

The Riordan IVC Protocol 2009

Intravenous Ascorbate (IVC) as a Chemotherapeutic and Biologic Response Modifier

IMPORTANT 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. 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!

Jackson JA, Hunninghake RE, et al. False positive blood glucose readings after high-dose intravenous vitamin C. *J Orthomol Med*, 2006; 21(4):188-190.

Introduction:

1. For over three decades investigators have researched the use of ascorbic acid to treat cancer.
2. The investigation of vitamin C as a treatment for cancer was pioneered by Klenner, Cameron, Pauling, Campbell, Hoffer, and Riordan (see references).
3. Both oral ascorbic acid (hence forth called vitamin C) and intravenous ascorbate (IVC) have been used to treat cancers in primary (known residual tumor) and adjuvant (after tumor removal) settings.
4. Oral vitamin C supplementation (and other antioxidants) has been used to help prevent cancer onset and its recurrence.
5. Standard chemotherapy and radiation protocols have used adjuvant IVC to augment their effectiveness and decrease their side effects.
6. Primary IVC therapy with or without other nutritional supplementation has shown success in decreasing symptoms, improving quality of life, and prolonging survival in cancer patients.
7. This protocol is named for Hugh D. Riordan, M.D. and his research team’s groundbreaking work in defining the therapeutic range for IVC therapy as a chemotherapeutic and biologic response modifier.

Treatment Rationale and Biological Response to IVC:

1. The Center has reported on numerous IVC case studies in patients with various types of cancer (see references).
2. Figure 1 (see below) shows the response of four tumor cell lines to increasing amounts of vitamin C and figure 2 shows the cytotoxic effect of vitamin C on human colon cancer cells in three different models of cancer cell growth (see next page).
3. Oral vitamin C does not produce a blood level high enough to kill cancer cells. From our studies, we concluded that tumor cells become susceptible to high-dose vitamin C at plasma levels of **350 to 400 mg/dL**, where redox cycling creates cellular peroxidation. This pro-oxidant effect of IVC

induces apoptosis in catalase-deficient cancer cells while sparing non-cancerous cells from oxidative damage.

Figure 1. - The responses to increasing doses of vitamin C of four human tumor cell lines grown in dense monolayers in a medium of human serum.

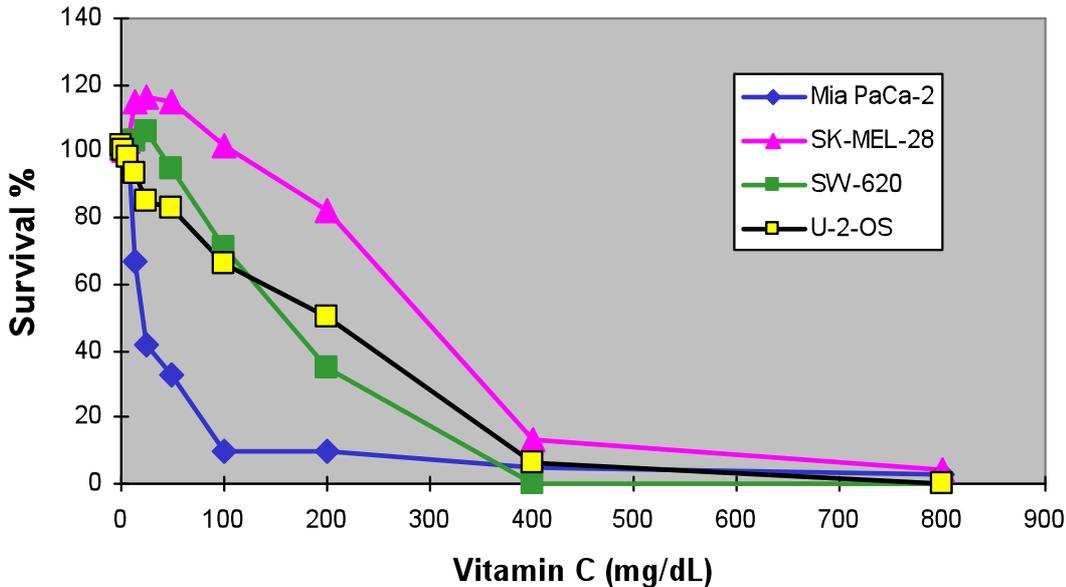


Figure 1. is a mean of 12 samples of the tumor cell lines Mia PaCa-2 (human pancreatic carcinoma), SK-MEL-28 (human melanoma); SW-620 (human colon carcinoma), and U-2-OS (human osteogenic sarcoma), all from ATCC, Rockville, MD. Results reflect total viable cells. Maintenance medium DMEM High-glucose medium (Irvine Sci.) w/10% heat-inactivated fetal calf serum + antibiotics + Fungizone, 5% CO2 humidified incubator at 37 degrees C. Experimental medium was human serum from patients with diagnoses of respective human tumors, cultured for 3 days after supplementation with vitamin C. Absolute quantitation of live cells determined using previously described microplate fluorometer method.

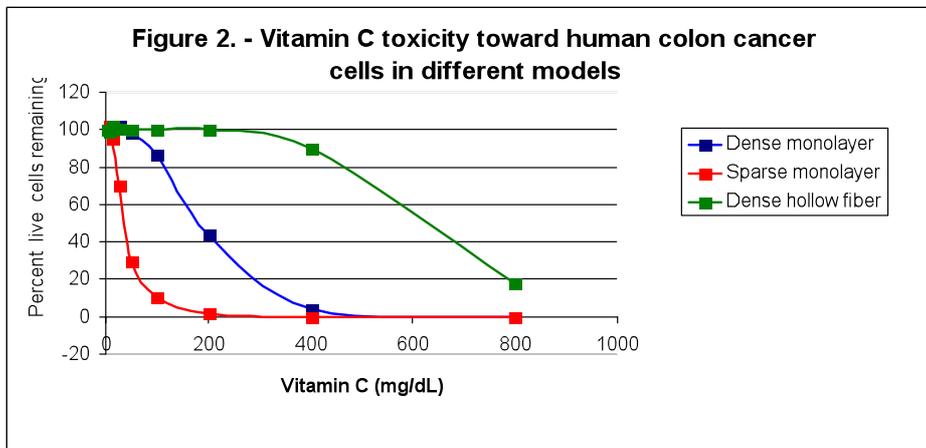


Figure 2. Human sera was used as a culture media to include serum inhibitory activity. Lower concentrations of vitamin C inhibited human colon cancer cells grown as a thin **monolayer** compared to the same cells grown as a thick monolayer. The 3-dimensional dense hollow fiber model attempts to replicate the characteristics of a human tumor. Much higher concentrations of vitamin C were required to inhibit cancer cells in this model.

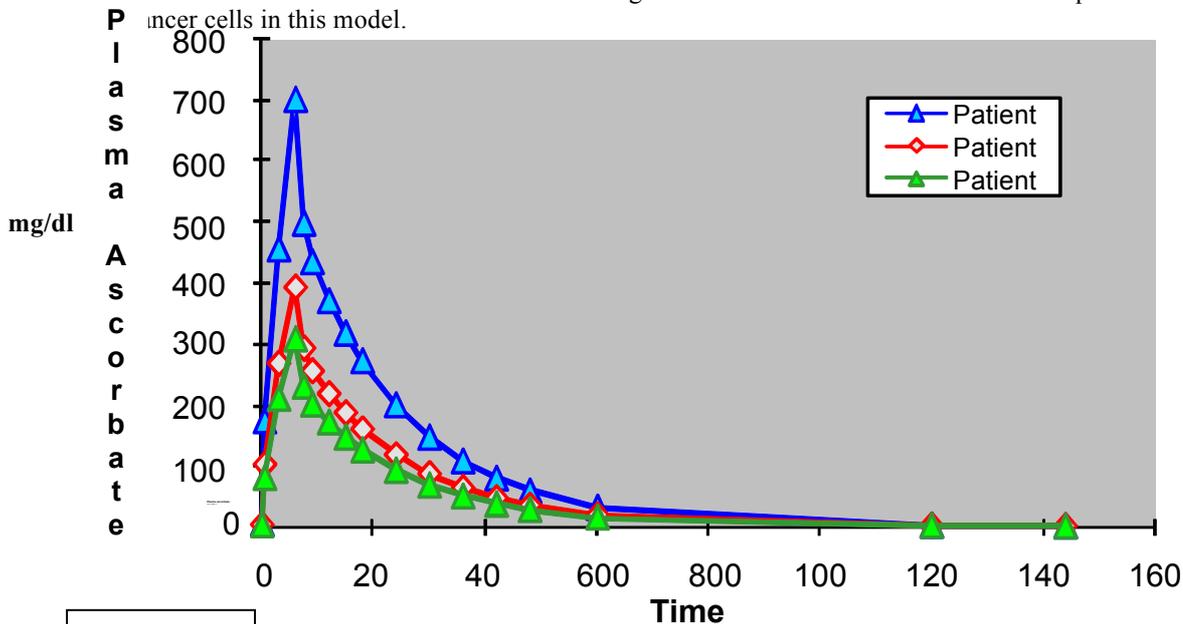


Figure 3

Patient 1 was a 74-year-old male with a diagnosis of non-metastatic prostate carcinoma, who had received >30 IVC infusions in the two years prior to the study.
Patient 2 was a 50-year-old male with a diagnosis of non-Hodgkin’s lymphoma who had received 16 IVC infusions prior to study
Patient 3 was a 69-year-old male with a diagnosis of metastatic carcinoma of the jejunum who had received 16 IVC infusions prior to study.

4. At 350 to 400 mg/dL, vitamin C is delivered as a pro-drug to the extracellular space where it interacts with metal ions in a Fenton reaction, generating significant interstitial H₂O₂. Normal cells are not affected while cancer cells, due to the catalase deficiency, are destroyed. Due to increased glucose receptors on the cancer cell membranes, vitamin C may accumulate up to five times the concentration than in normal cells.
5. Vitamin C promotes healthy mitochondria function, stimulates the immune system to produce interferon, to increase NK cell numbers, phagocytosis with enhanced migration and killing function. Vitamin C reduces oxidative damage to the p53 (apoptosis-regulating) gene due to chemo and radiation. This helps to prevent the DNA damage and mutation that would otherwise render cancer cell apoptosis and death nonfunctional.
6. Vitamin C helps in the production of collagen and carnitine for fibrous tissue formation that helps to “wall off” the tumor. It also helps in the formation of connective tissue, cartilage, bone matrix, tooth dentin, skin, and tendons.

7. Vitamin C helps in the conversion of amino acids to neurotransmitters; decreases the production of prostaglandin E₂ and, therefore, the inflammatory response; and enhances stem cell production for normal tissue healing.

Inclusion criteria and candidates for the Riordan IVC protocol:

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:

1. In our 25 years of clinical 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.
2. The danger of diabetics on insulin incorrectly interpreting their glucometer finger stick has already been mentioned. 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.
3. Tumor necrosis or tumorlysis syndrome has been reported in one patient after high-dose IVC. For this reason, the protocol always begins with a small 15 gram dose (see *Administration* below).
4. 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.
5. Hemolysis has been reported in patients with G6PD deficiency when given high-dose IVC. The G6PD level should be assessed before beginning IVC. (At our Center, G6PD readings have yielded

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- five cases of abnormally low levels. Subsequent IVC at 25 grams or less showed no hemolysis or adverse effects.)
6. 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.
 7. 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. 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.) 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.
 12. Table 1 lists the calculated osmolality of various amounts of fluid volume. Our experience has found that an osmolality of less than 1200 mOsm/kg H₂O is tolerated by most patients. A low infusion rate (0.5 grams IVC per minute) also reduces the tonicity, although up to 1.0 grams per minute can be used in order to achieve higher post IVC saturation levels. (Pre and post serum osmolality measurements are advisable at this dose.)
 13. We presently use a sodium ascorbate solution, MEGA-C-PLUS®, 500 mg/mL, pH range 5.5-7.0 from Merit Pharmaceuticals, Los Angeles, CA, 90065.

Table 1. – The Riordan IVC Protocol (with no solution removed from bag)

Vitamin C (A.A.) # Grams (# cc)	Diluent Type	MgCl Added	Infusion Time (~0.5 gram/minute)	Osmolality (calculated**)
15 grams (30cc)	250cc Ringer's Lactate	1cc	~30 minutes*	827 mOsm/L
25 grams (50cc)	250cc Sterile Water	1cc	~50 minutes	800 mOsm/L
50 grams (100cc)	500cc Sterile Water	2cc	~100 minutes	900 mOsm/L
75 grams (150cc)	1000cc Sterile Water	2cc	~150 minutes	703 mOsm/L
100 grams (200cc)	1000cc Sterile Water	2cc	~200 minutes	893 mOsm/L

* The patient's first introduction to high-dose IVC is infused more slowly...usually 45-60 minutes

** Data for actual measurements of both pre and post serum osmolality is available on request.

Administration of IVC:

1. 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.
2. The Riordan IVC Protocol dosing schedule depicted above has served as a “safe start” for cancer patients new to IVC. For the past 25 years The Center for the Improvement of Human Functioning International in Wichita, Kansas, has administered over 40,000 onsite IVC infusions according to this protocol. Zero fatalities and rare side effects attest to its remarkable safety.
3. The initial three infusions are monitored with post IVC infusion plasma vitamin C levels. As noted in the *Treatment Rationale* section above, research and experience has shown that a therapeutic goal of 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, but no additional clinical benefit has been gained.)
4. 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.
5. 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.
6. 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.
7. 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.
8. If the patient remains in a sub-therapeutic range, the IVC dosage is increased to the 100 gram level (as listed in Table 1.)
9. 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.
10. 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.
11. 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.
12. 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.

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13. 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.
14. 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.

Concurrent Therapy:

1. Mechanisms: Chemo – drugs of different mechanisms of action synergistically promote maximum cell kill. IVC – intravenous vitamin C when given in gram amounts to achieve a therapeutic range of 350-400 mg/dL acting as a prodrug producing H₂O₂ in cancer tissue which causes tumorlysis.
2. Toxicity: Chemo – drugs must have different toxicities that allow for safety of combination. IVC – protects higher oxygenated, noncancerous, tissues due to its antioxidant effect...while simultaneously performing as a selective prodrug in cancer tissue
3. Interactions: Chemo – drugs used in combination must not interfere with individual mechanisms of action. IVC – does not interfere with the majority of chemo agents as evidenced by in vitro research and in vivo clinical experience (as noted below.)
4. Predicted Response: Chemo – drugs used each must have a 5% predicted complete response (C.R.) rate and a 30% or greater partial response (P.R. – 50% reduction of measurable tumor volume.) IVC – Pauling, Cameron, Hoffer, Riordan, Simone, and Prasad record a range of approximately 3% C.R. rate and an approximately 80% improvement in long term survival.
5. Dose Dense Delivery: Chemo – drugs in combination allow for at least one to be used in a dose dense delivery fashion. Dose dense delivery allows for more frequent administration. IVC – allows for selected chemotherapeutic agents to be used in a dose dense fashion by virtue of its immune support and stem cell enhancement.

Conclusions:

1. IVC can be effective as a stand alone therapy, but is most commonly used in combination with conventional chemotherapeutic and radiation regimens.
2. Concurrent IVC with chemo/radiation may reduce side effects and enhance quality of life.
3. Concurrent IVC helps to preserve immunocompetence during chemotherapy and radiation.
4. Peer reviewed research documents over 7000 patients who have benefited from either IVC therapy or other concurrent antioxidant regimens.

Note: This document is an updated modification of an original protocol published by the Bio-Communications Research Institute and copyrighted in 2000. These modifications were completed by Hunninghake, Jackson, and Hyland in September of 2009. For copies, please contact Patricia Jobst at The Center for the Improvement of Human Functioning Int., Inc. at 3100 N. Hillside, Wichita, Kansas 67219 – USA – 316.682.3100 Fax # 316.682.5054

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