

Ascorbic Acid in Combination with Chemotherapeutic Agents for Cancer

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Abstract: Cancer accounts for nearly one-quarter of deaths in the United States. The life expectancy after standard treatment for these patients is dismal. New treatment modalities should be considered and evaluated. Ascorbic Acid (AA, Vitamin C) is a relatively low cost and safe nutrient even when given at very high doses (intravenous) that could be a very relevant co-adjuvant in cancer treatment. *In vitro* and *in vivo* studies have shown benefit of using high dose intravenous vitamin C as adjuvant therapy in cancer patients. There is significant supporting evidence of the benefits of the use vitamin C with chemotherapy.

Keywords: Ascorbic acid, Vitamin C, Chemotherapy.

INTRODUCTION

Cancer accounts for nearly one-quarter of deaths in the United States. Main reason why the government of the United States spends millions of dollars in cancer research. Even though millions have been spent in the research and treatment of cancer, the life expectancy after standard treatment for these patients is still under 5 years [1]. This is an indicator that new treatment modalities should be considered and evaluated. Ascorbic Acid (AA, Vitamin C) is a relatively low cost and safe nutrient even when given at very high doses (intravenous) that could be a very relevant co-adjuvant in cancer treatment [2].

Chemotherapy is the standard treatment recommended by clinical guidelines and remains to be the most reliable source of treatment as far as the conventional medical world is concerned. Chemotherapy has been used during the past fifty years and still patients' survival rate in 5 years is dismal [3]. Also the many side effects such as nausea, anemia, thrombocytopenia and others are uncomfortable, in addition to increasing the health care cost and negatively impacting the quality of life of cancer patients. The search for reliable alternative and complementary treatments by scientists, physicians and patients is necessary. The possibility of having available different options for treatment that will be effective, reasonably priced and with fewer side effects is attractive.

Antioxidants in general have been considered an option to be utilized in cancer treatment, studies have been conducted to determine the efficacy as adjuvants in chemotherapy regimen.

The use of antioxidant supplements by patients with cancer is estimated between 13% and 87%. [4]. Patients may take antioxidant supplements while undergoing chemotherapy to help ameliorate negative side effects from toxic chemotherapies and to increase the efficacy of the treatment. The principle that supports the use of antioxidant supplementation in cancer patients is based on redox therapy. This form of therapy involves the use of high doses of antioxidant molecules, especially vitamin C usually as intravenous sodium ascorbate [4]. The main mechanism in which vitamin C kills cancer cells, is by acting as a pro-oxidant. In the redox cycle in cancer cells, vitamin C interchanges between ascorbate and dehydroascorbate. In this process, in the presence of oxygen; hydrogen peroxide is produced within the cell. Cancer cells, unlike normal cells, have low amounts of antioxidant enzymes such as catalase, superoxide dismutase, glutathione peroxidase [4]. In a healthy cell, catalase would convert peroxide to oxygen and water. However, in a cancer cell, the peroxide is built up to toxic levels and causes apoptosis [4-6].

However, the use of antioxidants supplements is controversial, because some health professionals believe that antioxidants may interfere with the mechanism of action of the chemotherapy by diminishing the oxidative damage and subsequently decreasing its efficacy [7]. The chemotherapy

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mechanism of action is destruction of tumor tissue by introducing powerful oxidative species (potent free radicals). The aim is to kill all the malignant cells in the tumor tissue; since vitamin C is a powerful water-soluble antioxidant some health professionals believe that it must not be given with chemotherapy. The truth is that evidence to support this statement is lacking and investigation *in vivo* and *in vitro* demonstrates the contrary [8,9].

Others argue that antioxidant supplements are useful in conjunction with chemotherapy because they act synergistically, enhancing the efficacy of chemotherapy, moreover, reducing toxic side effects. This allows patients to tolerate chemotherapy for the appropriate full course of treatment and possibility at higher doses of the medication [10]. As a result, patients may have better tumor response rate and increased chance of survival. A literature analysis was done to evaluate the possibility of adding Vitamin C to a chemotherapeutic regimen to reduce negative side effects and improve patient's survival.

***In Vitro* Treatment**

Vitamin C has demonstrated to induce apoptosis in cancer cells, without affecting normal cells [11]. Induction of cell cycle arrest causing cell death of cancerous cells have been shown in lymphoma, leukemia, melanoma, brain tumor, prostate cancer and stomach cancer cells [12-16]. Since vitamin C therapy has been successful *in vitro* to treat cancer cells, studies to evaluate the possibly of adding it to chemotherapy are necessary.

Several studies in the past, have demonstrated that vitamin C enhances the inhibitory effects of most of the agents used in cancer treatment [17]. *In vitro* studies with various types of cancer cells, treated with doxorubicin cisplatin, paclitaxel [18], dacarbazine [19], fluorouracil [20] and bleomycin [21] demonstrated that vitamin C boost the cytotoxic activity of these drugs when combined. Increased drug accumulation resulting in a better pharmacological effect was also associated with vincristine and vitamin C in human non-small cell lung cancer [22].

In a study with cervical carcinoma cells treated with cisplatin, etoposide, adriamycin or bleomycin the growth inhibitory effect of vitamin C was assessed. It was found that cisplatin with vitamin C produce the maximum additive growth inhibitory effect *in vitro*, followed by etoposide, whereas adriamycin and bleomycin showed only moderate effects. It was

concluded that vitamin C increased the drug sensitivity of chemotherapeutic agents and that it should be evaluated as an innovative co-adjuvant approach for cancer therapy [23]. Other study published in 2002 showed that antioxidants including vitamin C, enhance the effect of paclitaxel and carboplatin in the treatment of human lung squamous cell carcinoma. This study recommends a 24-hour pretreatment with an antioxidant mixture followed by chemotherapy [23].

***In Vivo* Treatment in Animals**

In vivo Studies have demonstrated that Vitamin C may have benefits in cancer treatment. Chen *et al.* [24] studies in rats demonstrated that pharmacologic concentrations of ascorbate in plasma (>0.2 mM) had a positive effect in the tumors. They noted that metastases were present in 30% of athymic mice grafted with glioblastoma tumors, whereas no metastases were detected in similar mice injected i.p. with ascorbate [25]. The findings of Chen *et al.* strongly suggests that peroxide is responsible for the anti cancer activity of vitamin C [24]. This studies that are mentioned were made in mouse models, and there is a impediment because these animals are able to synthesize ascorbic acid and do not require dietary vitamin C.

Casciari *et al.* [25] measured tumor growth rates and intra-tumor ascorbate concentrations in tumor bearing guinea pigs treated with injected or orally administrated sodium ascorbate. They chose a guinea pig model because of their inability to produce vitamin C. Their findings demonstrated a possible role of high doses intravenous ascorbate in treating cancer.

Other related studies show a therapeutic gain of the combined administration of radiation and ascorbic acid; however, caution must be exercised before radiation dose escalation is applied clinically concomitant with Vitamin C, particularly since there have been no studies on the combined effects of radiation and ascorbic acid.

***In Vivo* Treatment in Humans**

It has been estimated that more than 60% of cancer patients use some kind of dietary supplement even though most oncologists do not recommend them during standard therapy [26]. On the other hand, cancer cells have been known to use more glucose and more vitamin C than normal cells for which they have specific GLUT receptors [4].

Medical professionals have debated over the benefits and disadvantages of using Ascorbic Acid (vitamin C) during the treatment of cancer since the review of Pauling, Cameron, and Leibovitz [27] reported scientific basis for the support of Ascorbic Acid as a therapeutic agent in the treatment of cancer was published.

It is known that the behavior of every human cancer is determined, to a significant extent by the natural resistance (immune system) of the patient to his disease [27]. Therefore, if Ascorbic Acid helps increase the patient's resistance (immune system) it could be deemed beneficial not only during the course of chemotherapy but before and after as a preventative and therapeutic method.

An important role of vitamin C is to prevent scurvy, a deficiency disease that appears due to a lack of ascorbate in the patient's system. Scurvy can be a life-threatening disease if untreated. The symptoms of the final stages of advanced Scurvy can include: anemia, cachexia, extreme lassitude, hemorrhages, ulceration, susceptibility to infections, and abnormally low tissue, plasma, and leukocyte ascorbate levels, with terminal adrenal failure. All these symptoms are similar to those of a patient in the final stages of advanced cancer. Furthermore, there are health professionals that regard Scurvy as an "omnifocal" variety of a neoplastic disease. Dr. William McCormick may have been the first person to notice the similarities between cancer and scurvy; he concluded that if many of the symptoms of scurvy and human cancer are similar and since scurvy can be treated with vitamin C it should have the same effects in cancer [27].

Unlike other mammals, humans and primates are completely dependent on their dietary intake of fruits and vegetables to satisfy all their vitamin C requirements [28]. Humans cannot synthesize vitamin C from glucose due to a L-glunolactone oxidase deficiency. It is believed that this deficiency happened because of a negative evolution where the kidneys lost their abilities to synthesize vitamin C, to make way for other functions performed in the kidneys. Even though humans can no longer synthesize ascorbate, it is necessary to ensure the efficient working of the immune system. These low levels of ascorbate in cancer patients indicate an increased utilization and requirement for the vitamin [27].

In their review, Cameron, Pauling, and Leibovitz [27], concluded that most cancer patients exhibit diminished immunocompetence and almost always

have low lymphocyte ascorbate content. They believed that the most simple and safest way to enhance immunocompetence in cancer patients and to ensure that their humoral and cell-mediated defense systems are working at maximum efficiency is to increase their ascorbate intake. This way if a patient's intake of vitamin C is increased to satisfy the demands imposed by the disease, the immunological mechanisms may be able to work at their full potential against the cancer.

Vitamin C is believed to increase the patient's resistance against cancer by enhancing lymphocyte functions. In addition, it increases the resistance of the intercellular ground substance to tumor cell metastasis [4].

High intravenous doses of Vitamin C are given before irradiation or chemotherapy to enhance the effects on the cancer cell, while protecting normal cells, is the main mechanism proposed for the use of ascorbic acid [26]. Intravenous ascorbic acid bypasses the gut and higher circulation levels are achieved for longer periods of time. Intravenous vitamin C can produce *in vivo*, plasma concentrations as high as 15,000 $\mu\text{mol/L}$; and at these concentrations of vitamin C has been proven to be selectively toxic towards cancer cells [26]. Ascorbic Acid is nontoxic at high concentrations and very rarely shows negative side effects [30].

Drisko *et al.* [31]. described two patients that choose to add intravenous ascorbic acid to their standard chemotherapy, both patients showed good signs of improvement and their results suggest that intravenous ascorbic acid improved the efficacy of chemotherapy. Later Padayatty *et al.* [32] reported three cases of patients suffering from different cancers that received intravenous Vitamin C and declined standard chemotherapy; all three patients went into remission and two were still alive after 10 years with no signs of cancer. Another case of a 70-year old white male with a renal adenocarcinoma that requested his cancer would only be treated with vitamin C showed improvement and no signs of cancer for 3.5 years [29]. This information presented herein shows that intravenous vitamin C can be beneficial for the treatment and prevention of cancer. Nevertheless, intravenous ascorbic acid is an off-label treatment and an appropriate informed decision must be made before subjecting a patient to this course of action [30].

CONCLUSION

There is significant supporting evidence of the benefits of the use vitamin C with chemotherapy. Most

of the evidence advocates the use of intravenous ascorbic acid, due to long list of benefits it could provide cancer patients with.

In vitro studies presented herein demonstrated the inhibitory effect that vitamin C in addition to chemotherapy could have in the proliferation of cancer cells. If this conclusion is extrapolated to human cancer, vitamin C presents a very promising co-adjuvant to treat cancer.

Animal cancer studies also demonstrate a beneficial response of the use of vitamin C. These studies in general show the efficacy of high doses of vitamin C in decreasing tumor cell growth. If these findings are extrapolated to human, again vitamin C presents a very promising co-adjuvant to treat cancer.

Human studies have also shown benefits of the use of high dose intravenous ascorbic acid as a therapeutic approach in cancer. Vitamin C is considered safe and effective therapy not only to prevent and treat cancer, but also to improve the quality of life of the patients.

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Received on 02-09-2022

Accepted on 01-10-2022

Published on 07-10-2022

<https://doi.org/10.30683/1929-2279.2022.11.03>© 2022 Gonzalez *et al.*; Licensee Neoplasia Research.

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