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Mini Review

A Mini-Review of Sildenafil's Paradoxical Roles in Oncology

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ABSTRACT

Sildenafil, a renowned Phosphodiesterase type 5 (PDE5) inhibitor, has a well-established role in managing erectile dysfunction by promoting Nitric Oxide (NO)-mediated relaxation of the corpus cavernosum. Beyond its urological applications, emerging research underscores its anti-tumoral efficacy in diverse cancers. However, concerns arise from its potential pro-tumoral role, with several studies indicating an association between Sildenafil use and increased melanoma risk. Although causality remains debated, the drug's dual oncological potential necessitates a discerning evaluation of its therapeutic application. This mini-review seeks to amalgamate information about the therapeutic and anti-tumor consequences of sildenafil in oncology, aiming to furnish guidance for its more prudent use.

Keywords: Sildenafil; Nitric oxide; Erectile dysfunction; Cancer; Melanoma

INTRODUCTION

Sildenafil operates as a distinct inhibitor of Phosphodiesterase type 5 (PDE5), concentrating its action on cyclic Guanosine Monophosphate (cGMP) [1]. The intracellular concentration of cGMP is dependent on two ways, including the activity of guanylate cyclase and Phosphodiesterases (PDEs) [2]. PDE5, crucial for the metabolic degradation of cGMP, plays a role that is amplified by Nitric Oxide (NO), and operates within the corpus cavernosum, initiating its contraction [3,4]. Consequently, through the inhibition of PDE5, Sildenafil obstructs the degradation of cGMP, activates Protein Kinase G (PKG), and promotes the production of NO, subsequently amplifying the previously mentioned relaxative impact of NO on the corpus cavernosum. Pertaining to erectile functionality, during sexual excitation, characterized by localized NO emission, Sildenafil maintains heightened cGMP concentrations within the corpus cavernosum through PDE5 inhibition [5]. This encourages smooth muscle relaxation, allows blood to flow into the penis, and consequently induces an erection. Additionally, within the domain of reproductive and sexual wellbeing, sildenafil has displayed effectiveness in addressing premature ejaculation [6].

LITERATURE REVIEW

Famed for its therapeutic application in alleviating Erectile Dysfunction (ED) [7], Sildenafil has also drawn notable attention in the region of oncology [8]. A growing body of research signals that sildenafil plays a crucial role in treating various cancers, including those originating in the lung, liver, colon, and ovaries [9]. Simultaneously, a noteworthy quantity of recent academic investigations has unveiled a clear link between sildenafil use and the emergence of melanoma [10]. This mini-review seeks to amalgamate information about the therapeutic and anti-tumor consequences of sildenafil in oncology, aiming to furnish guidance for its more prudent use.

Antitumoral impacts of Sildenafil

Experimental and preclinical findings substantiate the anti-neoplastic effectiveness of Sildenafil, highlighting its prospective utility in the realm of oncology. Such efficacy has been

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demonstrated not only in isolation but also, notably, in conjunction with other anti-neoplastic compounds and therapeutic approaches, serving as a chemotherapeutic adjunct. Numerous inquiries have probed into the antineoplastic efficacy of Sildenafil against lung cancer, particularly in conjunction with additional chemotherapeutic agents. Researches [11] executed in vitro studies to scrutinize the impacts of coupling Sildenafil with Pemetrexed, a chemotherapeutic compound clinically employed for the management of lung cancer and ovarian cancer. Regarding mechanisms of action, it appears that the majority of Sildenafil's impacts are contingent on NO/PDE5 inhibition, which leads to apoptosis activation, either independently or by bolstering the efficacy of established cytotoxic chemotherapies across various tumoral cell lines [12,13]. The pro-apoptotic influence has been demonstrated across various cancer types, such as colorectal, and myeloma. Furthermore, the participation of autophagy in the anti-neoplastic effects of Sildenafil has been thoroughly chronicled in the literature. An investigation revealed that Sildenafil, with differential magnitudes, augmented the ability of Pemetrexed to initiate cellular demise across a spectrum of ten distinct lung cancer cell lines. This was accomplished by the suppression of the PI3K/Akt/mTOR/p70S6K pathway, whereupon the pharmaceutical pairing enhanced the quantity of autophagosomes, and, consequently, autophagy within the cells subjected to treatment. In conjunction with apoptosis, inhibition of PDE5 has been associated with an amplified anti-tumoral immune response [14,15]. A notably finding is the immune-modulatory effect exhibited by the pairing of Pemetrexed and Sildenafil. More precisely, this duo has been shown to augment the expression of class I Major Histocompatibility Complex (MHC), MHCA, while concurrently diminishing the levels of PD-L1 and PD-L2 across diverse cancer cell lines [16].

DISCUSSION

Pro-tumoral impacts of sildenafil

Sildenafil harbors the potential to amplify susceptibility to particular cancers, such as various types of melanoma. Major public health concerns have been raised about severe adverse drug reactions related to Sildenafil. A study identified a correlation between self-reported sildenafil use and an elevated melanoma risk [17]. However, crucial data about the timing, duration, and dosage of Sildenafil, tumor stage, and usage sildenafil was absent in this study. The relationship between Sildenafil and melanoma skin cancer continues to be a subject of debate. Two synchronized case-control investigations conducted in 2016 revealed scant evidence to substantiate a direct causative association between Sildenafil and the risk of melanoma [18]. A recent analysis of the Surveillance, Epidemiology, and End Results (SEER) database revealed that post the 1998 introduction of Sildenafil, the malignant melanoma diagnosis rate trend did not exhibit substantial alterations [19]. However, inherently, the SEER didn't permit control for sun exposure intensity, introducing a potential confounder to their results. Our preceding study discovered that all stages of malignant melanoma were associated with Sildenafil [20], consistent with findings reported by others. A retrospective dataset revealed that Sildenafil amplified the indication for both malignant melanoma and basal cell carcinoma. Additional reports frequently and disproportionately highlighted malignant melanoma in association with adult use of sildenafil and tadalafil for sexual dysfunction. Moreover, without controlling for gender, age, indication, and administration route, a 40-fold greater time for sildenafil malignant melanoma was observed. Nevertheless, up to now, no evidence for a biological gradient was discovered. An investigation revealed the suppression of PDE5A across diverse melanoma cell lines expressing oncogenic BRAF, suggesting the potential of this inherent phenotype to serve as a biomarker indicative of increased invasiveness and a less favorable prognosis. Although a theoretical potential exists for drugs targeting PDE5A to expedite melanoma metastasis, the administration of sildenafil did not amplify the colonization of melanoma cells in the lungs within murine models.

CONCLUSION

The dichotomous role of sildenafil in oncology unveils a complex narrative of therapeutic potential juxtaposed with tangible public health concerns. On one frontier, sildenafil demonstrates considerable anti-tumoral impacts, enhancing the efficacy of established chemotherapies and exhibiting noteworthy anti-cancer capabilities across diverse malignancies through its modulation of cellular apoptosis and autophagy. Conversely, its potential association with heightened melanoma risk warrants cautious and discerning utilization, mandating a critical appraisal of its risk-benefit axis. Future research endeavors should prioritize meticulously designed, comprehensive studies to decipher the mechanistic underpinning of sildenafil's pro-tumoral activities, while concurrently exploring its anti-cancer efficacy in clinical trials.

AUTHOR CONTRIBUTION

Bin Zhao, Meiqi Lu, and Zheng Wan designed the study. Zheng Wan, Anran Sun, and Bin Zhao wrote the draft. All members participated in discussion. All authors approved the final manuscript.

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CONFLICTS OF INTERESTING

All authors declare no conflict of interest.

ETHICS

Not applicable.

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