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Vitamin C as an Antioxidant: Evaluation of Its Role in Oral Squamous Cell Carcinoma

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Abstract

Introduction: Oral Squamous Cell Carcinoma (OSCC) is the eighth most frequent cancer worldwide, with an 8-year overall survival rate of 50% to 60%. In OSCC and broader Head and Neck Squamous Cell Carcinoma (HNSCC), the sixth most common malignant tumor, oxidative stress plays a pivotal role in the oncogenic process, both as a cause and a result of altered redox metabolism, a state in which Vitamin C (VC) may have an impact.

Methods: A systematic review of databases, such as PubMed, Scopus, and Google Scholar, was performed to investigate the anticancer potential of VC in OSCC. Published research to date has focused on the molecular and biochemical profile, oxidative stress and signaling pathways, clinical results, and adverse effects of VC administration in patients with OSCC.

Results: Current evidence illuminates the promising preventive and adjunctive therapeutic capacity of VC in OSCC. Reactive Oxygen Species (ROS) increased by VC cause alterations in the tumor microenvironment, DNA damage, ATP reduction, and activation of tumor suppressor genes. Those were translated as an inhibition of xenograft OSCC tumor growth in mice and enhancement of cisplatin-mediated apoptosis.

Conclusions: VC demonstrated anticancer activity through ROS recruitment and signaling pathway alterations in OSCC models, necessitating future expansion of this observation in large clinical trials.

Keywords: Antioxidant; Reactive oxygen species; Anticancer

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Introduction

High mortality rates have been reported worldwide in patients with Head and Neck Squamous Cell Carcinoma (HNSCC), an entity that represents a global public health issue [1]. Endogenous and environmental risk factors have been described especially for Oral Squamous Cell Carcinoma (OSCC), with tobacco and alcohol consumption causing different biological profiles than those caused by HPV infection [2]. The treatment protocol of OSCC consists of surgery, chemotherapy, immunotherapy, and radiotherapy; however, a significant improvement in the overall survival rates for OSCC has not been reported in recent decades [3]. Therefore, a necessity emerged to highlight the preventive and adjunct therapeutic properties of substances that may offer to the patients a favorable efficacy/safety ratio [3]. L-ascorbic acid, also called vitamin C (VC), has an established, natural, antioxidant, redox profile that can be expressed only with intravenous administration targeting malignant tumor cells (Ngo et al. [4]). This innovative treatment modality of VC can be implemented to shift redox balance towards oxidative stress in malignant cells by elevating Reactive Oxygen Species (ROS) in the bloodstream. In our systematic review, recent experimental and clinical evidence will be described to investigate the preventive and adjunct therapeutic potential of VC in patients with OSCC.

Methods

Current literature has been reviewed in our study, featuring the levels of biochemical markers that affect redox imbalance, to assess the preventive and adjunct therapeutic role of VC in OSCC, with tumor cells' normal signaling pathways disrupted by ROS imbalance, overcoming endogenous protective mechanisms [5]. Our methodology is based on the interaction of VC with ROS and free radicals as byproducts of intracellular metabolism in a VC dose-dependent pattern at the tumor microenvironment [6]. Genomic instability of initially healthy cells can lead to definitive proliferation and metastatic potential at the experimental level, with a downstream pathological

consequence of redox metabolism in oncogenesis that can be interrupted by VC administration [7]. Oral cancer models have been used to synthesize current knowledge for cell cycle interruption with concentration-related VC toxicity against malignant cells [3].

Result

Observational studies investigated the potential impact of VC in HNSCC; for instance, a large-scale cohort study with 5959 cases and 12248 controls showed that the risk for OSCC was reduced in patients with regular consumption of VC [8]. Additionally, a prospective cohort study demonstrated that higher dosages of oral VC reduced the incidence of OSCC [9]. Nevertheless, VC has debatable therapeutic properties as shown in a randomized controlled trial that patients with oral leukoplakia consumed daily per os 500 mg VC and β-carotene, without remission of leukoplakia or prevention of malignant transformation [10]. The antineoplastic action of VC in OSCC models was identified in CAL27 cell lines, in which intravenous administration of VC led to a rapid, dose-dependent intracellular ROS accumulation, causing oxidative stress, disruption, and autophagy of mitochondria, depletion of intracellular ATP, and a reduction in neoplastic clone-forming ability [3]. Furthermore, this VC-mediated lack of cell energy activated, at a molecular level, the tumour suppressor genes in the p53/p21 axis, arrested the cell cycle at the G0/G1 phase, and activated caspase-dependent apoptosis by altering the Bax/Bcl-2 ratio, not allowing malignant cell migration and expansion [3]. Finally, an OSCC-implanted mouse model showed in vivo that intravenous high-dose VC twice daily restricted tumor burden and enhanced antineoplastic activity of cisplatin when administered concomitantly [3].

Discussion

Patients with OSCC initially present with advanced-stage disease, while adverse events or acquired resistance to platinum chemotherapy hinder clinical management [11]. Historically, oral VC intake has not proven to be efficient [12]. Recent studies have shown that intravenously administered high doses of VC are bioavailable in the cytoplasm [4]. The concentration-dependent VC preventive role in patients with OSCC has also been demonstrated by increased dietary consumption [8], whereas a standard VC supplementation pattern was inadequate for remission of leukoplakia [10]. As a result, VC in high dosage is clinically effective as a pro-oxidant factor that promotes ROS accumulation, targeting metabolic mechanisms of malignant cells [3]. Energy deficiency, caused by high intracellular ROS concentrations and mitochondrial damage, has also been described for other substances, such as thymol and icaritin [13,14]. Specifically, the VC-mediated cascade leads to mitochondrial autophagy, a decrease in anti-apoptotic Bcl-2, Bax activation, and cell-cycle arrest at the G0/G1 checkpoint, limiting tumor invasion and migration, as well as recurrence and mortality [3]. The combination of VC with cisplatin can enhance DNA damage and tumor suppression in vivo, limiting maybe the required cisplatin dosage and toxicity [15,3].

Conclusion

High-dose VC may play a pivotal role in the treatment algorithm of OSCC, as shown by large-scale epidemiological studies with increased dietary supplementation, as well as *in vitro* and *in vivo* assays with intravenous administration, especially when combined with cisplatin [3,8]. Standard dietary supplementation cannot lead to oral leucoplakia withdrawal [10]. In contrast, high doses of intravenous VC may rapidly achieve high cytoplasmic concentrations, enabling ROS generation and oxidative stress of tumor cells [4]. The synergistic action of VC with cisplatin in tumor regression of OSCC models in vivo indicates a promising treatment modality that needs further evaluation in prospective randomized clinical trials [3].

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