WHITE PAPER

Vitamin C Foundation Oral Dosage Recommendations to Achieve CSC-Lethal Concentrations of Ascorbate

This information is new and this document should be shared with your oncologist and other professional caregivers. The Vitamin C Foundation believes on the weight of the existing science, that vitamin C can complement conventional cancer treatments, such as chemotherapy and radiation. This means that vitamin C can help cancer patients live longer and feel better while undergoing conventional therapy. This new information, based on both first-time ever *in vitro* research and a xenograft experiment in live mice (with a reported 40% reduction in pancreate tumor size) suggests optimal vitamin C dosing. After your doctors have been informed, and are given time to study the new research, we strongly suggest you follow their advice and guidance.

A 1 g oral dose of Ascorbic Acid (AA) can raise plasma AA to 130 µmol/L within an hour and such doses at intervals of about two hours throughout the day can maintain ~230 µmol AA/L (Krone & Ely, 2002).

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This White Paper assigns oral vitamin C dosages to the optimal numbers found in the landmark Sen, *et. al.* study***, Opposing effects of low versus high concentrations of water soluble vitamins/dietary ingredients Vitamin C and niacin on colon cancer stem cells (CSCs).*** http://onlinelibrary.wiley.com/doi/10.1002/cbin.10830/full

Basic Vitamin C Oral Dosing Recommendation for Cancer Patients

Vitamin C in a daily dosage of **1,000 mg (1 gram) or less would create the concentrations that cause CSC proliferation** *(5 to 25 µM/L)* and should be avoided by cancer patients.

Supplement vitamin C, at least 1 gram every 2 hours, as often as possible, no matter what other cancer therapies you are on. (*12,000 mg or 12 g per day*) to maintain a blood level of at least 100 µM/L.

Higher doses, e.g. **2 or 4 grams every 3 to 4 hours would be even more optimal.** (*16,000 mg – 24,000 mg (16 g - 24 g) per day.*)

The highest dosages, up to 40 to 80 g per day of vitamin C should maintain the highest optimal CSC killing range studied by Sen, *et. al.*

Even higher vitamin C dosages are being investigated intravenously (Drisko), but their optimality w/r to CSCs was not investigated by Sen, and may be contraindicated.

Bottom Line: Oral Vitamin C Dosages Can Achieve Cancer Stem Cell (CSC) Destruction to Avoid Colon Cancer Stem Cell Proliferation.

For the first time in the history of science, a group of researchers in India have studied the optimal dosing of vitamin C with respect to the "seeds of cancer," i.e., colon cancer stem cells (CSCs). Sen, *et. al.*, found that higher doses of vitamin C and Niacin, or vitamin B3, destroy cancer stem cells.

About a decade ago, a leading US cancer center at the University of Michigan issued press release that conventional therapies are targeting only one type of class of cancer cell -

ordinary, rapidly dividing malignant cancer cells, but that cancers emanate from seed cells, or cancer stem cells (CSCs). Since then , Cancer Stem Cells have become the focus of research because these cells do not divide rapidly enough for chemo and radiation to kill them. If CSCs proliferate, their progeny becomes even stronger malignant cancer cells.

When you are fighting cancer - you are fighting both enemies.

The new, first-ever study found that vitamin C and Niacin, at the proper concentrations, could KILL these CSCs - the seeds of ordinary malignant cells. However, too small concentrations of vitamin C (and Niacin) actually promote the proliferation of these cancer-seed cells. Bottom line: There are two different types of cancerous cells, and they are killed differently.

Published in the journal *Cell Biology International*, the landmark study investigated both low and high doses of vitamin C and Niacin on stem cells tumors of the intestine. Different dosages produced opposite effects.

Study Abstract

Colorectal cancer is one of the global causes of cancer deaths. Cancer stem cells (CSCs) inside the tumour niche responsible for metastasis and relapses, and hence need to be targeted for cancer therapeutics. Although dietary fibre and lifestyle changes have been recommended as measures for colorectal cancer prevention, no such recommendations are available for using water soluble vitamins as prophylaxis measure for colorectal cancers. High dose of Vitamin C has been proven to selectively kill colon cancer cells having BRAF and KRAS mutations by inducing oxidative stress. In this study, we show for the first time the opposing effects of the low and high dose of Vitamin C and vitamin B3 on colon CSCs isolated from HT-29 and HCT-15 colorectal carcinoma cell lines. At small doses, both of these vitamins exerted a cell proliferative effect only on CSCs, while there was no change in the proliferation status of non-stem cancer cells and wild-type (WT) populations. On the other hand, the death effects induced by high doses of Vitamin C and B3 were of the order of 50–60% and ~30% on CSCs from HT-29 and HCT15, respectively. Interestingly, the control fibroblast cell line (NIH3T3) was highly refractory all the tested concentrations of Vitamin C and B3, except for the highest dose – 10,000 µg of Vitamin C that induced only 15% of cell death. Hence, these results indicate the future scope of use of therapeutic doses of Vitamin C and B3 especially in patients with advanced colorectal cancer.

If this landmark test tube research translates into *in vivo* blood concentrations in humans, we now know that when taking vitamin C to create a blood concentration of 5-25 micromole/L of vitamins C and B3, which is a low concentration, there is a process of active reproduction of stem cells tumors of the intestine. At high dosages (creating concentrations of 100 to 1,000 micromoles/L) these stem cells are destroyed. Higher dosages, e.g. 10,000 micromoles/L caused renewed CSC proliferation.

A new major British epidemiological *(in vivo*) study with a cohort of of 38,812 was just published (Egnell, 2017). This large study found that increased dietary levels of antioxidants such as vitamin C, E, β-carotene, and selenium are associated with lower risk of developing colon cancer. On the basis of the evidence, the authors wrote: *"Healthcare professionals may promote intake of these antioxidants in healthy amounts in order to reduce the incidence of this type of malignancy."*

There is no known harm or toxicity from taking vitamin C, so there is no reason for cancer patients to wait for more studies.

The next table from the Sen *et. al.*, study shows relative proliferation based on dosage of vitamin C. (*There is a similar table in the study showing the proliferation rates for Niacin*.) Numbers above 100 indicate proliferation, while numbers less than 100 indicate apoptosis or cell death.

Table 2. **Percentage of cell proliferation upon exposure to low (5–25 μM) and high concentration ranges (100–10,000 μM) of vitamin C/ascorbic acid in various cell populations obtained from HT-29 and HCT-15 colorectal carcinoma cell lines respectively.** Table showing the respective percentages of cell proliferation of the cell populations WT, CSCs ($CD44^+$) and non-stem cancer cells ($CD44^-$) with respect to various concentrations (5–10,000 μM) of Vitamin C/Vitamin C from HT-29 and HCT-15 cell lines. The untreated control cells for each of the cell type WT, CSCs ($CD44^+$) and non-stem cancer cells ($CD44^-$) have been assigned an arbitrary value of 100% cell proliferation.

	Cell types and percentage of cell proliferation					
Vitamin C conc. μM	**HT-29 WT**	**HCT-15 WT**	**HT-29-$CD44^+$**	**HCT-15 $CD44^+$**	**HT-29-$CD44^-$**	**HCT-15 $CD44^-$**
0	100	100	100	100	100	100
5	114	108	172	107	86	122
10	104.7	114	160.8	107.26	93.11	121.01
15	95.81	121.03	172	110.15	97.1	106
20	90.57	94.19	169.73	115.01	99.2	93.79
25	88.48	90.01	169.73	116.32	86.59	98.13
100	21.51	89.01	68.28	93.79	14.23	96.15
200	21.81	88.06	69.34	73.58	14.13	96.52
500	23.56	85.42	67.23	72.01	12.68	95.16
1,000	24.34	83.12	65.81	69.56	11.59	88.06
10,000	27.06	226	61.18	304.10	14.13	233.03

The Vitamin C Foundation nonprofit recommends that on the basis of the Sen, *et. al.* landmark study, all cancer patients be advised to supplement vitamin C in oral amounts that can achieve at least a 100 micromoles/liter concentration in their blood for as long as possible.

The major problem is that the kidney constantly reduces vitamin C concentrations to less than this amount steady state, e.g. 85 micromoles/liter, with a half-life of 30 minutes. **Our initial estimates are that 1 gram or less of oral vitamin C daily creates the concentrations that promote CSC proliferation**, and that 4 grams creates the minimum required 100

micromole/litter concentration, at least for a little while. If this work translates, dosages up to 80 grams would be appropriate and safe.

Continuous Oral Dosing May Work Better than Intravenous Vitamin C

The Vitamin C Foundation calculates that continuous oral supplemental oral intakes of vitamin C can achieve the study's reported cancer-lethal concentrations in the blood. The normal laboratory range for vitamin C in the USA is 0.4 mg/dl to 1.5 mg/dl, (23 to 85 µM/L). The Indian study results indicate that a 100 µM concentration (1.76 mg/dl) is the low end of the cancer-lethal range, or just above steady state (1.5 mg/dl). Sustaining this above-steady state blood level requires continuous vitamin C supplementation, as long advocated by vitamin C experts Steve Hickey and Hilary Roberts, PhDs.

While intravenous vitamin C can exceed the 10,000 µM by 2.5 times (e.g. 440 mg/dl or 24,983.2 µM/L) this level was not investigated, may be suboptimal spurring CSC proliferation, and it is difficult to keep people on constant intravenous vitamin C infusions.

The low range (5 to 25 µM) that promotes the growth of cancer stem cells equals a lab range of 0.08 to 0.44 mg/dl which is below normal and can easily be raised through regular vitamin C supplementation.

Note: The Sen, et. al., measurements indicate that daily amounts of one gram or less of vitamin C promote CSC proliferation. This new finding indicates that the government approved RDA for Vitamin C, and the low amount currently recommended by the Linus Pauling Institute at Oregon State, are dangerous for cancer patients. Much more vitamin C is needed to avoid CSC proliferation and malignancy relapse, at least 12 grams daily as long recommended by Linus Pauling.

I Have Cancer, How Much Vitamin C Should I Take Based on The Sen, et. al. Test Tube Study?

On the basis of research conducted in New Zealand, (Krone/Ely 2002) we believe that **the minimum dosage to maintain a cancer-killing concentration is 1,000 mg every 2 hours.**

A 1 g oral dose of AA can raise plasma AA to 130 µmol/L within an hour and such doses at intervals of about two hours throughout the day can maintain ~230 µmol AA/L

Self-reported daily intake varied from 0 to 20 g/day. The plasma AA levels ranged from 11.4 to 517 µmol/L and correlated well with the reported intake (Krone & Ely, 2002).

The 1 gram/2 hour minimum protocol requires a daily dosage of 12,000 milligram (12

grams).
Note: 8 hours of sleep requires a loading dose before bed, or timed release vitamin C. This minimum oral protocol maintains a 230 µM concentration, which is at the low-end of the optimum cancer killing range (100µM to 1,000µM).

Sen, *et. al.* did not investigate the mid-range vitamin C concentrations, from 26 µM to 99 µM.

The low, CSC stimulating concentrations (<26µM) would be expected from taking 1,000 mg (1 gram) of vitamin C or less daily.

We calculate that without the short half-life, approximately 40,000 mg (40 grams) of Vitamin C daily would reach a maximum optimal concentration of 1,000 µM . But high levels of vitamin C do not remain in the blood. Because of the short 30-minute half-life, we believe that 80 grams of vitamin C would be safe, and achieve the 1,000 µM concentration, on average, over a longer duration.

It is believed that conventional therapies destroy ordinary aggressive malignancies by creating oxidative stress. Very high dose vitamin C does produce hydrogen peroxide by overcoming enzyme systems (e.g. catalyze) that would otherwise prevent this. As the Sen, *et. al.*, abstract points out, IV/C. has been proven to treat ordinary cancer cells by creating oxidative stress. Therefore, rather than stopping vitamin C during conventional chemotherapy and/or radiation, increasing the dosage using very high dose IV/C may provide better results in conjunction with these therapies. Drisko is currently researching 200 gram IV/C in conjunction with conventional therapies.

The Vitamin C Foundation is not competent to assign Vitamin B3 (Niacin) dosing values based on the Sen, *et. al.* Study. Niacin was about 50% as effective as vitamin C killing Cancer Stem Cells (CSCs). However, we note that Vitamin B3 expert A. Hoffer, MD, PhD, in his book *Vitamin C and Cancer: Discovery, Recovery, Controversy (2000)* reported excellent results prescribing equal amounts of vitamin C and Niacin to cancer patients.

Summary of Recent Science: Vitamin C versus CSCs Proliferation

In 2001, the University of Michigan Cancer Center proclaimed that current chemotherapy targets the “wrong” cells. The Ann Arbor researchers discovered that not all cells in a tumor are equally malignant. Only tiny minorities of tumor cells are actually capable of inducing new cancers; the rest are relatively harmless. "These tumor-inducing cells have many of the properties of stem cells," said Michael F. Clarke, MD, a professor of internal medicine, who directed the study. "They make copies of themselves --a process called self-renewal -- and produce all the other kinds of cells in the original tumor" (Reya, 2001).

The 2017 first-ever study from India found that vitamin C, and Niacin to a lesser extent, at the proper concentrations can kill CSCs - the seeds of ordinary malignant cells. Importantly, they also demonstrated that too small concentrations of vitamin C (and Niacin) actually promote

the proliferation of these cancer-seed cells (Sen, 2017).

Last June, Professor Michael Lisanti from the University of Salford, UK, published two studies that found vitamin C and antibiotics could be up to 100 times more effective at killing cancer stem cells (CSCs) than standard-of-care drugs. According to Lisanti, giving the antibiotic doxycycline followed by vitamin C effectively starves cancer stem cells of their fuel, resulting in their death in the lab, the researchers said (De Francesco & Lamb, 2017).

Then last August, another research groups located in the UK and USA published their findings that injections of vitamin C could help fight blood cancers. Luisa Cimmino and Benjamin Neel at the New York University School of Medicine and their colleagues have discovered that, by injecting vitamin C, cancer growth could be prevented. Researchers halted the progression of leukemia in mice by promoting the function of a specific gene through high doses of vitamin C.

In the same month, researchers at Children's Medical Center Research Institute at UT Southwestern discovered that stem cells absorb “unusually high” levels of vitamin C, which reportedly regulate function and suppress the development of leukemia. Dr. Michalis Agathocleous, lead author of the study, said stem cells use vitamin C to regulate chemical modifications on DNA, which turn genes on and off. “When stem cells don’t receive enough vitamin C, these [DNA-regulating mechanisms] can become damaged in a way that increases stem cell function but also increases the risk of leukemia.” Thus, if humans take up more vitamin C than normal, this vitamin will regulate and stabilize stem cell function and suppress the chances of developing leukemia (Cimmino & Meacham, 2017).

Physician Daniel Couturier commented, “Available studies indicate that vitamin C, at doses of 4 g/kg b.w., a pancreatic tumor mass reduction of more than 40% could be achieved in a xenograft animal model" (Chen, 2008).

The new research settles the Linus Pauling/Arthur Robinson Cancer and Vitamin C Controversy. Both men were right. While low doses promote cancers in patients with cancer, high doses can kill cells that spawn new cancers.

Discussion

Many factors can affect ascorbate (vitamin C) blood concentrations, including the short 30-minute half-life, stress and illness, the type of vitamin C that is taken orally (e.g. ascorbic acid versus sodium ascorbate or liposomal vitamin C), the amount of sugar (glucose) in the diet, and the ability of the patient to consume high amounts of vitamin C, often called Bowel Tolerance.

In 1976, biochemist Sherry Lewin, PhD reported in her book *VITAMIN C: Its Biology and Medical Potential* that when vitamin C is administered at the same time carbohydrates are eaten, the vitamin breaks down in the intestinal tract, and less is absorbed into the blood stream. In contrast, when vitamin C is eaten with a protein, the amino acids chelate with the vitamin, protecting it during digestion, making the vitamin more bioavailable. There are many

products on the market that offer both vitamin C and the amino acid lysine together.

The Vitamin C Foundation's recently published *BIOAVAILABILITY OF VITAMIN C* paper in the Townsend Letter for Doctors and Patients is based on original research. The Foundation demonstrated the different rates of absorption between ascorbic acid, and the salt sodium ascorbate. Previously unknown, ascorbic acid entry into the blood stream is very rapid, probably through the stomach wall, and concentrations can exceed an IV/C, at least for a short time. On the other hand, sodium ascorbate enters the blood stream more slowly, more like a timed release, and probably travels down the GI Tract and is absorbed through the intestines. If sodium ascorbate is not taken with protein, it is probable that more of the vitamin would break down and not be bioavailable, indicating that a higher dosage may be required.

Some people have low bowel tolerances, meaning they cannot achieve even the minimum daily protocol of 1 gram every 2 hours. Liposomal technology may be the answer because more vitamin C is absorbed when encapsulated in liposomes, and the liposomes persist 4 to 6 times longer in the blood stream. It is unknown whether the vitamin encased in a 150-nanometer liposome would have the same CSC killing effect. Sen reports on a study that found liposomes made from fat-soluble vitamin C (ascorbyl palimate) were more potent than ordinary vitamin C injections in breast cancers.

> *"However, intravenous administration of palmitoyl ascorbate liposomes proved to be more potent, as compared to, free Vitamin C injection in Balb/c mice model of mammary carcinoma" (Sawant et al., 2012).*

Dosing Summary

Our advice to all cancer patients is to supplement vitamin C, at least 1 gram every 2 hours, no matter what other therapies you are on. (*12,000 mg or 12 g per day*)

Do supplement vitamin C, and do not supplement less than one gram per day.

Higher doses, e.g. 2 or 4 grams every 3 to 4 hours would be even more optimal. *16,000 mg (16 g) to 24,000 mg (24 g) per day.*

The highest dosages, up to 40 to 80 g per day should maintain the highest optimal CSC killing range.

This confirms Dr. Robert's Cathcart, II, MD's clinical experience that the bowel tolerance range for cancer patients is a daily amount 15 g to 100 g
https://vitamincfoundation.org/FDAapproved/pdfs/Vitamin_C_Dosage_in_Disease.pdf

While much higher dosages are being investigated intravenously (Drisko), the optimality of these dosage w/r to CSCs was not investigated by Sen. These high doses create oxidative stress in or near cancer cells, which may enhance conventional therapies.

It is interesting that the 12,000 grams of vitamin C would also achieve Linus Pauling's recommended therapeutic dosages for cardiovascular disease.

References

Daniel Couturier wrote: "I cannot comprehend why even proponents of high dose vitamin C consider it to be an inferior resource when it comes to antagonizing malignancies, considering the fact that available studies indicate that at doses of 4 g / kg b.w. a pancreatic tumor mass reduction of more than 40% could be achieved in a xenograft animal model. "

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Pharmacologic doses of ascorbate act as a prooxidant and decrease growth of aggressive tumor xenografts in mice

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Abstract

Ascorbic acid is an essential nutrient commonly regarded as an antioxidant. In this study, we showed that ascorbate at pharmacologic concentrations was a prooxidant, generating hydrogen-peroxide-dependent cytotoxicity toward a variety of cancer cells in vitro without adversely affecting normal cells. To test this action in vivo, normal oral tight control was bypassed by parenteral ascorbate administration. Real-time microdialysis sampling in mice bearing glioblastoma xenografts showed that a single pharmacologic dose of ascorbate produced sustained ascorbate radical and hydrogen peroxide formation selectively within interstitial fluids of tumors but not in blood. Moreover, a regimen of daily pharmacologic ascorbate treatment significantly decreased growth rates of ovarian ($P < 0.005$), pancreatic ($P < 0.05$), and glioblastoma ($P < 0.001$) tumors established in mice. Similar pharmacologic concentrations were readily achieved in humans given ascorbate intravenously. These data suggest that ascorbate as a prodrug may have benefits in cancers with poor prognosis and limited therapeutic options.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2516281/

This next study released late 2017 showed that increased dietary levels of antioxidants such as vitamin C, E, β-carotene, and selenium are associated with lower risk of developing colon cancer. This major epidemiological (in vivo) study had a cohort of of 38,812. On the basis of

the evidence, the authors wrote: "Healthcare professionals may promote intake of these antioxidants in healthy amounts in order to reduce the incidence of this type of malignancy."

Resource: Egnell, M., et al. (2017). **Antioxidant intake from diet and supplements and risk of digestive cancers in middle-aged adults: results from the prospective NutriNet-Santé cohort.** British Journal of Nutrition. doi:10.1017/S0007114517002392

Abstract:

The results of the study showed that increased dietary levels of antioxidants such as vitamin C, E, β-carotene, and selenium are associated with lower risk of developing colon cancer. This important study has demonstrated the link between antioxidants and digestive cancer risk. The harmful effects of alcohol and smoking are also apparently reduced by the intake of selenium and vitamin E, respectively. Overall, antioxidants in the diet may reduce the risk of developing gastrointestinal cancers. Healthcare professionals may promote intake of these antioxidants in healthy amounts in order to reduce the incidence of this type of malignancy. https://www.ncbi.nlm.nih.gov/pubmed/28927476

Linus Pauling and his associate, Ewan Cameron, MD, did not claim that vitamin C cured cancer, only that it extended lives making the patient feel better. This Korean study supports the Pauling /Cameron claim of longer and better lives for terminal cancer patients.

J Korean Med Sci. 2007 Feb;22(1):7-11.
Changes of terminal cancer patients' health-related quality of life after high dose vitamin C administration.
Yeom CH1, Jung GC, Song KJ.

Abstract

Over the years there has been a great deal of controversy on the effect of vitamin C on cancer. To investigate the effects of vitamin C on cancer patients' health-related quality of life, we prospectively studied 39 terminal cancer patients. All patients were given an intravenous administration of 10 g vitamin C twice with a 3-day interval and an oral intake of 4 g vitamin C daily for a week. And then we investigated demographic data and assessed changes in patients' quality of life after administration of vitamin C. Quality of life was assessed with EORTC QLQ-C30. In the global health/quality of life scale, health score improved from 36+/-18 to 55+/-16 after administration of vitamin C (p=0.001). In

functional scale, the patients reported significantly higher scores for physical, role, emotional, and cognitive function after administration of vitamin C ($p<0.05$). In symptom scale, the patients reported significantly lower scores for fatigue, nausea/vomiting, pain, and appetite loss after administration of vitamin C ($p<0.005$). The other function and symptom scales were not significantly changed after administration of vitamin C. In terminal cancer patients, the quality of life is as important as cure. Although there is still controversy regarding anticancer effects of vitamin C, the use of vitamin C is considered a safe and effective therapy to improve the quality of life of terminal cancer patients.

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