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HIGH DOSE VITAMIN C INTRAVENOUS THERAPY FOR CANCER

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ABSTRACT

Several studies have found vitamin C or Ascorbic acid therapy effective to treat cancer of lungs, liver, pancreas, ovaries, mesothelioma, sarcoma, prostate. Cancer cells are unable to grow at high vitamin C concentration and possibly it may cause tumour shrinkage. It is shown to have number of benefits in reducing cholesterol, neutralises free radicals, promotes collagen, breakdown of histamine, reduces risk of premature death etc. There are several pathways like epigenetic, antioxidant, chemopreventive, immunologic, collagen, and "adjuvant" anticancer effect that vitamin C undergoes during cancer treatment. Parenteral transfusion of vitamin C is believed to be selective as cancer cells have a low level of antioxidant enzyme like catalase, superoxide dismutase, and glutathione peroxidase than normal cells. In the cytosole dehydroascorbic acid (DHAA) is converted to vitamin C that depletes glutathione (GSH) and causes redox imbalance and oxidative stress. Oxidative stress triggers a cascade of processes that include glyceraldehyde 3-phosphate dehydrogenase (GAPDH) inactivation, glycolysis inhibition, and energy crisis, all of which culminate in cancer cell death. Vitamin C combined with chemotherapy perquisites in enhancement of chemotherapy, low toxicity, suppress tumour, and improve quality of life. Ascorbic acid is contraindicated in glucose-6-phosphate dehydrogenase (G6PD) and hemochromatosis. Clinical trials have shown that ascorbic acid is well tolerated with conventional anti-cancer drugs, reduces anti-cancer drug related toxicity. High-dose vitamin C increases radiosensitivity of glioblastoma multiforme cells, causing more cell death as compared to radiation.

KEYWORDS: epigenetic, antioxidant, chemopreventive, immunologic, collagen, and "adjuvant".

INTRODUCTION

Chemically known as l-ascorbic acid, vitamin C is water-soluble antioxidant and is used for many decades. In addition to several uses of vitamin C such as for heart, diabetes, common cold, tissue healing, fertility, atherosclerosis several studies have found vitamin C therapy as an effective therapy to treat cancer. First discovery for benefits of treating vitamin C in cancer was discovered by a scientist named Cameron in the year 1949. A study showed that high-dose ascorbic acid can enhance the survival rate of patients in terminal cancer.[1] In the past, many of the studies have proven that different types of cancer cells are unable to grow at high vitamin C concentration and possibly it may cause tumour shrinkage. Scientific studies have also highlighted the ability of vitamin C to hamper metastasis, inflammatory cytokine secretion, and tumour growth, and inflammatory cytokine secretion, encapsulation of tumours.[2]

Benefits of vitamin C

Being an essential nutrient, Vitamin C performs a number of beneficial functions in the human body which are explained in the following chart.

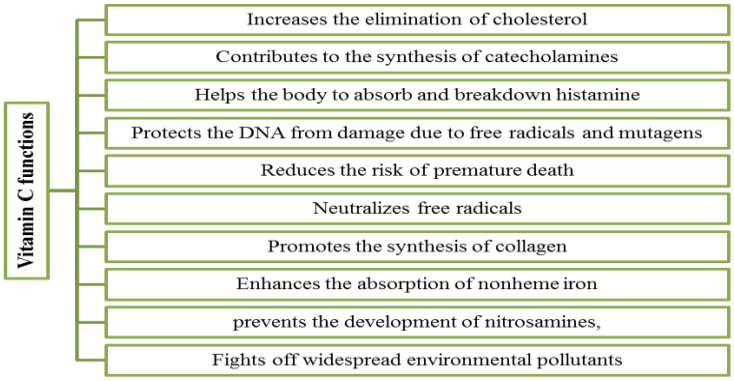

Figure 1: Functions of vitamin C.

Mechanism of action of vitamin C therapy in cancer

With respect to the anticancer properties of vitamin C, authors have suggested several pharmacological pathways for anticancer action of vitamin C which are explained below in Figure 2.[3]

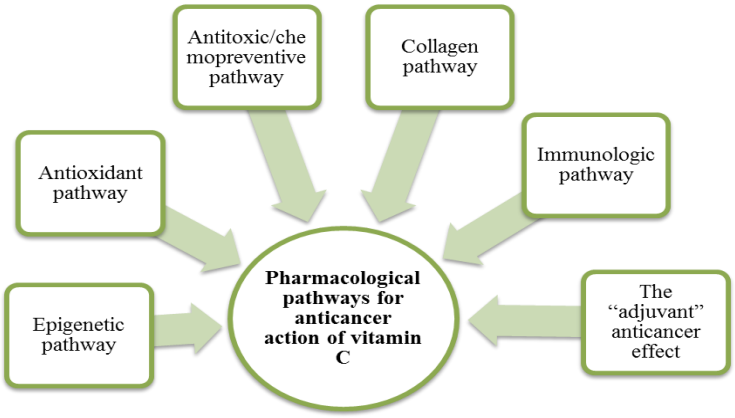

Figure 2: Pharmacological pathways for anticancer action of vitamin C.

1. The pro-oxidant pathway

Vitamin C acts as a pro-oxidant and are dispensed in high concentrations using high concentration dose as intravenous infusion (I.V). I.V transfusion of vitamin C in high doses acts as an effective pro-oxidant instead of an antioxidant forming a compound H_2O_2 which causes oxidative damage to cancer cells.

Yun et al. study showed vitamin C is a pro-drug of H_2O_2 destroying selective cancer cells.[4,5,6] The oxidative damage and eventual death of cancer cells undergo a pathway of a peroxide delivery system for the formation of sustainable Ascorbate radical and H_2O_2 in the extracellular space. Parenteral transfusion of vitamin C is believed to be selective as cancer cells have a low level of antioxidant enzyme like catalase, superoxide dismutase, and glutathione peroxidase than normal cells. The accumulation of H_2O_2 causes cellular damage further leading to redox imbalance and oxidative damage to numerous cellular structures.[7]

High amount of DHAA entering the cancer cells due to overexpressed GLUT-1 receptors was observed in glycolysis-addicted KRAS and BRAF mutated cell lines [Figure 3]. Inside the cells, DHAA is converted to vitamin C, which depletes glutathione (GSH) and causes redox imbalance and oxidative stress. Following that, oxidative stress triggers a cascade of processes that include GAPDH inactivation, glycolysis inhibition, and energy crisis, all of which culminate in cancer cell death.[4] As a pro-oxidant, vitamin C causes an increase in intracellular reactive oxygen species (ROS), which causes DNA damage. This is followed by the activation of poly ADP-ribose polymerase (PARP), an enzyme that repairs damaged DNA. Because to NAD^+ depletion and subsequent ADP depletion, PARP activation consumes NAD^+, resulting in an energy crisis and the death of cancer cells.[8]

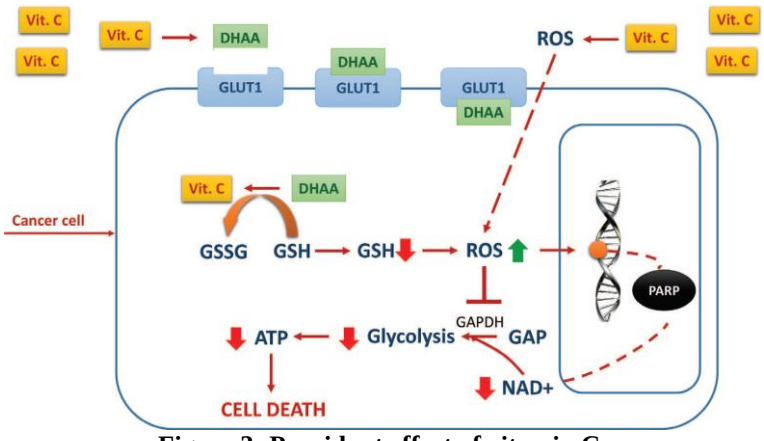

Figure 3: Proxidant effect of vitamin C.

Vit. C = vitamin C, ATP = adenosin triphosphate, DHAA = dehydroascorbic acid, GSH = glutathione, GSSG = glutathione disulfide, GAP = glyceraldehyde 3-phosphate, GAPDH = glyceraldehyde 3-phosphate dehydrogenase, GLUT = glucose transporter, NAD = nicotinamide adenine dinucleotide, ROS = reactive oxygen species, PARP = poly ADP-ribose polymerase.

2. Antioxidant activity

Vitamin C is also a cofactor of the enzyme responsible for the formation of hydroxyproline collagen prolyl-4-hydroxylase (c-p4h), which is the essential component of collagen. Prolyl-hydroxylases are a whole family of enzymes, also called 2-oxoglutarate-dependent dioxygenases (2-ogdds) having numerous biological functions,[9] and hif-hydroxylases vitamin C – the dependent enzyme belongs to this family.[10] These enzymes have proven their importance in tumour biology as hypoxia and induction of hifs are a hallmark of MEN tumours.[11]

The major role of vitamin C is the synthesis of hif-1 α hydroxylases. In this case it reduces levels of vitamin C thereby tumour growth and development. High the level of hif high is the tumour cell sensitivity to vitamin C induced toxicity.[12,13] Briefly noting, vitamin C stops the growth of human leukemic cells not just by generating H_2O_2 but primarily via the down regulation of hif-1α transcription.[17]

3. The epigenetic pathway

There are a lot of advantageous actions of vitamin C, especially its role as an electron donor for maintaining the redox state of iron-containing enzymes. A study reported that Fe_2^+-dependent oxidative modification activities in normal tissue homeostasis.[7] The role indicates that these activities are epigenetic defects and also compromised cell differentiation or developmental potential.

Features of epigenetic gene regulation mechanism of vitamin C are:

- The regulation of DNA demethylation as a crucial cofactor for TET dioxygenases.
- The regulation of histone demethylation as a major cofactor for Jumonji C (JmjC) domain-containing hi-stone demethylases.
- An Acting linkage between the genome and environment.
- An important role in retaining the epigenome, especially at early embryonic stages.
- The development of dopamine neuron differentiation in fetal midbrain, the introduction of the pluripotent state in mouse embryonic stem cells.[20,21]
- Improvement in the demethylating activity of 5-azacytidine, and elicitation of cytotoxicity.[22,23]
- Suppression of the malignant phenotype on melanoma cells in vitro, by partly regenerating 5-hydroxymethylcytosine (5-hmC) and the sequential alteration in the transcriptome.[24]
- The up regulation of microRNA (miRNA) involved in tumour suppression and drug resistance, the most crucial of which associated with enhanced overall survival of breast cancer or nasopharyngeal carcinoma.[25]
- Impediment of the proliferation, migration, and epithelial-mesenchymal-transition (EMT) of lens epithelial cells via destabilizing HIF-1α.[26]

4. The immunologic pathway

It has been know that immune system has a crucial role in fighting cancer and eliminating tumour cells. This discovery was made by a German scientist Paul Ehrlich in 1909.[27]

The presence of vitamin C in the plasma and leukocytes reduces due to exposure to infection and stress. Consumption of vitamin C on regular basis elevates many immune related functions like antimicrobial and natural killer (NK) activities, Chemotaxis, lymphocyte proliferation, and delayed-type hypersensitivity. It maintains redox balance protecting the immune system from ROS.[28, 29]

Whenever there is a lowering of ascorbic acid at intracellular level it gives rise to apoptosis of immunity cells and immunosuppression. The role of ascorbic acid proves to be an important factor in synthesis of immunoglobulin.[31] Active phagocytosis[32] synthesis of interferon[33] and suppresses the synthesis of interleukin-18 (IL-18) which is a key regulator in malignant skin tumours.[34]

The antioxidant property of vitamin C is where the "booster" element is inherited. Thus, ROS-dependent expression of pro inflammatory interleukin genes, via inhibition of transcription of NF-κB (nuclear factor kappa-light chain-enhancer of activated B cells) is down regulated by vitamin C, which, in turn, regulates the expression of pro-inflammatory cytokines, such as IL-1 and tumour necrosis factor-alpha (TNFα).[35] It has been reported that vitamin C increases antioxidant defence of T-cells[36] and elevates T-cell responsiveness to antigens, proving that it has a role in regulating immune function.[37]

5. The collagen pathway

About 60 years ago, it was discovered that the reason for cancer could be defect in the metabolism of collagen.[38] Deficiency in vitamin C hinders with the synthesis of collagen that makes the surrounding environment more exposed for the growth and spread of cancer to other organs and tissues.

Sometime ago; the role of basement membrane (BM) in the dynamic regulation of cell behaviour and cell-signalling pathways has come into the picture. The basement membrane plays important role in defining the tumour microenvironment and providing substantial host acquired regulatory signals throughout the progression of tumour growth and metastasis. A study goes to show that there is a disruption of the normal assembly and organization of the basement membrane in cancer progression. A vital component considered at the basement membrane is type IV collagen. An

experimental in vitro data has shown that cancer cells are when incubated in a nutrient mixture containing vitamin C, L-lysine, L-proline, and epigallocatechin gallate (EGCG), they cannot further invade the collagen matrix[39,40] and spread at distant sites.

6. The "adjuvant" anticancer effect

As mentioned previously vitamin C has a role to play in the protection of the healthy normal cells from the oxidative, genotoxic effects of chemotherapeutic agents, and there is no counteraction in the cytotoxic effects of cancer chemotherapy and radiation.

The earlier literature goes to prove the use of vitamin C combined with chemotherapy benefits in enhancement of chemotherapy, low toxicity levels, suppress tumour growth, improved quality of life, morbidity & mortality of patient's life

• Helps low-dose methotrexate (MTX) in inducing cell death in Hep3B cells.[42]

• Synergizes arsenic trioxide for acute promyelocytic leukemia.[41]

• Enhances chemosensitivity of ovarian cancer while decreasing, the toxicity of chemotherapy.[43]

• Sensitizes tumour cells toward cytostatic drugs.[44]

• Increases morbidity and mortality rate of patients on chemotherapy/ radiation.[45,46]

Toxicity /safety of vitamin C therapy

Based on clinical data till now high-dose vitamin C given by IV has been established as an effective therapy for cancer, although serious side effects can be observed in patients having hemochromatosis, kidney disease, glucose-6-phosphate dehydrogenase (G6PD) deficiency.

While undergoing treatment with vitamin C for leukemia and lymphoma, there are cytotoxic effects from many antineoplastic agents like doxorubicin, methotrexate, and cisplatin ranging between30-70%.[47]

Patients suffering from preexisting renal problems have reported renal failure after ascorbic acid treatment.[48] There was an evidence showing fluid overload because of ascorbic acid infusion although it was due to improper method of administration and not the product. One study reported fluid overload related to ascorbic acid infusion, but this may be caused by the delivery method and not the product.[50]

People deficient with glucose-6-phosphate dehydrogenase (G6PD) are at a risk of developing hemolysis with administration of high doses of vitamin C.[51,52,53]

Vitamin C is contraindicated in patients with hemochromatosis. The bioavailability of iron enhanced by Vitamin C.[54]

Laboratory/preclinical studies

Several studies proven that ascorbic acid lowers cell proliferation in a variety of cancer cell lines.[58,59]

A study reported one high-dose vitamin C increases radiosensitivity of glioblastoma multiforme cells, causing more cell death as compared to radiation.[60]

Treatment with vitamin C stops the tumour growth in animals for following cancers:

- Liver cancer.[57]
- Pancreatic cancer.[58,61,62]
- Ovarian cancer.[58]
- Mesothelioma.[63]
- Sarcoma.[64]
- Prostate cancer.[65]

1. Pancreatic cancer model

The combination of standard treatment with vitamin there is reduction in size and weight providing synergistic effect. This was tested in a mouse model suffering with pancreatic cancer. A dose of gemcitabine (30 or 60 mg/kg every 4 days) and Vitamin C (4 g/kg daily) resulted in a reduction in the tumour.[62]

2. Lung cancer model

A study reported that a combination treatment with chemotherapy (carboplatin temozolomide for glioblastoma) plus radiation therapy along with injunction. Vitamin C (4 g/kg/d) lead to higher morbidity rates as compared to only chemotherapy treatment.[15]

3. A significantly high tumor reduction was observed with a combination therapy of ascorbate (4 g/kg) and gemcitabine (60 mg/kg) or radiation therapy (12 Gy in 2 fractions). The control group resulted in greater survival rate and minimal toxicity targeting cancer-cell selective toxicity.[66]

4. Dehydroascorbate is another oxidized form of vitamin C that readily passes into the cells and reduces to vitamin C. This combination of ascorbic acid with doxorubicin in lymphoma-xenograft mice resulted in smaller tumour than treatment with doxorubicin alone.[67]

Clinical studies

Various clinical studies have demonstrated vitamin C as their primary therapy. There were additional treatment along with vitamin C like combination with minerals, vitamins and botanicals. The quality of life and survival rate improved after administration of vitamin at recommended doses of 15-65g, for 1-2 weeks for many months.

Two pilot clinical trials were conducted University of Iowa[69] patients were treated with non-small cell lung carcinoma (NSCLC) and glioblastoma multiforme (GBM).[70] One of the group in both trails were given conventional therapy along with IV vitamin C, with dosing individualized to achieve a 20 mM peak

plasma concentration of vitamin C in each patient. The clinical study was a phase I design of 13 total patients. IV vitamin C was added with both radiation therapy and temozolomide. There was less toxicity, progression-free survival, and survival rate were compared favourably with the outcomes measures. While NSCLC clinical trial was a phase II design with 14 patients having advanced cancer who received both chemotherapies along with IV vitamin C (median maximum plasma concentration, 16.4 mM). Disease control and confirmed objective response rates of the study group were compared favourably with those of historical controls. Limitations of this study were the use of historical controls and small numbers of enrolled participants.

Phase I study showed intravenous administered ascorbic acid easily reach 25-30 mM a dose of 100g. This study indicated that plasma concentrations around 10 mM were sustained for at least 4 hours which based on preclinical studies, is adequate to kill cancer cells.[71]

The following table gives a brief idea about some of the clinical trials:

Reference	Trial Design	Condition or Cancer Type	Dose	Results	Concurrent Therapy Used
[52]	Phase I, open-label trial	Metastatic stage IV pancreatic cancer	50 g/infusion, 75 g/infusion, or 100 g/infusion 3x/wk for 8 wk	Ascorbic acid was well tolerated with gemcitabine and erlotinib	Gemcitabine, erlotinib
[73]	Phase I, open-label trial	Stage IV pancreatic adenocarcinoma	15 g/wk until the plasma level reached at least 350 mg/dL (20 mM)	Ascorbate acid was well tolerated with gemcitabine	Gemcitabine
[74]	Pilot phase I/IIA trial	Stage III/IV ovarian cancer	Up to 75 g or 100 g 2x/wk for 12 mo	Ascorbate acid added to carboplatin and paclitaxel therapy reduced chemotherapy-related toxicities	Carboplatin, paclitaxel
[75]	Single-arm	Advanced tumours	Five cohorts treated with 30, 50, 70, 90, and 110 g/m2 for 4 consecutive days for 4 weeks.	Grade 3 and grade 4 hyponatremia, hyperkalemia. 3 patients had stable disease, 13 had progressive disease. The recommended dose is 70–80 g/m2. Thistranslates to approximately 125 g becausethe average patient has a body surface areaof 1.6–1.9 m2.	Multivitamin and Eicosapentaenoic acid
[76]	Single-arm	Advanced pancreatic adenocarcinoma	15–125 g twice weekly	No dose-limiting adverse effects Mean plasma ascorbate levels were significantly higher than baseline. Mean survival time of subjects completing 8 A week of therapy was 13 _ 2 months.	Gemcitabine
[77]	Randomized trial	Stage 3/4 ovarian cancer	75 or 100 g twice weekly for 12 months (target plasma concentration 20–23 mM)	Ascorbate did not increase grade 3/4; grade 1 and 2 toxicities were substantiallydecreased 8.75-month increase in PFS in the AA-treatedarm. The trend to the improved OS in the AA group; nonumerical data reported.	Carboplatin and paclitaxel
[78]	Single-arm	Locally advanced or metastatic prostate cancer	Phase I: An escalating dose of IVC from 25 g to 100 g and gemcitabine alone at 1000 mg/m2 (week 3) with a few patients receiving reduced doses and gemcitabine	Low toxicity; Increased thirst and nausea were caused by IVC. Patients experienced a mix of stable disease, partial response and disease progression.	IVC and gemcitabine

			with IVC (week 4) Phase IIa: no gemcitabine for 1 week and then continuous treatment of gemcitabine until disease progression or unacceptable toxicity and IVC 3 times per week		
[79]	Phase 2 study, single-arm	Advanced stage non-small cell lung cancer	1 cycle is 21 days; IV carboplatin (AUC 6, 4 cycles), IV paclitaxel (200 mg/m2, 4 cycles), IV pharmacological ascorbate (two 75 g infusions per week, up to 4 cycles)	No grade 3 or 4 toxicities related to ascorbate Imaging confirmed partial responses to therapy (n = 4), stable disease (n = 9),disease progression (n = 1)	Carboplatin, paclitaxel, and ascorbate
[80]	single arm	Various cancer types (lung, rectum, colon, bladder, ovary, cervix, tonsil, breast, biliary tract)	1.5 g/kg body weight infused three times (at least one day apart) on weekdays during weeks when chemotherapy was administered (but not on the same day as intravenous chemotherapy) and any two days at least one day apart during weeks when no chemotherapy was given.	Increased thirst and increasedurinary flow; these adversesymptoms did not appear tobe caused by the ascorbate molecule	Standard care chemotherapy
[81]	single arm	Advanced cancer or hematologic malignancy	1.5 g/kg body weight three times weekly	No dose-limiting adverse effects.	High dose IV ascorbate only
[82]	single arm	Castration-resistant prostate cancer	5 g during weekly week 1, 30 g weekly during week 2, and 60 g weekly during weeks 3–12	Multiple grades 3 events includinghypertension and anemia; two patients experienced pulmonary embolism. Adverse events were thought to be morelikely related to disease progression thanascorbic acid.	High dose IV ascorbate only
[83]	single arm	Late-stage terminal cancer patients	150–710 mg/kg/day for up to eight weeks	Two Grade 3 adverse events: onepatient with a history of renal calculi developed a kidney stone afterthirteen days of treatment and another the patient experienced hypokalemia after six weeks of treatment.	High dose IV ascorbate only

CONCLUSION

Numerous growing research studies show evidence of improvement in cancer patients with effective dose of vitamin C. The upcoming research gives us a clear idea on the therapeutic effects and potential biomarkers that further helps us in showing effectiveness in patient population suffering from cancer and responding to high-dose vitamin C therapy.

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