Intravenous ascorbic acid protocol for cancer patients: scientific rationale, pharmacology, and clinical experience

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ABSTRACT:

Background: Ascorbic acid (vitamin C, ascorbate) has been shown to protect cells against various types of oxidant injury at physiologically relevant concentrations. Vitamin C has been suggested as having both   a preventative and therapeutic role in a number of pathologies when administered at much higher-than-recommended dietary allowance levels**.** This article reviews the scientific rational for intravenous vitamin   C as a potential treatment for cancer.

Many mechanisms of action for ascorbate efficacy against cancer have been proposed over the years. Cancer patients are often deficient in vitamin C, and require large doses to replenish depleted stores. It has been demonstrated *in vitro* and in animal studies that vitamin C is preferentially toxic to tumor cells at millimolar concentrations; moreover, pharmacokinetic data suggest that these concentrations are clinically achievable when ascorbate is administered intravenously. Data suggests that ascorbate may serve as a biological response modifier, affecting inflammation and angiogenesis as well as improving immune function parameters.

While Phase II clinical trials using ascorbate in cancer therapy are under way, vitamin C is not subject to the regulations that synthetic drugs are and therefore has been used clinically for decades to treat cancer patients. This clinical experience suggests the therapy is safe, and may be effective in some instances. Attached to this article is the Riordan IVC Protocol, which details an intravenous vitamin C protocol that can be safely administered to cancer patients.

Keywords: Cancer, inflammation, C-reactive protein, inflammatory cytokines, high-dose vitamin C

INTRODUCTION:

Vitamin C is a major water-soluble antioxidant that increases extracellular collagen production and is important for proper immune cell functioning [1, 2]. It plays key roles in L-carnitine synthesis, cholesterol metabolism, cytochrome P-450 activity, and neurotransmitter synthesis [3].

Intravenous vitamin C (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 [4, 5]. While IVC may have a variety of possible applications, such as combating infections [6], treating rheumatoid arthritis [7], or treating fatigue, it has generated the most interest for its potential use in adjunctive cancer care.

Vitamin C was first suggested as a tool for cancer treatment in the 1950's; its role in collagen production and protection led scientists to hypothesize that ascorbate replenishment would protect normal tissue from tumor invasiveness and metastasis [2, 8]. Also, since cancer patients are often depleted of vitamin C [1, 9], replenishment may improve immune system function and enhance patient health and well-being [10]. Cameron and Pauling observed fourfold survival times in terminal cancer patients treated with intravenous ascorbate infusions followed by oral supplementation [11]. However, two randomized clinical trials with oral ascorbate alone conducted by the Mayo clinic showed no benefit [12, 13]. Most research from that point is 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:

- 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 (study with guinea pigs) at intra-tumor concentrations of 1 mM or higher.
- Plasma ascorbate concentrations in the millimolar range can be safely achieved with IVC infusions. Phase I clinical studies indicate that IVC can be administered safely with relatively few adverse effects.
- Published case studies report anti-cancer efficacy, improved patient well-being, and decreases in markers of inflammation and tumor growth.

The Riordan Clinic has treated hundreds of cancer patients (Figure 1) using the developed protocol.

We have 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 trial. The Riordan IVC protocol, along with the research results that have motivated its use, is described below.

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 [14-16]. According to the study [17], the plasma levels in healthy adults stayed below 100 μM, even if 2.5 grams were taken when administered once daily by the oral route.

Cancer patients tend to be depleted of vitamin C: fourteen out of twenty-two terminal cancer patients in our phase I study were depleted of vitamin C, with ten of those having zero detectable ascorbate in their plasma [9]. In a study of cancer patients in hospice care, thirty

percent of the subjects were deficient in vitamin C [18]. Deficiency (below 10 µM) was correlated with elevated inflammation marker C-reactive protein (CRP) 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.
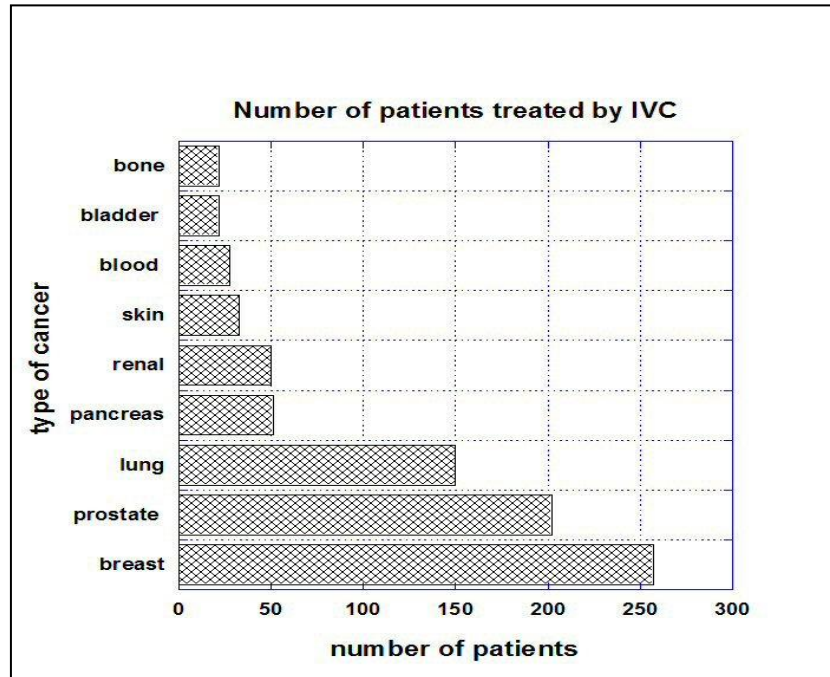
Figure 1. Types of cancers treated with IVC by the Riordan Clinic. Cancer patients from the database of patients for whom plasma ascorbic acid levels before and after treatment were available along with laboratory tests of inflammation marker CRP and cancer markers.

When vitamin C is given by intravenous infusion, peak concentrations over 10 mM can be attained [19, 20] without significant adverse effects to the recipient. Figure 2 shows plasma ascorbate concentrations attained via IVC infusion, while Figure 3 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. Using the pharmacokinetic model shown in Figure 3, a 50 gram infusion over one hour would yield a peak plasma concentration of about 18 mM. This suggests that IVC may be more effective than oral supplementation in restoring depleted ascorbate stores in cancer patients.

The pharmacokinetic data can be summarized as follows: IVC produces peak plasma ascorbate concentrations (30-50 min after beginning of infusion) on the order of ten millimolars. Results are highly variable from patient to patient, with the following tendencies observed:

• Lower peak plasma concentrations are obtained in cancer patients than in healthy subjects. Figure 4 shows peak plasma ascorbate concentrations attained after 25 gram IVC

infusions in cancer patients and healthy volunteers. Cancer patients who are deficient in vitamin C prior to therapy tend to achieve lower plasma levels post infusion.

• Patients with higher inflammation or tumor burdens, as measured by CRP levels or tumor antigen levels, tend to show lower peak plasma ascorbate levels after IVC (Figure 5, data for inflammation [22]).

•Patients with metastatic tumors tend to achieve lower post infusion plasma ascorbate levels than those with localized tumours (Figure 6, [22]).
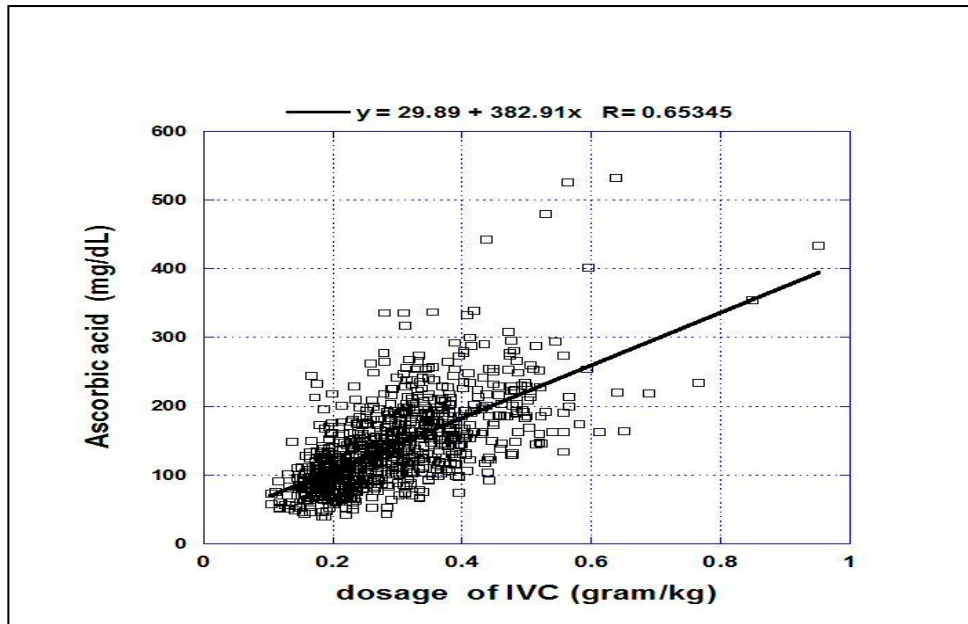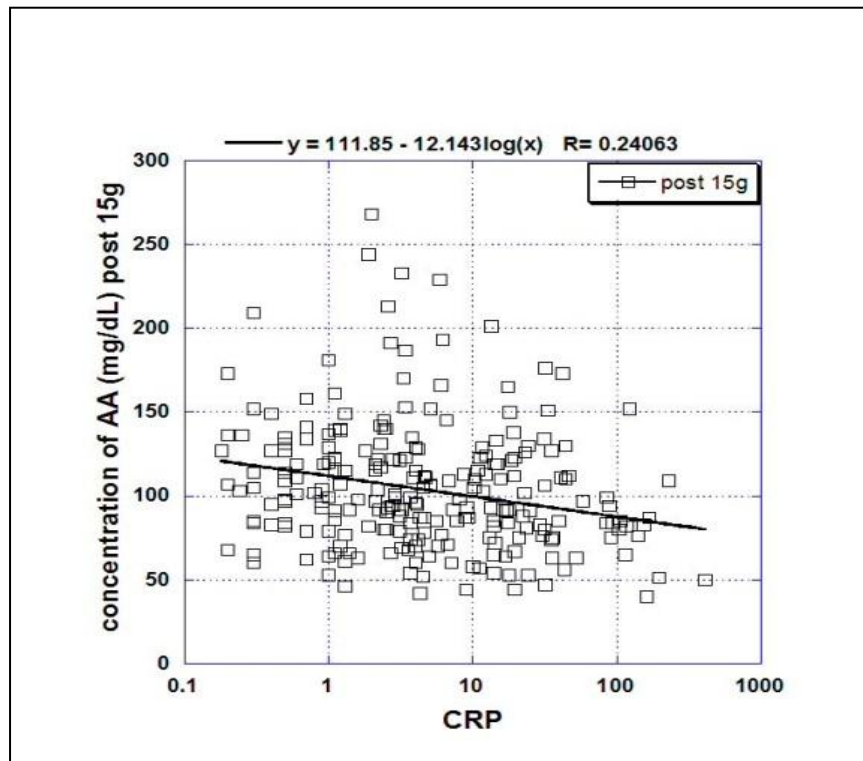

Figure 2. Peak plasma ascorbate concentrations (mg/dL) versus IVC dose (mg/kg) for 900 subjects given treatments at the Riordan Clinic
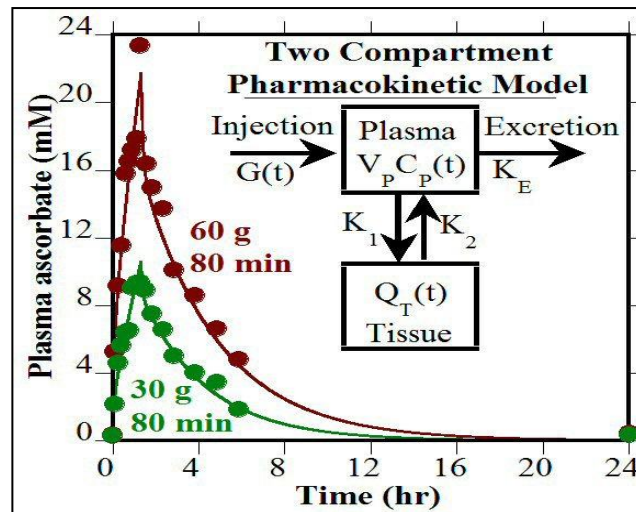
Figure 3. Vitamin C concentrations in plasma during and after an 80 min intravenous infusion of sixty or thirty grams IVC. The curves represent fits of the data to the two compartment pharmacokinetic model pictured in the figure inset [21].
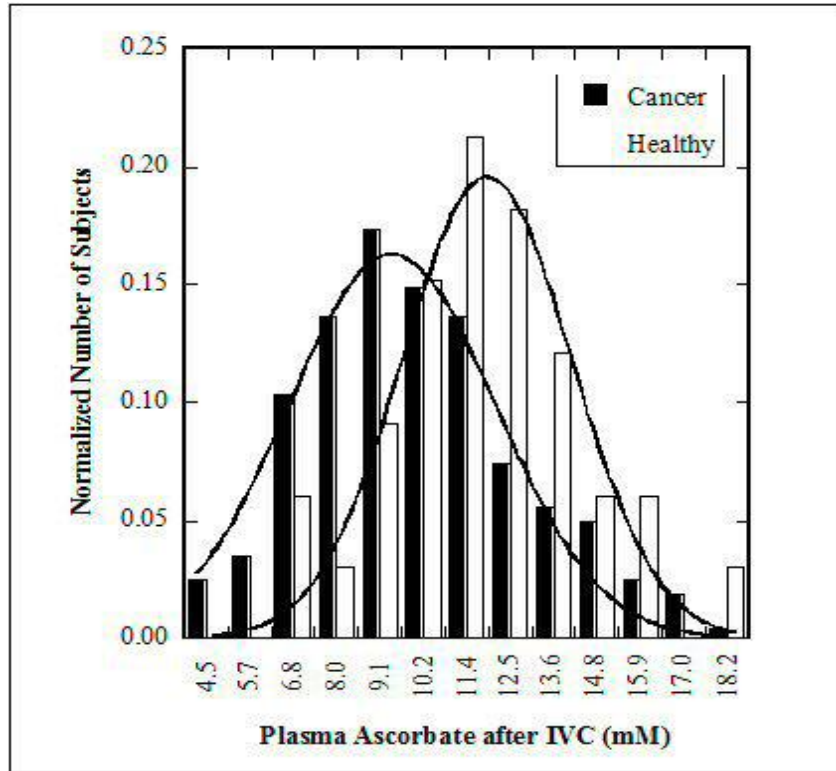
Figure 4. Distribution of peak plasma ascorbate levels in healthy adults and cancer patients given 25grams IVC [22]

Figure 5. Plasma concentration in mg/dL after 15g IVC as a function of CRP.
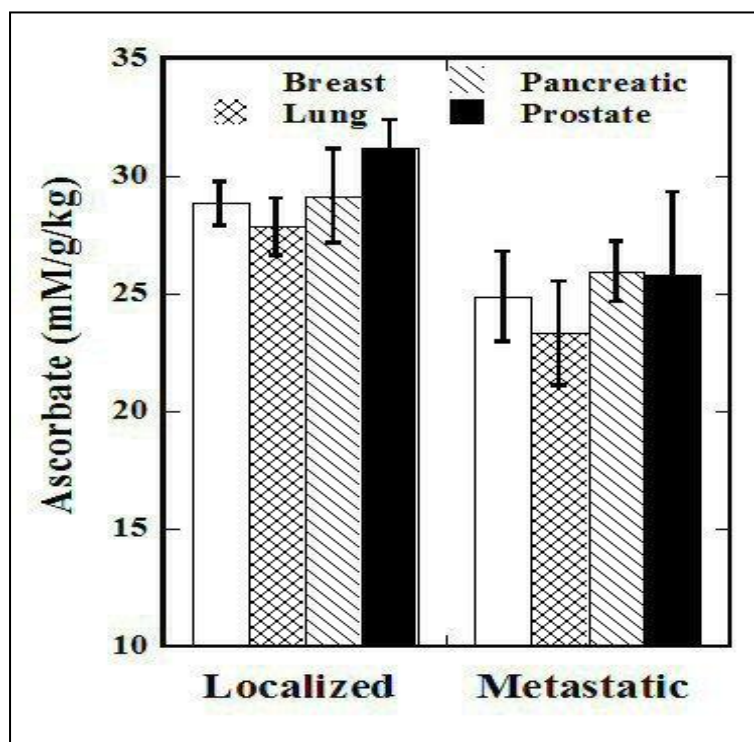
Figure 6. Mean value of the relative plasma ascorbate (plasma concentration in mM divided by dose in g/kg) in patients with various types of localized or metastatic cancer after their first 15 gram IVC infusion.

In addition to providing ascorbate replenishment, IVC may allow oncologists to exploit some important anti-cancer properties, including high dose IVC's ability to induce tumor cell apoptosis, inhibition of angiogenesis, and reduction of inflammation. *In vitro* and *in vivo* data supporting these potential mechanisms of action, discussed below, suggest that they may be relevant at ascorbate concentrations on the order of millimoles.

Peroxide-based Cytotoxicity: Vitamin C, at normal physiological concentrations (0.1 mM), is an antioxidant [3]. At concentrations on the order of 1 mM ascorbate can cause a build-up of hydrogen peroxide, which is preferentially toxic toward tumor cells [19, 23-26], leading to autophagy or apoptosis. In addition, the data presented in studies [24, 25] show that ascorbic acid selectively killed cancer but not normal cells, using concentrations that could only be achieved by IVC.

To examine the cytotoxic effect in a three dimensional model, we employed hollow-fiber *in vitro* solid tumor model (HFST), in which colon cancer cells were grown inside hollow fibers [19]. Ascorbate concentrations required for toxicity in this model (LC_{50} = 20 mM), were much higher than those typically observed in cell monolayers. Moreover, the cytotoxic threshold could be reduced significantly (LC_{50} = 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 [27] or copper containing compounds [28].

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 [29-34].

We analyzed the effect of ascorbic acid on tumor suppression by using the L-10 model in guinea pigs [35]. The animal study was approved by the Institutional Review Board and conducted in accordance with the Office of Laboratory Animal Welfare regulation. The ascorbate dosage used in this study was 500 mg/kg/day. The overall tumor burden (primary plus metastases) was then determined after 30 days of tumor growth and 18 days of ascorbate therapy. The intra-tumor ascorbate concentrations were measured, and it was found that the correlation between tumor mass and tumor ascorbate concentration is strong regardless of the mode of ascorbate administration (Figure 7). The precentage of tumor growth inhibition, relative to controls, was roughly 50% at intra-tumor ascorbate concentrations of 1 mM and roughly 65% once the intra-tumor ascorbate level went above 2 mM.
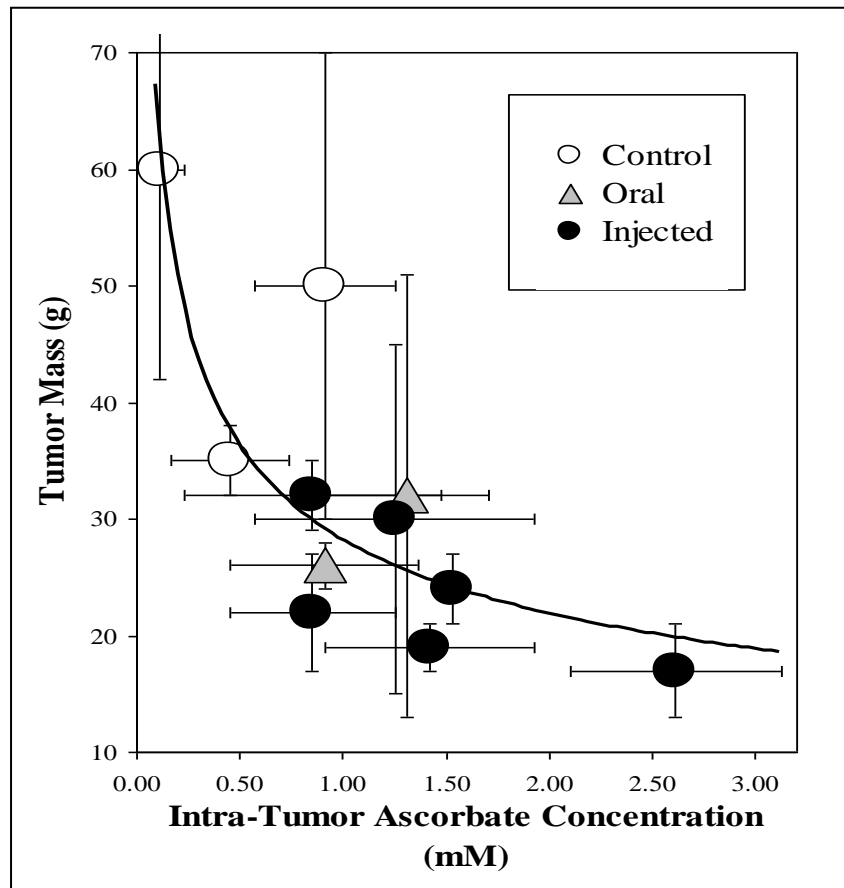
Figure 7. Correlation between intra-tumor ascorbate concentrations and tumor masses in L-10 tumor bearing quinea pigs.

In addition, we looked at survival times of BALP/C mice with S180 sarcomas. The mice were inoculated by S-180 sarcoma cells ($1*10^6$ cells/mouse) subcutaneously in front left armpit.

After 12 days 0.1ml of ascorbic acid at the concentration of 700mg/kg/day was administered once every other day around the tumor intraperitoneally (IP). The control group was injected by the same volume of normal saline. The survival time results are shown in Figure 8. The median survival time for the untreated mice was 35.7 days post implantaion, while that for ascorbate treated mice was 50.7 days. The efficacy observed in these animal studies may be due to some combination of direct cytotoxicity and other factors, such as angiogenesis inhibition [33] or other biological response modifications [2].
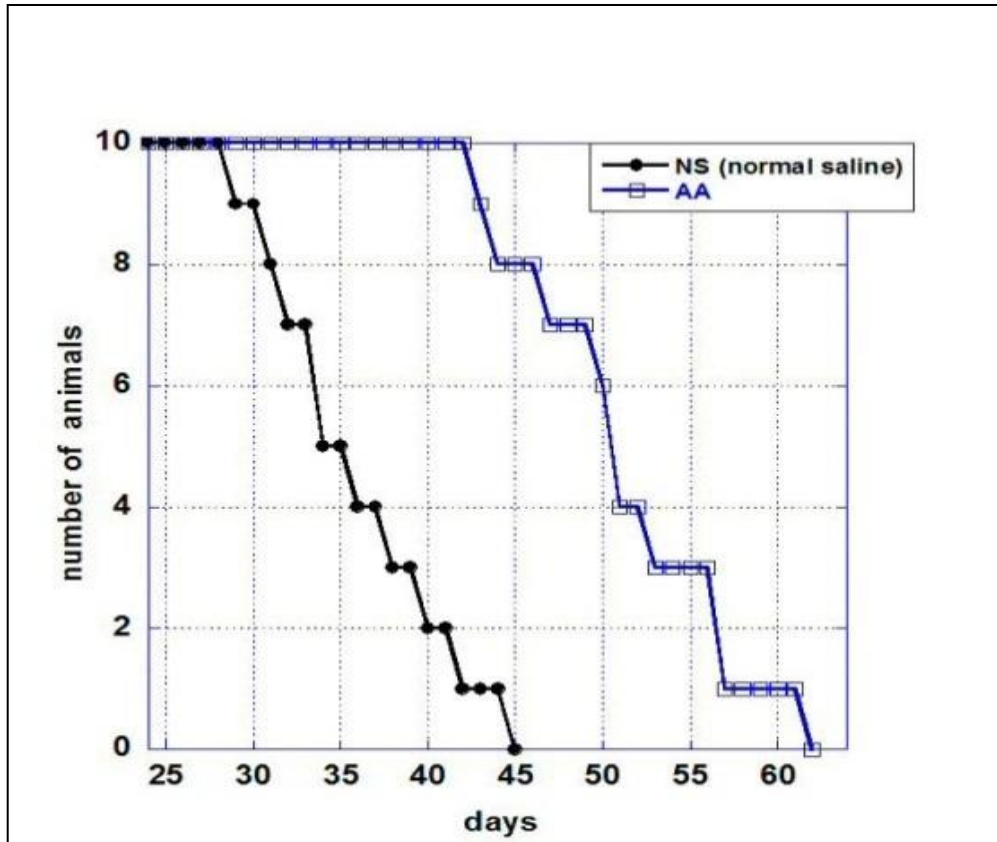

Figure 8. Survival time of sarcoma bearing BALP/C mice control and treated IP starting on day 12 with 700 mg/kg ascorbate

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 [36], that ascorbate can inhibit genes necessary for angiogenesis [32], and that it might influence angiogenesis through its effect on hypoxia inducable factor [37].

In our studies the angiogenesis inhibition was evaluated using several different experimental models [7, 38]. We examined the effects of ascorbate at levels, relevant during intravenous infusion therapy, on angiogenesis using an *ex vivo* rat aortic ring assay, an *in vivo* Matrigel plug assay, and an *in vitro* Matrigel assay. In all cases, there is an inhibitory effect on angiogenesis at millimolar concentrations of ascorbate. According to our data, concentrations of

ascorbate higher than 100 mg/dl suppressed capillary-like tube formation on Matrigel for all cells tested (Figure 9), and the effect was more pronounced for progenitor cells in comparison with mature cells. In addition, cell migration was assessed using an *in vitro* wound healing model. The rate at which endothelial cells can migrate on a petri dish to fill a gap between them was reduced when millimolar concentrations of ascorbate were added. These dosages reduced ATP production in cells less than 20% and did not affect viability. The results of these experiments showed an inverse correlation between concentration of ascorbate and rate of cell migration.
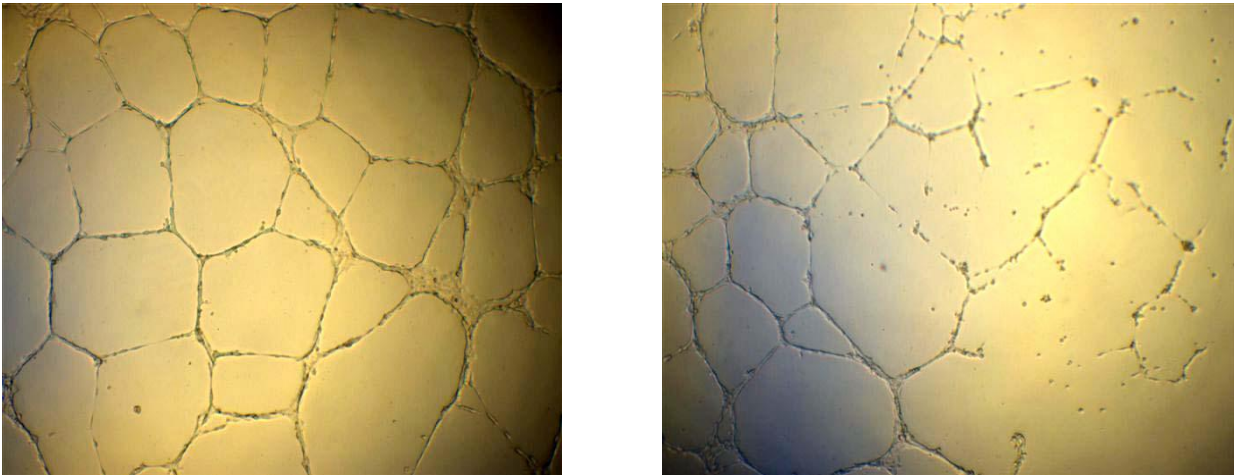
Figure 9. The effect of high doses of ascorbic acid on capillary tube formation by mature endothelial cells. Capillary tube formation by HUVECs in control well without addition of ascorbate (left) and in well treated by 3 mg/ml of ascorbic acid (right).

The growth of new micro-vessels from aortic rings *ex vivo* is inhibited by ascorbate at concentrations 5mM or more, as shown in Figure 10.
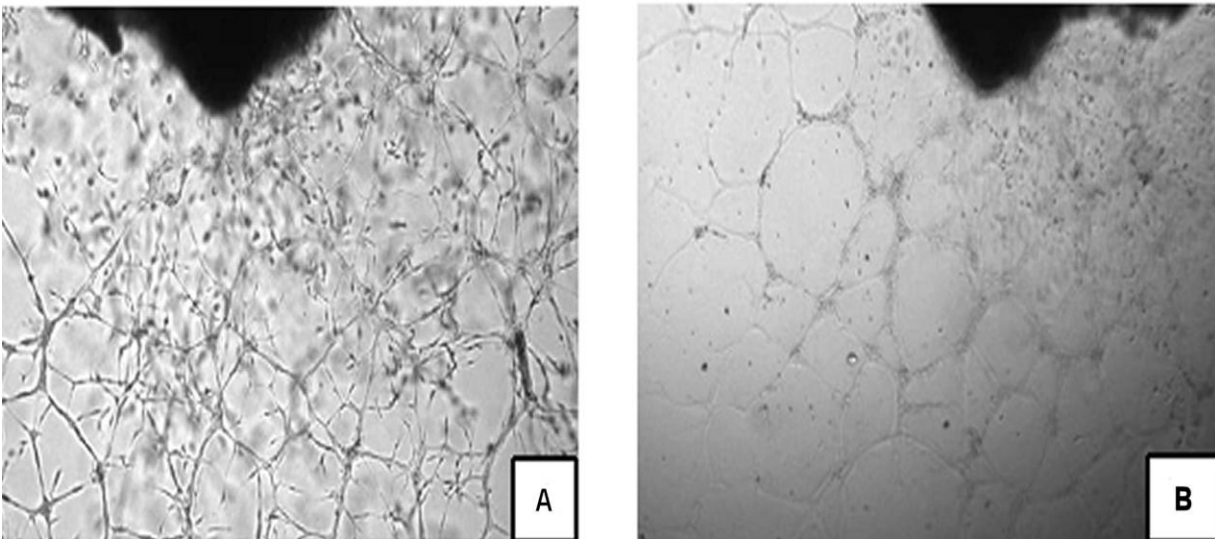
Figure 10. Endothelial microvessel growth out of aortic rings: control (A) versus treated by 5mM of ascorbate (B).

For Matrigel plugs implanted subcutaneously in mice, the micro-vessel densities were significantly lower in mice treated with 400 mg/kg every other day for two weeks; numbers of vessels and vessel densities in plugs from treated mice were roughly 30% less than those in plugs from untreated mice.

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 [39]. C-reactive protein was used as a marker of inflammation, as reports in the literature indicate that elevated CRP correlates with poor patient prognosis [40]. Over sixty percent of analyzed cancer patients have CRP levels above 10mg/L prior to IVC therapy. Patients were treated at the clinic by high doses of vitamin C (7.5g -100g) after standard treatments by conventional methods. The information about treatment and laboratory tests were analyzed for patients with prostate cancer, breast cancer, bladder cancer, pancreatic cancer, lung cancer, thyroid cancer, skin cancer, and B-cell lymphoma. The median follow-up time was 7.2 years. Concentrations of ascorbic acid in blood, CRP and tumor markers were measured by a routine analysis. In addition, serum samples were collected before and after IVCs for the cytokines' test to see the trend of IVC on cytokines.

According to our data, positive response of treatment on inflammation, which was demonstrated by measurements of C- reactive protein, was found in 75% of patients and progression of the inflammation in 25% of patients. Comparisons of individual values of CRP before and after treatments are shown in Figure 11 (a). Prostate specific antigen (PSA) levels also improved in most subjects as shown in Figure 11(b).

There was correlation between tumor markers (PSA, CEA, CA27.29 and CA15-3) and changes in the levels of C-reactive protein. IVC treatments of several aggressive stage cancer patients (cancers of lung, pancreas, colon, and bladder) demonstrated the poor response of treatment.

Since many of the subjects in this database were prostate cancer patients, prostate specific antigen (PSA) levels were analyzed before and after therapy. Most of the prostate cancer patients showed reductions in PSA levels during the course of their IVC therapy. In those for whom both tumor marker and CRP data were available before and after IVC therapy, there was a strong correlation ($r^2 = 0.6$) 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 [41].

The potential effect of IVC in reducing inflammation was also supported by our cytokine data analysis: serum concentrations of the pro-inflammatory cytokines IL-1α, 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 [39].

The results of our study supported the hypothesis that the high dose intravenous ascorbic acid therapy affects C-reactive protein levels and pro-inflammation cytokines in cancer patients and that modulation of inflammation by IVC correlated with decreases in tumor marker levels.
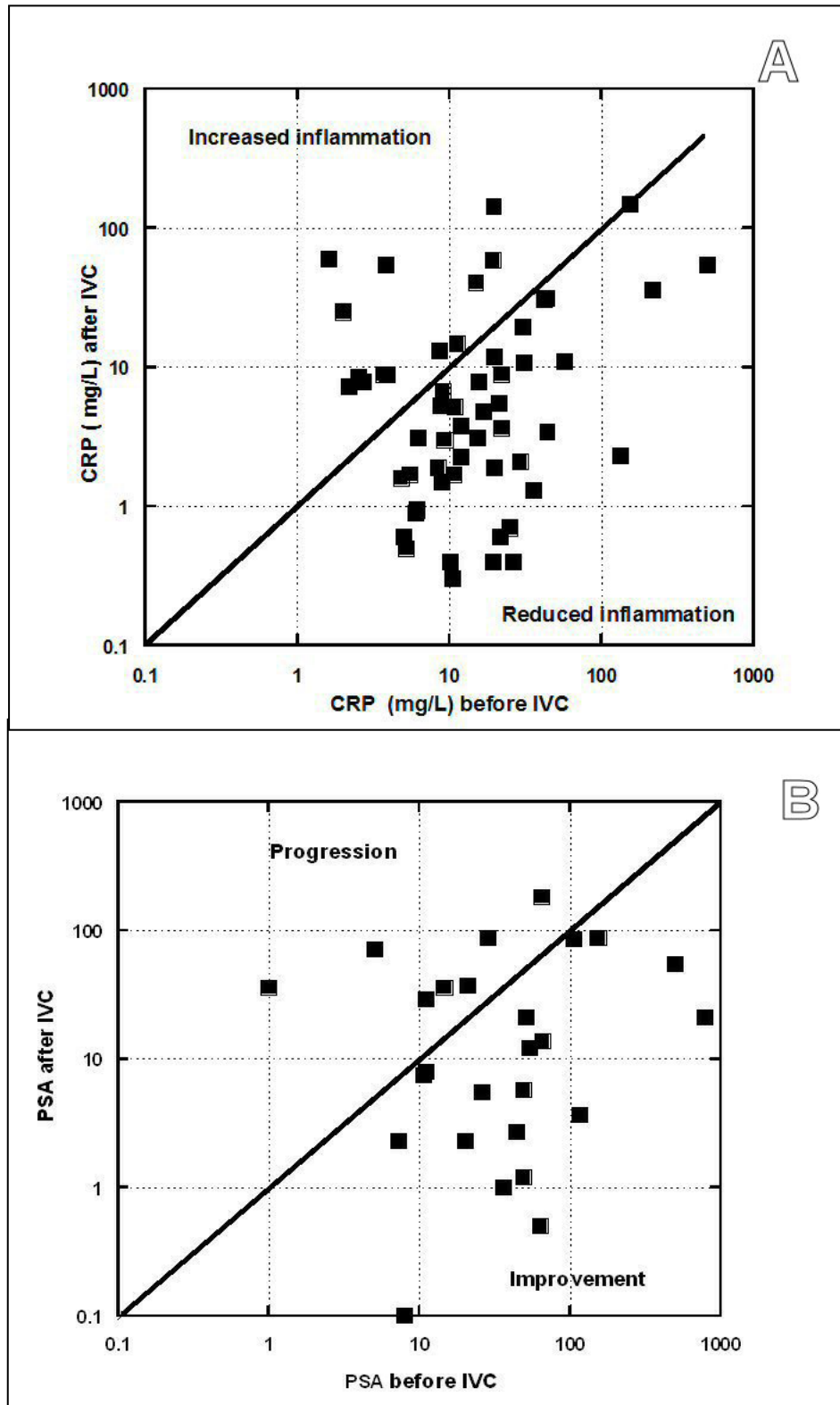
Figure 11. Changes in inflammation and PSA markers for cancer patients treated at the Riordan Clinic after IVC therapy.

In addition, we analyzed the effect of ascorbic acid on transcriptional factor NK-kB. When stimulated by tumor necrosis factor (TNF-α), cancer cells up-regulate production of NF-κB, a molecule that is the key to inflammation and is thought to promote tumor angiogenesis and tumor invasiveness. Our experiments, using a HeLa cancer cell line transfected with the bioluminescence marker luciferase added to the promoter region of the gene for NF-κB, indicate that vitamin C might lessen the up-regulation of this inflammation marker. The effect of the reduced form of ascorbic acid and its oxidized form, dehydroascorbate (DHA), on NF-κB production in HeLa cell in the presence of TNF- α is shown in Figure 12.
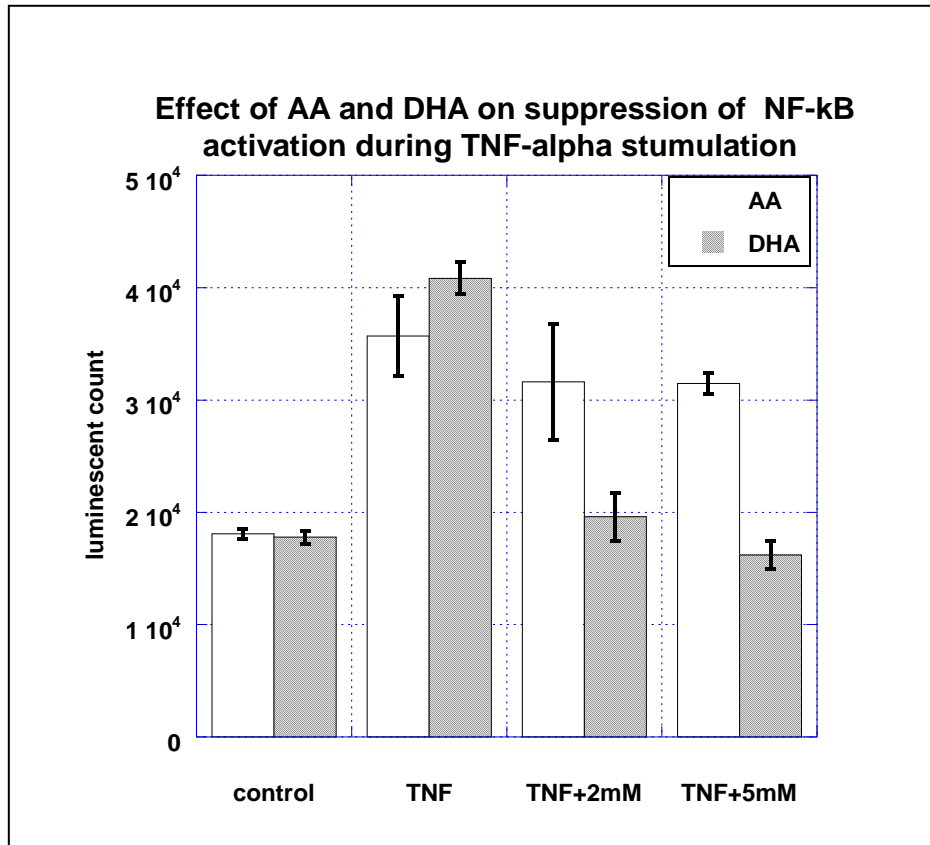
Figure 12. Vitamin C inhibits NF-kB activation by TNF-α in confluent monolayers of HeLa cells pretreated with 2 mM or 5 mM of ascorbate or DHA before stimulation by 10 ng/ml TNF-α. Control cells were left un-stimulated.

The data suggest that addition of DHA in medium inhibited cellular NF-κB production in a concentration dependent fashion. The greater efficacy of the oxidized form of ascorbate (DHA) may be related to a preference of HeLa cells toward uptake of DHA, as the most cells accumulate ascorbic acid (AA) intracellularly by transporting the oxidized form of the vitamin, dehydroascorbic acid (DHA). The DHA-loaded cells showed significantly decreased TNF alpha-induced nuclear translocation of NF-kB.

Chemotherapy Controversy: The observations that ascorbate is an antioxidant and that it preferentially accumulates in tumors [42] have raised fears that ascorbate supplementation would compromise the efficacy of chemotherapy [43]. 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 [44].   Questions have been raised, however, whether the experimental conditions used in this study are clinically or biochemically relevant, considering, among other issues, that dehydroascorbic acid rather than ascorbic acid was used [45].

A variety of laboratory studies suggest that, at high concentrations, ascorbate does not interfere with chemotherapy or irradiation and may enhance efficacy in some situations [46-52]. 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 regiments [53, 54].

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 [11, 55]. There have been several case studies published by the Riordan Clinic team [56-58] and collaborators [59, 60]. 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.

Several other clinical studies looked into the effect 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 [60]. In a recent German study, breast cancer patients receiving IVC along with standard therapy were compared to subjects receiving standard therapy alone [61]. 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 [9, 63, 64]. The first Phase I study was conducted with twenty-four terminal cancer patients (mostly liver and colorectal cancers) [9]. The study used doses up to 710 mg/kg/day. Blood chemistry parameters were monitored during treatment. Of particular interest were those associated with renal function: BUN, creatinine, and glucose levels in urine remained stable during treatment, while uric acid levels 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 "possibly related" to the agent were reported: a kidney stone in a patient with a history of renal calculus and a patient who experienced hypokalemia. These patients were generally vitamin C deficient at the start of treatment, and plasma ascorbate concentrations did not exceed 3.8 mM.

In the study by Hoffer and coworkers [63], twenty-four subjects with advanced cancer or hematologic malignancy not amenable to standard therapy were given IVC at doses of 0.4 g/kg to 1.5 g/kg (equivalent to a range of 28 to 125 grams in a 70 kg adult) three times weekly. In this study, peak plasma concentrations in excess of 10 mM were obtained, and no serious side effects were reported. Subjects at higher doses maintained physical quality of life, but no objective anti-cancer response was reported. The study by Monti and coworkers [64], 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, and 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 [9]. In cases where there are preexisting renal problems, however, caution is advised. In addition to a kidney stone forming in one patient with a history of stone formation [9], a patient with bilateral urethral obstruction and renal insufficiency suffered acute oxalate neuropathy [65]. A full blood chemistry and urinalysis work-up is thus recommended prior to the onset of intravenous ascorbate therapy.

Campbell and Jack [66] 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-phosphate dehydrogenase deficiency. It is thus recommended that G6PD levels be assessed prior to the onset of therapy. The treatment is contra-indicated in situations where increased fluids, sodium, or chelating may cause serious problems. These situations include congestive heart failure, edema, ascites, chronic hemodialysis, unusual iron overload, and inadequate hydration or urine void volume [67].

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.

The next key step in researching the use of IVC for cancer would be Phase II studies, some of which are currently underway. IVC may also have a variety of other applications, such as combating infections, treating rheumatoid arthritis, and treating ADHD and other mental illnesses where inflammation may play a role.

APPENDIX:
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 care-giver) 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 necessary if relapse and symptom progression has occurred since diagnosis.)
    b)   Appropriate tumor markers, CT, MRI, PET scans, bone scans, and x-ray imaging.
    c)   Prior cancer treatments, the patient's response to each treatment type, including side effects.
    d)   The patient's functional status with an ECOG Performance Score.
    e)   Patient weight.

Precautions and Side Effects: 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 give 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 [68].

2) Tumor necrosis or tumor lysis syndrome has been reported in one patient after high-dose IVC [66]. For this reason, the protocol always begins with a small 15 gram dose.

3) Acute oxalate nephropathy (kidney stones) was reported in one patient with renal insufficiency who received a 60 gram IVC. Adequate renal function, hydration, and urine voiding capacity must be documented prior to starting high-dose IVC therapy. In our experience, however, the incidence of calcium oxalate stones during or following IVC is negligible [9].

4) Hemolysis has been reported in patients with G6PD deficiency when given high-dose IVC. The G6PD level should be assessed before beginning IVC.

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.

10) As with any I.V. infusion, infiltration at the site is possible. This is usually not a problem with ports.

11) IVC should only be given by slow intravenous drip at a rate of 0.5 grams per minute. Rates up to 1.0 gram/minute are generally tolerable, but close observation is warranted. Patients 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 1000 mOsm/kg H_2O 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.)

Table 1. The calculated osmolality of various amounts of fluid volume. We presently use the sodium ascorbate solution, MEGA-C-PLUS®, 500 mg/mL, pH range 5.5-7.0,   Merit Pharmaceuticals, Los Angeles, CA, 90065.

Treatment volume of ascorbic acid	Solution Volume		Inject volume of AA into solution	Inject volume of MgCl₂ into solution	Osmolarity of solution (mOsm)	Infusion rate	Total infusion time
	Ringer Lactate	Sterile water					
15 grams (30cc)	250cc		30cc	1cc	939	0.5-1.0 g/min	~0.5 h
25 grams (50cc)		250cc	50cc	1cc	1029	0.5-1.0 g/min	~ 1 h
50 grams (100cc)		500cc	100cc	2cc	1013	0.5-1.0 g/min	~1.5 h
75 grams (150cc)		750cc	150cc	2ccc	1005	0.5-1.0 g/min	~2.5 h
100 grams		1000cc	200cc	2cc	1002	0.5-1.0 g/min	~3.5 h

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 two consecutive IVC infusions at the 15 and 25 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 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.

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 burden, chemo/radiation damage, hidden infection, or other oxidative insult, such as smoking.

Following the first IVCs, the patient can be scheduled to continue either a 25 or 50 gram IVC dose (doctor's discretion) twice a week until the post IVC plasma level results are available from the 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 require 100 grams IVC infusions 3x/week. Post IVC plasma levels serve as an excellent clinical guide to this special dosing.

In our experience, the majority of cancer patients require 50 gram IVC infusions 2-3x/week to maintain therapeutic IVC plasma levels. All patients 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.

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