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Cardiomyocyte Morphology with Repeated Doses of Cockle shell derived Calcium Carbonate Nanoparticle loaded with Doxorubicin

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ABSTRACT

Doxorubicin is a potent widely used anticancer for several types of cancers, including haemopoietic, solid and soft tissue sarcomas, since cancer is considered as one of the most challenging healthcare conditions. The major side effect is on the mitochondria structural morphology resulting dysfunction and impairment of energy required for muscular contraction, thus, leading to heart failure. Although, several therapeutic strategies are put in place to ameliorate the effect of doxorubicin on cardiomyocytes, using either nanocarrier for doxorubicin delivery or cardio-protectant in combination with antioxidant. It is widely acknowledged that doxorubicin induces cardio-dysfunction, by interacting with cardiomyocyte organelles which enable energy production. This review is focussed on the histomorphological structure of cardiomyocytes upon the repeated dose of cockle shell derived calcium carbonate nanoparticle loaded with doxorubicin and its current potential strategies in reducing doxorubicin-induced cardiomyocytes changes.

Keywords: Cardiomyocytes, Doxorubicin, Mitochondria, Nanotechnology

INTRODUCTION

Doxorubicin (DOX) is one of the most successful and widely used anthracycline group of anticancer agents. However, its repeated doses are associated with myocadiac cell damages, which is currently a primary concern in cancer treatment over the years [8]. Despite its efficacy in the management of both hematopoietic and solid cancers, its usage is being hampered by inducing cardiac toxicity [26]. However, cardiomyopathy caused by DOX is a major concern for its clinical use due to several alterations on the cardiomyocytes. Recent advances in early cancer diagnosis have paved the way for new approaches in the management of cancer. However, the therapeutic strategies are still hampered due to off targeted effect of the most potent drugs [25].

Notwithstanding serious search for a palliative route for the prevention of the toxicity induced by DOX using fewer toxic analogues or subclinical doses by researchers, there is no consensus on the best strategy to prevent DOX cause toxicity especially cardiomyopathy [24]. Although, modified medicine strategies have been employed to avoid chemotherapy-induced toxicity by the use of nanocarrier for drug delivery or with cardio-protectant in combination with antioxidants [32]. However, the clinical use of DOX is restrained by chronic and cumulative cardiotoxicity manifested as a dilated congestive heart failure [24]. Cardiotoxicity induced by DOX could either be acute or chronic. However, acute changes are infrequent, thus manifest as acute tachyarrhythmia, asymptomatic electrocardiography, chest pain and heart failure, which occurs within 2-3 days of administration [27]. However, dose-dependent chronic DOX myocardial toxicity is associated with cardiomyopathy, cardiac dysfunction and heart failure [1,33]. Due to the high risk of the cardiotoxic effect of DOX, patients are currently deprived of therapy to avoid the development of the detrimental effects such as cardiomyopathy. This review is focused on the histomorphology of cardiomyocytes of the animal model given repeated doses of cockle shell derived calcium carbonate nanoparticle loaded with doxorubicin, its mechanism, and the current potential strategies in reducing DOX-induced cardiomyocytes changes. Hence, the review

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will also briefly highlight a few histological alterations of myocardial tissue on ultrastructure and histology induced by chronic DOX and DOX-loaded nanocarrier.

Mechanism of DOX-induced cellular alteration on cardiomyocytes

DOX-induced cellular alteration ~~is~~ through multifactorial pathways [3,10]. The exact mechanism is somewhat controversial, although two leading theories are associated with the mechanism. The antineoplastic mechanism of DOX has been attributed to intercalation of the planar anthracycline ring into the DNA helix [10] and covalent binding to proteins involved in DNA replication and transcription. Such interactions result in inhibition of DNA, RNA, and protein synthesis, leading ultimately to cell death [15,28]. However, the common pathway frequently associated with DOX induction tissue damage is through ion transfer in the process of activation of DOX to semi-quinone active metabolite within the mitochondrial structural complex resulting to the production of the superoxide anion [25]. However, DOX act on the neoplastic cells either by intercalation into the DNA structure or by disruption of topoisomerase II-mediated DNA repair and by free radicals' generation [31].

From a molecular perspective, DOX-dependent iron overload originates from the ability of the drug to interfere with the activity of iron-transporting and binding proteins [28]. DOX-induced reactive oxidative stress (ROS) irreversibly converts the iron-free [23,35]. The abundant of cardiolipins within the inner membrane of the mitochondrial of cardiomyocytes as compared to other tissues with low antioxidant justify the reason for more injury to the heart tissue than other tissues [19]. Thus, damage of the mitochondrial membrane potentiates the resulting influx of cytochrome c and other anti-apoptotic proteins which activate cell death [5,11,34].

Cardiomyopathy and Doxorubicin

Marked dilation of the sarcoplasmic reticulum and mitochondrial damage are primary evidence of the cardiomyopathy [21] were previously observed in the myocardium after DOX administration in both healthy and cancer patients. The contractile ability of atria and ventricular are significantly reduced, accompanied by myocyte vacuolization, myofibrillar loss with increase sarcoplasmic reticulum and T-tubule size associated with cytoplasmic vacuolation [22]. However, with the nuclear region changes such as chromatin and nucleolar shrinkage, with segregation of granular and fibrillar components are mostly observed ultra-structurally [29]. These alterations are reported to be more prominent with accumulative doses of the drug, but not with a more prolonged period of perfusion per administration. DOX disrupt cellular function leading to increase oxidative stress, mitochondrial damage, apoptosis and cell death [25].

Variation in the location of cell damage and the number of the organelles (sub sarcolemma, intermyofibrillar, mitochondrial concentration) involved depends on the concentration DOX in which the tissue interacted [33]. Ventricular remodeling as a result of the DOX is a crucial pathway explaining the pathogenesis of the tissue damage to the architecture morphology [22]. The changes observed with the ventricular response to the DOX insult are ranging from cardiomyocytes hypertrophy, fibroblast proliferation, with increase protein deposit within the extracellular matrix and collagen infiltration between the fiber [17].

Potential strategies in reducing DOX induced cardiomyocytes morphological alteration

Considering the pathways involved in DOX induction of the cardiomyocyte morphological alterations, many strategies have been employed to ameliorate the effects. Emphases are made in science to reduce the adverse impact of cumulative doses of DOX, which are mostly towards dose reduction, with the use of DOX analogue or modifying the administration schedules protocol. However, the most common method used in the past involved the use of antioxidant and iron chelators which are mostly from synthetic material [13]. The incomplete knowledge of cancer biology persists relatively, thus the use of nanoscale material for new oncology therapeutics. Moreover, no doubt that some highly innovative studies have been revealed in clinical space with few approvals in cancer management [8], and rapid expansion of the clinical application of cockleshell derived calcium carbonate nanoparticle loaded with DOX in treatment of solid cancer in dogs [8]. The use of advance nanotechnology has paved ways in chemotherapeutic approach in the management of cancer with several nano-formulations available for usage, using both passive and active drug delivery approach [12,16]Cockleshell derived calcium carbonate nanoparticle load with DOX, Cytarabine, docetaxel and other active chemotherapeutic drugs has proved to effective in managing adenomas and sarcoma in different models and clinical trials [7,8,14,18], with no sign on the nuclei, mitochondria and structural fibrous proteins with the cardiomyocytes of the dogs with osteosarcoma given repeated doses of the conjugate. Although, the cardiomyocytes of the dogs given DOX alone expresses mitochondrial depolarization and fragmentation associated with membrane blebbing [4]. Cockleshell derived calcium carbonate nanoparticle loaded with DOX overcome the non-specific delivery of DOX, which causes significant effects on health and cancerous cells in the body [7,8]. This conjugate has shown promising efficacy as compared to the conventional chemotherapeutic drugs with excellent biological behavior with chronic repeated administration. Cockleshell derived calcium carbonate nanoparticle has proved to be potent when conjugated with cytarabine, docetaxel and ciprofloxacin in the treatment of haemopoietic tumor, breast cancer and osteoporosis [2,14,18,20]. The conjugate showed little or effect on other healthy rapid multiplying cell as when compared to the respective active compound, taking advantage of the targeting and pH-responsive mechanism

properties of the nanocarriers and microenvironment of the tumor as a delivery strategy for the delivery drug [6].

CONCLUSION

The optimal strategy for preventing chemotherapy-induced cardiotoxicity remains unclear. The used of biogenic biodegradable cockle shell derived calcium carbonate nanoparticle loaded with doxorubicin as shown to be promising in the treatment of naturally occurring solid tumors in dogs with improving the survival rate and excellent quality of life. Thus, highly recommend for clinical application in the management of solid tumors.

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