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A COMPREHENSIVE REVIEW OF THE MECHANISMS OF ACTION AND CARDIOTOXICITY OF DOXORUBICIN

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ABSTRACT

Doxorubicin (DOX), an anthracycline antibiotic, is a chemotherapeutic agent used to treat various cancers, including breast cancer, leukemia, and lymphomas. Primary mechanisms of action are DNA intercalation and topoisomerase II inhibition to disrupt DNA replication and transcription, inducing apoptosis in rapidly dividing cancer cells. Its clinical utility is significantly limited by dose-dependent cardiotoxicity, driven by the generation of reactive oxygen species (ROS), mitochondrial damage, and inflammatory cytokine activation, often leading to irreversible heart failure. This review highlights recent insights into doxorubicin's mechanisms of action and toxicity, emphasising pathways such as mitochondrial dysfunction and apoptotic signalling in cardiomyocytes. Advanced delivery systems, including liposomal formulations

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and nanoparticle-based platforms, are explored for their ability to enhance tumor targeting while minimising exposure to healthy tissues. Notably, pH-sensitive and stimuli-responsive nanoparticles offer improved specificity, reducing systemic toxicity. Emerging strategies such as biomarker-guided therapy and pharmacogenomics enable early detection of cardiotoxicity and personalised dosing regimens. Predictive modelling using cardiac biomarkers and genetic profiling hold promising for identifying high-risk patients. Combination therapies, particularly with immune checkpoint inhibitors, provide opportunities to enhance efficacy while reducing doxorubicin doses and associated toxicities. Future advancements in precision medicine, green chemistry, targeted delivery system approaches are expected to mitigate doxorubicin's cardiotoxic effects, broadening its clinical applicability and improving patient outcomes.

Keywords: doxorubicin, Reactive oxygen species (ROS), cardiomyocytes, topoisomerase, green chemistry.

AIMS AND BACKGROUND

This review highlights the anticancer mechanisms with respect to the molecular action of doxorubicin (DOX) elucidates DNA intercalation and topoisomerase II inhibition, both of which inhibit DNA transcription and replication and thus cause selective apoptosis of tumor cells. Further, this review investigates the dose-dependent cardiotoxic mechanisms of doxorubicin, focusing on ROS generation, mitochondrial malfunction, and pro-inflammatory cytokine release accompanies often with an irreversible status of heart failure. Hence, the review turns into the applications of advanced drug-delivery systems such as liposomal formulations and nanoparticle-based platforms to increase targeting to tumors while reducing systemic toxicity. These are put forward with regard to their application in anticancer therapy. Currently, approaches such as biomarker-based therapy in combination with pharmacogenomics, plus predictive modelling with cardiac biomarkers, are also considered for the early detection of cardiotoxicity and dose optimisation. The really promising strategy for further improving effectiveness with lower toxicity is combination therapy, especially when combined with immune checkpoint inhibitors. It is expected that advances in precision medicine, drug targeting, and AI-based technologies will counteract the toxic effects of doxorubicin, and thus increase the therapeutic usage of the drug and improve patient outcomes.

Doxorubicin (DOX) has played a important role in treating various cancers, including breast cancers and some blood disorders. This drug was discovered from the late 1960s onwards, during which time numerous investigations showed its mechanism of action as intercalates the DNA and inhibits the action of topoisomerase II. The structure of doxorubicin is represented in Fig. 1. These two actions together inhibit cell growth and finally trigger apoptosis. However, effective though it may be, the use of doxorubicin in the clinic has been considerably hampered for a considerable time by its dose-dependent cardiotoxic action, occasionally resulting in severe cases of heart failure in patients. The balance between optimum therapeutic efficacy and reduction

of cardiac risk remains difficult for clinicians, so continued research is directed to reveal mechanisms of toxicity and new therapeutic approaches[1]. Recent research has endeavoured to investigate the ways that doxorubicin influences the cardiac cells on a molecular scale, with such research demonstrating the oxidative stress, mitochondrial dysfunction, and cellular apoptosis to all significantly contribute to reported cardiotoxicity. Breakthroughs in delivery and individual patient therapies through methods of liposomes and genetic marking have presented avenues for less toxicity, but those patients with greater risk continue to be at high risk for untoward cardiac action[2].

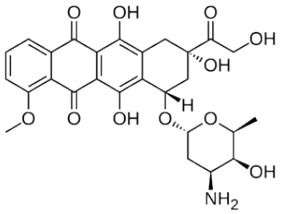

Fig. 1. Structure of doxorubicin

MECHANISMS OF DOXORUBICIN

DNA INTERCALATION AND TOPOISOMERASE II INHIBITION

The mechanisms of action, through which doxorubicin delivers its antitumor activities, could be divided into two broad categories. These are the inhibition of the enzyme topoisomerase II and DNA intercalation. The planar structure of such compound enables doxorubicin to insert itself between the DNA helix bases, thereby preventing necessary processes of transcription and replication in cancer cell growth[3]. Doxorubicin inhibits topoisomerase II activity by stabilising the covalent topoisomerase II–DNA cleavage complex and preventing the re-ligation of DNA strands, thereby causing the accumulation of double-strand breaks and inducing apoptosis. This could be the reason why doxorubicin is not very selective since it harms normal highly proliferative cells like those in bone marrow and cardiac muscle[4]. Recent studies indicate differences in DNA damage response and repair pathways in cancer and cardiac cells, potentially offering the prospect of selective therapeutic targeting. Without repair pathways, cancer cells are exquisitely sensitive to both the doxorubicin-induced double-strand break and the DNA-intercalating agent relative to normal cells, which use these pathways to evade apoptosis. Raising the differential doxorubicin responses between these two cell types might therefore offer novel directions for therapeutic approaches to prevent off-target toxicity.

GENERATION OF REACTIVE OXYGEN SPECIES (ROS)

ROS production has been thoroughly reported to be one mechanism by which doxorubicin triggers apoptosis in cancer cells by mainly oxidative damage to DNA,

proteins, and lipids. This very process is also involved in cardiotoxicity induced by doxorubicin, were ROS damage cardiomyocytes and initiate cell death and subsequent cardiac dysfunction. The heart, with a high oxygen requirement and compromised antioxidant protection, is especially vulnerable to oxidative damage. Doxorubicin is also lowered in cardiac mitochondrial membranes through redox cycling, which adds to surplus production of ROS and enhances cellular stress and mitochondrial damage[5].

IMMUNOGENIC CELL DEATH (ICD)

ICD is widely researched in relation to doxorubicin. DAMPs release in doxorubicin-induced ICD, such as ATP and HMGB1, further promotes antigen-presenting cells to elicit adaptive immunity against tumor cells. It transdifferentiates tumors into sources of antigens to provoke a larger sustained immune response to reduce the size of tumor cells even upon chemotherapy. This immunogenicity has now been read as beneficial, particularly in conjunction with the immunotherapies that are checkpoint inhibitors, which act to enhance T-cell activation against tumor cells[6]. The combination of doxorubicin and immune checkpoint inhibitors is being evaluated in clinical trials. In addition, the ICD effect of doxorubicin can enhance treatment in immune-resistant tumors resistant to immune checkpoint blockade alone. The flow points of ICD are illustrated in Fig. 2. The approach is designed to produce a maximum of tumor suppression via chemotherapy-induced immunity and hence offer new directions in treatment that are broader than classical cytotoxicity[7].

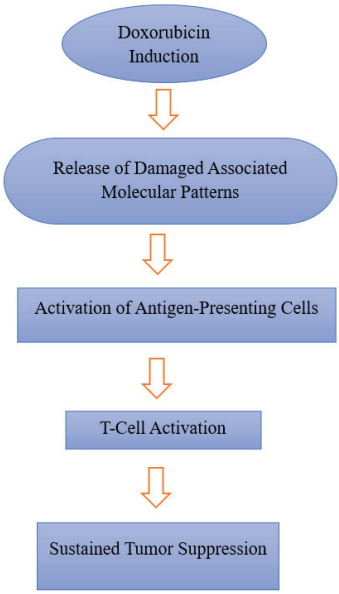

Fig. 2. Flow points of ICD

APOPTOTIC PATHWAYS: CASPASE-DEPENDENT AND CASPASE-INDEPENDENT

Doxorubicin not only causes caspase-dependent apoptosis but is also reported to cause alternative forms of cell death, including necroptosis and autophagy that can be implicated in mechanisms of resistance in some cancers[8]. There is interest in caspase-independent mechanisms because they can bypass the tumor's resistance mechanisms for evading apoptotic death by caspase inhibition Among the various forms of regulated death, necroptosis has been elicited as one of the forms contributing to apoptotic activity of doxorubicin in a few cancers, and it may very well aggravate, in this regard, the cardiac inflammation and damage, warranting subsequent modulation[9].

DOXORUBICIN-INDUCED CARDIOTOXICITY

OXIDATIVE STRESS AND MITOCHONDRIAL DYSFUNCTION

Cardiotoxicity still stands as the greatest dose-limiting side effect of doxorubicin therapy resulting from an obvious increase in oxidative burden and mitochondrial dysfunction within cardiomyocytes. ROS is considered the leading factors in triggering oxidative stress and DNA damages[10]. The heart's characteristic redox conditions exacerbate the cytotoxic features of doxorubicin as mitochondrial ROS are produced and accumulated. The resulting ROS exert their damaging influence directly on cellular membranes, proteins, and mitochondrial DNA, destabilising cell integrity, and launching signalling pathways for cardiomyocyte apoptosis. Ultimately, this has been an accumulation of cell injury over a long period, resulting in reduced cardiac contractility, leading to heart failure in significantly advanced stages[11].

There are many types of mitochondrial-targeted therapies with antioxidants and compounds such as MitoQ that show promise in their ability to selectively protect the heart from ROS, while still maintaining doxorubicin's antitumor action. Research is currently being conducted on these compounds in clinical trials involving patients who are undergoing treatment with doxorubicin; results from early trials appear to indicate their potential in terms of reduced cardiotoxicity biomarkers. This represents an evolving strategy to one of the major problems associated with doxorubicin therapy.

FERROPTOSIS AND LIPID PEROXIDATION

Ferroptotic cell death is a recently identified key mechanism of doxorubicin-induced cardiotoxicity, in addition to apoptosis. In cardiomyocytes with a relatively high iron load, ferroptosis, a controlled process of cell death driven by lipid peroxidation and dependent on iron is especially harmful[12]. Ferroptosis produces lipid peroxidation products that damage cell membrane integrity, resulting in cell death and doxorubicin's cumulative cardiotoxicity.

Application of ferroptosis inhibitors, including liproxstatin-1, has been promising in preclinical models of doxorubicin-induced cardiotoxicity by minimising cell death and maintaining cardiac function. These results highlight the potential to target

ferroptosis as a new strategy to prevent cardiotoxicity, especially for individuals receiving high cumulative doses of doxorubicin[13].

INFLAMMATORY RESPONSE AND FIBROSIS

Doxorubicin induction leads to persistent inflammation in cardiac tissue, enhanced cytokine production, and immigration of immune cells. This inflammatory condition would activate fibroblasts, allowing remodelling in the extracellular matrix and fibrosis which may further endorse cardiac function[14]. It is a type of irreversible damage, and even acute survivors of cardiotoxicity might evolve to experiences of progressive heart failure because of chronic remodelling and fibrosis. If MI takes place in the individual, it could lead to irreparability.

Since inflammatory cytokines like TNF-α and IL-6 have a well-established role in doxorubicin-induced cardiotoxicity, it is possible that some of these effects could be lessened by targeted immunosuppressive or anti-inflammatory treatments. Cytokine inhibitors are being tested in preclinical and clinical trials to lessen fibrosis, with encouraging initial findings regarding reduced fibrosis and preserved cardiac function[15].

STRATEGIES TO MITIGATE DOXORUBICIN TOXICITY

LIPOSOMAL FORMULATIONS

Liposomal drug formulations of doxorubicin, such as Doxil, have greatly improved the delivery of this agent by diminishing considerably the cardiotoxicity of doxorubicin by entrapping it in a lipid bilayer. The lipid bilayer delivery is favorable to tumor tissue-directed delivery via the enhanced permeability and retention (EPR) effect, and hence cardiomyocyte exposure is minimised. There are reduced incidences of acute and chronic cardiotoxicity without compromising antitumor activity[16]. Success with Doxil and the emerging clinical adjuncts that liposomal formulations have afforded to other anticancer drugs such as cytarabine has, of course, achieved new impetus for innovation in drug delivery using nanoparticles. Target ligands that have been the subject of much current research to be incorporated into the liposomal formulation are mentioned. These ligands will, therefore, target a receptor inside the cancer cell, allowing the drug to accumulate more in the tumor than in other healthy tissues, such as the heart.

ANTIOXIDANT THERAPY

The best study in reducing the cardiotoxicity of doxorubicin is adjunctive antioxidant use to minimise ROS production and oxidative damage. Doxorubicin has been shown to induce the formation of doxorubicin-iron complexes that catalyse ROS production. Thus, dexrazoxane, a non-iron chelation iron-chelating agent, is the sole FDA-approved cardioprotective medication shown to be doxorubicin related. While dexrazoxane is a potent way of coping with this, concerns over its potential blockade against doxorubicin's antitumor effect have prompted the testing of other antioxidants[17].

PHARMACOGENOMICS AND PRECISION MEDICINE

Pharmacogenomics is an intriguing area of study that personalises treatment with doxorubicin and predicts toxicity. The basis of individual variability in doxorubicin toxicity due to heterogeneity of genes associated with drug disposition, oxidative stress response, and cardiac physiology explain variability of drug induced cardiotoxicity[18]. Efficacy and variability of toxicity have been connected to polymorphisms in CYP2D6, a drug metabolising enzyme. Polymorphisms in the antioxidant defense enhancing genes NQO1 and SOD2 have also been connected to increased risk for cardiotoxicity[19].

Genomic information allows clinicians to better characterise individual risk, and personalise doxorubicin dosing regimens to enhance effectiveness while minimising toxicity. Pharmacogenomic testing will be especially advantageous in the identification of high-risk populations and committing to cardioprotective or alternative treatments, as early as possible. Advancements in genome-wide association studies (GWAS) and next-generation sequencing technologies have already prompted research in the pharmacogenomics of anthracyclines. Application and adoption of these technologies in clinical practice may soon make personalised treatment for doxorubicin therapy an expected norm.

BIOMARKER-GUIDED MONITORING

The serial monitoring of cardiac injury biomarkers being a crucial aspect of patient care for those on doxorubicin therapy, cardiac biomarkers such as troponins, natriuretic peptides (BNP and NT-proBNP), and galectin-3 become meaningful indicators of myocardial stress and have demonstrated the ability to foresee very beginning signs of cardiotoxicity[20]. Rising levels of these biomarkers during a course of therapy indicate subclinical cardiac injury that can instigate measures to forestall further injury[21].

Current studies now mainly include new upcoming biomarkers as well as routine biomarkers regarding circulating microRNAs (miRNAs) and specific cardiac proteins that are thought to serve as more appreciable and specific markers for diagnosis with doxorubicin-induced cardiotoxicity[22]. For instance, miR-208 and miR-499 trigger some early manifestation of use for detecting cardiotoxic effects, and their non-invasiveness and their rapidness in application are currently being studied. Integration of such markers into clinical practice may refine the observation and limit the long-term cardiotoxicity effects in cancer survivors.

ALTERNATIVE FORMULATIONS – PRODRUG DEVELOPMENT

PRODRUG STRATEGIES

Prodrug approach has been recently introduced as an effective strategy to improve selective delivery and decrease systemic toxicity of doxorubicin. The Prodrug is an inactive analog that gets converted to the active drug by metabolisation at the site of action, resulting in lower off-target side-effects seen in healthy tissues[23]. Scientists

are able to optimise prodrugs structure-activity by modification of doxorubicin and rationalise cardiotoxic erosion. For instance, some novel prodrugs are reported to have been conjugated with hydrophilic polymers or tumor cell-targeting ligands that promote tumor tissue accumulation of doxorubicin to minimise taking systemic exposure[24].

Some prodrug formulations are made so that they only take on bioactive form in the highly acidic environment that typifies most solid tumors in an effort to direct delivery of the doxorubicin dose directly into the tumor with little to no exposure of the healthy surrounding tissues. The minimal formation in the cardiac cells of ROS caused by this treatment reduces the extent of cardiotoxic side effects[25]. Prodrug formulations-for example, those that use glutathione-sensitive linkages-target the high-glutathione cellular environment in cancer cells and provide targeted release of doxorubicin.

ADVANCED BIOMARKER UTILISATION AND PREDICTIVE MODELLING

BIOMARKER-DRIVEN TREATMENT ADJUSTMENTS

Biomarkers are increasingly critical to optimise doxorubicin use, especially in identifying risk of cardiotoxicity and for personalised dosing. Troponin, brain natriuretic peptide (BNP) and circulating microRNAs (miRNAs) are among the cardiac biomarkers that have been well recognised to predict early cardiac insult. Biomarker monitoring enables dose adjustments according to real time biomarker values leading to dose optimisation and˜ personalised therapy with less toxicity without loss of activity against cancer[26].

In the last few years biomarkers like circulating miRNAs and exosomes reflecting stress and damage in cardiac myocyte have been identified[27]. Specific to myocardial cell miRNAs such as miR-208a and miR-499 have a potential role as proximal biomarkers of doxorubicin cardiotoxicity that may lend themselves to preventive therapy in an effort to intervene before full, irreversible injury. Development of all-encompassing biomarker panels to facilitate real-time treatment strategies may emerge as a core component of personalised doxorubicin therapy to increase safety and outcome.

PREDICTIVE MODELLING FOR CARDIOTOXICITY RISK

Patient Specific Predictive modelling with genetic variants and patient-specific components is an entirely new way for identifying cardiotoxicity risk before commencing therapy. Using the model to generate personalised risk estimates based on genetic data, biomarker concentration, and clinical history helps clinicians identify high-risk patients so that treatment plans can be adjusted accordingly. For instance, the information on genes which affects molecular level of oxidative stress pathways (NQO1 and SOD2 for pharmacogenomic standpoint), is employed by these models to deduce if an individual is at higher susceptibility due to ROS-induced damage[28].

COMBINATION THERAPIES TO ENHANCE EFFICACY AND REDUCE TOXICITY

SYNERGISTIC USE WITH TARGETED THERAPIES

Doxorubicin in conjunction with targeted agents such as TKIs and PARP inhibitors is likely to heighten therapeutic efficacy while at the same time presenting an opportunity to lessen the required dosage such that cardiotoxicity may be minimised. These TKIs act by disrupting cancer cell growth factor signalling and have had synergistic effects with doxorubicin, especially in highly proliferative tumors[29]. Therefore, through these combinations, oncologists can obtain enhanced anti-cancer effects at any given time with lower doses, thereby decreasing the toxicity associated. In addition to PARP inhibitors taken together with doxorubicin to enhance its efficacy, certain cancers exist whereby DNA repair is purposely handicapped. In BRCA-mutated cancers, where DNA repair is already weakened, in conjunction with PARP inhibitors, diverting or further effort on DNA Repair from Dox is really good. The combination has been very successful in breast and ovarian cancers, providing a therapeutic avenue that will keep efficacy while reducing dosing.

IMMUNE CHECKPOINT INHIBITORS AND IMMUNOTHERAPY

The increasing popularity of immunotherapy, investigations have focused on combining doxorubicin with immune checkpoint inhibitors (ICIs) such as PD-1 and CTLA-4 blockers in order to promote immunogenic cell death and sustain the anti-tumor immune responses. Doxorubicin may induce the immunogenic cell death (ICD) responsible for activating the immune system for long-term protection against cancer cells[30].

In particular, this combination is showing promise in aggressive or immune-resistant cancers where traditional chemotherapy might not suffice alone. Clinical studies are currently being conducted with the combination of doxorubicin and ICIs, and preliminary data suggest improved overall survival as well as progression-free survival for patients receiving these regimens.

CONCLUSIONS

Doxorubicin is one of the most important anticancer agents in cancer treatment because of its potent cytotoxicity but the use is severely limited by dose-limiting cardiotoxcity. The biological mode of action in doxorubicin- DNA intercalation and ROS generation, immunogenic cell death as well as apoptotic pathways-based approach has unfolded new strategies to minimise toxicity while retaining anticancer efficacy. Attempts to attenuate cardiotoxicity resulted in the creation of novel agents, from new drug formulations such as liposomal doxorubicin, nanoparticle-based drug-delivery systems, and/or prodrug strategies to improve than ever tumour-selective drug delivery. Doxorubicin (and other cardioprotective agents like dexrazoxane; mitochondrial-targeted antioxidants; ferroptosis inhibitors) is probably going to decrease the amount of pos-

sible damage done to the heart. The use of pharmacogenomics in combination with biomarker-led monitoring enables more tailored therapy, which is associated with improved safety and efficacy.

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