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Vitamin C and its Action on Cancer Cells

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Abstract**—** *Vitamin C is a substance that has been the subject of debate over the years because of its numerous documented uses. Benefits have been shown in some cases, from use as prevention and shortening the duration of colds to reviewing vitamin C and its effects on diseases such as cancer. Therefore, vitamin C has been studied to evaluate the different mechanisms of action of vitamin C in relation to cancer; even vitamin C has been used as monotherapy or in combination with chemotherapy to demonstrate or eliminate its role in cancer. The aim of this review is to show whether the effects of vitamin C are effective and whether it makes sense to use it as monotherapy or in combination with chemotherapy; and even more to confirm or deny its positive effect in cancer.*

Keywords**— Vitamin C, DNA, Apoptosis, Carcinogenic cells**

I. INTRODUCTION

The World Health Organization estimates that about 9.6 million people died of cancer in 2018. The main types of cancer in women are: breast, lung, cervix, and thyroid; in men, they include: prostate, colon, stomach, lung, and liver. With this factor in mind, several studies have been conducted to alleviate and even treat different types of cancer with different drugs. Several recent studies have demonstrated that intravenous vitamin C at pharmacological doses selectively kills tumor cells [1].

Studies have shown that ascorbic acid is a cofactor for hydrolases that regulate gene transcription and cell signaling pathways [2].

II. INTRODUCTION TO VITAMIN C

Vitamin C, also known as ascorbic acid, is a substance obtained from food sources or from the liver. The substance enters cells via the sodium-dependent vitamin C transporter type 1 and type 2 [SVCT). This transporter is primarily responsible for the absorption and reabsorption of ascorbic acid in intestinal and renal cells. However, type 2 transporters are responsible for distribution to all tissues. Ascorbic acid is oxidized to dehydroascorbic acid [DHA)

by donating a single electron to various oxidants such as oxygen radicals, peroxides, and superoxides. DHA enters cells via the GLUT glucose transporter. Inside the cell, it is reduced to ascorbic acid [3]. Vitamin C is anionic and therefore soluble in water. Therefore, it diffuses slowly through the plasma membrane. In the stomach (pH 1) and intestinal environment (pH 5), the proportion of ascorbic acid increased to 99% and 15%, respectively; therefore, passive diffusion may play a more important role. Upon ingestion of vitamin C, cellular release of vitamin C into the blood has been demonstrated due to the rapid absorption of vitamin C at gastric and intestinal levels through anion channels present in epithelial cells (maximum plasma residence time of approximately 3 hours). The half-life of DHA is several minutes; however, it is reduced to ascorbic acid by enzymes. However, it must be taken into account that the recycling process may be insufficient during illness as smokers; therefore, higher vitamin C intakes are required to maintain homeostasis in these individuals [4].

III. PLASMA CONCENTRATIONS OF VITAMIN C AND ITS ACTION ON CANCER CELLS

Among the physiological effects, it was found that the ascorbic acid plasma concentrations necessary to induce cytotoxicity in cancer cells could only be achieved by intravenous administration of vitamin C. In a study by Hoffer LJ et al. It has been found that with an intravenous infusion of 100 grams of vitamin C, vitamin C concentrations can reach 25-30 mmol; 10 mmol remains in the blood for at least 4 hours. From this they concluded that this concentration and time were sufficient to slow the growth of cancer cells. This is critical for the safety and efficacy of high-dose ascorbic acid in the treatment of various types of cancer, such as ovarian, brain, prostate, and lung cancer, whether as monotherapy or in combination with chemotherapy [5].

However, in another study by Padayatty and Levine, when ingested at 100 mg/day, the plasma concentration of vitamin C was shown to be 56 µM, and when ingested at 400 mg/day, the plasma concentration in men was 70 µM. For women, a daily intake of 100 mg corresponds to 62 micromoles and a daily intake of 400 mg corresponds to 73 micromoles [6].

EVALUATED DOSES OF VITAMIN C

It has been determined that plasma concentrations of vitamin C administered via the venous route can reach up to 21000 uM/L at doses of 60 gr/day; in contrast, plasma concentrations after oral administration of 3 grams per day, reach a maximum of 220 uM/L caused by the intestinal absorption limit. Likewise, it was determined that the pro-oxidant effect due to the generation of hydrogen peroxide, affects tumor cells in concentrations between 1000 to 5000 uM/L. In phase I studies related to metastatic gastric or colorectal cancer, it was found that doses of 1.5 g/day were used without finding toxicity or adverse effects and without interaction with chemotherapy. In another similar study, symptomatic improvement was determined, especially in the increase of functional capacity [7].

In several investigations, it has been reported that there is a beneficial effect of the venous administration of vitamin C in high doses in cancer patients; this is due to the pro-oxidant effect that this vitamin causes, by causing apoptotic death of cancer cells in the periphery of the tumor, preventing the development of angiogenesis and metastasis. In a meta-analysis of 2019, it was even concluded that the administration of 100 mg daily of vitamin C decreases mortality associated with the development of breast cancer by 20% [8].

MECHANISMS OF ACTION IN RELATION TO CANCER CELLS

One of the properties of vitamin C is reversible oxidation, which causes catalytic activity. One of the examples is the reduction of ferric ion to ferrous ion. This change is of vital importance, as it plays a special role in DNA synthesis. Another effect produced by vitamin C is the regulation of the levels of the transcription factors HIF1 (hypoxia-inducible factor-1) by enzymes of the hydrolase group, dependent on the action of ascorbic acid (Fe2+/2-oxoglutarate-dependent dioxygenase). If there is a deficiency of cofactors, the activity of hydrolases is altered, generating an increase in the stabilization and activation of HIF-1. HIF regulates cell immortality, angiogenesis or cell resistance to chemotherapy or radiation by regulating the transcription of hundreds of genes. Thus, elevated proliferation generates uncontrolled access of cancer cells to nutrients, including glucose and oxygen, causing anaerobic metabolism in cells. The level of HIF1 in cells depends on the amount of oxygen, which can be increased by activation of oncogenes. Vitamin C is considered one of the epigenetic modulators, because it is related to the reprogramming of cellular hydrolases such as 2OG-dioxygenase or TET protein; in which, vitamin C induces a demethylation in TET1/TET2. Because of this, it has been shown that vitamin C induces proper transcription coordinated by TET1. Vitamin C deficiency reduces the number of germ cells and leads to inadequate expression of the TET1-dependent gene. The importance of the TET gene is for its suppressor property, which is observed in several genes, where it is mutated, and where its expression is reduced. It has been shown that TET expression can be inhibited by K-Ras, leading to the reduction of 5-

hydroxymethylcytosine (5hmC). As a result, this leads to decreased expression of pro-apoptotic genes [9].

Several studies demonstrate the toxicity of ascorbic acid to cancer cells, although the exact mechanism has not been clear. The effect is presumed to be through the pro-oxidative activity of ascorbic acid, leading to H2O2 formation and oxidative stress. The pro-oxidative activity of ascorbic acid depends on the presence of the amount of iron; and interestingly, oxygen free radicals promote increased levels of labile iron. With all this in mind, elevated iron levels recognized in active iron-dependent cancer cells induce adaptation to hypoxia and stimulate proliferation. In high doses of vitamin C in cancer treatment, with in vitro studies, it has been shown that various tumor lines, whether epidermoid, pancreatic, cervical, colonic and breast carcinoma, are sensitive to high doses of vitamin C. A study by Kaźmierczak-Barańska et al in 2021 showed that 5 of 6 tests of various prostate cancer lines are sensitive to millimolar levels of ascorbic acid. The effect of high doses of ascorbic acid on cancer cells is by the formation of H2O2 in the extracellular space. Due to this, stress-induced oxidative autophagy is generated in cancer cells [9]. In short, vitamin C has been shown to act as both an antioxidant and a pro-oxidant [10].

Another characteristic of cancers is the presence of a marked deficiency of vitamin C; therefore, if physiological levels of this vitamin are restored or recovered, the growth of malignant cells can be slowed down. As is well known, low concentrations of vitamin C are administered venously, its action is primarily antioxidant and maintains sufficient levels of iron in the ferrous state, which promotes the activity of dioxygenases. At higher doses, it has pro-oxidant actions, which cause oxidative stress and depletion of reduced glutathione, leading to the accumulation of reactive oxygen species. Likewise, vitamin C in high doses has been found to increase the sensitivity of multiple hematopoietic neoplasms to the use of arsenic trioxide, in addition to increasing the chemosensitivity and radiosensitivity of several cancer cells, such as ovarian glioblastoma, pancreatic and non-small cell lung carcinoma cells. As a curious fact, increased labile iron and glutathione depletion are causative of ferroptosis, which is a form of non-apoptotic cell death caused by lethal lipid peroxidation. With this in mind, the following argument for vitamin C will make sense. High-dose vitamin C promotes increased iron mobilization along with redox activity and glutathione depletion; however, it may even induce ferroptosis as an additional mechanism for its anticancer effect. Therefore, TET-mediated DNA oxidation induced by vitamin C mimics a response to DNA damage in Acute Myeloid Leukemia cells, making it hypersensitive to Poly ADP ribose polymerase (PARP) inhibition, which makes it more sensitive to tumor DNA damage caused by chemotherapy, and therefore, to cell lethality [11].

One of the effects of vitamin C is the inhibition of adenylate cyclase, which stops the expression of several genes that are under the control of the cyclic AMP pathway. In a 2009 study, it was determined that vitamin C decreases the expression of several subunits of translation initiation factor, RNA transfer and genes that regulate cell cycle progression and stops the S-phase of proliferative cells. In in vivo studies, vitamin C inhibited the growth of leukemic progenitor cells in patients with acute myeloid leukemia. The concentrations used in vitro to generate toxicity in cancer cells can be achieved by intravenous administration. Similar to glutathione oxidation, formation and accumulation of hydrogen peroxide (H2O2) occurs, leading to apoptosis. This role of apoptosis induction by H2O2 in acute myeloid leukemia has been confirmed by using catalase to abrogate vitamin C-induced apoptosis [12].

In a meta-analysis by Camarena and Wang in 2016, the benefit of vitamin C administration in reducing mortality caused by breast cancer was evidenced in 17,000 patients. Likewise, overexpression of TET1 in breast cancer and TET2 in melanoma has been demonstrated, which leads to restoring the normal 5hmC profile in cancer cells and decreasing their malignancy and invasiveness. Vitamin C acts as a cofactor of TET, which enhances and maximizes the catalytic activity of existing TETs in cancer cells [3].

In a 2018 study by Shenoy, Creagan, Witzig, and Levine in mice, they determined that orally consumed ascorbate may be effective as an agent to prevent or postpone the development of certain types of malignancy in genetically prone individuals. An example is individuals with hematopoietic cells with TET2 mutation, haplodeficiency VHL individuals, who predispose to renal cell carcinoma [13].

In a 2019 publication by Lykkesfeldt and Tveden-Nyborg, they measured the concentrations of high doses of vitamin C in tumor tissues in mice; where it was evidenced that, daily administration was necessary to delay tumor growth and suppress the transcription of hypoxia-inducible factor 1 (HIF-1). Likewise, it was demonstrated that the infusion administration allowed a delayed elimination by the tumor tissue. In poorly vascularized tumor tissues, it was proposed that high-dose vitamin C, combined with the hypoxic tumor environment, induces the formation of cytotoxic levels of, for example, hydrogen peroxide (H2O2); providing a pivotal role for ascorbic acid in cancer treatment. Therefore, it is suggested that plasma millimolar concentrations, administered venously, normalize to physiological levels in approximately 16 hours. Interestingly, these values may

remain elevated for approximately 48 hours in tumor tissue [4].

REDOX IMBALANCE, UNEXPECTED AND NECESSARY PATHWAY

In the cancerous cells, the presence of oxidative stress is greater because there is an increase in defective mitochondria and an increased metabolic rate. Due to the increase in free oxygen radicals, the imbalance in the genetic composition that motives the tumoral growth increases and at the same time, cell proliferation. The elevated levels of these are dangerous for the same cancerous cells since they do not present ways of adequate signalization. Therefore, since free oxygen radicals induce cancer development, the antioxidant treatment should be studied and considered anti-cancerous. Must remember that, as cancerous cells produce more hydrogen peroxide and OH, it has become more susceptible to Vitamin C effect [1].

SPECIFIC EFFECT ON CANCERS

In recent studies in colorectal cancerous cells, the KRAS and BRAF mutated genes, show that are vulnerable to high doses of Vitamin C. The effect produced by the glucose (induced and necessary glycolysis for the cancerous cells), and ascorbic acid have a similar structure that the DHA, which allows it to be absorbed by KRAS and BRAF. Inside these cells, vitamin C transforms into glutathione, nicotinamide, and adenine dinucleotide phosphate (NADPH), producing free oxygen radicals inside the cancerous cells. This NADPH posteriorly reduce to nicotinamide and adenine dinucleotide (NAD+), that inhibit the action of glycerate 3-phosphate dehydrogenase (GAPDH) (glycolytic enzyme necessary for the glucose use and glycolysis), deactivated by the same free oxygen radicals generate inside of the cells for the transformation of vitamin C in the mentioned co-factors. Finally, the GAPDH inhibition in this type of KRAS and BRAF cells, very dependent on glucose and glycolysis, presents an energy lack, which generates the death cell of these cancerous cells.

In relation to the vitamin C effect at melanoma, it was proposed that vitamin C acts like an enzymatic cofactor that unites directly to TET dominium, which causes an increase of enzymatic activity. Plasmatic concentrations between 100 and 200 μM, induce apoptosis in certain melanoma cells by negative regulation of clusterin, with posterior BAX activation and Bcl-XL kidnapping in mitochondria, producing apoptosis in these cells [1].

A study realized and published in Albany in 2019 for cancer treatment, used doxycycline, which acts like an inhibitor of mitochondrial ribosome (28S), whose effect traduce in the mitochondrial protein translation inhibition. In vitro evidence has been supporting the inhibitor effects of doxycycline in the cancer growth by the propagation inhibition of cancerous mother cells, showing a 40% descent expression of these mother cells markers in breast cancer tumor samples. Now, two more agents were added: azithromycin and vitamin C. The azithromycin action inhibits the big mitochondrial ribosome (39S), in addition of being an established inducer of autophagy, and whose effect can carry at mitophagy, that is the active elimination of dysfunctional mitochondria, an added effect is the implication for aging. Instead, vitamin C acts like a soft pro-oxidant, which can produce free radicals and induce mitochondrial biogenesis. This combination therapy looked to stimulate the mitochondrial biogenesis, while inhibited the translate of mitochondrial proteins, causing an ATP depletion, and at the same time an effective blockade to the production of encoded proteins for the mitochondrial DNA, necessary for oxidative phosphorylation.

With therapy based on the combination of doxycycline and azithromycin, the rate of mitochondrial and oxidative metabolism, and glycolysis was considerably reduced. In this same investigation, studied the metabolic profile of doxycycline, azithromycin, and vitamin C; in plasmatic concentrations of 1 μM, 1 μM and 250 μM respectively, for three days. During this time, oxidative mitochondrial metabolism reduced by 50%, glycolysis increased, and glycolytic reserve decreased on the cancerous cells. Therefore, observations at the action level of vitamin C translate in a soft pro-oxidant and stimulate the mitochondrial biogenesis, boosting a higher mitochondrial metabolism and an elevated ATP production [14].

Between several studies [14], it has proposed that vitamin C reduces the effects produced by chemotherapy, thanks to the antioxidant properties. Other studies [15] had demonstrated that combination of vitamin with therapies against cancer, help to inhibit the tumoral growth in pancreas, liver, prostate, ovary cancer, sarcoma, and malignant mesothelioma, along with this, has had revealed the increase of life quality; and physical, mental and emotional functions in patients that have been administered intravenous vitamin C; jointly the decrease of adverse effects like fatigue, nausea, vomits, pain and loss of appetite. The vitamin C intravenous dose had good tolerance, including 1,5 g/kg dose. Patients with breast cancer and metastatic pancreatic cancer experienced fewer side effects due to chemotherapy after administered intravenous vitamin C. In some studies, showed that the simultaneous administration of vitamin C and Oxaliplatin or Irinotecan, inhibited the in vivo tumoral growth and the effect was major with this combination. Vitamin C is a chemosensitizer with combination therapy with Gefitinib in non-small cell lung cancer. Other studies showed that vitamin C high doses administered in ovary cancer induce damage in DNA of cancerous cells, a cellular

ATP depletion and activation of stress signation kinase, ATM (ataxia-telangiectasia mutated), and activated protein by the kinase AMP. The combination of vitamin C with the administration of chemotherapeutic agent carboplatin and paclitaxel reduced the toxicity associated with these chemotherapeutic in ovarian cancer [15].

Vitamin C in pharmacological doses has an effect, in this specific case, is pro-oxidative, hugely different from vitamin C in physiological conditions. The pro-oxidative effect of vitamin C in high doses and in certain conditions leads to the production of free oxygen radicals, protein glycation and damage in the DNA.

In millimolar concentrations, it has been shown that vitamin C produced the destruction of several types of cancerous cells, both in vivo and in vitro studies by the production of these free radicals. Other vitamin C effects is the sensibility increase of cancerous cells at the ionization radiation combined with chemotherapy, all these caused by brought out increase at the free oxygen radicals and labile iron with redox activity, producing a selective sensibility and pro-oxidative toxicity from the ascorbate in high doses [16].

Controlled randomized studies made by Van Gorkom, et al., in 2019, revealed that, in seven or ten studies, there was a positive effect on survival by vitamin C administration. One of these studies was made in acute myeloid leukemia (AML) patients treated with decitabine, whose in vitro effect is related to TET2 expression, apoptosis, and tumor cell proliferation. These patients received intravenous low doses of vitamin C and their survival growth at six months.

In another analysis of study, overall survival improved when adding vitamin C to chemotherapy for ovary cancer, nonetheless, the limiting factor was that the patient group was exceedingly small, so, overall survival increase was not significantly. It was observed that intravenous administration of vitamin C brought about a positive effect on survival, while oral administration did not influence survival. In nine studies analyzed to evaluate clinical response, six displayed improvements. In the first study made, a 10% tumoral regression was determined, although this regression was measured in function of clinical findings and not images, and early tumor progression or metastasis were not always evaluated for histology. Unfortunately, fourteen patients evaluated by intravenous administration of vitamin C did not have a tumor regression. Fifteen patients evaluated for bone metastasis, 53% of them caused pain relief with intravenous administration of vitamin C, versus the 13% treated with chemotherapy, additionally a decrease in the stupefacient use. In another group with twenty patients with prostate cancer, 75% had a PSA decrease after intravenous vitamin C administration, nonetheless, the effect was not confirmed since in another study made in twenty-three patients, it did not have such decrease. Finally, the major goal obtained was in patients with acute myeloid leukemia, where response rates significantly matter after use of chemotherapy that without the same [17].

In a retrospective observational study made for Klimant, et al. [18], in 2018, was revealed fifty-three patients treated with 7,5 g intravenous vitamin C for four weeks, more own therapy against cancer (chemotherapy, radiation, hormonal treatment), depressive disorders like: fatigue, appetite, sleep disorders decreased considerably. Although it should be mentioned the study was limited by the missing of randomization, the potential bias and absence of survival results.

In other study analyzed in base of life quality in patients with advanced cancer, was noticed that patients which receive 12,5 g to 100 g vitamin C twice a week during four weeks, moreover oral doses of 2 at 4 g/day showed that there was a significantly drop in insomnia, constipation and fatigue afterward 2 weeks and, pain reduction and better cognitive function afterward four weeks.

Degradation and redesign of the extracellular matrix can be inhibited and prevent bone metastasis into cancerous cells by the weakening of IL-1beta effects over MMP-3 and MMP-9 in the chondrocytes and the RNA level decrease at the MMP-9 in chondrocytes. Vitamin C can also reduce the activity of hyaluronidases to inhibit cancer metastasis. Hence, vitamin C not just promotes the proliferation and maturation of T cells and natural killer (NT), but also reduces the effects in relationship with cancer growth and metastasis, by decreasing the extracellular tramps of neutrophiles.

In a case of multiple lungs metastasis caused by an hepatocarcinoma in a 74-year-aged woman, had complete regression after 10 months of high doses of vitamin C treatment. Other studies showed high doses of vitamin C could stop the migration and invasion of cell lines of breast cancer for the suppression of epithelial-mesenchymal transition. Even, high doses of vitamin C inhibit the tumor growth by activation of AMPK stress signaling kinases (activated kinases protein by AMP) and ATM (ataxia-telangiectasia mutated). According to scientific evidence, vitamin C is effective when it is administered to intravenous doses of 1 g/kg for 2 hours twice a week or more often [19].

VITAMIN C AND BREAST CANCER: THE GATES OF REGULATION.

A study made by Sant, et al. [20], in 2018, showed that 100μM plasmatic levels of vitamin C keeps an elevated level of 5hmC in MDA-MB-231 cells (human cell line of breast adenocarcinoma, more used in vitro studies). Due to this cell line having TET enzymes, vitamin C can

effectively catalyze the hydroxylation reaction. The 5hmC increase conduces a change in DNA methylation-demethylation, what leads (theoretically) changes at the transcriptome (sequential-RNA), all these generated by the administration of vitamin C. Another vitamin C effect is the codification and positively regulation at TRAIL expression (apoptosis-inducing ligand related to TNF), responsible for the apoptosis induction [20].

As an additional information, was determined the caspases effect for the apoptosis induction, who results increased, hence, was determined in this study that vitamin C induce apoptosis in breast cancer cells by the TRAIL increased expression, that activate caspases and BAX (pro-apoptotic inductor), reduce the Bcl-xl (anti-apoptotic regulator) and releases including cytochrome C that activates apoptosome, who activates the caspase-9, and, in turn this, activates the caspase-3 and this triggers apoptosis.

In the study by Lee, et al. [21], in 2019, it was figured out that vitamin C high doses inhibit the cell growth of TAM-R/MCR-7 (line cell of breast cancer), where there existed selective antiproliferative effects on chemotherapy-resistant breast cancer cells.

IV. CONCLUSION

We always must take in charge the vitamin C actions, the pro-oxidant role run out glutathione that depletes them, what produce a cellular oxidative stress and apoptosis, even their role in the inhibitory function on glycolysis (by action in GAPDH) it is also present. In vivo trials have evidence that vitamin C acts in cancer cells, showing a reduction of the ability in the effect on self-renovation, survival and genetic expression of hepatocellular carcinogenic cells. Likewise, it was noticed that vitamin C effect in hepatocellular carcinogenic cells produce DNA damage and ATP depletion, which activates the cyclin-dependent kinase inhibitor p21, stopped the cell cycle in G2/M phase, and in turn, activates caspase-dependent apoptosis. Due to vitamin C effects only having been discovered minimally, it is important to continue the investigations and discover new pathways and actions of vitamin C, not only related to cancer, but also other diseases.

V. FINAL STATEMENT

This review is based on an article of Santiago Vintimilla and Antonieta Flores called “Vitamina C y su acción en Células Cancerígenas”, whose authors authorized the translation and rewriting from the spanish language version to the english language version; moreover, the original authors are included in this review and they were the substantial part of this work.

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