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Review

On the Efficacy of High-dose Ascorbic Acid as Anticancer Treatment: A Literature Survey

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Abstract

Vitamin C (ascorbic acid, ascorbate) has a controversial history in cancer treatment. Emerging evidence indicates that ascorbate in cancer treatment deserves re-examination. As research results concerning ascorbate pharmacokinetics and its mechanisms of action against tumor cells have been published, and as evidence from case studies has continued to mount that ascorbate therapy could be effective if the right protocols were used, interest among physicians and scientists has increased.

Key Words: Vitamin C; Antioxidant; Anticancer

Introduction

Ascorbic acid (vitamin C, ascorbate) has been shown to protect cells against various types of oxidant injury at physiologically relevant concentrations. Vitamin C has been suggested as having both a preventative and therapeutic role in a number of pathologies when administered at much higher-than-recommended dietary allowance levels. Despite some initial skepticism on the use and efficacy of high-dose Vitamin C as anticancer treatment, some recent findings seem to support such a practice. Here we will survey some recent literatures around this controversial topic. There is even one book devoted to the use of Vitamin C for anticancer [1].

Vitamin C (ascorbic acid, ascorbate) has been well documented to reduce the incidence of most malignancies in humans. What has been hotly debated is whether vitamin C has any therapeutic effect in the treatment of cancer. Cameron and Pauling reported in 1976 and 1978 that highdose vitamin C (typically 10 g/day, by intravenous infusion for about 10 days and orally thereafter) increased the average survival of advanced cancer patients and for a small group of responders, survival was increased to up to 20 times longer than that of controls [2]. According to Cameron and Pauling, results of the use of Vitamin C to extend live of patients are encouraging. See table 1 below.

(after Cameron & Pauling [2])

Other researchers reported benefit consisting of increased survival, improved well-being and reduced pain. However, two randomized clinical trials with oral ascorbate conducted by the Mayo Clinic showed no benefit. These negative results dampened, but did not permanently extinguish, interest in ascorbate therapy or research. Some research groups conducted rigorous research, particularly in the area of administering mega-doses of ascorbate intravenously [3].

History

A more complete historical account of Vitamin C can be found in Gonzalez & Miranda-Massari [1].

Such an early development around 60s and 70s have been supported by later findings, therefore the use of highdose Vitamin C for anticancer purpose has become more or less accepted. But the remaining question is: what are the exact mechanism of Vitamin C as anticancer agent?

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TABLE 1
Differences in Average Survival Times of Ascorbate-Treated Patients and Matched Controls

Primary Tumor Type	Number of Patients		Mean survival times (days) Measured from date of first hospital attendence		Measured from date of "untreatability"		Increased survival times of ascorbate-treated patients (days)		
			A	B	C	D	E	F	G
	Test	Controls	Test	Control	Test	Control	A-B	C-D	
Colon	17	170	458+	316	352+	33	142+	319+	324+
Bronchus	17	170	219+	118	186+	31	101+	155+	184+
Stomach	13	130	286+	159	182+	32	127+	150+	134+
Breast	11	110	1396+	1020	487+	52	376+	435+	378+
Kidney	8	80	774+	492	381+	39	282+	342+	348+
Bladder	7	70	1669+	420	355+	21	1249+	334+	226+
Rectum	7	70	634	336	270	43	298	227	247+
Ovary	6	60	884	366	183	69	518	114	157+
Others	14	140	706+	279	278+	37	427+	241+	189+
All	100	1000	681+	360	293+	38	321+	255+	234+

A. Mean survival time for ascorbate-treated patients measured from date of first hospital attendance. B. Corresponding time for controls. C. Mean survival time for ascorbate-treated patients measured from date of "untreatability." D. Corresponding time for controls. E. Additional survival time of ascorbate-treated patients, A-B. F. Additional survival time of ascorbate-treated patients, C-D. G. Additional survival time of first set of ascorbate-treated patients with first set of controls, ref. 1, to May 15, 1978, when seven were still living (measured from the date of "untreatability").

Figure 1: Differences of Average Survival Times of Ascorbate-treated Patients

Pharmacokinetics

According to Mikirova et al.

"Vitamin C is water-soluble, and is limited in how well it can be absorbed when given orally. While ascorbate tends to accumulate in adrenal glands, the brain, and in some white blood cell types, plasma levels stay relatively low. According to the study, the plasma levels in healthy adults stayed below 100 μM, even if 2.5 grams were taken when administered once daily by the oral route.

Cancer patients tend to be depleted of vitamin C: fourteen out of twenty-two terminal cancer patients in our phase I study were depleted of vitamin C, with ten of those having zero detectable ascorbate in their plasma. In a study of cancer patients in hospice care, thirty percent of the subjects were deficient in vitamin C. Deficiency (below 10 μM) was correlated with elevated inflammation marker C-reactive protein (CRP) and shorter survival times. Given the role of vitamin C in collagen production, immune system functioning, and antioxidant protection, it is not surprising that subjects depleted of ascorbate would fare poorly in mounting defenses against cancer. This also suggests that supplementation to replenish vitamin C stores might serve as adjunctive therapy for these patients"[4].

While generally speaking, such use of high dose of Vitamin C is considered harmless, there are potential side effects as reported by Unlu et al. [5].

Possible Mechanism

We shall emphasize here that many mechanisms of action for ascorbate efficacy against cancer have been proposed over the years. Cancer patients are often deficient in vitamin C, and require large doses to replenish depleted stores. It has been demonstrated in vitro and in animal studies that vitamin C is preferentially toxic to tumor cells at millimolar concentrations; moreover, pharmacokinetic data suggest that these concentrations are clinically achievable when ascorbate is administered intravenously. Data suggests that ascorbate may serve as a biological response modifier, affecting inflammation and angiogenesis as well as improving immune function parameters [4].

More descriptions of mechanism of Vitamin C as anticancer agent can be found in Gonzalez & Miranda-Massari [1].

Frei and Lawson also add some interesting fact that Vitamin C is able to kill cancer cells without harming normal cells. They wrote[6]:

"Why is it important to understand how vitamin C can produce H_2O_2 and kill cancer cells but not normal cells? Because without this detailed knowledge, we do not have a scientific rationale to revisit the question of whether i.v. infusion of vitamin C may have value in treating cancer patients. The potential cancer-therapeutic activity of vitamin C has a long and controversial history. In 1973, Linus Pauling and Ewan Cameron postulated that vitamin C inhibits tumor growth by enhancing immune response and stabilizing glycosaminoglycans

of the extracellular matrix by inhibiting hyaluronidase. Cameron and Campbell reported on the response of 50 consecutive patients with advanced cancer to continuous i.v. infusions (5–45 g/d) and/or oral doses (5–20 g/d) of vitamin C. No or minimal response was observed in 27 patients; 19 patients exhibited tumor retardation, cytostasis, or regression; and 4 patients experienced tumor hemorrhage and necrosis. The first clinical study by Cameron and Paulingcompared survival times between 100 patients with terminal cancer treated with i.v. and oral vitamin C, usually 10 g/d, and 1,000 comparable patients not given vitamin C. Patients treated with vitamin C survived approximately four times longer than controls, with a high degree of statistical significance (P 0.0001). A follow-up study reported that patients given vitamin C had a mean survival time almost 1 year longer than matched controls. Overall, 22% of vitamin C-treated patients but only 0.4% of controls survived for more than 1 year."

Chemotherapy Controversy

With regards to possible interaction with chemotherapy, Mikirova et al. have reported:

"The observations that ascorbate is an antioxidant and that it preferentially accumulates in tumors have raised fears that ascorbate supplementation would compromise the efficacy of chemotherapy. In support of this, Heaney and coworkers found that tumor cells in vitro and xenografts in mice were more resistant to a variety of anticancer agents when the tumor cells were pretreated with dehydroascorbic acid. Questions have been raised, however, whether the experimental conditions used in this study are clinically or biochemically relevant, considering, among other issues, that dehydroascorbic acid rather than ascorbic acid was used [7]. A variety of laboratory studies suggest that, at high concentrations, ascorbate does not interfere with chemotherapy or irradiation and may enhance efficacy in some situations. This is supported by meta-analyses of clinical studies involving cancer and vitamins; these studies conclude that antioxidant supplementation does not interfere with the toxicity of chemotherapeutic regiments" [4].

A Few Recent Reports

There are a number of recent studies which indicate that interest in the efficacy of ascorbic acid for preventing and cure of tumor and cancer cells have revived. We will review a few of these recent literatures:

a. Ali Ghanem et al. reported: "The notion of mega doses of ascorbic acid (vitamin C) for cancer treatment has recently been revived. Besides animal experimentation, evidence from cellular and molecular research suggests a combined oxidative and metabolic mechanism behind the specific cytotoxicity of vitamin C towards cancerous cells. Here we investigate the efficacy of vitamin C against breast cancer cell lines. This work showcases a distinctive metabolic shift induced by ascorbate across multiple cell lines, disruption in the RedOx homeostasis, and the consequent cytotoxic effects. To further define the source of ascorbate'stoxicityweprobedthepotentialuptakeroutsofbothascorbicacidand dehydroascorbate (the oxidized form of ascorbic acid) and the extra and intra cellular ROS resulting from ascorbate treatment"[8].

b. But what kind of mechanism of anticancer effect of ascorbic? A number of recent papers try to elucidate these question. In a report, Birandra K. Sinha et al. suggests that Topotecan may hold an answer. Their abstract goes as follows: "Topotecan, a derivative of camptothecin, is an important anticancer drug for the treatment of various human cancers in the clinic. While the principal mechanism of tumor cell killing by topotecan is due to its interactions with topoisomerase I, other mechanisms, e.g., oxidative stress induced by reactive free radicals, have also been proposed. However, very little is known about how topotecan induces free radical-dependent oxidative stress in tumor cells. In this report we describe the formation of a topotecan radical, catalyzed by a peroxidase-hydrogen peroxide system. While this topotecan radical did not undergo oxidation-reduction with molecular O_2, it rapidly reacted with reducedglutathione and cysteine, regenerating topotecan and forming the corresponding glutathiyl and cysteinyl radicals. Ascorbic acid, which produces hydrogen peroxide in tumor cells, significantly increased topotecan cytotoxicity in MCF-7 tumor cells. The presence of ascorbic acid also increased both topoisomerase Idependent topotecan-induced DNA cleavage complex formation and topotecan-induced DNA double-strand breaks, suggesting that ascorbic acid participated in enhancing DNA damage induced by topotecan and that the enhanced DNA damage is responsible for the synergistic interactions of topotecan and ascorbic acid. Cell death by topotecan and the combination of topotecan and ascorbic acid was predominantly due to necrosis of MCF-7 breast tumor cells"[9].

C. Jiliang Xia et al. also conclude that pharmacologically-dosed ascorbic acid can help to kill multiple myeloma tumor cells. Their abstract goes as follows: "High-dose chemotherapiesto treat multiple myeloma (MM) can be life-threatening due to toxicities to normal cells and there is a need to target only tumor cells and/or lower standard drug dosage without losing efficacy. We show that pharmacologically-dosed ascorbic acid (PAA), in the presence of iron, leads to the formation of highly reactive oxygen species (ROS) resulting in cell death. PAAselectively kills CD138+MM tumor cells derived from MM and smoldering MM (SMM) but not from monoclonal gammopathy undetermined significance (MGUS) patients. PAA alone or in combination with melphalan inhibits tumor formation in MM xeno graft mice. This study shows PAA efficacy on primary cancer cells and cell lines *invitro* and *invivo*"[10].

d. But there is caveat too, other report shows that pyruvate diminishes the anticancer effect of ascorbic acid. Their abstract goes as follows: "The anticancer potential of ascorbic acid (AA) has been controversially discussed for decades. Although the cytotoxic effect of pharmacologic concentrations of ascorbic acid has already been successfully demonstrated in numerous studies *invitro,* it could not be verified to the same extent *invivo*. We propose that the ubiquitous metabolite pyruvate diminishes the effect of AA by reacting with its presumable cytotoxic mediator hydrogen peroxide (H_2O_2). MTT assays confirm that co-incubation with 1.4 mM pyruvate abolishes the cytotoxic effect of pharmacologic concentrations of AA in all cancer cell lines tested (human melanoma (WM451-Lu), breast (MCF-7) and hypopharyngeal cancer cells (FaDu)). We further investigated whether pyruvate diminishes the anticancer effect of AA by interfering with the generation of (H_2O_2). Therefore, we analyzed the concentration of AFR, a proposed intermediate in the AA-dependent formation of H_2O_2, by electron paramagnetic resonance spectroscopy, during incubation with AA and pyruvate in WM451-Lu cells as a model system. In addition, we measured H_2O_2 concentration by indirect detection with Clark-type oxygen electrode. AFR concentration was not significantly influenced by pyruvate, whereas H_2O_2 concentration was significantly reduced. In parallel, pyruvate concentrations of the stimulation medium declined with increasing AA and consequently H_2O_2 concentrations. In summary, pyruvate diminishes the cytotoxic activity of ascorbic acid in vitro. The AFR concentration measured remains unaffected by pyruvate whereas the H_2O_2 concentration is reduced; confirming that pyruvate directly reacts with AA-induced H_2O_2, without influencing its formation" [11].

Concluding Remarks

We have discussed some real positive effects on the use and efficacy of ascorbic acid as anticancer treatment.

To conclude this short review, allow us to quote Cameron & Pauling: "There is good evidence that high intakes of ascorbate potentiate the immune system in various ways: increasing the production and effectiveness of antibodies and crucial components of the complement cascade, enhancing lymphocyte blastogenesis, stimulating macrophage chemotaxis, improving phagocytic ability, amplifying lymphocyte trapping, and increasing the proliferation and differentiation of antigen-triggered lymphocytes.

Ascorbate offers some protection against oncogenic viruses and against a variety of known chemical and physical carcinogens, and is also involved in a number of biological processes, discussed in this review, that are known to contribute to host resistance to neoplastic disease. There is a growing suspicion that "host resistance to cancer," no matter how measured, is largely dependent upon the dietary intake of this simple nutrient"[2].

Nonetheless, this short review is not sufficient, it is recommended to continue further studies and procedures to maximize such positive impact of ascorbic acid as anticancer treatment.

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