



The Riordan IVC Protocol for Adjunctive Cancer Care

Intravenous Ascorbate as a Chemotherapeutic and Biological Response Modifying Agent

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 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 (McCormick, 1959; Cameron, et al., 1979). Also, since cancer patients are often depleted of 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:

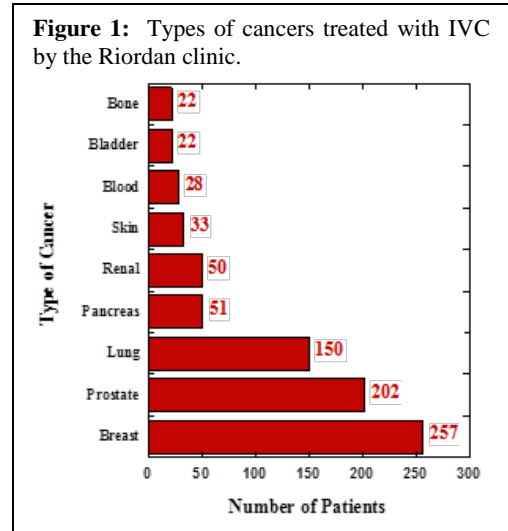
- Plasma ascorbate concentrations in the millimolar range can be safely achieved with IVC infusions.
- At millimolar concentrations, ascorbate is preferentially toxic to cancer cells in vitro and is able to inhibit angiogenesis in vitro and in vivo.
- Vitamin C can accumulate in tumors, with significant tumor growth inhibition seen (in guinea pigs) at intra-tumor concentrations of 1 mM or higher.

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- 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.

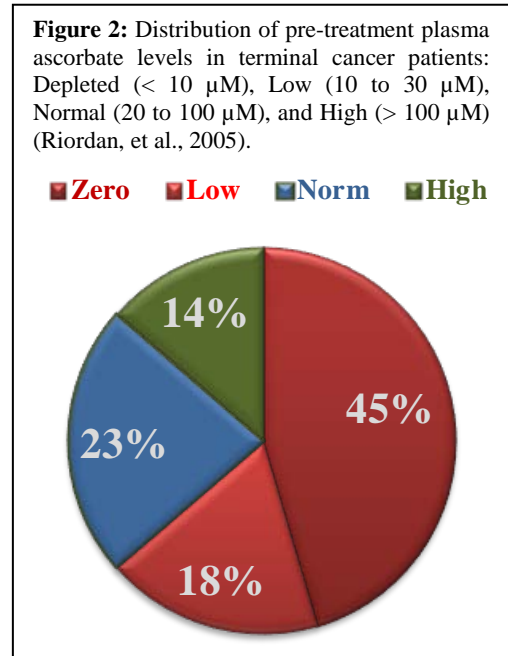


SCIENTIFIC BACKGROUND

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 100 μ M, even if 2.5 grams were taken when administered once daily by the oral route. (Levine, et al., 1996).

Cancer patients tend to be depleted of vitamin C: fourteen out of twenty-two terminal cancer patients in a phase I study we depleted of vitamin C, with ten of those having zero detectable ascorbate in their plasma (Riordan, et al., 2005).



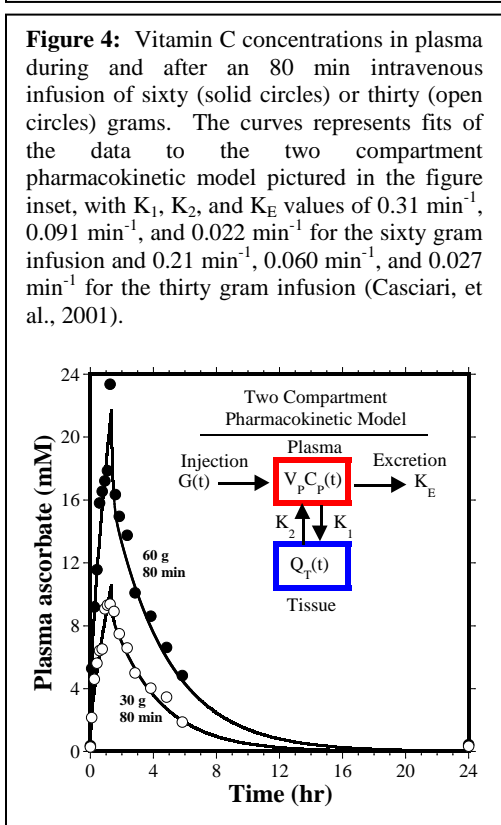
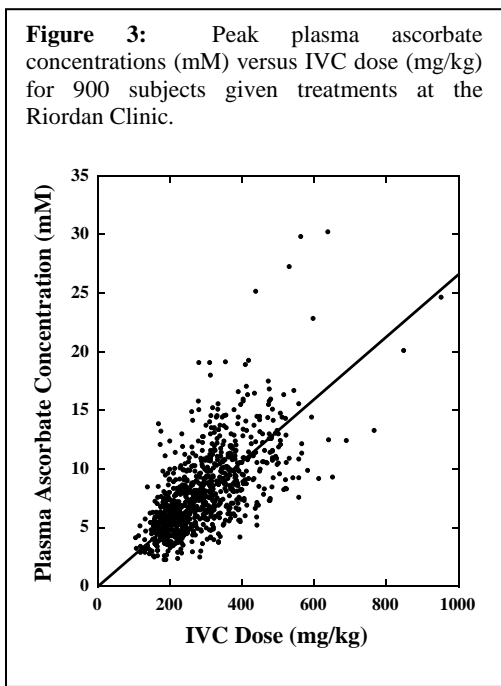
This is shown in Figure 2. In a study of cancer patients in hospice care, Mayland and coworkers found

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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.

When vitamin C is given by intravenous infusion, 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.



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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 concentrations on the order of 2 mM. As shown in Figures 3 and 4, these concentrations are attainable in plasma using progressive dosing of IVC. A 2-compartment model can be used to predict peak and “average” (over 24 hours) plasma ascorbate concentrations for an average sized adult at a given IVC dose. This calculation suggests that a 50 gram, 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.

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 al., 1969; Riordan, et al., 1995; Casciari, et al., 2001; Chen, et al., 2005; Frei & Lawson, 2008), often leading to autophagy or apoptosis. To examine this cytotoxic effect in a three dimensional model, the RCRI employed hollow-fiber in vitro solid tumors (HFST). Figure 6 shows a histological section of colon cancer cells growing in this configuration. Dual staining annexin V and propidium iodide flow cytometry

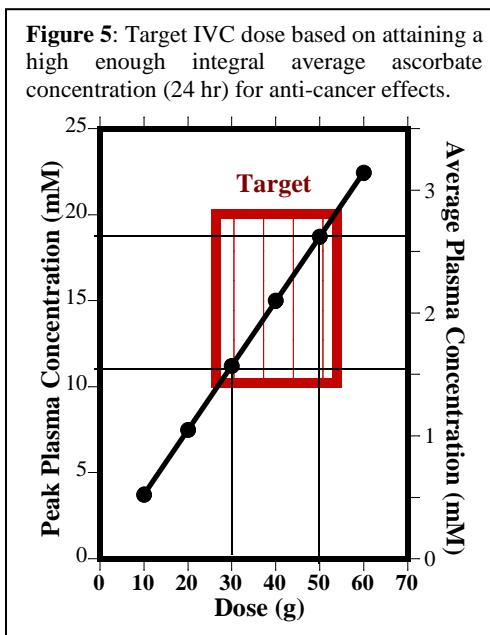
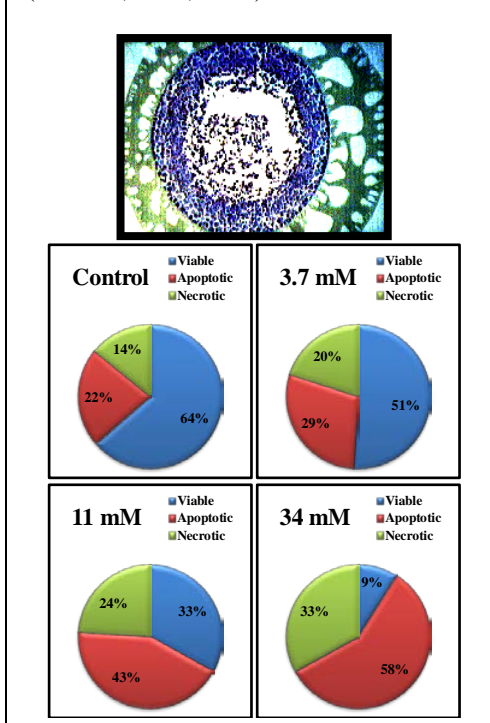


Figure 6: Histological cross section of an SW620 hollow fiber tumor (HFST) along with viable, apoptotic, and necrotic fractions after 2 days ascorbate treatment (Casciari, et al., 2001).



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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 ($LC_{50} = 20$ mM), with only two days incubation, were much higher than those typically observed in cell monolayers. 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 (Verrax, et al., 2004) or copper containing compounds (Gonzalez, et al., 2002).

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 shows data using the L-10 model in guinea pigs. L-10 tumor cells implanted subcutaneously metastasize to the lymph nodes. The overall tumor burden (primary plus metastases) was then determined after 30 days of tumor growth and 18 days of ascorbate therapy. Note that here the actual intra-tumor ascorbate concentrations were 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%

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

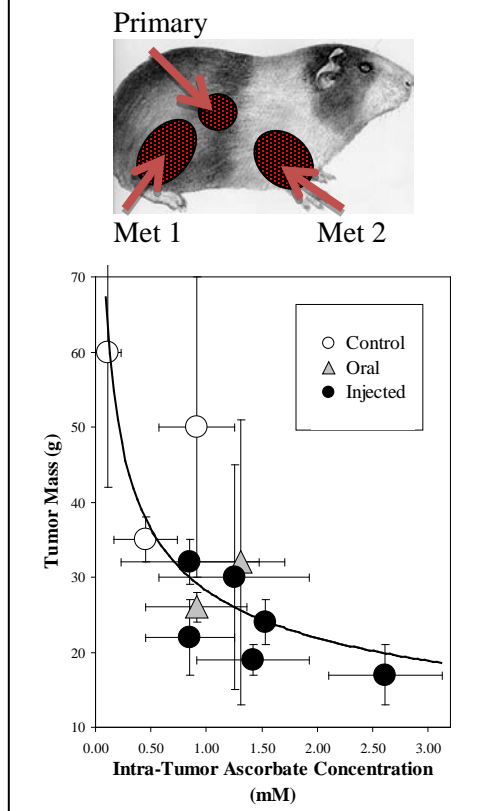
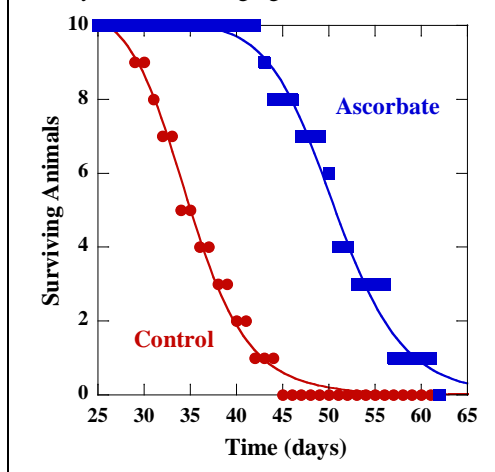


Figure 8: Survival time of sarcoma bearing BALP/C mice control and treated IP starting on day 12 with 700 mg/kg ascorbate.



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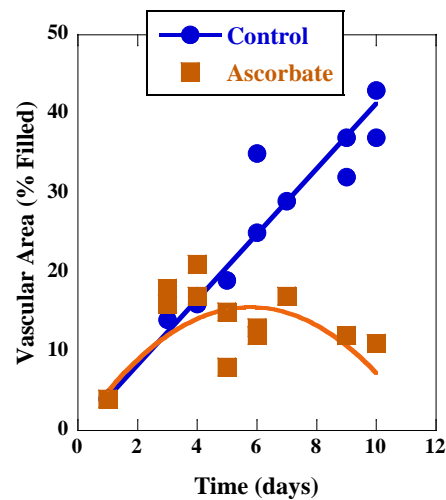
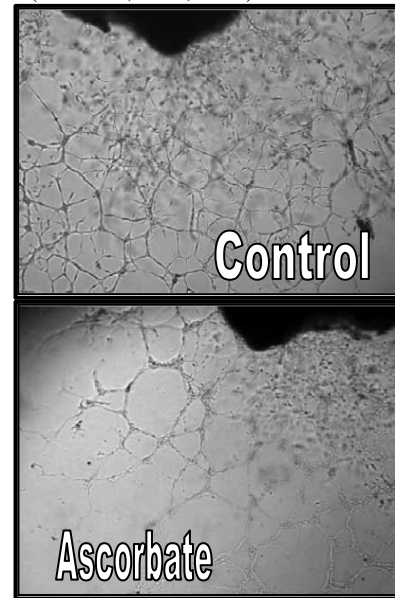
once the intra-tumor ascorbate level went above 2 mM. The ascorbate dosage used in this study was 500 mg/kg/day. Our scientists also looked at survival times of BALP/C mice with S180 sarcomas. The results are shown in Figure 8. The median survival time for the untreated mice was 35.7 days post implantation, 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).

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).

Figure 9: A: Endothelial microvessel growth out of aortic rings: control versus ascorbate treated (5.7 mM, 4 days). **B:** Graph of vascular area near aortic ring as a function of time (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.
- Ascorbate inhibits endothelial cell tubule formation in Matrigel in vitro in a concentration dependent fashion. Number of intact tubule loops was decreased by half at concentrations of 11 mM for endothelial progenitor cells and 17 mM for HUVEC cells.

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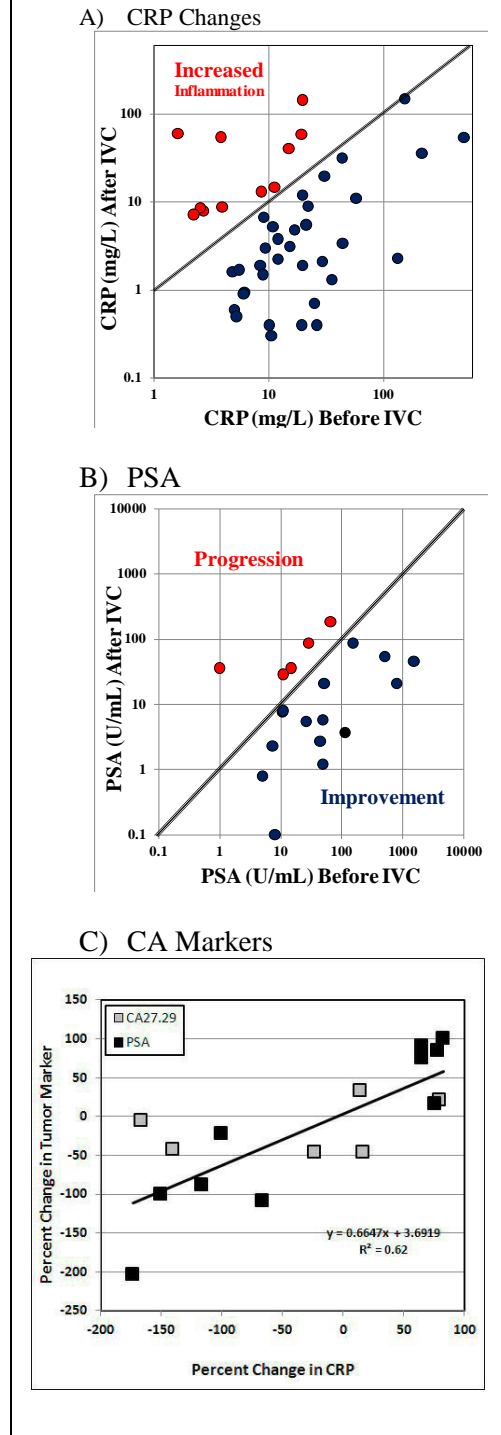
- The rate at which endothelial cells can migrate on a petri dish to fill a gap between them was reduced when 5.7 mM ascorbate was added after the gap was created. The ascorbate also reduced ATP production in these endothelial cells by twenty percent, but did not affect cell viability.
- For Matrigel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

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 $76 \pm 13\%$ of these subjects, IVC reduced CRP levels. This improvement was more prevalent, $86 \pm 13\%$, 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 (PSA) levels before and after therapy. This is shown in Figure 10B. Most of the prostate cancer patients showed reductions in PSA levels during the course of their IVC

Figure 10: Change in key parameters for cancer patients at the Riordan Clinic after IVC therapy (Mikirova, et al., 2012)



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therapy. This was not true with other markers, as shown in Figure 10C. In some subjects, both tumor marker and CRP data were available both before and after IVC therapy. In those cases, 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).

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).

Chemotherapy Controversy

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 that the goal of IVC is to attain millimolar intra-tumor concentrations (for the reasons described above) and thus the accumulation of ascorbate in tumors is considered an advantage.

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 (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

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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:

- A) A 51 year old female with **renal cell carcinoma** (nuclear grade III/IV) and **lung metastasis** declined chemotherapy and instead chose to intravenous ascorbate at an initial dose of 15 grams. Her dose was increased to 65 grams after two weeks. She continued at this dose for ten months. Patient received no radiation or chemotherapy. The patient supplemented with thymus protein extract, N-acetylcysteine, niacinamide, beta-glucan, and thyroid extract. 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).
- B) 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).
- C) 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-

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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 showed no clinical signs of lymphoma after one year. Ten years diagnosis, the patient remained in normal health (Padayatti, et al., 2006).

- D) A 55 year old woman with stage_IIIC papillary **adenocarcinoma of the ovary** and an initial CA-125 of 999 underwent surgery followed by six 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).
- E) 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.

Note that these case studies involve a variety of cancer types, sometimes involve the use of IVC in conjunction with chemotherapy or irradiation, and usually involve the use of other nutritional supplements by the subject.

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

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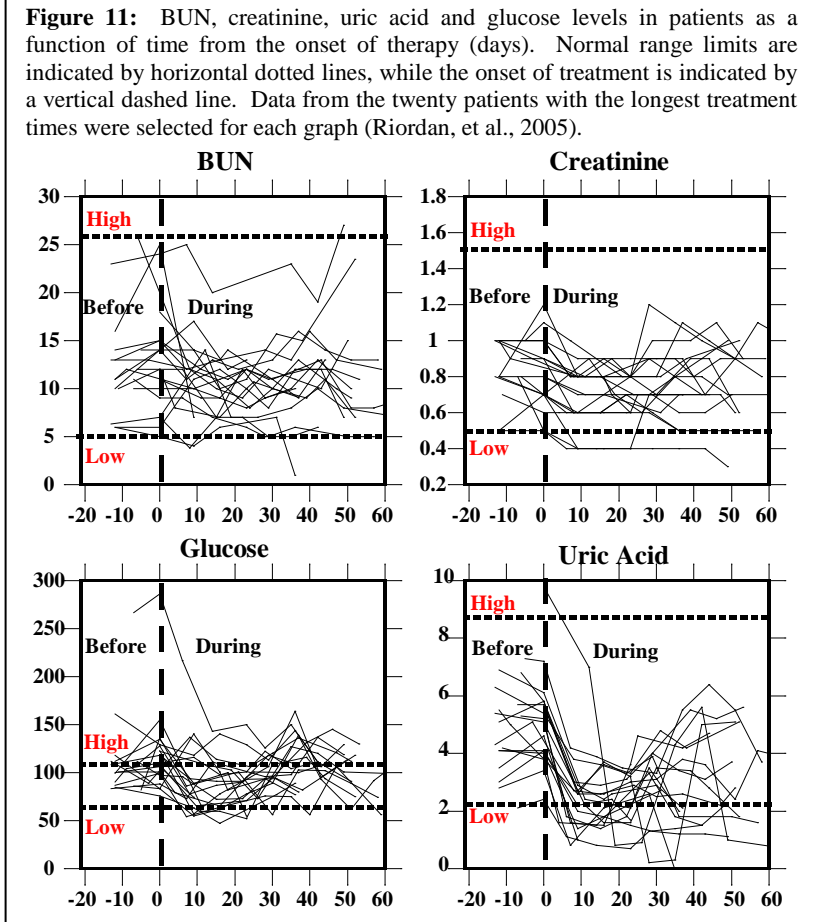
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less fatigue, reduction in nausea and vomiting, and improved appetite (Yeom, et al., 2007). In a recent German study, breast cancer patients receiving IVC along with standard therapy were compared to subjects receiving standard therapy alone (Vollbracht, 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



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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 (Hoffer, et al., 2008), 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 (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-phosphate dehydrogenase deficiency. It is thus recommended that G6PD levels be

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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 (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 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.

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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.
- 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 (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.

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- 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 is very reliable with rare infiltrations (depending upon the status of the patient's veins!)
- 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 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

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

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solution, MEGA-C-PLUS®, 500 mg/mL, pH range 5.5-7.0 from Merit Pharmaceuticals, Los Angeles, CA, 90065.

Treatment volume of Ascorbic acid	Solution Volume		Withdraw from solution and discard	remaining solution	Inject volume of AA into solution	inject volume of MgCl ₂ into solution	final volume	Infusion rate	total infusion time
	Ringer Lactate	Sterile water							
15 grams (30cc)	250 cc		31cc	219 cc	30 cc	1 cc	250 cc	0.5-1.0 g/min	~ 0.5 h
25grams (50cc)	500cc		51cc	449cc	50cc	1cc	500cc	0.5-1.0 g/min	~ 1 h
50 grams (100cc)		500cc	102cc	398 cc	100 cc	2cc	500cc	0.5-1.0 g/min	~ 1.5 h
75 grams (150cc)		750cc	152cc	598cc	150cc	2cc	750cc	0.5-1.0 g/min	~ 2.5 h
100grams		1000cc	202cc	798cc	200cc	2cc	1000cc	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 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 burden, chemo/radiation damage, hidden infection, or other oxidative insult, such as smoking.

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Following the first three 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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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.

REFERENCES

- Agus, D., Vera, J. & Golde, D., 1999. Stromal cell oxidation: a mechanism by which tumors obtain vitamin C. *Cancer Res.*, Volume 59, pp. 4555-8.
- Ashino, H. et al., 2003. Novel function of ascorbic acid as an angiostatic factor. *Angiogenesis*, Volume 6, pp. 259-69.
- Belin, S. et al., 2009. Antiproliferative effect of ascorbic acid is associated with inhibition of genes necessary to cell cycle progression. *PLoS ONE*, Volume 4, p. e4409.
- Benade, L., Howard, T. & Burk, D., 1969. Synergistic killing of Ehrlich ascites carcinoma cells by ascorbate and 3-amino-1,2,4-triazole. *Oncology*, Volume 23, pp. 33-43.
- Berlin, S. et al., 2009. Antiproliferative effect of ascorbic acid is associated with inhibition of genes necessary for cell cycle progression. *PLoS ONE*, Volume 4, pp. E44-0.
- Block, K. et al., 2008. Impact of antioxidant supplementation on chemotherapeutic toxicity: a systematic review of the evidence from randomized controlled trials. *Int J Cancer*, Volume 123, pp. 1227-39.
- Cameron, E. & Pauling, L., 1976. Supplemental ascorbate in the supportive treatment of cancer: Prolongation of survival times in terminal human cancer. *PNAS USA*, Volume 73, pp. 3685-9.

The Riordan IVC Protocol for Adjunctive Cancer Care

Intravenous Ascorbate as a Chemotherapeutic and Biological Response Modifying Agent

- Cameron, E., Pauling, L. & Leibovitz, B., 1979. Ascorbic acid and cancer, a review. *Cancer Res*, Volume 39, pp. 663-81.
- Campbell, A. & Jack, T., 1979. Acute reactions to mega ascorbic acid therapy in malignant disease. *Scott Med J*, Volume 24, p. 151.
- Campbell, G., Steinberg, M. & Bower, J., 1975. Letter: ascorbic acid induced hemolysis in a G-6-PD deficiency.. *Ann Intern Med*, Volume 82, p. 810.
- Casciari, J., Riordan, H., Miranda-Massari, J. & Gonzalez, M., 2005. Effects of high dose of ascorbate administration on L-10 tumor growth in guinea pigs. *PRHSJ*, Volume 24, pp. 145-50.
- Casciari, J., Riordan, N. S. T. M. X., Jackson, J. & Riordan, H., 2001. Cytotoxicity of ascorbate, lipoic acid, and other antioxidants in hollow fibre in vitro tumours. *Br. J. Cancer*, Volume 84, pp. 1544-50.
- Chen, Q. et al., 2008. Pharmacologic doses of ascorbate act as a prooxidant and decrease growth of aggressive tumor xenografts in mice. *PNAS USA*, Volume 105, pp. 11105-9.
- Chen, Q. et al., 2005. Pharmacologic ascorbic acid concentrations selectively kill cancer cells: action as a pro-drug to deliver hydrogen peroxide to tissues. *PNAS USA*, Volume 102, pp. 13604-13609.
- Creagan, E. et al., 1979. Failure of high-dose vitamin C (ascorbic acid) therapy to benefit patients with advanced cancer: A controlled trial. *NEJM*, Volume 301, pp. 687-690.
- Drisko, J., Chapman, J. & Hunter, V., 2003. The use of antioxidants with first-line chemotherapy in two cases of ovarian cancer. *Am J Coll Nutr*, Volume 22, pp. 118-23.
- Du, J. et al., 2010. Mechanisms of ascorbate-induced cytotoxicity in pancreatic cancer. *Clin Cancer Res*, Volume 16, pp. 509-20.
- Espey, M. et al., 2011. Pharmacologic ascorbate synergizes with gemcitabine in preclinical models of pancreatic cancer. *Free Radic Biol Med*, Volume 50, pp. 1610-19.
- Espey, M., Chen, Q. & Levine, M., 2009. Comment re: vitamin C antagonizes the cytotoxic effects of chemotherapy. *Cancer Research*, Volume 69, p. 8830.
- Frei, B. & Lawson, S., 2008. Vitamin C and cancer revisited. *PNAC USA*, Volume 105, pp. 11037-8.
- Fromberg, A. et al., 2011. Ascorbate exerts anti-proliferative effects through cell cycle inhibition and sensitizes tumor cells toward cytostatic drugs.. *Cancer Chemother Pharmacol*, Volume 67, pp. 1157-66.
- Fujita, K. et al., 1982. Reduction of adriamycin toxicity by ascorbate in mice and guinea pigs. *Cancer Res*, Volume 42, pp. 309-16, p. 42.
- Geeraert, L., 2012. *CAM-Cancer Consortium. Intravenous high-dose vitamin C*. [Online] Available at: <http://www.cam-cancer.org/CAM-Summaries/Other-CAM/Intravenous-high-dose-vitamin-C>.
- Ginter, E., Bobeck, P. & Vargova, D., 1979. Tissue levels and optimal dosage of vitamin C in guinea pigs.. *Nutr Metab*, Volume 27, pp. 217-26.
- Gonzalez, M. et al., 2002. Inhibition of human breast cancer carcinoma cell proliferation by ascorbate and copper.. *PRHSJ*, Volume 21, pp. 21-3.
- Heaney, M. et al., 2008. Vitamin C antagonizes the cytotoxic effects of antineoplastic drugs. *Cancer Res*, Volume 68, pp. 8031-8.
- Henson, D., Block, G. & Levine, M., 1991. Ascorbic acid: biological functions and relation to cancer. *JNCI*, Volume 83, pp. 547-50.
- Hoffer, L. et al., 2008. Phase I clinical trial of i.v. ascorbic acid in advanced malignancy. *Ann Oncol*, Volume 19, pp. 1969-74, p. 19.
- Hoffman, F., 1985. Micronutrient requirements of cancer patients.. *Cancer*, 55(Suppl. 1), pp. 145-50.
- Hornig, D., 1975. Distribution of ascorbic acid metabolites and analogues in man and animals. *Ann NY Acad Sci*, Volume 258, pp. 103-18.
- Jackson, J. & Hunninghake, R., 2006. False positive blood glucose readings after high-dose intravenous vitamin C. *J Ortho Med*, Volume 21, pp. 188-90.

The Riordan IVC Protocol for Adjunctive Cancer Care

Intravenous Ascorbate as a Chemotherapeutic and Biological Response Modifying Agent

- Jackson, J., Riordan, H., Hunninghauke, R. & Riordan, N., 1995. High dose intravenous vitamin C and long time survival of a patient with cancer of the head and pancreas. *J Ortho Med*, Volume 10, pp. 87-8.
- Keith, M. & Pelletier, O., 1974. Ascorbic acid concentrations in leukocytes and selected organs of guinea pigs in response to increasing ascorbic acid intake. *Am J Clin Nutr*, Volume 27, pp. 368-72.
- Kuether, C., Telford, I. & Roe, J., 1988. The relation of the blood level of ascorbic acid to tissue concentrations of this vitamin and the histology of the incisor teeth in the guinea pig. *J Nutrition*, Volume 28, pp. 347-58.
- Kurbacher, C. et al., 1996. Ascorbic acid (vitamin C) improves the antineoplastic activity of doxorubicin, cisplatin, and paclitaxel in human breast carcinoma cells in vitro. *Cancer Lett*, Volume 103, pp. 183-9.
- Levine, M. et al., 1996. Vitamin C pharmacokinetics in healthy volunteers: evidence for a recommended dietary allowance. *PNAS USA*, Volume 93, pp. 3704-9.
- Lin, A., Chen, K., Chung, H. & Chang, S., 2010. The significance of plasma c-reactive protein in patients with elevated serum prostate-specific antigen levels. *Urological Sci*, Volume 21, pp. 88-92.
- Mayland, C., Bennett, M. & Allan, K., 2005. Vitamin C deficiency in cancer patients. *Palliat Med*, Volume 19, pp. 17-20.
- McCormick, W., 1959. Cancer: a collagen disease, secondary to nutrition deficiency. *Arch. Pediatr.*, Volume 76, pp. 166-171.
- Mikirova, N., Casciari, J. & Riordan, N., 2012. Ascorbate inhibition of angiogenesis in aortic rings ex vivo and subcutaneous Matrigel plugs in vivo. *J Angiogenesis Res*, Volume 2, pp. 2-6.
- Mikirova, N., Casciari, J., Taylor, P. & Rogers, A., 2012. Effect of high-dose intravenous vitamin C on inflammation in cancer patients. *J Trans Med*, Volume 10, pp. 189-99.
- Mikirova, N., Ichim, T. & Riordan, N., 2008. Anti-angiogenic effect of high doses of ascorbic acid.. *J Transl Med*, Volume 6, p. 50.
- Mikirova, N., Rogers, A., Casciari, J. & Taylor, P., 2012. Effects of high dose intravenous ascorbic acid on the level of inflammation in patients with rheumatoid arthritis. *Mod Res Inflamm*, Volume 1, pp. 26-32.
- Moertel, C. et al., 1985. High-dose vitamin C versus placebo in the treatment of patients with advanced cancer who have no prior chemotherapy: a randomized double-blind comparison.. *NEJM*, Volume 312, pp. 137-41.
- Monti, D. et al., 2012. Phase I evaluation of intravenous ascorbic acid in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. *PLoS One*, Volume 7, p. e29794.
- Murata, A., Morishige, F. & Yamaguchi, H., 1982. Prolongation of survival times of terminal cancer patients by administration of large doses of ascorbate. *Int J Vitam Res Suppl*, Volume 23, pp. 103-13.
- Okunieff, P. & Suit, H., 1987. Toxicity, radiation sensitivity modification, and combined drug effects of ascorbic acid with misonidazole in vivo on FSaII murine fibrosarcomas. *JNCI*, Volume 79, pp. 377-81.
- Padayatti, S. et al., 2006. Intravenous vitamin C as a cancer therapy: three cases. *CMAJ*, Volume 174, pp. 937-42.
- Padayatti, S. & Levine, M., 2000. Reevaluation of ascorbate in cancer treatment: emerging evidence, open minds and serendipity. *J Am Coll Nutr.*, Volume 19, pp. 423-5.
- Padayatti, S. et al., 2010. Vitamin C: intravenous use by complementary and alternative medical practitioners and adverse effects. *PLoS ONE*, Volume 5, p. 11414.
- Padayatti, S. et al., 2004. Vitamin C pharmacokinetics: implications for oral and intravenous use. *Ann. Intern. Med.*, Volume 140, pp. 533-37.
- Page, E. et al., 2007. Hypoxia inducible factor-1 (alpha) stabilization in nonhypoxic conditions: role of oxidation and intracellular ascorbate depletion. *Mol Biol Cell*, Volume 19, pp. 86-94.

The Riordan IVC Protocol for Adjunctive Cancer Care

Intravenous Ascorbate as a Chemotherapeutic and Biological Response Modifying Agent

- Pollard, H., Levine, M., Eidelman, O. & Pollard, M., 2010. Pharmacological ascorbic acid suppresses syngenic tumor growth and metastases in hormone-refractory prostate cancer. *In Vivo*, Volume 2012, pp. 249-55.
- Raloff, J., 2000. Antioxidants may help cancers thrive. *Science News*, Volume 157, p. 5.
- Riordan, H. et al., 2005. A pilot clinical study of continuous intravenous ascorbate in terminal cancer patients. *PR Health Sci J*, Volume 24, pp. 269-76.
- Riordan, H. et al., 2003. Intravenous ascorbic acid: protocol for its application and use. *PR Health Sci. J.*, Volume 22, pp. 225-32.
- Riordan, H., Jackson, J., Riordan, N. & Schultz, M., 1998. High-dose intravenous vitamin C in the treatment of a patient with renal cell carcinoma of the kidney. *J Ortho Med*, Volume 13, pp. 72-3.
- Riordan, N., JA, J. & Riordan, H., 1996. Intravenous vitamin C in a terminal cancer patient. *J Ortho Med*, Volume 11, pp. 80-2.
- Riordan, N., Riordan, H. & Meng, X., 1995. Intravenous ascorbate as a tumor cytotoxic chemotherapeutic agent. *Med Hypotheses*, Volume 44, pp. 207-13.
- Rivers, J., 1987. Safety of high-level vitamin C ingestion. In: Third Conference on Ascorbic Acid. *Ann NY Acad Sci*, Volume 489, pp. 95-102.
- Shinozaki, K. et al., 2011. Ascorbic acid enhances radiation-induced apoptosis in an HL60 human leukemia cell line. *J Radiat Res*, Volume 52, pp. 229-37.
- Simone, C., Simone, N. S. V. & CB, S., 2007. Antioxidants and other nutrients do not interfere with chemotherapy or radiation therapy and can increase survival, part 1. *Altern Ther Health Med*, Volume 13, pp. 22-8.
- St. Sauver, J. et al., 2009. Associations between c-reactive protein and benign prostatic hyperplasia lower urinary tract outcomes in a population based cohort. *Am J Epidemiol*, Volume 169, pp. 1281-90.
- Taper, H., Keyeux, A. & Roberfroid, M., 1996. Potentiation of radiotherapy by nontoxic pretreatment with combined vitamins C and K3 in mice bearing solid transplantable tumor. *Anticancer Res*, Volume 16, pp. 499-503.
- Verrax, J. et al., 2004. Ascorbate potentiates the cytotoxicity of menadione leading to an oxidative stress that kills cancer cells by a non-apoptotic caspase-3 independent form of cell death. *Apoptosis*, Volume 9, pp. 223-33.
- Verrax, J. & Calderon, P., 2009. Pharmacologic concentrations of ascorbate are achieved by parenteral administration and exhibit antitumoral effects. *Free Radic Biol Med*, Volume 47, pp. 32-40.
- Vollbracht, C. et al., 2011. Intravenous vitamin C administration improves quality of life in breast cancer patients during chemo-radiotherapy and aftercare: results of a retrospective, multicentre, epidemiological cohort study in Germany. *In Vivo*, Volume 82, pp. 983-90.
- Wong, K. et al., 1994. Acute oxalate nephropathy after a massive intravenous dose of vitamin C. *Aust NZ J Med*, Volume 24, pp. 410-1.
- Yeom, C., Jung, G. & Song, K., 2007. Changes of terminal cancer patients health related quality of life after high dose vitamin C administration. *Korean Med Sci*, Volume 22, pp. 7-11.
- Yeom, C. et al., 2009. High-dose concentration administration of ascorbic acid inhibits tumor growth in BALB/C mice implanted with sarcoma 180 cancer cells via the restriction of angiogenesis. *J Transl Med*, Volume 7, p. 70.