REVIEW ARTICLE

Orthomolecular Oncology: a Mechanistic View of Intravenous Ascorbate's Chemotherapeutic Activity.

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The effect of vitamin C in cancer has been a subject of great controversy; mainly because of the inconsistent results obtained by oral intakes of ascorbate when used as an anticancer agent. We believe the intravenous application of ascorbate will provide more consistent results in cancer patients since Vitamin C blood levels attained are substantially higher in a range proven cytotoxic to malignant cells. In this article we will present and discuss our proposed mechanism on the chemotherapeutic activity exhibited by ascorbate.

Key words: Vitamin C, Cancer, Oncology

The effect of ascorbic acid on cancer has been reevaluated in view of new evidence of its anticancer activity when provided by intravenous administration (1-3). In this paper we are proposing the main mechanism by which intravenous ascorbic acid (IAA) is capable of eliciting a chemotherapeutic effect. Ascorbic acid (AA) and its salts are preferentially toxic to tumor cells in vitro and in vivo. A has the potential to selectively kill tumor cells in a manner similar to other cytotoxic chemotherapeutic agents but without the accompanying adverse effects.

Discussion

An increased glucose consumption rate has been observed in malignant cells (1-3). Glucose molecular structure is similar to that of ascorbate. Warburg postulated that the respiratory process of malignant cells was impaired and the transformation of normal cells to malignant was mainly due to defects in aerobic respiratory pathways (4). Szent -Gyorgyi also viewed cancer as originating from insufficient availability of oxygen (4). Oxygen by itself has an inhibitory action on malignant cell proliferation (5) by directly interfering with anaerobic respiration (fermentation, lactic acid production). In addition certain oxidation intermediates have demonstrated antineoplastic activity (6). In order to be able to divide and proliferate the cell needs to reduce its cohesiveness and dismount part of its structure. This unstable state of cellular organization facilitates free radical damage by oxidative species in the malignant cell and at the same time predisposes normal cells to the malignant state. Interestingly, during differentiation there is an increased cellular production of oxidants that appear to provide one type of physiological stimulation for changes in gene expression that lead to a terminal differentiated state (7). Ascorbic acid not only has antioxidant properties but also pro-oxidant activity capable of selective cytotoxic effects on malignant cells at high concentrations (8).

It has been suggested that ascorbate promotes oxidative metabolism by inhibiting utilization of pyruvate for aerobic metabolism (9). Also an inhibitory effect on growth of several types of tumor cells has been produced by ascorbate and/or its derivatives. This inhibitory action was not observed in normal fibroblasts (10). This cytotoxic activity produced by ascorbate in an array of malignant cell lines has been associated to its pro-oxidant activity (11-16). Ascorbate can generate hydrogen peroxide (a reactive species) upon oxidation with oxygen in biological

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systems (17). Hydrogen peroxide may further generate additional reactive species such as the hydroxyl radical and aldehydes which can compromise cell viability (18). These reactive species may induce strand breaks in DNA, disrupt membrane function via lipid peroxidation or deplete cellular ATP (18). The failure to maintain ATP content may be a consequence of oxidative inactivation of key enzymes of the aerobic pathway. The cytotoxicity induced by ascorbate seems to be primarily mediated by hydrogen peroxide generated intra -cellularly by ascorbate's metabolic oxidation to dehydroascorbate (19-23) In addition this anti-proliferative action of ascorbate in cultured cells, animal and human tumors has been increased by the addition of the cupric ion, a catalyst for the oxidation of ascorbate (19). It has also been suggested that the selective toxicity of ascorbate in malignant cells may be due to reduced level of catalase in these cells, leading to cellular damage through the accumulation of hydrogen peroxide (19-26). There is a 10 to 100 fold greater content of catalase in normal cells that in tumor cells (19). For this reason the combination of mega-doses of ascorbate together with oxygen and copper seems logical as part of a non-toxic treatment protocol for cancer patients (26).Moreover, lack of superoxide dismutase (SOD) has been detected in the mitochondria of cancer cells (27).This deficiency will impair the function of the Krebs cycle forcing anaerobic metabolism and the concomitant production of lactic acid. Intravenous administration of ascorbate can yield very high plasma vitamin C levels which seem to be necessary for ascorbate's toxic effect on malignant cells (28-30). Interestingly ascorbate concentrations in blood achievable through oral supplementation, although not cytotoxic, are capable of increasing collagen production by tumor cells which can probably restrict their metastatic potential (30). The concentrations of ascorbate toxic to cancer cells in vitro can be achieved clinically by intravenous administration (28-30). Furthermore it has been reported that lipoic acid decreases the dose of ascorbate required to kill 50% of the tumor cells (29-30) probably by restoring ascorbate's redox capabilities and/or by enhancing oxidative pathways.

Conclusion

The evidence presented herein supports the hypothesis that the main chemotherapeutic action of ascorbate can be attained in vivo by intravenous administration and potentiated by lipoic acid. Ascorbate's cytotoxic effect seems to be due mainly by the in situ formation of hydrogen peroxide for which the cancer cells have no defense because of their lack of the enzymes catalase and super oxide dismutase. Intravenous ascorbic acid seems as a very attractive anticancer therapy due to its specific cytotoxicity against cancer cells and its lack adverse effects.

Resumen

El efecto de vitamina C en cáncer ha sido un tema de gran controversia, mayormente por los resultados inconsistentes obtenidos por ingestas orales de ascorbato al ser utilizado como agente anti-cáncer. Creemos que el uso intravenoso de ascorbato proveerá resultados más consistentes en pacientes de cáncer ya que los niveles de vitamina C en sangre que se obtienen son substancialmente más altos que vía oral y en un rango citotóxico contra células malignas. En este artículo presentamos y discutimos nuestro mecanismo propuesto de la actividad quimioterapéutica de ascorbato.

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