Ascorbic Acid as an effective Agent in Cancer Therapy

Adeela khurshid, Aqeela Khurshid, Zubair Anwar, Adeel Arsalan, Iqbal Ahmad*

ABSTRACT

Ascorbic acid (vitamin C) is a cofactor for a number of metabolic enzymes and is an undeniable essential vitamin C for humans. However, the prospects of ascorbic acid as an anticancer agent have been a topic of argument. A number of earlier reports have addressed both the positive aspects and restrictions of ascorbate in cancer therapy. In this review, we briefly sum up the potential antitumor effects of ascorbate have been described and its prospects for clinical use have been discussed. The biological role of ascorbic acid has been highlighted and its advantages in cancer therapy have been discussed.

Key Words: Ascorbic acid, vitamin C, cancer, ascorbate

The role of ascorbic acid (vitamin C) in cancer treatment is a subject with a notorious history. ' The core of this controversy is the need of reproducibility of the therapeutic effects of ascorbate on cancer patients, a difficulty compounded by uncertainties associated with deficiencies of independent pathologic verification and failure to include appropriate placebo groups in clinical studies. ¯ However, more recent studies on the beneficial effects of ascorbate have provided a clearer understanding of its effect in cancer action. The action of ascorbate in cancer cells has also been more evidently defined by in vitro studies. In this review, the new conclusion in the field and the biological mechanism of action of ascorbate in cancer therapy have been discussed.

HISTORY OF CANCER TREATMENT

Several decades ago, McCormick, Cameron and Rotman, postulated two hypotheses concerning the use of ascorbate for cancer therapy ¯ .One hypothesis was that ascorbate exerts an antitumor effect by rising collagen synthesis ' .The other proposed that the anticancer effects of ascorbate were due to hang-up of hyaluronidase, which decomposes hyaluronic acid. Pauling, Cameron and Leibovitz provided a scientific basis to maintain these hypotheses, which they later popularized. '

On the basis of an initial study of the antitumor effects of ascorbate in 50 patients with superior cancer, Cameron and colleagues defined that high-dose ascorbate enhanced treatment outcome. Cameron and Pauling subsequently published the results of one more clinical study in 1978,' showing that the long-term survival of cancer patients who established high-dose ascorbate supplements was 20 times greater than that of patient in the control group (). In addition, a prospective study published in 1991 showed that endurance of ascorbate-treated patients was 343 days compared to 180 days for controls who did not receive ascorbate . However, Moertel and Mayo concluded that there was no major difference in survival between ascorbate-treated and -untreated groups.' The divergence between the findings of these studies may reproduce differences in the route of ascorbate administration: Cameron administered ascorbate both orally and intravenously, whereas Moertel administered ascorbate entirely through the oral route. These results are summarized in Fig.1.¯ In addition, the Mayo study was criticized because a greater part of the enrolled patients had received prior chemotherapy, unlike the Cameron study, in which a minority of patients (4/100) had been formerly treated with radiation and chemotherapy. Although the effectiveness of ascorbate against cancer should be reassessed, the results from clinical studies disagree that ascorbate may be a potential anticancer agent. The detailed analyses of ascorbate actions

in cancer cells were predicated on the basis of these results.

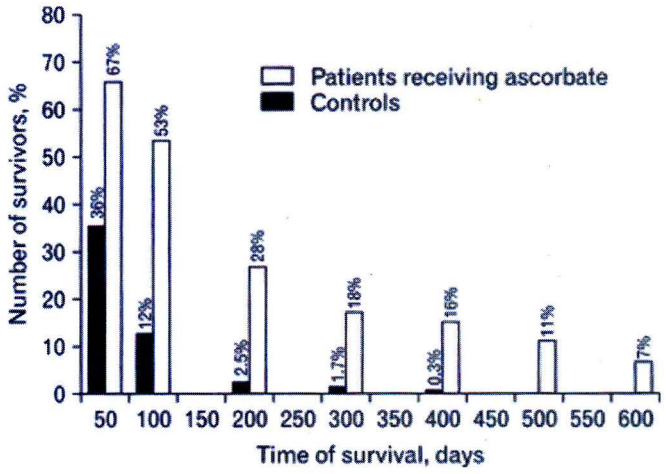

Fig1. History of cancer treatment

BIOLOGICAL ROLE

One biochemical function of ascorbate is to increase hydroxylation in a huge number of biosynthetic reactions.[1] In a majority of these biosynthetic processes, ascorbate provides essential electrons to participating enzymes and is a requisite to achieve full enzymatic activity. The distinctive function of ascorbate is as a cofactor for prolyl and lysyl hydroxylase enzymes. Ascorbate is also required for cholesterol metabolism, cytochrome p450 activity, neurotransmitter synthesis and the synthesis of carnitine from lysine.[1] Importantly, ascorbate has twin properties in oxidative processes, acting as both an antioxidant and a prooxidant. Ascorbate is considered to be an vital antioxidant in extracellular fluid, it also protects against aqueous radicals in blood and defends plasma lipids from peroxidative breakdown caused by peroxyl radicals. Thus, in this capacity, ascorbate protects a number of cells and tissues all the way through the body from oxidative stress. Conversely, ascorbate also speed up oxidative metabolism by avoiding the use of pyruvate for glycolysis. This property helps to inhibit the propagation of tumor cells, but not normal cells.[-] In a great number of malignant cancer cell lines, it is interesting to observe that the cytotoxic effect of ascorbate is associated with its prooxidant activity.[-]

VITAMIN C IN CANCER TREATMENT

Vitamin C as an immune-modulator Ascorbate boosts resistance against pathogens by stimulating the immune system,[-] Recently, we reported that ascorbate restrains production of IL-18, a key controller in malignant skin tumors, as well as melanomas and squamous cells carcinomas (). IL-18 is acknowledged as an interferon-ã-inducing factor, and is proficient of stimulating interferon-ã production by natural killer (NK) cells, activated macrophage, and T cells. Prominently, it has been lately reported that IL-18 expression is positively associated with various tumors. (Fig.2.)

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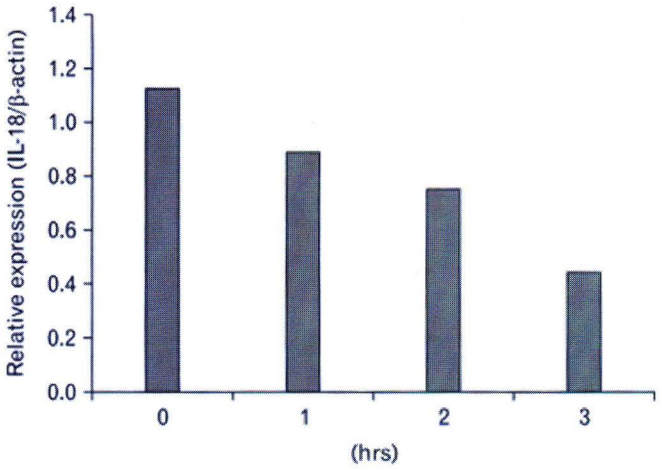

Fig.2. A model inhibiting IL-18 complexes by ascorbate. Ascorbate inhibits IL-18-induced the immune break out of various cancer cells, including gastric, breast, leukemia, and melanomas.

In gastric cancer cells, IL-18 production is improved by vascular endothelial growth factor (VEGF), follow-on in increased IL-18-mediated tumor cell migration. In breast cancer cells, IL-18 persuades the expression of transferring, which is a positive controller of cell growth and proliferation. Thus, one method by which ascorbate may be effective next to cancer is through down-regulation of IL-18, which plays an important role in scheming the escape of various cancer cells, counting melanimas, gastric, and breast cancer cells, from immune surveillance given below (Fig. 3.).

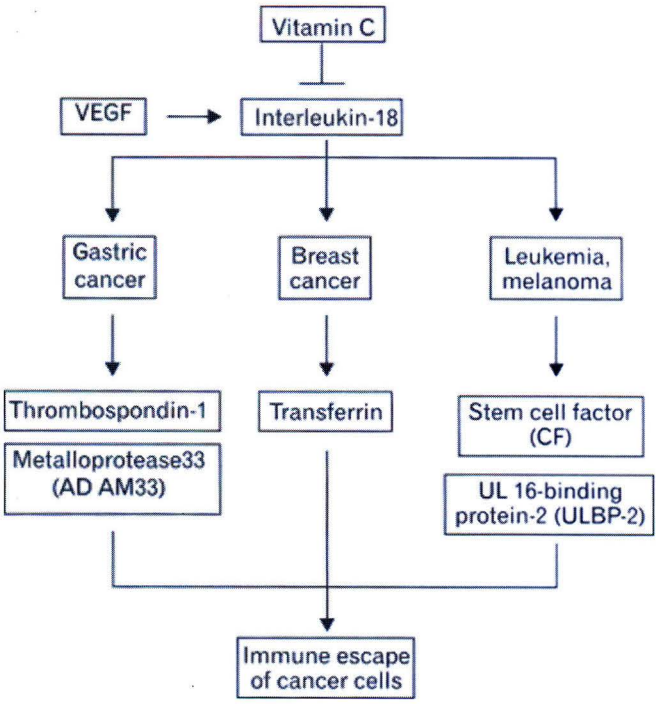

Fig.3. A mechanism of preferential arrangement of ascorbate radicals (Asc-) and H2O2 in extracellular fluid evaluated with blood. Adapted from Levine

Importantly, dosage is a key to the efficiency of ascorbate as an immune-modulator. On the basis of the above information, it has recently been claimed that a dose of ascorbate, 100~250 μM may help avoid the immune escape of cancer cells. These dosages can be attained by daily oral supplements of ascorbate.

Alternative properties of vitamin C as an antioxidant and prooxidant

Ascorbate is the abridged form of vitamin C, which also subsists physiologically in the oxidized form, dehydroascorbic acid (DHA). DHA is taken up into cells by glucose regulator.s' Inside the cell, it is abridged to ascorbic acid ' and diminishes intracellular ROS levels, thus acting originally as an antioxidant.[-]

In a recent study, Conner and colleagues reported that all antineoplastic drugs tested created mitochondrial dysfunction, as well as loss of

mitochondrial membrane potential and an raise in ROS levels, and showed that this occurrence was inhibited by vitamin C. They hypothesized that vitamin C acts as an antioxidant to defend cells against mitochondrial dysfunction induced by antineoplastic agents, and thus antagonizes the cytotoxic effects of antineoplastic drugs.[50] In a similar vein, Blair cautioned that because vitamin C/d (200 mg) provoked decomposition of lipid hydroperoxides to endogenous genotoxins, it might be counterproductive in cancer management.'[52] This study did not support the concept that vitamin C induces lipid peroxidation[53]

However, the importance of these studies in the potential antioxidant properties of vitamin C neglects the capacity of ascorbate to operate as a prooxidant. In the previous studies, it has shown that ascorbate provokes apoptosis in B16F10 murine melanomas through mitochondrial dysfunction.[54] A high dose of ascorbate induced a decrease in mitochondrial membrane strength and a discharge of cytochrome c from mitochondria to cytosol, which acted to support apoptosis. A low dose of ascorbate induced cell-cycle seize of cancer cells. ' Thus, the effect of ascorbate on cancer cells was intervened by an increase in intracellular ROS levels. In addition, we showed that ascorbate, performing as a prooxidant, inhibited cancer cell growth through other mechanisms, including introduction of endoplasmic reticulum stress, suppression of insulin-like growth factor creation, and inhibition of angiogenic factor production.' Levine and colleagues have also reported anticancer actions of ascorbate that were attributable to its prooxidant properties, presenting that ascorbate acts as a prooxidant and reduces tumor growth in mice.[59] It was shown that ascorbate formed hydrogen peroxide-dependent cytotoxicity in various cancer cells without disturbing the normal cells. More importantly, Levine suggested that ascorbate-induced development of hydrogen peroxide preferentially occurs in extracellular fluid evaluated with blood.[60] These studies supply a mechanistic basis for applying ascorbate as a prooxidant therapeutic agent for cancer healing.(Fig.4.)

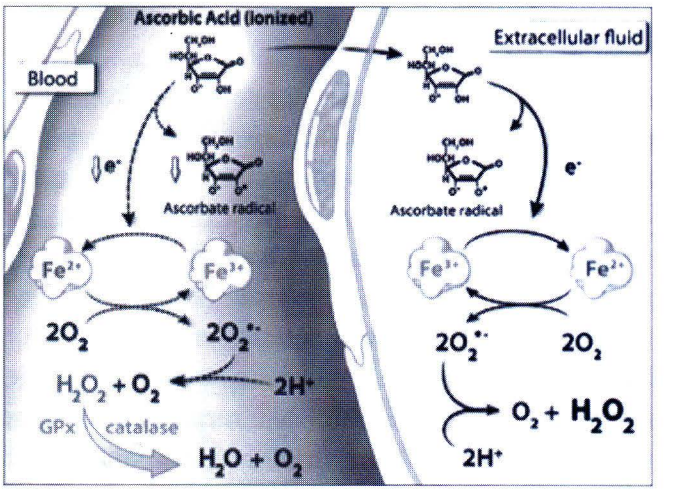

Fig. 4. Clinical studies of ascorbate and cancer survival.[17]

Although ascorbate has exposed inhibitory effects in a diversity of cancer cells, including melanomas, brain tumor, prostate cancer, and stomach cancer cell, the comparative chemosensitivity of different cancer cells to ascorbate is not clear. This possible drawback in an otherwise positive profile has not so far been fully addressed, despite a number of studies that have tried to clarify the mechanism-of-action of ascorbate in cancer cells.

CLINICAL TRIALS

Inoue suggested that the application of US National Cancer Institute (NCI) Best-Case Series guidelines () is one way to proceed the clinical possibility of ascorbate for the cancer therapy.'[62,63] These guidelines cover several standards. First, there must be a credible diagnosis of cancer based on a clinic examination, preferably counting a tissue biopsy. Second, the patient should not be treated parallel with ascorbate and other therapeutic modalities, including emission and chemotherapy. Third, the treatment history of patient should be recognized. One such study of three carcinoma cases renowned by Padayatty and conducted in accordance with NCI Best-Case Series guidelines'[64] showed that cancer development was significantly suppressed by high-dose intravenous vitamin C therapy. [64] Further clinical studies are needed to strengthen the scientific support for the clinical plausibility of the use of vitamin C in the

management of cancer.

CONCLUSION

Several scientific studies supports that ascorbate improves the health and survival of cancer patients, particularly when administered intravenously. The valuable effects of ascorbate in cancer handling reflect the ability of ascorbate to reduce cancer cell proliferation. The oral administration of ascorbate can inhibit the immune escape of cancer cells during suppression of IL-18 expression. Since ascorbate is not cytotoxic towards normal cells, it may be a model antineoplastic agent, prolonging survival and improving the worth of life through specific inhibition of tumor growth.

Based on the previous studies, it may be suggested that acorbate, particularly intravenous ascorbate, would be a useful medicine in cancer therapy, and more in vitro preclinical studies are required to verify its detailed mechanisms-of-action in cancer cells.

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