

High-dose intravenous vitamin C as an Anticancer Agent - A Literature Review

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Abstract: Ascorbate (vitamin C) is a cofactor for a number of metabolic enzymes and is an indisputable essential vitamin C for humans. However, the potential of ascorbate as an anticancer agent has been a topic of controversy. A number of previous reports have addressed both positive aspects and limitations of ascorbate in cancer therapy. In this review, we briefly summarize the potential antitumor effects of ascorbate and its prospects for clinical use.

Keywords: Ascorbate, ascorbic acid, vitamin C, cancer, intravenous, cytotoxicity, antioxidant.

INTRODUCTION

Vitamin C is also known as L-ascorbic acid or as sodium L-ascorbate. The richest natural sources of vitamin C are fruits and vegetables, and a balanced diet usually meets the daily requirements. Vitamin C is synthesized from D-glucose or D-galactose by many plants and animals. However, humans lack the enzyme L-gulonolactone oxidase required for ascorbic acid synthesis and must obtain vitamin C through food or supplements.¹ Thus, it is sold as a nutritional supplement in a variety of forms. Vitamin C can be administered via several routes including orally but physiological concentrations of vitamin C (L-ascorbate or L-ascorbic acid) in the body are controlled through intestinal absorption, tissue accumulation, and renal reabsorption and excretion. Therefore, intravenous administration is used to achieve pharmacologic doses.

Head and neck cancer is the sixth most common human cancer², representing 3% of all types of cancer. They are located in the oral cavity in 48% of cases, and 90% of these are oral squamous cell carcinoma³. They are sometimes preceded by precancerous lesions, such as leukoplakia and erythroplakia. More than 300,000 new cases of oral squamous cell carcinoma are diagnosed annually⁴. The most common site for intraoral carcinoma is the tongue, which accounts for around 40% of all cases in the oral cavity proper. Tongue cancers most frequently occur on the posterior-lateral border and ventral surfaces of the tongue. The floor of the mouth is the second most common intraoral location. Less common sites include the gingival, buccal mucosa, labial mucosa, and hard plate.

In the context of cancer, high-dose intravenous vitamin C (> 0.5 g per kg body weight) is claimed to have several effects: a) cytotoxicity for cancer cells, but not for normal tissue, b) improved quality of life for cancer patients, c) protection of normal tissues from toxicity caused by chemotherapy, and d) reinforcement of the action of radiation and some types of chemotherapy. High-dose vitamin C is essentially non-toxic. Reported side-effects are minor if patients are adequately screened for renal disease and glucose 6-phosphate dehydrogenase deficiency, and when doses are gradually increased with careful monitoring of the patient. Vitamin C might reduce the therapeutic response to conventional anti-cancer therapy.

Vitamin C is well known for its antioxidant activity although it is only one of a large variety of dietary antioxidants. Vitamin C has been well documented to reduce the incidence of most malignancies in humans⁵. What has been hotly debated is whether vitamin C has any therapeutic effect in the treatment of cancer. In the 1950s, vitamin C was originally

hypothesized to be protective against cancer,^{6, and 7} but in the 1970s, Ewan Cameron and Linus Pauling suggested that it also had a therapeutic effect, reporting increased survival of patients with advanced cancer following high-dose IV vitamin C treatment (typically 10 g/day, by intravenous infusion for about 10 days and orally thereafter)⁸. Other researchers reported benefit consisting of increased survival, improved well-being and reduced pain^{9,10}. In contrast, several subsequent randomized controlled trials (RCTs) of high-dose oral vitamin C failed to demonstrate a similar benefit,¹¹⁻¹³ opening the issue of therapeutic effectiveness to controversy. Some research groups conducted rigorous research, particularly in the area of administering mega-doses of ascorbate intravenously¹⁴.

Intravenous administration was found to increase plasma ascorbate concentrations by an order of magnitude compared to what may be achieved orally¹⁵. This may explain the discrepancy between Cameron and Pauling's success and the negative results observed at the Mayo Clinic. To date, no randomized controlled clinical trial with high-dose intravenous vitamin C has been published. A limited number of Phase I clinical trials confirm the non-toxic character of the treatment, and give some indications that the treatment may improve quality of life, but do not suggest distinct anti-cancer effects. Several case reports argue for a positive effect on survival time, even reporting cancer remission, and improved quality of life. This article presents a literature review of the role of high dose intravenous vitamin C as an anticancer agent.

HISTORICAL BACKGROUND OF HIGH-DOSE VITAMIN C THERAPY

The earliest experience of using high-dose vitamin C (intravenous [IV] and oral) for cancer treatment was by a Scottish surgeon, Ewan Cameron, and his colleague, Allan Campbell, in the 1970s¹⁶. This work led to a collaboration between Cameron and the Nobel Prize-winning chemist Linus Pauling, further promoting the potential of vitamin C therapy in cancer management^{8,17}. As a result, two clinical trials on oral vitamin C were conducted in the late 1970s and early 1980s^{11,12}.

LABORATORY/ANIMAL/PRECLINICAL STUDIES - In Vitro Studies

Numerous studies have demonstrated that pharmacological doses of ascorbic acid (0.1–100 mM) decrease cell proliferation in a variety of cancer cell lines¹⁸⁻²². The potential mechanisms through which treatment with high-dose ascorbic acid may exert its effects on cancer cells have been extensively investigated. Several studies have demonstrated that the in vitro direct cytotoxic effect of ascorbic acid on various types of cancer cells is mediated through a chemical reaction that generates hydrogen peroxide^{18,23}. However, not all studies combining vitamin C with chemotherapy have shown improved outcomes.

Laboratory studies have shown the following:

1. Treatment with high-dose vitamin C slowed the growth and spread of prostate, pancreatic, liver, colon, malignant mesothelioma, neuroblastoma, and other types of cancer cells.
2. Combining high-dose vitamin C with certain types of chemotherapy may be more effective than chemotherapy alone:
3. Ascorbic acid with arsenic trioxide may be more effective in ovarian cancer cells.
4. Ascorbic acid with gemcitabine may be more effective in pancreatic cancer cells.
5. Ascorbic acid with gemcitabine and epigallocatechin-3-gallate (EGCG) may be more effective in malignant mesothelioma cells.
6. Another laboratory study suggested that combining high-dose vitamin C with radiation therapy killed more glioblastoma multiforme cells than radiation therapy alone.

However, not all laboratory studies combining vitamin C with anticancer therapies have shown benefit. Combining dehydroascorbic acid, a particular form of vitamin C, with chemotherapy made it less effective in killing some kinds of cancer cells.

Animal Studies

The effects of high-dose ascorbic acid in combination with standard treatments on tumors have been investigated. Using N-acetylcysteine (NAC) and vitamin C, researchers showed in 2007 that these compounds, both thought to act predominantly as antioxidants, may have anti-tumorigenic actions in vivo by decreasing levels of hypoxia-inducible factor (HIF)-1, a

transcription factor that targets vascular endothelial growth factor (VEGF) and plays a role in angiogenesis²⁴. There have also been reports of animal studies in which vitamin C has interfered with the anticancer activity of various drugs.

Human/Clinical Studies

Early Ascorbate-Only Trials

In the early 1970s, a consecutive case series was conducted in which 50 advanced cancer patients were treated with large doses of ascorbic acid¹⁶. These patients began ascorbic acid treatment after conventional therapies were deemed unlikely to be effective. Patients received intravenous (IV) ascorbic acid (10 g/day for 10 consecutive days; some patients received higher doses), oral ascorbic acid (10 g/day), or both. The subjects exhibited a wide variety of responses to treatment, including no or minimal response, tumor regression, and tumor hemorrhage. However, the authors noted that lack of controls prevented definitive assignment of any beneficial responses to the ascorbic acid treatment.

Recent Ascorbate-Only Trials

One study reported three case reports of cancer patients who received IV vitamin C as their main therapy. During vitamin C therapy, the patients used additional treatments, including vitamins, minerals, and botanicals. According to the authors, the cases were reviewed in accordance with the NCI Best Case Series guidelines. Histopathologic examination suggested poor prognoses for these patients, but they had long survival times after being treated with IV vitamin C¹⁵. Vitamin C was given at doses ranging from 15 g to 65 g, initially once or twice a week for several months; two patients then received it less frequently for 1 to 4 years. Studies have shown that vitamin C can be safely administered to healthy volunteers or cancer patients at doses up to 1.5 g/kg and with screening to eliminate treating individuals with risk factors for toxicity (e.g., glucose-6-phosphate dehydrogenase deficiency, renal diseases, or urolithiasis). These studies have also found that plasma concentrations of vitamin C are higher with IV administration than with oral administration and are maintained for more than 4 hours^{15,25}.

Ascorbate-Combination Trials

Studies of vitamin C combined with other drugs have shown mixed results:

- In a small study of 14 patients with advanced pancreatic cancer, IV vitamin C was given along with chemotherapy and treatment with a targeted therapy. Patients had very few bad side effects from the vitamin C treatment. The nine patients who completed the treatment had stable disease as shown by imaging studies.²⁶
- In another small study of 9 patients with advanced pancreatic cancer, patients were given chemotherapy in treatment cycles of once per week for 3 weeks along with IV vitamin C twice per week for 4 weeks. These patients had disease that did not progress for a period of months. The combined treatment was well tolerated and no serious side effects were reported.²⁷
- Patients with acute myeloid leukemia²⁸, refractory metastatic colorectal cancer²⁹, or metastatic melanoma³⁰ treated with vitamin C combined with other drugs had serious side effects and the disease got worse.

MECHANISM OF ACTION OF HIGH DOSE INTRAVENOUS VITAMIN-C

There are primarily two concepts in the mechanism of action of vitamin-C. First, vitamin-C is so rapidly removed from the body that the absorption rate and the secretion rate reach equilibrium in the blood stream at a relatively low oral dose of approximately 350mg. When given intravenously at a dose of 50-100 grams (more than 100 times higher than the oral dose), the blood concentrations can reach much higher levels. It is at these levels that vitamin-C can kill cancer cells.

Secondly, Vitamin C at a low physiological concentration of 0.1 mM is an anti-oxidant that inactivates reactive oxygen species³¹. However, at high pharmacologic concentrations of up to 20 mM it becomes a pro-oxidant generating oxidative species, i.e. extracellular hydrogen peroxide, which is lethal to cancer cells.^{32,33} According to the in-vitro studies performed in rats and mice, virtually the same cancer-killing hydrogen peroxide concentrations were found in extracellular fluid, but not in blood, after intravenous administration of high-dose vitamin C oral doses did not result in generation of hydrogen peroxide^{20,21,34}. It has been proposed that extracellular hydrogen peroxide diffuses into cancer cells and mediates toxicity by ATP depletion, thereby causing cell death. Moreover, hydrogen peroxide toxicity compromises membranes, glucose

metabolism, and DNA integrity. Normal cells are unaffected by both the concentrations of vitamin C. In normal cells hydrogen peroxide is readily neutralized by antioxidant enzymes like catalase, glutathione peroxidase, and superoxide dismutase, while levels of these antioxidant enzymes are low or imbalanced in most human cancers³⁵. Mega dose vitamin C selectively targets cancer cells while providing healthy cells protection against oxidative stress. Vitamin C increases intracellular production of hydrogen peroxide which selectively destroys cancer cells due to their relative deficiency of the enzyme Catalase. Catalase metabolizes Hydrogen peroxide into water and free oxygen in healthy cells but is absent in cancer cells. Researchers have found that diets high in vitamin C significantly reduce the risk of oral cancer. Research shows that a combination of both vitamin C and beta-carotene are important factors in reducing your risk for cancer. It is best to eat foods high in Vitamin C whenever possible, and only take supplements when in special need.

Cancer patients are normally tired, listless, bruise easily, and have a poor appetite. They don't sleep well and have a low threshold for pain. This adds up to a very classic picture of scurvy that generally goes unrecognized by their conventional physicians. When cancer patients receive high dose of intravenous vitamin C they report that their pain level goes down, and that they are better able to tolerate their chemotherapy. They bounce back quicker since the high dose of vitamin C reduces the toxicity of the chemotherapy and radiation without compromising their cancer cell killing effects.

ORAL VERSUS INTRAVENOUS VITAMIN-C

There is much research regarding the use of vitamin C (ascorbic acid) in cancer therapy. IV vitamin C has a significantly greater effect on immune enhancement than the conventional oral route of administration. Oral doses of vitamin C can only achieve maximum blood concentrations of 220 micromoles per liter. At this concentration, vitamin C acts as an antioxidant, protecting healthy cells from oxidative stress and against some bacteria and viruses. However, Research shows that blood levels greater than 1,000 micromoles per liter are toxic to cancer cells and are attained by intravenous administration of vitamin-C. These levels cannot be achieved by taking oral vitamin C.

ADVANTAGES OF INTRAVENOUS VITAMIN C:

1. Prolongs survival times.
2. Improves quality of life.
3. Enhances the tumour killing effect of some chemotherapeutic agents.
4. Reduces damage done by some chemotherapeutic agents.

SIDE EFFECTS OF IV VITAMIN C THERAPY:

There are very few side effects associated with high doses of intravenous vitamin C. High dose vitamin C is contraindicated in patients with an iron overload disease. It is also contraindicated in patients with renal insufficiency or renal failure, or those undergoing dialysis.

Is vitamin-c safe alone and in conjunction with chemotherapy and radiotherapy?

Vitamin C is generally regarded as an innocuous compound with a favorable therapeutic index. While many centers have used high doses, there is limited published data around the safety at these doses. Cases of acute hemolysis in patients with underlying glucose-6-phosphate dehydrogenase (G6PD) deficiency have been reported in patients treated with high dose patients should be screened for G6PD deficiency prior to starting vitamin C therapy.³⁶

Caution should also be taken in patients with a history of renal stones.³⁷ Acute obstructive renal failure secondary to oxalate stones has been reported in a patient with underlying renal impairment.³⁸ The effect of vitamin C on oxalate excretion is controversial with some believing excessive ingestion of AA increases the formation of oxalate stones.³⁷ In patients with widespread and rapidly proliferating tumors, vitamin C has been reported to cause tumor acceleration and precipitate tumor hemorrhage and necrosis.^{16,39} The initial Cameron and Campbell trial described four patients in this category.¹⁶ Potentially, this could also be explained by the natural history of the underlying cancer. Dyspepsia, nausea and altered bowel habit are the most frequently reported side effects, particularly following oral administration.^{37, 40} High doses of oral vitamin C have been shown to affect iron absorption and interfere with many routine laboratory parameters.^{37, 40} In patients with congestive heart failure and ascites, the high fluid intake associated with administration may exacerbate their condition.³⁷

Role of vitamin c in combination with chemotherapy and radiation

The literature reports that 30–95% of patients with cancer try unconventional therapies, with the majority using these as adjuncts to their standard care with the intention to improve their quality of life and symptom control.^{41–43} Despite this wide use, it remains unclear whether the concurrent use of antioxidants with chemotherapy and radiotherapy is beneficial or detrimental.⁴⁴ Because of the paucity of clinical trial evaluation, the evidence to date is mostly derived from in vitro and in vivo data, and observational records. There are no published RCTs examining high-dose IV vitamin C in conjunction with chemotherapy or radiotherapy, making it difficult to definitively assess safety and efficacy. Vitamin C has been studied in combination with a number of cytotoxic agents in vitro 7 in vivo with conflicting outcomes on efficacy^{45–48}. It is theorized that vitamin C may sensitize refractory cancers to radiotherapy and chemotherapy.^{45–49} Koch and Biaglow studied dehydroascorbic acid alongside radiation in hypoxic Ehrlich cells in ascites in vivo, demonstrating increased inhibition of cell growth with half the radiation dose.⁵⁰ Similar findings were found in neuroblastoma and glioma cell lines treated with 5-fluorouracil (5FU), sodium d-ascorbate and radiation.⁵¹ Contrary to this, Witenberg et al. demonstrated a reduction in apoptosis from ionizing radiation in myeloid leukemia cells treated with dehydroascorbic acid.⁵² This sensitizing effect is postulated to be due to the increased H2O2 generation secondary to vitamin C administration. However, vitamin C may also result in a reduction in HIF-1, which in xenograft models has been shown to be associated with heightened radiation sensitivity.⁵³ In keeping with this theory, putative small-molecule inhibitors of HIF-1 have demonstrated enhanced tumor responsiveness to radiation in vitro, supporting the use of this as a target in association with conventional therapies.⁵⁴ High-dose vitamin C is also postulated to reduce the toxicity of chemotherapy because of restoration of plasma vitamin C concentrations and thus antioxidant capacity.⁵⁵ In vitro evidence has also suggested that vitamin C may reduce the cardiac toxicity associated with doxorubicin without compromising efficacy, postulated to be related to peroxidation of cardiac lipids.⁵⁶

DISCUSSION

When evaluating new innovative cancer treatments we need to ensure that three basic requirements are met:

1. There is a clinical plausibility, i.e. credible case reports exist.
2. There is a biological plausibility, i.e. the mechanism of action is clear.
3. Proven clinical effectiveness, i.e a randomized controlled trial has been conducted.

The high dose intravenous vitamin-C therapy has met the first two requirements but unfortunately, the third one i.e the randomized controlled trials have not been met yet. Based on a vast pool of clinical experience, the intravenous administration of high dose of vitamin-C has been shown to essentially have minimal side effects unlike chemotherapy drugs and radiation therapy. Since vitamin-C works just like chemotherapy and radiation therapy by releasing free radicals, there are no contraindications for their simultaneous use. In fact vitamin-C may work synergistically with chemotherapy and potentiate its effect. Thus, High dose intravenous vitamin-C therapy can be used as an anti-cancer agent. However, experimental data demonstrating the effectiveness of vitamin-C against cancer in animal models, and most importantly, data from randomized clinical controlled trials (the gold standard) are still needed.

THE FUTURE OF IV VITAMIN C

Lab studies reveal that this therapy is effective against many types of cancer, including lung, brain, colon, breast, pancreatic, and ovarian. Animal studies show that when human cancers are grafted into animals, high-dose IV vitamin C decreases tumor size by 41 to 53 percent “in diverse cancer types known for both their aggressive growth and limited treatment options.” Additionally, numerous patient case reports have been written up in medical journals.

IV vitamin C is not a cure-all for cancer. However, it is one of the brightest lights on the horizon. Vitamin C may also be used in conjunction with other alternative and conventional therapies—in fact, when given on the same day as chemo, the two have synergistic effects. It remains uncertain whether the use of vitamin C in conjunction with chemotherapy and radiotherapy has a beneficial or detrimental interaction. Trials using vitamin C alongside chemotherapy need to include analyses of the pharmacokinetic properties of both vitamin C and the chemotherapeutic agent. In vitro and in vivo data suggest vitamin C may overcome chemoresistance and improve chemosensitivity.^{45–49} This has been demonstrated in vivo in pancreatic cancer cell lines in combination with gemcitabine, making this a potential population to start with.⁴⁵

Role of high-dose intravenous vitamin-c as anticancer agent for the treatment of oral cancer needs to be studied.

CONCLUSION

Although the rates of utilization of vitamin C therapy remain uncertain, its popularity has increased over the years since the first suggestion of its chemotherapeutic activity in the 1970s. Although there is currently no definitive evidence that IV vitamin C improves quality of life, progression-free or overall survival, the published RCT data do not negate potential benefit based on an improved understanding of vitamin pharmacokinetics.

Based on in vitro data, it is now recognized that the plasma levels necessary for cytotoxicity requires IV dosing. However, a phase I trial of 24 patients did not demonstrate objective responses despite using IV doses of up to 1.5 g/kg.⁵⁷

Vitamin C is well known for its antioxidant activity, but it is the proposed pro-oxidant activity at high concentrations that remains controversial. This situation is perpetuated by the lack of a defined mechanism of action. While intracellular and extracellular generation of H₂O₂ is the most common theory, clarification of this and determination whether this will translate to a clinical benefit is critical in future research. Although high-dose IV vitamin C appears relatively innocuous given alone, it does have the potential to cause harm in patients with G6PD deficiency and previous renal stones. It remains uncertain whether vitamin C is clinically safe when given alongside chemotherapy and radiotherapy.

Studies to determine the effectiveness of high dose intravenous vitamin-C as an anticancer therapeutic agent in the treatment of oral cancers are required. There are highly polarized views on the use of highdose vitamin C for cancer treatment, with passionate advocates balanced by passionate critics. This is a key reason for why carefully controlled clinical trials, rather than a review of the literature, are needed to obtain a clear view of this field.

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