INTRAVENOUS VITAMIN C and CANCER

INTRODUCTION:

Vitamin C has long been known for its effects on immune stimulation and function. Because of vitamin C's role in maintaining normal immune function, many people use it for treating and preventing infectious conditions such as the common cold. Activity of several major immune cells and the messengers they produce seem to be increased by vitamin C. An additional viewpoint is that vitamin C serves as an antioxidant and increased intake from either foods or dietary supplements may promote good health.

HISTORICAL CONTEXT:

The World Health Organization recommends a daily intake of 45 mg/day of vitamin C for healthy adults. Vitamin C is necessary for production of collagen and other biomolecules, and for the prevention of scurvy. Vitamin C is an antioxidant, which has led to its endorsement by some researchers as a complementary therapy for improving quality of life.

Primates, including humans, and guinea pigs do not synthesize vitamin C internally. Nearly all other animals synthesize vitamin C internally, maintaining cellular vitamin C concentrations that are considerably higher than those achieved with the Recommended Daily Intake set for humans. Irwin Stone coined the term *hypoascorbia* to describe the low level of vitamin C maintained in humans through their diet compared to the level other animals maintain through their internal production. He proposed that hypoascorbia is caused by a genetic defect in humans and most primates. Animals that produce ascorbate internally produce considerably higher amounts when they are stressed. *This is why higher intake of Vitamin C is necessary when we are stressed or ill.*

Vitamin C has been promoted by naturopathic physicians as a treatment for the common cold, cancer, polio and various other illnesses. The evidence for these claims is mixed. Orthomolecular-based megadose recommendations for vitamin C are based mainly on theoretical speculation and observational studies, such as those published by Fred R. Klenner from the 1940s through the 1970s. Since the 1930s, when it first became available in pure form, some physicians have experimented with higher than recommended vitamin C consumption or injection.

> *NOTE: One of these physicians, Linus Pauling (known as the father of intravenous vitamin C therapy), found that he could reduce, and at times reverse the effects of polio and measles on subjects when employing intravenous Vitamin C. To test "definitively" whether ascorbate was effective, a later physician, Dr. Moertel, conducted two randomized placebo controlled studies randomized to* **oral** *ascorbate; neither study showed benefit. Subsequently, ascorbate treatment was considered useless. However, it was not recognized until approximately 15 years later that oral and intravenous ascorbate have strikingly different pharmacokinetics. At this time – it became increasingly difficult to prove to the current medical community that IVC may effectively act to combat chronic diseases. Although becoming more main stream – to this date, it remains difficult to advocate the use of IVC to most conventional medical practitioners.*

VITAMIN C and CANCER

Ascorbate (ascorbic acid, vitamin C, AscH) is one of the early unorthodox therapies for cancer, based on two unsupported hypotheses. McCormick postulated that ascorbate protects against cancer by increasing collagen synthesis, while Cameron hypothesized that ascorbate could have anti-cancer action by inhibiting hyaluronidase and thereby prevent cancer spread. These hypotheses were subsequently promoted by Cameron and Pauling. Cameron and Campbell initially published case reports of 50 patients; some seemed to have benefited from high dose ascorbate. Cameron and Pauling then published results of 100 patients with terminal cancer that were given intravenous ascorbate. The ascorbate-treated patients were compared to 1000 retrospective controls with similar disease. Patients who received ascorbate survived 300 days longer than controls.

Recent studies have characterized the administration of IV vitamin C and its effectiveness at tumorlysis (tumor cell death). There are now multiple studies with animal data showing tumor reduction and improved survival with high dose ascorbic acid administration using pharmacologic doses achievable in humans. Other investigators have found increased survival outcomes in terminal cancer patients receiving high dose vitamin C alone and combined with chemotherapy. The phase I clinical trial by Hoffer, Levine et al. concluded that high dose intravenous ascorbic acid was well-tolerated and safe in patients with previously treated malignancies. In that trial, i.v. ascorbic acid was administered in a dose (1.5g/kg several times weekly) sufficient to sustain plasma ascorbic acid concentrations >10 mmol/l for several hours in line with current data and previous evidence regarding its potential in anti-cancer activity. Another study combined first line chemotherapy and intravenous vitamin C for use in ovarian cancer in humans with 2 cases showing benefit and long-term survival beyond expectation for the disease state. There are numerous case reports showing evidence for application of high dose intravenous vitamin C for increased survival and more favorable outcomes. Much of the pioneering work in the use of intravenous high dose vitamin C therapy lays the groundwork for further use in its application as an adjunct tool in cancer therapy. In particular, a very recent study elucidated and further confirmed the mechanisms of i.v. ascorbic acid's role in non-caspase mediated cell death in pancreatic cell lines treated with pharmacologic doses of ascorbate achievable in humans.

THE DIFFERENCE BETWEEN ORAL and INTRAVENOUS IVC

Vitamin C is well absorbed by tablet or capsule at low doses, but the absorption of vitamin C decreases as the dose increases. Approximately 87% of a 30 mg oral dose is absorbed, 80% of a 100 mg dose is absorbed, 63 % of a 500 mg dose is absorbed, and less than 50% of a 1250 mg does is absorbed. Most of what is absorbed is excreted in the urine. Decreased absorption with increasing dose and increased excretion in the urine limits the ability of the blood plasma to become high in Vitamin C.
Research in this field has shown that high blood plasma levels of vitamin C allow the nutrient to be carried to the area where tumors exist in the body. When given intravenously, it is possible to elevate blood plasma levels of antioxidant Vitamin C over longer periods of time which may fight cancer and produce health benefits.

It is important to note that normal levels of Vitamin C are important. These levels function to block free radical generation and maintain the oxidation reduction reaction intracellularly; i.e., its principle action is as an anti-oxidant. However, to act as a pro-oxidant, cancer fighter, intravenous administration is imperative.

HOW IVC WORKS: THE DEATH OF CANCER CELLS and THE INTEGRITY OF NORMAL CELLS

In research that defines the cytotoxic effect that pharmacologic concentrations of ascorbic acid may have on tumor growth in vivo, it was found that administration resulted in the formation of both ascorbate radical and H_2O_2 in the extracellular fluid of the tissue parenchyma. Hydrogen peroxide has the action of compromising membranes, disrupting glucose metabolism and degrading DNA integrity. With sustained increase in H_2O_2 after ascorbate treatment, Q Chen et al noted intra-tumoral concentrations of H_2O_2 increased similar to endogenous levels evident in dermal wound sites 2-5 days after injury. Further it was seen in vivo that in contrast to the wound healing process, the regimen of daily pharmacologic ascorbate treatment in animal models produced episodic and chronic peroxide formation which manifested as an overall diminished tumor growth and suppression of cancer compared to control subjects. In vivo, because red blood cells exhibit both catalase and glutathione peroxidase activities, ascorbate toxicity is completely inhibited in the presence of blood which delivers the pro-drug ascorbic acid to the tissues where H_2O_2 formation acts on catalase deficient cancer cells which have a greater sensitivity toward oxidative stress. Both in vitro and in vivo data support the idea that ascorbate induces the production of extracellular hydrogen peroxide leading to oxidative stress and necrotic cell death of susceptible cancer cells. Ascorbate readily donates an electron to redox-active transition metal ions such as iron and copper which therefore react with oxygen to produce superoxide ions which in turn may dismutate to produce H_2O_2.

WHY ADD VITAMIN K TO IVC?

Vitamin K (K1, K2, K3, K4) is a group of structurally similar, fat soluble vitamins that are needed for the posttranslational modification of certain proteins, required for blood coagulation and are involved in metabolic pathways in bone and other tissue.

Vitamin K3 (2-methyl-1,4-napthoquinone), has been shown to promote "oncosis," a form of stress-activated ischemic cell death to which tumor cells are particularly susceptible. Because of their high growth rate, tumor cells can rapidly outgrow their blood supplies. Furthermore, their high metabolism means they use up oxygen rapidly, making them especially vulnerable to oxidant stress—much more so than the healthy tissues around them. Vitamin K targets these tumor cells for destruction by stimulating oxidative stress, without toxicity to healthy tissues. . Numerous studies now point to the benefits of combining a form of Vitamin K – Vitamin K3, with vitamin C to produce a greater anti-cancer effect.

When Vitamin K is combined with Vitamin C, the H2O2 generated is of a higher degree resulting in even greater death to those susceptible cells – i.e., cancer cells.

When combined into a single mixture administration of Vitamin C and 2-methyl-1,4-napthoquinone (vitamin K3) demonstrated a synergistic inhibition of cell growth at **10 to 50 times lower concentrations.** When combined both vitamins have demonstrated anti-cancer effects on human ovarian, breast, endometrial, prostate, hepatocellular carcinoma and skin cancer cell lines. Similar anti-cancer results have been cited for animal studies. These vitamins are not toxic to normal human cells. In addition**, the combination of sodium ascorbate and vitamin K$_3$ may also prevent metastasis.**

VITAMIN C and CHEMOTHERAPY:

The promise of ascorbic acid in the treatment of advanced cancer may lie in combination with cytotoxic agents, where high concentrations of this redox-active compound might modify either toxicity or response. There are currently several FDA approved clinical trials that are combining i.v. ascorbic acid with chemotherapy as first-line treatment in advanced stage non-small-cell lung cancer, pancreatic cancer, colorectal, and breast cancer.

An example: *IVC and Gemcitabine in Pancreatic Cancer*

Preclinical data has shown that HDIVC has anti-tumor effect in pancreatic cancer via the formation of H_2O_2 which mediates both chemosensitization of cells to gemcitibine as well as direct cytotoxic activity. There is also evidence to suggest that continuous infusion with lower levels of IVC after initial HDIVC over several hours, prolongs elevated plasma levels driving the increase in extracellular H_2O_2. In pre-clinical models the combined treatment with gemcitabine + HDIVC has shown no interaction or elevation of toxicity criteria in-vivo.

Extending survival and improving quality of life are primary considerations in the management and care of patients with cancer. With use of standard therapies, poor overall survival and reduced quality of life continue to be major obstacles despite recent advances in care. When patients with progressing disease who have undergone first, second and third line therapies continue to seek medical care with the intent to fight cancer, they may be offered a palliative approach with supportive measures. With few options, patients may turn to clinical trials, experimental medicine, or natural therapies looking for additional benefit to survival or relief from the symptoms of advanced pancreatic cancer.

Due to the safety of clinical trials of HDIVC in patients with advanced malignancy and in light of the proposed synergy between some chemotherapies and HDIVC the physicians and researchers leading this field from the National Institutes of Health and University research centers in Kansas and Iowa have urged their clinician colleagues in oncology to continue to move forward in this area of research.

PRECAUTIONS and SIDE EFFECTS

The side-effects of high-dose IVC are rare.
However, there are precautions and potential side-effects to consider.

1. 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 25 gram dose (see *Administration* below).

2. 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.

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

4. 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.

5. 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.

6. 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.

7. As with any I.V. infusion, infiltration at the site is possible. This is usually not a problem with Ports or Picc lines (as mentioned previously).

8. Approximately 75% of patients experience respiratory allergies to intravenous administration of Vitamin K. For this reason the dose of Vitamin K is increased slowly to assess tolerance. At times it is advisable to avoid addition of Vitamin K to infusions completely.

Blood Sugar and Intravenous Vitamin C

Vitamin C is structurally similar to glucose and subsequently results in the endogenous (body's own) production of insulin. When this occurs, any glucose in circulation is absorbed by cells causing blood sugar to drop. It is therefore important to eat prior to and, in many cases, during administration of IV Vitamin C. Bring snacks with you.

For those patients who are Diabetic: Although blood sugar may appear elevated post administration, this is a false result. As mentioned above, vitamin C is structurally similar to Glucose with resultant erroneous glucometer readings. Depending on the dose, false positive glucose and occasionally "positive ketone" readings may last for 8 hours after infusion. Blood taken from a vein and run in a laboratory using the hexokinase serum glucose method is not affected. Again, it is important that you bring food with you to eat during treatment – although your sugars may appear high they may actually drop with IV Vitamin C, requiring supplemental nutritional/caloric intake.

THE IVC PROTOCOL:

The dosage of Vitamin C typically involves 25, 50, or 75 gms. Initiation is always at 25 gm. 50 or 75 gm Vitamin C dosage is followed by serum IVC plasma levels in order to determine appropriate incremental dosage of Vitamin C. The lower than normal serum levels after a dose have been shown to 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.

Once the therapeutic level has been reached it is recommended patients remain at the given dose and receive 1-2 infusions weekly to maintain serum levels.

It is advised to orally supplement with at least 4 gms of Vitamin C daily, especially on the days when no infusions are given, to help prevent a vitamin C "rebound effect."

DOSING SCHEDULE:

G6PD testing (can be assessed either prior to or post initial 25 gm infusion) Must have prior to 50gm infusion.

(1) 250cc lactated ringers with 25gm Vitamin C over 45 minutes
(2) 500cc sterile H20 wit 50gm Vitamin C over 2 hours
(3) 900cc sterile H20 with 50 gm Vitamin C and Vitamin K over 3 hours (if allergic to Vitamin K will know at this time).
(4) 850cc sterile H20 with 75gm Vitamin V (with or without K) over 3 hours.
(5) Post IV draw Plasma Ascorbate level from opposite arm. Not: May repeat no. (5) until lab result is in.
(6) Assess lab indices and pursue appropriate intravenous therapy to reach desired serum indices.

DISCONTINUING IVC THERAPY:

Some patients are not able to continue IV therapy for a number of reasons. IV therapy *is not* the only viable therapy to manage cancer and/or prevent its recurrence. Additional recommendations and referrals are always available. Your care and follow-up is important and imperative for you to ensure your health, longevity and quality of life.

A heartfelt thank you for joining me in this lecture and sharing your time.

In health and blessings,

Kirsten West N.D.

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