadione (Verrax, et al., 2004) or copper containing compounds (Gonzalez, et al., 2002).



IVC-Protocol-Vitamin-C-Research-Riordan-Clinic-Hollow-Fiber-Tumor

Figure 6: Histological cross section of an SW620 hollow fiber tumor (HFST) along with viable, apoptotic, and necrotic fractions after 2 days ascorbate treatment (Casciari, et al., 2001).

Studies from many laboratories in a variety animal models, using hepatoma, pancreatic cancer, colon cancer, sarcoma, leukemia, prostate cancer, and mesothelioma confirm that ascorbate concentrations sufficient for its cytotoxicity can be attained in vivo, and that treatments can reduce tumor growth (Chen, et al., 2008; Verrax & Calderon, 2009; Du, et al., 2010; Belin, et al., 2009; Yeom, et al., 2009; Pollard, et al., 2010). Figure 7



measured, and the correlation between tumor mass and tumor ascorbate concentration is strong regardless of the mode of ascorbate administration. The percentage of tumor growth inhibition, relative to controls, was roughly 50% at intra-tumor ascorbate concentrations of 1 mM tumor and roughly 65% once the intra-tumor ascorbate level went above 2 mM. The ascorbate dosage used in this study was 500 mg/kg/day. Our scientists also looked at survival times of BALP/C mice with S180 sarcomas. The results are shown in Figure 8. The median survival time for the untreated mice was 35.7 days post implantation, while that for ascorbate treated mice (700 mg/kg/day) was 50.7 days. Of course, the efficacy observed in these animal studies may be due to some combination of direct cytotoxicity and other factors, such as angiogenesis inhibition (Yeom, et al., 2009) or other biological response modifications (Cameron, et al., 1979).

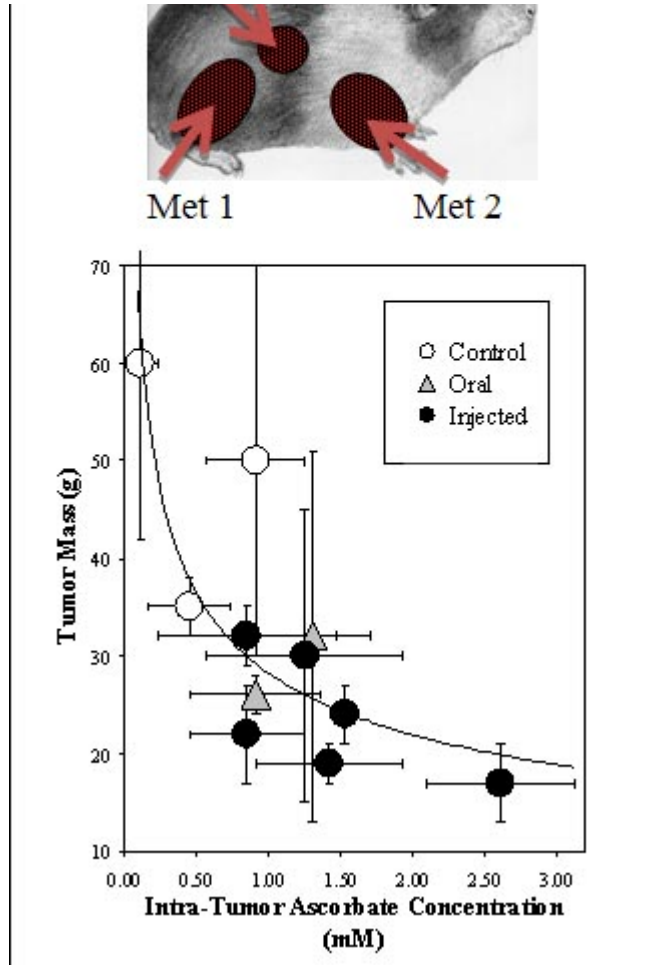


Figure 7: Correlation between intra-tumor ascorbate concentrations and tumor masses in L-10 tumor bearing guinea pigs. (Casciari, et al., 2005)

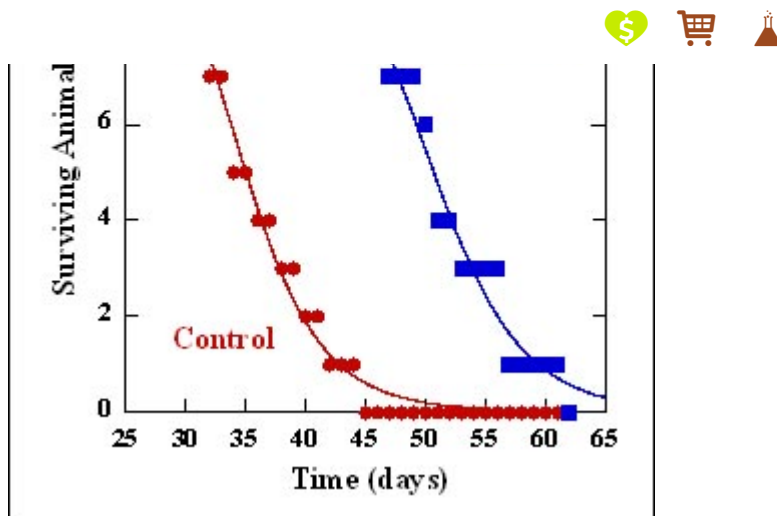


Figure 8: Survival time of sarcoma bearing BALP/C mice control and treated IP starting on day 12 with 700 mg/kg ascorbate.

Angiogenesis Inhibition

Tumor angiogenesis is the process of new blood vessel growth toward and into a tumor. It is considered to be critical in tumor growth and metastasis. Reports in the literature suggest that ascorbate's effect on collagen synthesis can act to inhibit formation of new vascular tubules (Ashino, et al., 2003), that ascorbate can inhibit genes necessary for angiogenesis (Berlin, et al., 2009), and that it might influence angiogenesis through its effect on hypoxia inducible factor (Page, et al., 2007).

The Riordan clinic researchers evaluated angiogenesis inhibition using four different experimental models. In all cases, there is an inhibitory effect on angiogenesis at ascorbate concentrations of 1 to 10 mM (Mikirova, et al., 2008; Mikirova, et al., 2012).

The growth of new micro-vessels from aortic rings ex vivo is inhibited by ascorbate at concentration 5 mM or more, as shown in Figure 9.



The rate at which endothelial cells can migrate on a petri dish to fill a gap between them was reduced when 5.7 mM ascorbate was added after the gap was created. The ascorbate also reduced ATP production in these endothelial cells by twenty percent, but did not affect cell viability.

Restores appropriate nerve function

For Matrigel plugs implanted subcutaneously in mice, the micro-vessel density was significantly lower in mice treated with 430 mg/kg every other day for two weeks.

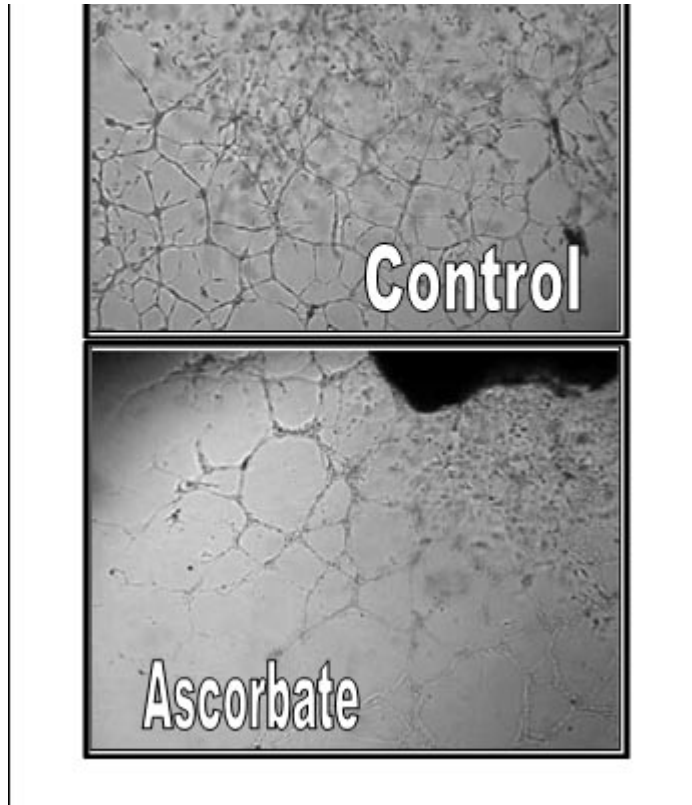


Figure 9 A): Endothelial microvessel growth out of aortic rings: control versus ascorbate treated (5.7 mM, 4 days).

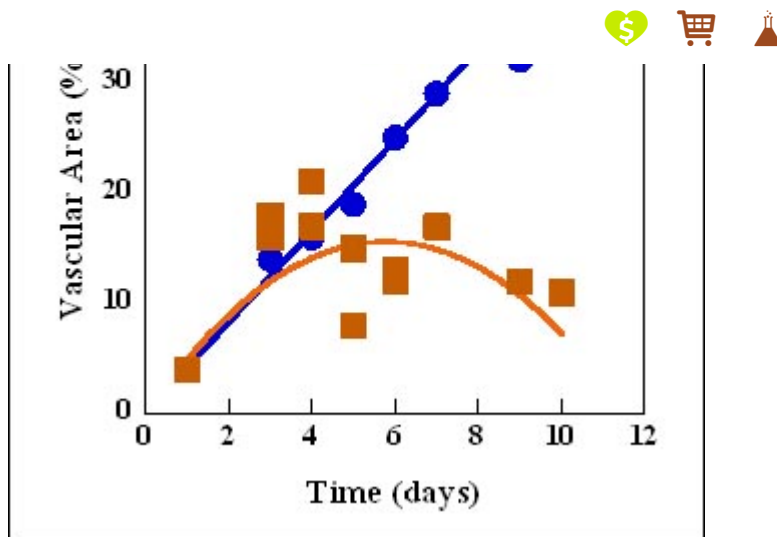


Figure 9 B): Graph of vascular area near aortic ring as a function of time (Mikirova, et al., 2012).

In animal experiments and clinical case studies where high ascorbate doses show efficacy against tumors, this benefit may represent therapeutic synergism due to both angiogenesis inhibition as well as to direct cytotoxicity or other causes.

Inflammation Modulation

Analysis of clinical data from the Riordan Clinic suggests that inflammation is an issue for cancer patients, and that it can be lessened during IVC therapy (Mikirova, et al., 2012). C-reactive protein was used as a marker of inflammation, as reports in the literature indicate that elevated CRP is correlated with poor patient prognosis (St. Sauver, et al., 2009). Over sixty percent of analyzed Riordan Clinic cancer patients had CRP levels above 10 mg/L prior to IVC therapy. In 76 3 13% of these subjects, IVC reduced CRP levels. This improvement was more prevalent, 86 3 13%, in subjects with elevated (above 10 mg/L) CRP. Comparisons of individual values before and after treatments are shown in Figure 10A. Since many of the subjects in this database were prostate cancer patients, we examined prostate specific antigen



there was a strong correlation ($r^2 = 0.62$) between the change in tumor marker and the change in CRP during IVC therapy. This is consistent with observations from the literature showing a correlation between CRP levels and PSA levels in prostate cancer patients (Lin, et al., 2010).

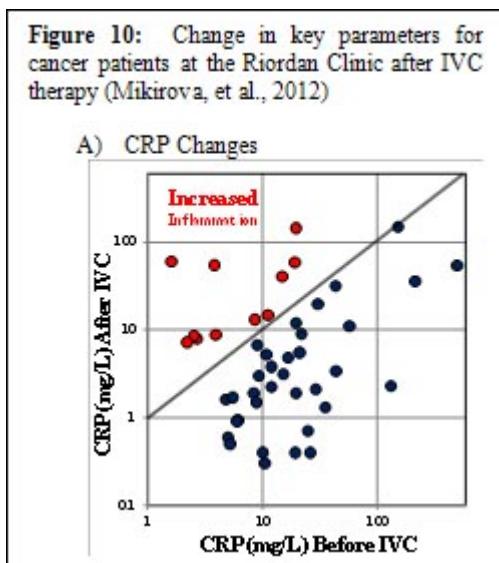


Figure 10 A): Endothelial microvessel growth out of aortic rings: control versus ascorbate treated (5.7 mM, 4 days)
A) CRP Changes

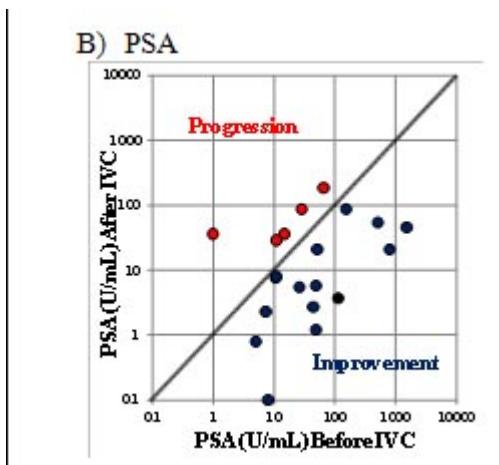


Figure 10 B): Endothelial microvessel growth out of aortic rings: control versus ascorbate treated (5.7

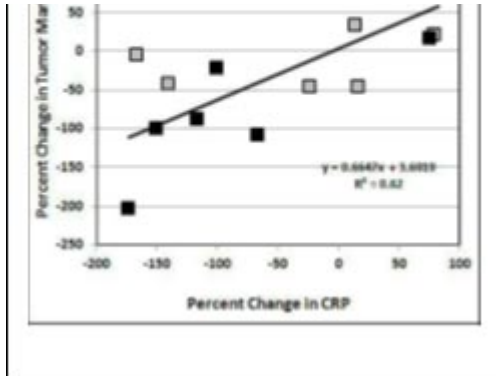


Figure 10 C): Endothelial microvessel growth out of aortic rings: control versus ascorbate treated (5.7 mM, 4 days)

C) CA Markers

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The potential effect of IVC in reducing inflammation is also supported by cytokine data: serum concentrations of the pro-inflammatory cytokines IL-1 α , IFN- γ , IL-8, IL-2, TNF- α and eotaxin were acutely reduced after a fifty gram ascorbate infusion, and in the case of the last three cytokines listed, reductions were maintained throughout the course of IVC therapy (Mikirova, et al., 2012).

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Inflammation Modulation

The observations that ascorbate is an antioxidant and that it preferentially accumulates in tumors (Agus, et al., 1999) have raised fears that ascorbate supplementation would compromise the efficacy of chemotherapy (Raloff, 2000). In support of this, Heaney and coworkers found that tumor cells in vitro and xenografts in mice were more resistant to a variety of anticancer agents when the tumor cells were pretreated with dehydroascorbic acid (Heaney, et al., 2008). Questions have been raised, however, whether the experimental conditions used in the Heaney study are clinically or biochemically relevant, considering, among other issues, that dehydroascorbic acid rather than ascorbic acid was used (Espey, et al., 2009). It should also be noted



chemotherapy or irradiation and may enhance efficacy in some situations (Fujita, et al., 1982; Okunieff & Suit, 1987; Kurbacher, et al., 1996; Taper, et al., 1996; Fromberg, et al., 2011; Shinozaki, et al., 2011; Espey, et al., 2011). This is supported by meta-analyses of clinical studies involving cancer and vitamins; these studies conclude that antioxidant supplementation does not interfere with the toxicity of chemotherapeutic regimens (Simone, et al., 2007; Block, et al., 2008).

CLINICAL DATA

Case Studies

The situation with intravenous ascorbate therapy is different from that with new chemotherapeutic agents in that FDA approval was not strictly required in order for physicians to administer IVC. As a result, clinical investigations tended to run concurrently with laboratory research. Two early studies indicated that intravenous ascorbate therapy could increase survival times beyond expectations in cancer patients (Cameron & Pauling, 1976; Murata, et al., 1982). There have been several case studies published by the Riordan Clinic team (Jackson, et al., 1995; Riordan, et al., 1998; Riordan, et al., 1996) and collaborators (Padayatti, et al., 2006; Drisko, et al., 2003). While these case studies do not represent conclusive evidence in the same way that a well-designed Phase III study would, they are nonetheless of interest for comparing methodologies and motivating future research, in addition to being of monumental importance to the individuals who were their subjects. Some key case studies are summarized here:

51 year old female with **renal cell carcinoma** (nuclear grade III/IV) and **lung metastasis** declined chemotherapy and instead chose to



Seven of eight lung masses resolved. Patient went four years without evidence of regression. Four years later, patient showed a new mass (consistent with small-cell lung cancer, not with recurrent renal carcinoma metastasis) and died shortly afterward (Padayatti, et al., 2006).

A 49 year old male with a **bladder tumor** (invasive grade 3/3 papillary transitional cell carcinoma) and **multiple satellite tumors** declined chemotherapy and instead chose to receive intravenous ascorbate. He received 30 grams twice weekly for three months, followed by 30 grams monthly for four years. Patient supplementation included botanical extract, chondroitin sulfate, chromium picolinate, flax oil, glucosamine sulfate, alpha-lipoic acid, lactobacillus acidophilus, L. rhamnosus, and selenium. Nine years after the onset of therapy, patient is in good health with no signs of recurrence or metastasis (Padayatti, et al., 2006).

A 66 year old woman with diffuse Stage III **large B-cell lymphoma** with a brisk mitotic rate and large left paraspinal mass (3.5 - 7 cm transverse and 11 cm craniocaudal) **showing evidence of bone invasion** agreed to a five-week course of radiation therapy, but refused chemotherapy and instead chose to receive intravenous ascorbate concurrent with radiation. She received 15 grams twice weekly for two months, once per week for seven months, and then once every two-three months for one year. Patient supplementation included coenzyme Q10, magnesium, beta-carotene, parasidal, vitamin B and C supplements, Parex and n-acetylcysteine. The original mass remained palpable after radiation therapy and a new mass appeared. Vitamin C therapy continued. Six weeks later, masses were not palpable. A new lymph mass was detected after four months, but the patient



cycles of chemotherapy (paclitaxel, carboplatin) combined with oral and parenteral ascorbate. Ascorbate infusion began at 15 grams twice weekly and increased to 60 grams twice weekly. Plasma ascorbate levels above 200 mg/dL were achieved during infusion. After six weeks, ascorbate treatment continued for one year, after which patient reduced infusions to once every two weeks. The patient also supplemented with vitamin E, coenzyme Q10, vitamin C, beta-carotene, and vitamin A. At the time of publication, she was over 40 months from initial diagnosis and remained on ascorbate infusions. All CT and PET scans were negative for disease, and her CA-125 levels remained normal (Drisko, et al., 2003).

A 60 year old woman with stage IIIC **adenocarcinoma of the ovary** and an initial CA-125 of 81 underwent surgery followed by six cycles of chemotherapy (paclitaxel, carboplatin) with oral antioxidants. After six cycles of chemotherapy, patient began parenteral ascorbate infusions. Ascorbate infusion began at 15 grams once weekly and increased to 60 grams twice weekly. Plasma ascorbate levels above 200 mg/dL were achieved during infusion. Treatment continued to date of publication. The patient supplemented with vitamin E, coenzyme Q10, vitamin C, beta-carotene, and vitamin A. Her CA-125 levels normalized after one course of chemotherapy. After the first cycle of chemotherapy, the patient was noted to have residual disease in the pelvis. At this point, she opted for intravenous ascorbate. Thirty months later, patient showed no evidence of recurrent disease and her CA-125 levels remained normal.



of vitamin C on quality of life in cancer patients. In a Korean study, IVC therapy significantly improved global quality of life scores, with benefits including less fatigue, reduction in nausea and vomiting, and improved appetite (Yeom, et al., 2007). In a recent German study, breast cancer patients receiving IVC along with standard therapy were compared to subjects receiving standard therapy alone (Vollbracht, et al., 2011). Patients given IVC benefited from less fatigue, reduction in nausea, improved appetite, reductions in depression and fewer sleep disorders. Overall intensity scores of symptoms during therapy and aftercare was twice as high in the control group as the IVC group. No side effects due to ascorbate were observed, nor were changes in tumor status compared to controls reported.

Phase I Clinical Trials

The safety of intravenous ascorbate has been addressed in recently published Phase I clinical studies (Riordan, et al., 2005; Hoffer, et al., 2008; Monti, et al., 2012). The first Phase I study was conducted with twenty-four terminal cancer patients (mostly liver and colorectal cancers) (Riordan, et al., 2005). The study used doses up to 710 mg/kg/day. Figure 11 shows how parameters associated with renal function changed during the course of treatment. These indicators remained steady or decreased over time; this is significant since they would be expected to rise during treatment if ascorbate was having an acute detrimental effect on renal function. Blood chemistries suggested no compromise in renal function, and one patient showed stable disease, continuing treatment for an additional 48 weeks. Adverse effects reported were mostly minor (nausea, edema, dry mouth or skin). Two grade three adverse events “possible related” to the agent were reported: a kidney stone in a patient with a history of renal calculus and a patient who

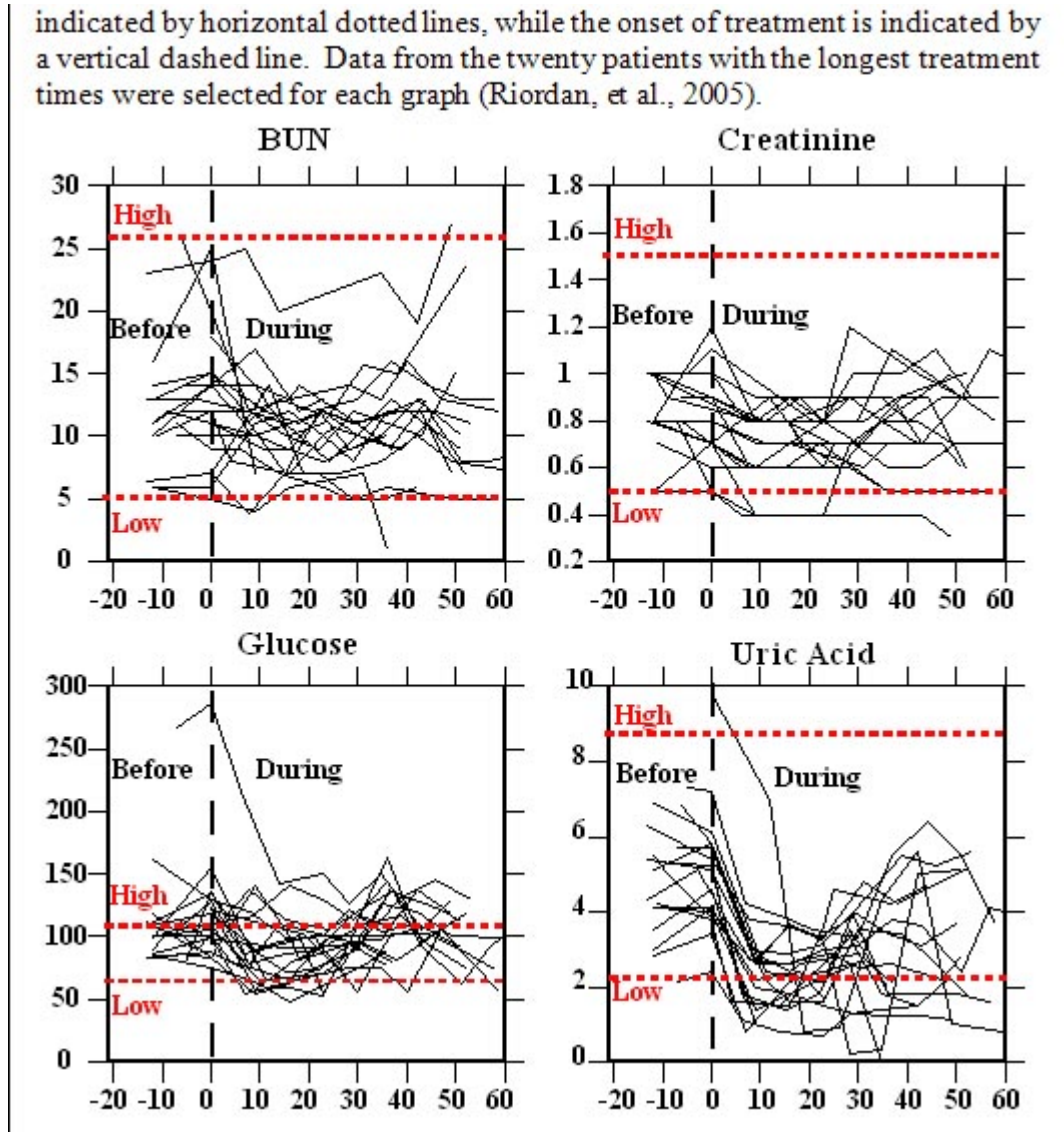


Figure 11: BUN, creatinine, uric acid and glucose levels in patients as a function of time from the onset of therapy (days). Normal range limits are indicated by horizontal dotted lines, while the onset of treatment is indicated by a vertical dashed line. Data from the twenty patients with the longest treatment times were selected for each graph (Riordan, et al., 2005).

In the study by Hoffer and coworkers (Hoffer, et al., 208), twenty-four subjects with advanced cancer or



quality of life, but no objective anti-cancer response was reported. The study by Monti and coworkers (Monti, et al., 2012), fourteen patients received IVC in addition to nucleoside analogue gemcitabine and the tyrosine kinase inhibitor erlotinib. Observed adverse events were attributable to the chemotherapeutic agents, but not to the ascorbate, but no added efficacy due to the ascorbate was observed.

Thus far, Phase I studies indicate that IVC can be safely administered to terminal cancer patients at high doses (10 to 100 grams or more), but anti-cancer efficacy of the sort reported in case studies has not yet been observed. Of course, the terminal subjects used in Phase I studies would be expected to be the most difficult to treat. Phase II studies, with longer durations, are needed at this point.

Safety Issues Reported In Literature

Evidence indicates that patients who show no prior signs or history of renal malfunction are unlikely to suffer ill effects to their renal systems as a result of intravenous ascorbate (Riordan, et al., 2005). In cases where there are preexisting renal problems, however, caution is advised. In addition a kidney stone forming in one patient with a history of stone formation (Riordan, et al., 2005), a patient with bilateral urethral obstruction and renal insufficiency suffered acute oxalate neuropathy (Wong, et al., 1994). A full blood chemistry and urinalysis work-up is thus recommended prior to the onset of intravenous ascorbate therapy.

Campbell and Jack (Campbell & Jack, 1979) reported that one patient died due to massive tumor necrosis and hemorrhaging following an initial dose of intravenous ascorbate. It is thus recommended that treatment start at a low dose and be carried out using slow “drip” infusion. Fatal Hemolysis can occur if a patient has glucose-6-



overload, and inadequate hydration or urine void volume (Rivers, 1987).

THE RIORDAN IVC PROTOCOL

Inclusion Criteria and Candidates

1. Candidates include those who have failed standard treatment regimens; those seeking to improve the effectiveness of their standard cancer therapy; those seeking to decrease the severity and carcinogenicity of side effects from standard cancer therapy; those attempting to prolong their remission with health-enhancing strategies; those declining standard treatment, yet wishing to pursue primary, alternative treatment.
2. Patient (guardian or legally recognized caregiver) must sign a consent-to-treat or release form for the IVC treatment. Patient should have no significant psychiatric disorder, end-stage CHF, or other uncontrolled co-morbid conditions.
3. Obtain baseline and screening laboratory:
 - a. Serum chemistry profile with electrolytes
 - b. Complete blood count (CBC) with differential
 - c. Red blood cell G6PD (must be normal)
 - d. Complete urinalysis
4. In order to properly assess the patient's response to IVC therapy, obtain complete patient record information prior to beginning IVC therapy:
 - a. Tumor type and staging, including operative reports, pathology reports, special procedure reports, and other staging information. (Re-staging may be



- d. The patient's functional status with an ECOG Performance Score.
- e. Patient weight.

Precautions and Side Effects

In the Riordan Clinic's experience giving over 40,000 onsite IVC treatments, the side-effects of high-dose IVC are rare. However, there are precautions and potential side-effects to consider.

1. The danger of diabetics on insulin incorrectly interpreting their glucometer finger stick has been found. It is important to notice to health care workers using this protocol for the treatment of cancer in patients who are also diabetic: high dose intravenous vitamin C (IVC) at levels 15 grams and higher will cause a false positive on finger-stick blood glucose strips (electrochemical method) read on various glucometers (Jackson & Hunninghake, 2006). Depending on the dose, the false positive glucose and occasionally "positive ketone" readings may last for eight hours after the infusion. Blood taken from a vein and run in a laboratory using the hexokinase serum glucose method is not affected! The electrochemical strip cannot distinguish between ascorbic acid and glucose at high levels. Oral vitamin C does not have this effect. Please alert any diabetic patients of this potential complication! Diabetics wishing to know their blood sugar must have blood drawn from a vein and run in the laboratory using the hexokinase glucose determination method.
2. Tumor necrosis or tumor lysis syndrome has been reported in one patient after high-dose IVC (Campbell & Jack, 1979). For this reason, the protocol always begins with a small 15 gram dose.



oxalate stones during or following IVC is negligible (Riordan, et al., 2005).

4. Hemolysis has been reported in patients with G6PD deficiency when given high-dose IVC (Campbell, et al., 1975). The G6PD level should be assessed before beginning IVC. (At the Riordan Clinic, G6PD readings have yielded five cases of abnormally low levels. Subsequent IVC at 25 grams or less showed no hemolysis or adverse effects.)
5. IV site irritation may occur at the infusion site when given in a vein and not a port. This can be caused by an infusion rate exceeding 1.0 gram/minute. The protocol suggests adding magnesium to reduce the incidence of vein irritation and spasm.
6. Due to the chelating effect of IVC, some patients may complain of shakiness due to low calcium or magnesium. An additional 1.0 mL of MgCl added to the IVC solution will usually resolve this. If severe, it can be treated with an IV push of 10 mL's of calcium gluconate, 1.0 mL per minute.
7. Eating before the IVC infusion is recommended to help reduce blood sugar fluctuations.
8. Given the amount of fluid used as a vehicle for the IVC, any condition that could be adversely affected by fluid or sodium overload (the IV ascorbate is buffered with sodium hydroxide and bicarbonate) is a relative contraindication; i.e. congestive heart failure, ascites, edema, etc.
9. There have been some reports of iron overload with vitamin C therapy. We have treated one patient with hemochromatosis with high-dose IVC with no adverse effects or significant changes in the iron status.
10. As with any I.V. infusion, infiltration at the site is possible. This is usually not a problem with ports. Our nursing staff has found that using #23 Butterfly needles with a shallow insertion



- can develop nausea, shakes, and chills.)
12. It should never be given as an IV push, as the osmolality at high doses may cause sclerosing of peripheral veins, nor should it be given intramuscularly or subcutaneously. The accompanying table lists the calculated osmolality of various amounts of fluid volume. Our experience has found that an osmolality of less than 1200 mOsm/kg H₂O is tolerated by most patients. A low infusion rate (0.5 grams IVC per minute) also reduces the tonicity, although up to 1.0 grams per minute can be used in order to achieve higher post IVC saturation levels. (Pre and post serum osmolality measurements are advisable at this dose.)
 13. We presently use a sodium ascorbate solution, MEGA-C-PLUS®, 500 mg/mL, pH range 5.5-7.0 from Merit Pharmaceuticals, Los Angeles, CA, 90065.

Ascorbate Mass(g) → Vol [†] (cc) ([†] 500 mg/mL stock)	Recommended Dilution and Osmolarity	
	Dilute	mOsm/L
15 g → 30 cc	250 mL Ringers	909
25 g → 50 cc	500 mL Ringers	795
50 g → 100 cc	500 mL H ₂ O	1097
75 g → 150 cc	750ml H ₂ O	1088
100 g → 200 cc	1000 ml H ₂ O	1085



	Ringer Lactate	Sterile water				
15 grams (30cc)	250 cc		31cc	219 cc	30 cc	1 cc
25grams (50cc)	500cc		51cc	449cc	50cc	1cc
50 grams (100cc)		500cc	102cc	398 cc	100 cc	2cc
75 grams (150cc)		750cc	152cc	598cc	150cc	2cc
100grams		1000cc	202cc	798cc	200cc	2cc

Table 2: Treatment Volume of Ascorbic Acid

Administration of IVC

Having taken all precautions listed above and having obtained informed consent from the patient, the administering physician begins with a series of three consecutive IVC infusions at the 15, 25, and 50 gram dosages followed by post IVC plasma vitamin C levels in order to determine the oxidative burden for that patient so that subsequent IVCs can be optimally dosed.

The initial three infusions are monitored with post IVC infusion plasma vitamin C levels. As noted above (Scientific Rational), research and experience has shown that a therapeutic goal of reaching a peak-plasma concentration of ~20 mM (350- 400 mg/dL) is most efficacious. (No increased toxicity for post IVC plasma vitamin C levels up to 780 mg/dL has been observed.) The first post IVC plasma level following the 15 gram IVC has been shown to be clinically instructive: levels below 100 mg/dL correlate with higher levels of existent oxidative stress, presumably from higher tumor



lab. If the initial 50 gram post IVC level did not reach the therapeutic range of 350 - 400 mg/dL, another post IVC vitamin C level should be obtained after the next scheduled 50 gram IVC. If the therapeutic range is achieved, the patient is continued on a 50 gram twice a week IVC schedule with monthly post IVC determinations to assure continued efficacy. If the therapeutic range is still not achieved, the IVC dosage is increased to 75 grams of vitamin C per infusion for four infusions, at which time a subsequent post IVC plasma level is obtained. If the patient remains in a sub-therapeutic range, the IVC dosage is increased to the 100 gram level.

If after four infusions the post IVC dosage remains sub-therapeutic, the patient may have an occult infection, may be secretly smoking, or may have tumor progression. While these possibilities are being addressed, the clinician can elect to increase the 100 gram IVC frequency to three times per week. Higher infusion doses beyond 100 grams are not recommended without serum osmolality testing before and after infusions in order to properly adjust the infusion rate to maintain a near physiologic osmolality range.

If higher dosages are not tolerated, or there is tumor progression in spite of achieving the therapeutic range, lower dosages can still augment the biological benefits of IVC, including enhanced immune response, reduction in pain, increased appetite, and a greater sense of well-being.

Very small patients, such as children, and very large obese patients need special dosing. Small patients < 110 lbs. with small tumor burdens and without infection may only require 25 gram vitamin C infusions 2x/week to maintain therapeutic range. Large patients > 220 lbs. or patients with large tumor burdens or infection are more likely to



reaching therapeutic range should still be monitored monthly with post IVC plasma levels to ensure that these levels are maintained long term. We advise patients to orally supplement with at least 4 grams of vitamin C daily, especially on the days when no infusions are given, to help prevent a possible vitamin C “rebound effect.” Oral alpha lipoic acid is also recommended on a case by case basis.

CONCLUSIONS

Vitamin C can be safely administered by intravenous infusion at maximum doses of one-hundred grams or less, provided the precautions outlined in this report are taken. At these doses, peak plasma ascorbate concentrations can exceed 20 mM.

There are several potential benefits to giving IVC to cancer patients that make it an ideal adjunctive care choice:

Cancer patients are often depleted of vitamin C, and IVC provides an efficient means of restoring tissue stores.

IVC has been shown to improve quality of life in cancer patients by a variety of metrics.

IVC reduces inflammation (as measured by c-reactive protein levels) and reduces the production of pro-inflammatory cytokines.

At high concentrations, ascorbate is preferentially toxic to tumor cells and is an angiogenesis inhibitor.



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IVC Patents:

[5639787](#) – Therapeutic method for the treatment of cancer

[6284786](#) – Treatment of cancer using lipoic acid in combination with ascorbic acid

[6448287](#) – Treatment of cancer using lipoic acid in combination with ascorbic acid

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