General Protocol

General protocol in oncology patients who are undergoing treatment for newly diagnosed or relapsed cancer.

Eligibility for Therapy

Each of the criteria must be met in order for a patient to be considered eligible for high-dose intravenous ascorbic acid therapy.

Inclusion:

1.1 G6PD status normal

1.2 Patients must have histologically or cytologically diagnosed neoplasm

1.3 The patient must screened for eligibility and have care approved by treating oncologist; the oncology care is to be dictated by the oncology team and patient.

1.4 Patients must be without evidence of spinal cord compression.

1.5 ECOG Performance Status 0-3. Must be able to take food and water by mouth.

1.6 Laboratory: ANC ≥ 1,500/mm3, Hemoglobin > 8 g/dL, platelets ≥ 100,000/mm3, total bilirubin ≤ 1.5 mg/dL, creatinine ≤2.0 mg/dL, transaminase (AST/ALT) ≤2.5 X upper limit, urine uric acid < 1,000 mg/d, urine pH <6, urine oxalate <60 mg/d.

1.7 Patients may be eligible for treatment if: there is no language barrier; they are cooperative; can give consent for treatment after being informed of medications and procedures.

Exclusion:

1.8 Patients with evidence of a significant psychiatric disorder by history/examination that would prevent informed participation.

1.9 ECOG Performance Status of 4.

1.10 Co-morbid condition that would affect survival: end stage congestive heart failure, unstable angina, myocardial infarction within 6 weeks of treatment, uncontrolled blood sugars ≥ 300 mg/dL, patients with known chronic active hepatitis or cirrhosis.

1.11 Patients who consume an excess of alcohol or abuse drugs (an excess of alcohol is defined as more than four of any one of the following per day: 30mL distilled spirits, 340mL beer, or 120mL wine) will not be allowed.

1.12 Patients who smoke tobacco products will not be allowed to participate.

Treatment Plan

2.1 Patient will have history and physical information and copies of the laboratory tests recorded in the medical record.

2.3 Patients may be newly diagnosed or relapsed neoplasm with histological or cytological confirmation provided and documented.

2.4 Patients may be currently undergoing chemotherapy and/or radiation therapy while enrolled in this protocol with approval of the medical or surgical oncologist.

2.5 History and physical examination and all laboratory analysis will be done within 14 days prior to instituting therapy.

2.6 The first visit will be a screening visit in the clinical setting (30 – 60 minutes) with review of medical records and laboratory work; decisions for follow-up visits will be based on the initial visit and mutually agreed upon by the patient and the treating physician (follow up visits - infusion visits will last approximately 60 minutes – 3 hours/ visit based on vitamin C dosing)

2.7 Patients will receive intravenous and oral nutrients at the discretion of the treating physician. The intravenous ascorbic acid will be given in a dose based on the plasma vitamin C level to reach a level of 350 - 450mg/dL.

2.8 Vitamin C infusions will be given on a schedule consistent with the study subjects' needs and

desires. The study subjects will be scheduled based on stage and status: option 1 for active disease - intravenous vitamin C infused 2 – 3 days per week, or option 2 for maintenance - intravenous vitamin C infused 1 time per week.

2.9 Patients will be encouraged to take oral supplemental nutrients on a daily basis and adhere to a whole foods diet free of processed carbohydrates and sugar.

2.10 After patient is disease-free, treatment is suggested to continue for 1-year. Thereafter, slow tapering is recommended with occasional administration of maintenance doses 1 to 2 times per month along with close monitoring.

Off Treatment

3.1 If there is evidence that the IV ascorbate infusions are no longer effective in tumor control.

3.2 Patient chooses to discontinue therapy.

Toxicities to be Monitored

4.1 Adverse events, whether volunteered by the patient, discovered by the treating physician during questioning, or detected by physical examination, laboratory tests, or other means will be collected and recorded in the medical record. Please note if this is directly related to the ascorbate infusions or to other therapies or disease process.

4.2 Patients experiencing Grade 4 neutropenia, Grade ≥3 thrombocytopenia, or Grade 2 peripheral neuropathy that do not recover will have treatment protocol discontinued.

4.3 Neutropenic fever is defined as fever >101° in the face of a granulocyte count <1,000.

4.4 Colony-stimulating factors will be prescribed at the discretion of the medical and/or surgical oncologist.

4.5 Hepatic dysfunction as defined as total bilirubin ≥ 1.5 mg/dL, creatinine ≥2.0 mg/dL, transaminase (AST/ALT) ≥2.5X upper limit.

4.6 Idiosyncratic intolerance of the therapies such as acute hypersensitivity will be recorded.

4.7 Intravenous ascorbic acid in the doses recommended has been shown not to be toxic. To ensure that these therapies are non-toxic, liver enzymes and creatinine will be monitored during the treatment phase.

4.8 **Common toxicity criteria will be defined by the NCI version 4.0 manual of toxicities**.

Administration of Intravenous Ascorbate

- **Intravenous ascorbic acid**: **Red blood cell hemolysis may occur in people found to be deficient in the G6-PD enzyme.** After the results of the G-6-PD laboratory test, a test dose of 25 grams of ascorbic acid (500 mg/mL; Bioniche Pharma or equivalent) in 500 mL Ringer's lactate is infused over 50 minutes. If this dose is tolerated, then the dose of ascorbic acid will be increased over the next 2 weeks until the plasma level reaches 350-450 mg/dL (see below). For clinical purposes: send samples to LabCorp, Quest Diagnostics, Biocenter Lab, Wichita Kansas or ARUP Lab for plasma C analysis– samples are drawn **immediately** after infusion is stopped. If using peripheral vein for infusion, use opposite arm for phlebotomy. If accessing a port, flush the port prior to withdrawing blood for analysis. Samples must be put on ice and transported immediately for processing.
- **Vitamin C degradation may occur during processing and storage and must be processed immediately**. Patients should not be sent to labs for blood draws after the infusions are finished because the clearance of ascorbate from the plasma occurs very quickly – this will give a falsely low value for plasma ascorbate.
- The protocol will include 2-3 infusions/ week including the weeks when chemotherapy is administered.

Infusion #1

- ***First Infusion of ascorbate***: Infusion rate will be given at 0.5 gram of ascorbic acid per minute; starting infusion of 25 grams of Vitamin C in appropriate carrier fluid (see table 1). The subsequent infusions may not be given less than 24 hours apart.

Infusions #2-3

The next 2 doses of ascorbic acid are 50 grams in the appropriate carrier fluid (see table 1) and infused at 0.5 gram per minute with 200 mg Mag Chloride added to the fluid to prevent vascular spasm. Approximately 10ccs of blood is collected following the second 50 gram infusion and sent to the diagnostic lab for plasma ascorbate analysis. Or prior to the infusion, check a finger stick blood sugar and record the value. Following the 50 gram infusion, flush line (or port) with 5 mL of saline, then draw back about 5 mL of blood to waste. Then collect approximately 10 mL of blood to send to the diagnostic lab for plasma ascorbate analysis. With this collected blood, also check another blood sugar value with the glucometer (or check via finger stick). You should expect the post infusion finger stick to read elevated because of the high ascorbic acid level in the serum. This is a testing artifact and the elevated reading should **not be treated with insulin**.

- The determination to increase from 50 to 75 grams is occasionally delayed for 1 week until results of plasma ascorbate levels are known. The practitioner may also recommend increasing the dose prior to receiving results of ascorbate testing.

Infusions #4-5

- The next 2 doses are 75 grams ascorbic acid in the appropriate carrier fluid (see table 1) with 400 mg Mag Chloride. These doses are infused at 0.5 gram per minute. After the second infusion of 75 grams, the plasma vitamin C level is reevaluated by laboratory analysis described above.

Once Plasma Level is Reached:

- Once the plasma ascorbate level reaches 350 to 450 mg/dL, then the patient may remain on the target dose two to three times per week. If the plasma level has not reached the appropriate plasma level on 75 grams, then dose escalation to 100 grams for 2 doses is undertaken with repeat of the plasma ascorbate level. At the dose where 350 to 450 mg/dL plasma concentration is obtained, that is the infusion dose for the remainder of the protocol. It may be necessary to increase the dose to as high as 125 grams in patients who have extremely aggressive tumors like pancreatic cancer, but this based on the plasma vitamin C level.

- **If the plasma level does not escalate appropriately with the increases in ascorbate doses, it is necessary to question the subject about surreptitious tobacco use and it may be indicated to check nicotine and continine levels. Additionally, patients must be taking oral nutrients and eating well.**

- **It is known that intravenous ascorbate is a pro-drug for hydrogen peroxide in the extracellular space. Because of this effect, concurrent use of intravenous glutathione may decrease therapeutic efficacy by decreasing levels of hydrogen peroxide formed in the tissues. We are currently NOT recommending IV and oral glutathione be administered on the same day, but this needs further investigation.**

Infusion Carrier Fluid

IV infusions will be administered in sterile water or lactated Ringers (see table 1) depending on the amount of ascorbate acid and other nutrients to be infused. Mag Chloride is also added to the solutions of 25 grams or higher ascorbic acid. See Table 1 bolded numbers for correct carrier solutions

Na Ascorbic Acid (calculated using 500mg/mL ascorbic acid)	Osmolarity calculated in Sterile Water			Osmaolarity calculated in Ringer's Lactate		
	250 mL	500 mL	1000 mL	250 mL	500 mL	1000 mL
1 gram	72	36	18	**347**	**312**	**297**
5 grams	261	131	65	**528**	**404**	**342**
10 grams	**499**	249	125	**754**	**517**	**399**
15 grams	**737**	**368**	184	**981**	**630**	**455**
25 grams	1212	**606**	**303**	1433	**857**	**568**
30 grams	1449	**725**	**362**	1660	**970**	**625**
50 grams	2400	1200	**600**	2565	1423	**851**
60 grams	2875	1437	**719**	3018	1649	**965**
75 grams	3588	1794	**897**	3697	1989	1134
100 grams	4776	2388	**1194**	4829	2555	1427

Note: Osmolarity is calculated by withdrawing the equivalent volumes of ascorbic acid and MgCl from the carrier fluid bag prior to injecting the ascorbic acid and MgCl into the bag: i.e for 1 gram (2 mL) of ascorbic acid and 2 mL MgCl, 4 mL is withdrawn from a 250 mL bag of Ringer's Lactate first. **See numbers that are black, bolded, and larger for correct carrier solutions**.