Review article

Vitamin C and Cancer

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Abstract: Vitamin C or ascorbic acid has been proposed as an anticancer agent, as an intervention to reduce cancer incidence, and also as a medication to reduce cancer treatment-related side effects. While there has been significant basic science research that has evaluated the potential tumoricidal mechanisms of action, clinical studies have been underpowered, retrospective, or poorly designed. Current systematic reviews have suggested that the outcome data from vitamin C therapy is limited. There is an important need for prospective clinical trials and pharmacologic studies to fully evaluate the potential of vitamin C as an anticancer agent.

Keywords: vitamin C; ascorbic acid; complementary and alternative therapy; cancer therapeutics

1.   Introduction

Intravenous and oral vitamin C or ascorbic acid has been used for decades with the hope of improving wound healing, reducing infections, boosting the immune system, and treating cancers [1]. It is a glucose-derived organic compound, which is a mild reducing agent and anti-oxidant. Vitamin C is an essential nutrient and deficiencies can lead to the life-threatening condition of scurvy [2].

Vitamin C was first proposed as an anticancer agent in 1959 when it was postulated to limit metastatic disease [3]. This hypothesis was expanded in the 1970s to suggest that ascorbate might inhibit hyaluronidases, through direct incorporation into a hyaluronidase inhibitor complex with

subsequent reduction in cancer cell proliferation [4]. Case reports then suggested that vitamin C slowed cancers and was "cancerstatic" [5].

A recent systematic literature review analyzed clinical reports of vitamin C in cancer therapy. The conclusion was that there is no definitive scientific evidence to show the efficacy of vitamin C in the treatment of cancers [6]. Despite the lack of clear clinical proof that vitamin C plays a role in cancer therapy, there continues to be significant interest in its use [7]. Much of the scientific controversy of the efficacy of vitamin C is related to a lack of agreement of the mechanism of action [8]. However, *in vitro* and *in vivo* studies hold promise [9]. This review summarizes the history, basic science, and clinical reports of vitamin C and cancer therapy.

2. Material and Methods

The PubMed and Embase were searched for relevant studies published before October 2015 using the following terms without restrictions: ("vitamin C" OR "ascorbic acid") AND ("cancer", OR "cancer prevention", OR "cancer treatment"). Furthermore, the reference lists from the relevant articles or reviews were also searched for additional eligible studies. The latest studies were selected when there were duplicates that report the same data or overlapping data.

3. Results and Discussion

3.1. Chemistry and pharmacokinetics of vitamin C

Vitamin C or L-ascorbic acid is a water-soluble cofactor that is important in at least eight enzymatic reactions. Three enzymes that are important for collagen synthesis include prolyl-3-hydroxylase, prolyl-4-hydroxylase, and lysyl hydroxylase [2]. Vitamin C functions as a cofactor for these enzymes to hydroxylate proline and lysine groups and allow collagen to assume a triple helix structure. The consequences of these enzymatic processes are crucial for the development of cartilage, scar tissue, and blood vessels. Vitamin C is important for several essential metabolic pathways in both plants and animals by functioning as a reducing agent in these pathways and scavenging oxygen free radicals.

Vitamin C is involved in the synthesis of carnitine, which is important for the transport of fatty acids into mitochondria and the generation of ATP. Two enzymes which interact with ascorbic acid, epsilon N-trimethyl-L-lysine hydroxylase and gamma butyrobetaine hydroxylase are required for this important mitochondrial role [10].

Finally vitamin C is a cofactor in three enzymes, dopamine beta hydroxylase, peptidyglycine alpha-amidating monooxygenase, and 4-hydroxyphenylpyruvate, which are important in peptide hormone synthesis [11].

The anticancer effect, in vitro, is dose dependent and is mediated by reactive oxygen and ascorbic radicals. This mechanism suggests that vitamin C catalyzes hydrogen peroxide production in tissues [12]. At high plasma concentrations of vitamin C, it generates hydrogen peroxide, which is thought to play a role in its cytotoxic role with transformed cells [13]. A high concentration of vitamin C has been reported to induce apoptosis [14]. Oral vitamin C is absorbed through the gastrointestinal tract and excreted by the kidneys [15]. Ascorbic acid is eliminated by simple first-order kinetics [16]. Orally administered ascorbic acid, even at very large and frequent dosing, will increase plasma concentrations only modestly, from 0.07 millimole (mM) to a maximum of 0.22 mM [17]. Intravenously administered vitamin C bypasses the gastrointestinal system and leads to a higher plasma concentration [18]. This has led to the recommendation that intravenous infusions are the method of choice for vitamin C therapy. In a systematic review of human studies with IV vitamin C, doses ranged from 1 gram to greater than 200 grams per IV infusion. The doses were administered two to three times weekly [19].

3.2.   Laboratory studies

In vitro studies suggest that ascorbic acid is capable of killing many different types of cancer cell lines [20]. In one series of *in vitro* experiments, exposure to ascorbic acid concentrations of up to 20 mM for one hour did not affect survival in the normal human cells tested, whereas more than half of the cancer cell lines tested showed a 50% decrease in survival after exposure to five mM or less [21]. The mechanism of action may involve the generation of superoxide and hydrogen peroxide in the extracellular space. While nontransformed cell lines are not impacted by vitamin C, cancer cell lines produce elevated levels of superoxide that make them susceptible to vitamin C's cytotoxic effects [13].

The selective tumorcidal effect of vitamin C in cancer cell lines is also augmented by the relative hypoxic state of transformed cells [22]. Another set of studies with MCF7 human breast adenocarcinoma and HT29 human colon cancer cells suggest that vitamin C inhibited energy metabolism through nicotinamide adenine dinucleotide (NAD) depletion, altered the pattern of the glycolytic metabolites, and induced cancer cell death [23]. Another series of experiments with NC160 cancer cell lines analyzed the influence of hypoxia-inducible factor-1 alpha (HIF) after vitamin C exposure. Resistance to the cytotoxic effects of vitamin C was directly related to hypoxia and HIF signaling [24]. This suggests that oxygenation is important for the cytotoxic efficacy of vitamin C. Venturelli et al have suggested combining hyperbaric oxygen or O_2 sensitizers with the use of vitamin C [12]. Another *in vitro* study of the cytotoxic effects of ascorbic acid on human myeloid cell lines showed a highly lethal effect of high doses of ascorbic acid [25].

3.3.   In Vitro and in Vivo studies of vitamin C in combination with cytotoxic agents

Numerous studies have examined the synergy of ascorbic acid with chemotherapeutic agents. The hypothesis is that reducing agents may increase the selectivity of cytotoxic agents for cancer cells. In a study of ovarian cancer cell lines, platinum with or without ascorbic acid and glutathione was evaluated [26]. They found a connection between reduction and activity of the platinum compound. Interestingly in another study, administration of cisplatin in Wistar aged rats led to a reduction in concentrations in reduced glutathione and ascorbic acid [27]. This led to a reduction in the activity of membrane bound ATPases and glutathione peroxidase suggesting a potential mechanism by which vitamin C may potentiate the action of platinum agents. Another *in vitro* study of Molt-4 human leukemia cells evaluated the addition of vitamin C and vitamin D3 and demonstrated an increased the cytoxicity of dihydroartemisinin [28]. In contrast, another study of concurrent chemoradiotherapy with alginate-hyaluronate microcapsules that release carboplatin did not show that addition of ascorbic acid increased antitumor effects [29].

3.4.   Clinical studies

3.4.1. Cancer risk reduction with vitamin C

There have been numerous retrospective reviews and case series that have analyzed the role of vitamin C in reducing the incidence of a variety of malignancies. To identify pharmacologic or nutrition interventions that reduce the development of cancer, large longitudinal epidemiologic studies are necessary. Most of the data on cancer risk reduction by vitamin C ingestion has used small cohort groups. The retrospective analyses of publications on this topic have pooled data from multiple small patient series. The antioxidant role of vitamin C has been postulated to play a role in disease prevention [1].

A 2013 Cochrane review found no evidence that vitamin C supplementation reduces the risk of lung cancer in healthy or high-risk (smokers and asbestos exposed) people [30]. A 2014 meta-analysis found weak evidence that vitamin C intake might protect against lung cancer risk [31]. A second meta-analysis found no effect on the risk of prostate cancer [32].

Two meta-analyses evaluated the effect of vitamin C supplementation on the risk of colorectal cancer. One found a weak association between vitamin C consumption and reduced risk, and the other found no effect of supplementation [33,34].

A 2011 meta-analysis failed to find support for the prevention of breast cancer with vitamin C supplementation [35]. In contrast more recently, a meta-analysis of 17 studies showed that vitamin C intake was significantly associated with reduced the risk of pancreatic cancer [36]. Another review of twenty previous publications using a technique called "dose-response analysis" suggested an inverse correlation of vitamin C intake and esophageal cancer risk [37].

3.4.2. Cancer treatment with vitamin C

There have been multiple case reports, series, and Phase I, II, and III clinical trials looking at the responses of a range of different cancers to both oral and intravenous vitamin C. An early, randomized trial evaluated one hundred and fifty patients with advanced cancer who participated in a controlled double-blind study to evaluate the effects of high-dose vitamin C on symptoms and survival. The median survival for all patients was about seven weeks, and the survival curves essentially overlapped. There was no therapeutic benefit of high-dose vitamin C treatment at the end of life [38]. It should be noted that this study evaluated oral vitamin C, which may not deliver adequate cytotoxic dosing based on in vitro studies [18].

After reviewing 25 case reports of high dose vitamin C, a 2001 National Cancer Institute panel determined that there was insufficient evidence to demonstrate that ascorbic acid was beneficial [39]. Since then, several systematic reviews of both oral and intravenous vitamin C as anticancer treatment cast doubt on the efficacy of vitamin C as an anticancer therapy [6,40].

Reports of oral vitamin C used for cancer treatment range from a case report [41], a phase II study [42], and a case of regression of liver metastases after high dose intravenous vitamin C [43]. In addition there have been three randomized controlled trials [38,44,45]. In half the studies, the patients who had multiple types of advanced cancer had concurrent chemotherapy. Overall survival was not significantly different with the addition of oral vitamin C.

Following upon the *in vitro* and *in vivo* studies of using vitamin C to enhance cytotoxicity of chemotherapy, the combination has been evaluated in human studies [25–29]. A retrospective study of thirty patients with relapsed multiple myeloma described the combination of ascorbic acid with arsenic trioxide and ifosfamide [46]. There was a 17% partial response rate and no patients attained a complete remission. However, side effects were tolerable with a progression free survival of 6 (2–8) months and an overall survival of 48 months (29–120). Without a control group, it is not possible to know how the addition of ascorbic acid improves response over chemotherapy alone.

Jacobs et al analyze 16 studies using intravenous vitamin C [6]. Thirty-seven percent (6 of 16) reports were case reports and eight were nonrandomized phase I or II studies. The one randomized trial of IV vitamin C showed a trend towards improvement in overall survival [47]. For the remainder of the studies without a control group, it is not possible to evaluate whether vitamin C had a treatment response beyond standard therapy.

In contrast, a meta-analysis of 10 studies of women with breast cancer analyzed the total mortality and breast cancer-specific mortality of women who used vitamin C as a nutritional supplement [48]. The relative risk of total mortality and breast cancer-specific mortality for women who used vitamin C was 0.81 (95% confidence interval (CI 0.72–0.91) and 0.85 (CI 0.74–0.99)). In another systematic review of thirty-seven studies of IV vitamin C for use in cancer patients from 1971 to 2013, two randomized controlled trials, fifteen uncontrolled trials, six observational studies, and fourteen case reports were identified [19]. Intravenous vitamin C did not increase toxicity of

conventional chemotherapy. Case reports, and uncontrolled trials document several instances of tumor regression. For instance, a Phase I trial of nine patients with pancreatic cancer received IV vitamin C along with gemcitabine. Mean survival of subjects completing at least two cycles (8 weeks) of therapy was 13 ± 2 months [49].

3.4.3. The role of vitamin C for cancer-related symptom management

Several early studies have documented subjective improvement in quality of life (QOL) in advanced cancer patients [17,50]. A prospective study of IV vitamin C in terminal cancer patients showed lower scores of fatigue, pain, and improved appetite [51]. In a phase I study of vitamin C, there was improvement in health-related QOL [16]. In another study of women with breast cancer receiving standard chemotherapy and radiation with or without IV vitamin C, symptom intensity scores were improved and toxicity scores were reduced in those receiving vitamin C [52]. Another study reported on the effects of ascorbic acid on 39 patients with bone metastases and compared to nine control patients [53]. The investigators noted a 50% median reduction in pain scores among the group who received vitamin C. Overall, multiple studies support the observations that there is improvement in fatigue, insomnia, anorexia, nausea, and pain seen in cancer pains using intravenous vitamin C [19,54].

3.4.4. Complementary and alternative medicine

Non-allopathic physicians have used vitamin C orally and parenterally for more than 60 years as a therapeutic agent [55]. Intravenous high dose vitamin C is currently widely used by complementary and alternative medicine (CAM) practitioners. In an analysis of fourteen European countries, CAM use among cancer patients ranged from 14.8% to 73.1% [56]. The main justification for the addition of agents such as vitamin C was to increase the body's ability to fight cancer or improve physical and emotional well-being. A survey of CAM practitioners revealed that 86% of them treated their cancer patients with IV vitamin C [57]. Vitamin C has also been part of trials looking that suggest a role for nutritional supplements during cancer therapy and long-term survival [58].

3.4.5. Side effects and toxicity of vitamin C

In general, high-dose IV vitamin C is well tolerated, and most adverse events are mild. Treatment-related nausea and headache are fairly common side effects. Some patients had moderate to severe hypernatremia and hypokalemia. Other reported adverse events were hypertension, insomnia, abnormal urine color, loss of appetite, fatigue, chills, and hyperglycemia [16].

IV vitamin C administered in gram doses can cause serious side effects in some patients. A metabolic end product of vitamin C metabolism is oxalate, and oxalate nephropathy has been

reported in patients with renal impairment given gram doses of IV vitamin C [59]. High doses have been associated with renal failure [60]. Acute hemolysis has been induced by high dose ascorbic acid in patients with glucose-6-phosphate dehydrogenase deficiency [61]. These toxicities of oxalate calculus, renal failure, hemochromatosis and glucose-6-phosphate-dehydrogenase deficiency are contraindications for high dose IV vitamin C therapy. In general, clinical studies and comprehensive survey data document the good tolerability of high-dose intravenous vitamin C in dosages up to 0.5 g per kg of body weight and in Phase I clinical trials where doses are up to 1.5 g per kg of body weight [57,62–64].

4.   Conclusion

Despite promising preclinical data, the question of clinical efficacy remains. There is no consistent clinical evidence of an antitumor effect or a cancer prevention role for vitamin C. A lot of clinical data is retrospective and underpowered. However, there are promising Phase I studies [47,49,63]. There are multiple small studies that suggest an improvement in quality of life and symptom management. These studies lack a placebo arm, which is the nature of non-interventional studies.

There are now many meta-analyses, which have tried to pool data and establish a better understanding of the preventative and therapeutic effects of vitamin C. However, meta-analyses have their own challenges with introducing bias into the interpretation of results. "Small study effects" can amplify the results in a meta-analysis and can lead to either an under- or over-interpretation of positive or negative results [65].

In vitro and *in vivo* laboratory studies have reported that vitamin C increases extracellular superoxide and hydrogen peroxides that are selectively cytotoxic to transformed cells. These effects are nonspecific and non-targeted. Vitamin C, at supra-nutritional doses, holds promise as a low-toxic therapeutic strategy to treat cancer. The clinical efficacy of vitamin C needs to be reassessed using proper dosing, route of administration, and controls.

Vitamin C continues to be studied intensively in the laboratory and in clinical scenarios. Well-powered, prospective, randomized studies with intravenous vitamin C are needed to establish the role of vitamin C in cancer therapy.

Conflict of Interest

The author declares no conflicts of interest in this paper.

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