

Mini Review

Ascorbic Acid, Still Controversial in using Against Cancer Resistance?

Torequul Islam M*

Department of Pharmacy and Postgraduate Program in Pharmaceutical Science, Southern University and Federal University of Piaiui, Mehedibag (Chittagong)-4000, Bangladesh

***Corresponding author:** Torequul Islam M,

Department of Pharmacy and Postgraduate Program in Pharmaceutical Science, Southern University and Federal University of Piaiui, Mehedibag (Chittagong)-4000, Bangladesh

Received: December 04, 2017; **Accepted:** February 14, 2018; **Published:** February 21, 2018

Abstract

Ascorbic acid is a known strong antioxidant and is evident to exert a pro-oxidative effect of high concentration/dose. Therefore, it can be used not only as a protective agent, but also as an adjuvant or direct cytotoxic agent. Resistance of cancer cells is a regular matter, stimulating scientist to search fighting tools against it. Evidences suggest that the use of ascorbic acid in cancer resistance is still controversial. This paper sketches a current scenario of ascorbic acid in cancer resistance, especially resistance occurring from chemotherapy and radiotherapy. Although, hopes are alive with the use of this vitamin in this case, but more research is needed to understand the fact clearly.

Keywords: Dietary supplements; Cancer resistance; Perspective**Introduction**

Ascorbic Acid (AA) (also known as vitamin C) is a vitamin found in many foods and used as a dietary supplement. It is well-known for its antioxidant activity [1] and can be used as a prooxidant, chemopreventive agent as well as adjuvant in the cancer therapy [2]. However, the effect of AA supplementation on cancer is still controversial [3], although a number of earlier reports suggesting its applicability in cancer therapy, especially in radiation and chemo-resistant carcinoma [4,5]. This paper sketches a current scenario of this vitamin in cancer resistance.

AA against cancer resistance

Cercek and Cercek suggested that tumors pre-treated with other drugs become resistant to growth inhibitory effects of ascorbate ions such as Young Multi-Drug Resistant (YMDR) cells resistant to the antitumor drug Methylene-Dimethanesulphonate (MDMS), HeLa cells pre-treated with colcemid, and Young Multi-Drug Susceptible (YMDS) cells pretreated with cytochalasin B [6]. In a study, liver tumor resistant to oncovin, in a separate pre-treatment with AA or vitamin K3 alone was without any effect [7]. However, the acquired vincristine resistance of the PC-9/VCR cell line was partially reversed by AA along with the reduced drug accumulation, higher efflux rate, and increased in drug uptake. In contrast, AA had no effect on drug tolerance in either PC-9 parental cells or known Multidrug-Resistant (MDR) cells. AA may act *via* P-glycoprotein-mediated MDR mechanism [8]. A similar result was also observed by Song et al. with a nontoxic concentration of L-ascorbic acid (25 µg/mL) [9]. In human neuroectodermal cells SK-N-BE (2) AA (10 nM to 1 mM) showed 43% cell death resistant. The cell death observed suggests a pro-oxidant, rather than an anti-oxidant role AA [10].

The ability of human cells to regenerate AA from dehydroascorbate is partially dependent on the glutathione redox status of the cell and the relative activity of dehydroascorbate reductases. The antioxidant role of AA was also seen in adriamycin-resistant human breast tumor cells (MCF-7 ADRR), where normal cell viability was observed with the increased ascorbate-dehydroascorbate levels

than the drug-sensitive cells [11]. As a prooxidant, AA is evident to induce cytotoxic effect through hydrogen peroxide (H₂O₂)-based mechanism. For an example, U937 cells resistant to H₂O₂ were also cross-resistant to ascorbic acid [12]. Ascorbic acid at 102-103 µM was found to increase the cytotoxicity in complete doxorubicin-resistant, moderate-cisplatin resistant and in sensitive paclitaxel two human breast carcinoma cell lines, MCF-7 and MDA-MB-231, possibly by synergistic effect [13]. Generally, the cells with high catalase activity are resistant to pro-oxidant concentrations of ascorbate since catalase can decompose H₂O₂ induction by the auto-oxidation of ascorbate in cells [14]. Thus, this physiological antioxidant may help the cancer cells to grow resistance to it. The melanoma cells may contribute to the intrinsic drug resistance. In this category cells, the gamma-glutamyltransferase-overexpressing clone was found to exhibit a low susceptibility to As₂O₃-induced apoptosis, associated with low reactive oxygen species induction and increased catalase activity. AA (subtoxic concentrations) co-treated with As₂O₃ resulted sensitization in apoptotic cell death [15]. The cancer cells are more sensitive to ascorbate/menadione than healthy cells because of their lack of antioxidant enzymes, mainly catalase. The mechanism underlying this cytotoxicity involves the oxidative cleavage of Hsp90 with a subsequent loss of its chaperone function, thus leading to degradation of wild-type and mutated Bcr-Abl protein [16].

Sakagami et al, suggested that human peripheral blood lymphocytes and polymorphonuclear cells, resistant to ascorbate were found to sensitive to the Acer nikoense Maxim. extract, or a combination of them. The extracts may stimulate the degradation of ascorbates *via* ascorbyl radical production and increases the incidence of cytotoxic activity of ascorbate [17]. On the other hand, the glioblastoma multiform tumor (T98G) cells were found in more resistant to ascorbate analogs than human renal carcinoma (TC-1) and HL-60 cells, possibly due to higher intracellular glutathione concentrations. It may be due to the reduced cyclic Adenosine Monophosphate (cAMP) activity in the T98G cells than the others [18]. But, AA (1,000 mg/day) was found to enhance the activity of arsenic trioxide (As₂O₃) (0.25 mg/kg/day) against drug-resistant

Multiple Myeloma (MM) *in vitro* by depleting intracellular glutathione (GSH) [19]. Furthermore, co-administration of AA and vitamin K3 may increase cytotoxic effects in tumor cells and increase the lifespan of animals [20], while AA and vitamin D₃ synergized with the anti-tumor effects of therapeutic genes driven by hOC increased cytotoxicity in advanced renal cell carcinoma cells [21].

AA in KCL22/SR cells overcome resistance to imatinib, possibly *via* inhibition of Nuclear Factor Erythroid 2-related factor 2 (Nrf2)-mediated gene expression [22]. On the other hand, ascorbate pretreatment enhanced the efflux of the Multidrug Resistant Protein (MRP) substrate, Carboxy-2',7'-Dichlorofluorescein (CDF), and it prevented the 4-Hydroxy-2(E)-Nonenal (HNE)-induced inhibition of CDF export from THP-1 cells, suggesting that the protective effect of ascorbate against HNE cytotoxicity is through modulation of MRP-mediated transport of GSH-HNE conjugate metabolites [23].

AA was found to enhance quinone 8 (a phenylaminopyrimido isoquinolinequinones)-mediated cytotoxicity in quinone 8 resistant human leukemia K562 cells [24]. Glioblastoma Multiforme (GBM) has a very poor prognosis because of its chemo- and radiation therapy resistance. Ascorbate at 5 mM caused inhibition of G2/M arrest in GBM cells and prevented radiation-induced G2/M arrest in combined treatment [25]. The effects of AA surely depend on its concentration. In a study, the breast carcinoma cell line BT-20 highly resistant to the exposure to AA at low concentration, silenced with specific sh-RNA, become susceptible to high concentrations of AA (50 and 100 mmol/L) [26].

Labile iron (iron that is weakly bound and is relatively unrestricted in its redox activity) can be used in cancer treatment, as labile iron may contribute to their mechanism of action through pharmacological ascorbate and ionizing radiation. Generally, labile iron enhances the rate of formation of H₂O₂ and can also react with H₂O₂. In a study, both pharmacological ascorbate and irradiation were found to increase the labile iron in tumor homogenates in a murine model of pancreatic cancer [27]. Moreover, the Manganoporphyrins (MnPs) in combination with pharmacologic ascorbic acid was found to increase cytotoxic efficacy in pancreatic cancer [28]. AA was also evident to reduce pain and increase in survival rate when compared to the control group in radiotherapy-resistant retrospective cohorts [29]. It also exhibited strong cytotoxicity against the vemurafenib-resistance cell line A2058, however, at low concentrations it promoted cell growth, migration and cell cycle progression, and protected against mitochondrial stress [30]. However, in clinical trials phase II, an infusion with 5-60 g of AA did not induce anticancer activity against metastatic Castration-Resistant Prostate Cancer (mCRPC) in a 12 week treatment [31].

Conclusive Talks

From the above findings, it can be demonstrated that, the activity of AA is concentration or dose dependent. At low concentration it is an antioxidant (cytoprotective) while cytotoxic at high. The cytotoxic activity of this vitamin may be due to its pro-oxidative effects in cells. However, the activity of it may be interfered with the action of physiological antioxidants (e.g. - catalase and glutathione); protein kinase (e.g. - cAMP), liable iron, or other drugs or chemicals.

Most of the anticancer drugs and radiation therapy act through

induction of oxidative stress in cancer cells. In some studies, AA was found to act against radiation-resistant tumor cells. It may be the further proof of this vitamin's potent reducing capability. Although, the applications of AA in overcoming cancer resistance are still controversial, but many of the evidence suggest positive results, especially with pharmacological dose. More research is highly appreciated to confirm the applicability of ascorbic acid in the prevention and treatment of cancers and overcome of cancer resistance.

References

1. Michels A, Frei B. Vitamin C. In Caudill MA, Rogers M. Biochemical, Physiological, and Molecular Aspects of Human Nutrition (3 ed.). Philadelphia: Saunders. 2012; 627-654.
2. Carvalho RM, Aguiar RPS, Islam MT, Alencar MVOB, Mata AMOF, Braga AL, et al. Cytogenotoxicological defense of retinyl palmitate in the front damage of antineoplastics. *Exp Toxicol Pathol* 2017; 69: 293-297.
3. Xu X, Yu E, Liu L, Zhang W, Wei X, Gao X, et al. Dietary intake of vitamins A, C, and E and the risk of colorectal adenoma: a meta-analysis of observational studies. *Eur J Cancer Prev.* 2013; 22: 529-539.
4. Schirmacher H, Schneider J. Limits and possibilities of vitamin A and C overdose therapy in inoperable and radiation-resistant carcinoma. *Z Geburtshilfe Gynakol.* 1955; 144: 172-182.
5. Shlemkevich MP. Effect of ascorbic acid on incorporation of 5-fluorouracil-6-3H into acid-soluble fraction and into RNA of sensitive and resistant to 5-fluorouracil cells of Ehrlich ascites carcinoma. *Biull Eksp Biol Med.* 1982; 93: 56-57.
6. Cercek L, Cercek B. Effects of ascorbate ions on intracellular fluorescein emission polarization spectra in cancer and normal proliferating cells. *Cancer Detect Prev.* 1987; 10: 1-20.
7. Taper HS, Roberfroid M. Non-toxic sensitization of cancer chemotherapy by combined vitamin C and K3 pretreatment in a mouse tumor resistant to oncovin. *Anticancer Res.* 1992; 12: 1651-1654.
8. Chiang CD, Song EJ, Yang VC, Chao CC. Ascorbic acid increases drug accumulation and reverses vincristine resistance of human non-small-cell lung-cancer cells. *Biochem J.* 1994; 301: 759-764.
9. Song EJ, Yang VC, Chiang CD, Chao CC. Potentiation of growth inhibition due to vincristine by ascorbic acid in a resistant human non-small cell lung cancer cell line. *Eur J Pharmacol.* 1995; 292: 119-125.
10. De Laurenzi V, Melino G, Savini I, Annicchiarico-Petruzzelli M, Finazzi-Agrò A, Avigliano L. Cell death by oxidative stress and ascorbic acid regeneration in human neuroectodermal cell lines. *Eur J Cancer.* 1995; 31: 463-466.
11. Wells WW, Rocque PA, Xu DP, Meyer EB, Charamella LJ, Dimitrov NV. Ascorbic acid and cell survival of adriamycin resistant and sensitive MCF-7 breast tumor cells. *Free Radic Biol Med.* 1995; 18: 699-708.
12. Sestili P, Brandi G, Brambilla L, Cattabeni F, Cantoni O. Hydrogen peroxide mediates the killing of U937 tumor cells elicited by pharmacologically attainable concentrations of ascorbic acid: cell death prevention by extracellular catalase or catalase from cocultured erythrocytes or fibroblasts. *J Pharmacol Exp Ther.* 1996; 277: 1719-1725.
13. Kurbacher CM, Wagner U, Kolster B, Andreotti PE, Krebs D, Bruckner HW. Ascorbic acid (vitamin C) improves the antineoplastic activity of doxorubicin, cisplatin, and paclitaxel in human breast carcinoma cells *in vitro*. *Cancer Lett.* 1996; 103: 183-189.
14. Nemoto S, Otsuka M, Arakawa N. A positive correlation between catalase activity and ascorbate uptake in the tissues of guinea pigs and cultured cells of mammals. *J Nutr Sci Vitaminol (Tokyo).* 1996; 42: 387-395.
15. Giommarelli C, Corti A, Supino R, Favini E, Paolicchi A, Pompella A, et al. Gamma-glutamyltransferase-dependent resistance to arsenic trioxide in melanoma cells and cellular sensitization by ascorbic acid. *Free Radic Biol Med.* 2009; 46: 1516-1526.

16. Beck R, Pedrosa RC, Dejeans N, Glorieux C, Levêque P, Gallez B, et al. Ascorbate/menadione-induced oxidative stress kills cancer cells that express normal or mutated forms of the oncogenic protein Bcr-Abl. An *in vitro* and *in vivo* mechanistic study. *Invest New Drugs*. 2011; 29: 891-900.
17. Sakagami H, Anzai S, Goto S, Takeda M. Enhancement of cytotoxic activity of ascorbate by Acer nikoense Maxim Extracts. *Anticancer Res*. 1997; 17: 4453-4456.
18. Makino Y, Sakagami H, Takeda M. Induction of cell death by ascorbic acid derivatives in human renal carcinoma and glioblastoma cell lines. *Anticancer Res*. 1999; 19: 3125-3132.
19. Bahlis NJ, McCafferty-Grad J, Jordan-McMurry I, Neil J, Reis I, Kharfan-Dabaja M, et al. Feasibility and correlates of arsenic trioxide combined with ascorbic acid-mediated depletion of intracellular glutathione for the treatment of relapsed/refractory multiple myeloma. *Clin Cancer Res*. 2002; 8: 3658-3668.
20. Calderon PB, Cadrobbi J, Marques C, Hong-Ngoc N, Jamison JM, Gilloteaux J, et al. Potential therapeutic application of the association of vitamins C and K3 in cancer treatment. *Curr Med Chem*. 2002; 9: 2271-2285.
21. Johnson NA, Chen BH, Sung SY, Liao CH, Hsiao WC, WK Chung L, et al. A novel targeting modality for renal cell carcinoma: human osteocalcin promoter-mediated gene therapy synergistically induced by vitamin C and vitamin D. *J Gene Med*. 2010; 12: 892-903.
22. Tarumoto T, Nagai T, Ohmine K, Miyoshi T, Nakamura M, Kondo T, et al. Ascorbic acid restores sensitivity to imatinib *via* suppression of Nrf2-dependent gene expression in the imatinib-resistant cell line. *Exp Hematol*. 2004; 32: 375-381.
23. Miranda CL, Reed RL, Kuiper HC, Alber S, Stevens JF. Ascorbic acid promotes detoxification and elimination of 4-hydroxy-2(E)-nonenal in human monocytic THP-1 cells. *Chem Res Toxicol*. 2009; 22: 863-874.
24. Vásquez DR, Verrax J, Valderrama JA, Calderon PB. Aminopyrimidoisoquinolinequinone (APIQ) redox cycling is potentiated by ascorbate and induces oxidative stress leading to necrotic-like cancer cell death. *Invest New Drugs*. 2012; 30: 1003-1011.
25. Herst PM, Broadley KW, Harper JL, McConnell MJ. Pharmacological concentrations of ascorbate radiosensitize glioblastoma multiforme primary cells by increasing oxidative DNA damage and inhibiting G2/M arrest. *Free Radic Biol Med*. 2012; 52: 1486-1493.
26. Klingelhoeffer C, Kämmerer U, Koospal M, Mühling B, Schneider M, Kapp M, et al. Natural resistance to ascorbic acid induced oxidative stress is mainly mediated by catalase activity in human cancer cells and catalase-silencing sensitizes to oxidative stress. *BMC Complement Altern Med*. 2012; 12: 61.
27. Moser JC, Rawal M, Wagner BA, Du J, Cullen JJ, Buettner GR. Pharmacological ascorbate and Ionizing Radiation (IR) increase labile iron in pancreatic cancer. *Redox Biol*. 2013; 2: 22-27.
28. Cieslak JA, Strother RK, Rawal M, Du J, Doskey CM, Schroeder SR, et al. Manganoporphyrins and ascorbate enhance gemcitabine cytotoxicity in pancreatic cancer. *Free Radic Biol Med*. 2015; 83: 227-237.
29. Günes-Bayir A, Kiziltan HS. Palliative Vitamin C Application in Patients with Radiotherapy-Resistant Bone Metastases: A Retrospective Study. *Nutr Cancer*. 2015; 67: 921-925.
30. Yang G, Yan Y, Ma Y, Yang Y. Vitamin C at high concentrations induces cytotoxicity in malignant melanoma but promotes tumor growth at low concentrations. *Mol Carcinog*. 2017; 56: 1965-1976.
31. Nielsen TK, Højgaard M, Andersen JT, Jørgensen NR, Zerahn B, Kristensen B, et al. Weekly ascorbic acid infusion in castration-resistant prostate cancer patients: a single-arm phase II trial. *Transl Androl Urol*. 2017; 6: 517-528.