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Review Article

DOXORUBICIN INDUCED CARDIOTOXICITY: POSSIBLE CAUSE AND PREVENTIONS

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ABSTRACT:

Doxorubicin/Adriamycin (Dox) is a powerful, well established and highly efficacious drug in the fight against many kinds of cancers like solid tumors, leukemia's, soft tissue sarcoma, breast cancer, small cell carcinoma of the lung and esophageal carcinomas. But its clinical usefulness is still restricted due to its specific toxicities to cardiac tissues. Congestive heart failure, cardiomyopathy, and electrocardiographic changes were demonstrated after cumulative Dox administration. The possible mechanisms proposed for cardiotoxic effects of Doxorubicin include free radical induced myocardial injury, lipid peroxidation, mitochondria damage, decreased activity of Na, K-adenosine triphosphate, vasoactive amine release, impairment in myocardial adrenergic signaling/regulation and cellular toxicity.

Increased oxidative stress and release free radicals, including super oxide anion (O_2^-) and other reactive oxygen intermediates as well as endogenous antioxidant deficits have been suggested to play a major role in Dox-induced cardiomyopathy and heart failure.

In the same context the possible cause of Dox inducing cardiotoxitiy will be discussed along with the various till date possibilities for its prevention.

Keywords: Doxorubicin, Adriamycin, Free radicals, Cardiiotoxicity, Cancer.

INTRODUCTION:

Discovery of Doxorubicin (Adriamycin), an antitumor antibiotic, in the early 1960's represented a major advancement in the fight against cancer, as the drug was found to be very effective in a variety of soft and solid human malignancies [1]. This enthusiasm quickly waned, however, when it became obvious that Doxorubicin had the very serious side effect of causing cardiomyopathy leading to congestive heart failure (CHF) [2]. During early clinical trials with Dox, electrocardiogram (EKG) modifications including tachycardia, ST segment depression and T wave changes were observed [3]. But it took a retrospective analysis of 399 patient charts to firmly establish the occurrence of CHF due to Adriamycin [4]. This study also made it clear that CHF was a dose dependent phenomenon. An incidence of >5% was seen at a 501- 550 mg/m^2 body surface area, increasing to >30% at over 601 mg/rn^2. Thus, the dose of 500mg was considered the upper limit in order to minimize the risk of Doxorubicin cardiomyopathy and CHF. Subsequent studies showed that cardiomyopathy could occur at a much smaller dose of Dox in patients with risk factors such as age, some underlying heart conditions, previous or concurrent radiation therapy and concomitant chemotherapy.

More recently, a long-term follow-up study revealed that patients who were asymptomatic of cardiac toxicity at the time of complete remission of cancer after treatment with Dox showed within the next 4 to 20 years an unusually high incidence of cardiovascular complications typical of Dox cardiomyopathy[5]. Because of its high antitumor efficacy, Dox, despite the risk, has remained in use. Although the use of Dox as a single agent has been restricted, it forms a valuable component of various regimens of chemotherapy. Therefore, there is still a need to find ways to avoid or minimize the cardiotoxic side effects of Dox in the treatment of cancer patients.

CHEMISTRY OF DOXORUBICIN:

Doxorubicin consists of a naphthacenequinone nucleus linked through a glycosidic bond at ring atom 7 to an amino sugar, daunosamine. Chemically, Doxorubicin hydrochloride is: 5,12-Naphthacenedione,10-[(3 - amino - 2, 3, 6 - trideoxy- alpha - L - lyxohexopyranosyl)oxy] - 7, 8, 9, 10 - tetrahydro - 6, 8, 11- trihydroxy - 8 -

(hydroxylacetyl)-1-methoxy-, hydrochloride (8S-cis). The molecule is amphoteric, containing acidic functions in the ring phenolic groups and a basic function in the sugar amino group. The structural formula is shown in Fig 1:

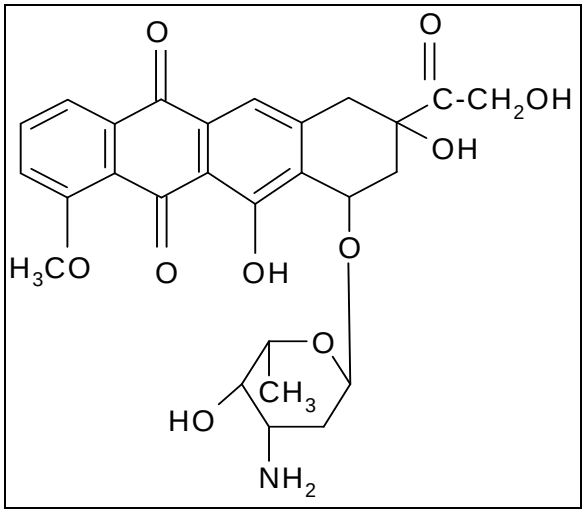

Fig No. 1: Structural formula of Dox

Doxorubicin binds to nucleic acids, presumably by specific intercalation of the planar anthracycline nucleus with the DNA double helix. The anthracycline ring is lipophilic, but the saturated end of the ring system contains abundant hydroxyl groups adjacent to the amino sugar, producing a hydrophilic center.

PHARMACOKINETICS OF DOXORUBICIN:

Dox is typically administered via infusion over a brief period, with the peak plasma concentration in humans varying between 5 and15 μmol/L and a half-life in the range 20–30 h [6]. It is imperative that physiologically relevant concentrations be considered when evaluating the multitude of studies on Dox. Clinically relevant doses are critical in deciphering the mechanism of Dox cardiotoxicity since excessive concentrations induce a variety of pathological effects unrelated to the true mode of action, as will be discussed in subsequent sections. In addition, Dox undergoes metabolic transformation to several derivatives in the body.

The chemical structure of the Dox consists of a tetracycline moiety containing a quinone and a conjugated amino sugar residue and is modified by several enzymes, predominantly in the liver, for elimination. Metabolites of Dox include an alcohol produced via carbonyl reduction and several aglycone derivatives. Dox is widely distributed throughout the body after administration in mice as the presence of the drug is noted in most organs

[7]. Additional data demonstrate that an appreciable portion of the drug is excreted in feces (and to a lesser extent in urine) in the alcohol and parent forms suggesting that conversion to metabolites is not extensive. The metabolism of Dox in the heart does not appear extensive.

Another hypothesis based in a comparison of the effects (toxicities of Dox and its major metabolite, Doxorubicinol, suggest that Doxorubicinol is more toxic to the heart than doxorubicin and points the same as a potential culprit in Dox induced cardiotoxicity [8].

Notable chemical species include the parent form and the alcohol, with no appreciable accumulation compared to other tissues such as liver or kidney. In human cardiac samples, the parent compound along with the alcohol, are again the most prominent chemical species present. Further investigation of the distribution of Dox reveals the presence of specific sites of drug accumulation within the cell. Isolated mitochondria have been shown to effectively accumulate the drug and studies using perfused rat hearts have shown that Dox is localized primarily to the nucleus and mitochondria of the cell [9].

CLINICAL ASPECTS AND MORPHOLOGICAL CHARACTERISTICS OF DOX-INDUCED CARDIOMYOPATHY

Chronic cardiomyopathy [10]:

Chronic cardiomyopathy usually occurs within the first year after therapy (early onset), but occasionally much later. Such late onset cardiac toxicity was documented especially in children. The probability of developing cardiomyopathy is clearly dose-dependent. At a dose of 550 mg/m2 the incidence is up to 7%. However, sub clinical cardiac damage can be observed at doses much lower than this threshold using echocardiography or radionuclide ventriculography. The clinical course and manifestation of Dox-induced cardiomyopathy is highly variable ranging from acute cardiogenic shock to gradually progressive deterioration and congestive heart failure.

Acute cardiomyopathy [11]:

Acute cardiotoxicity with anthracyclines occurring during or immediately after the treatment was reported in patients as relatively rare and usually transient. It is typically characterized by electrocardiographic

abnormalities, such as arrhythmias, non-specific ST-T alterations, QT-prolongation, and associated with reversible hypotension and pericarditis [12]. Of note, the electrical manifestations are not predictive of subsequent cardiomyopathy. Diastolic functional impairment arises first after Dox therapy.

Later on, diastolic dysfunction becomes more pronounced and is accompanied with alterations in systolic function [13]. Tissue Doppler imaging isovolumic relaxation time (an index for diastolic function), measured at the mitral annulus during early assessment was found to be shorter (<80 ms) in patients who developed subsequently an ejection fraction below 50% of original values and cardiomyopathy (positive and negative predictive value of 100% and 91%, respectively). Certain factors were identified to predispose to cardiomyopathy: age over 65 years , diabetes, pre-existing heart disease and hypertension, liver disease or mediastinal radiotherapy.

Although Dox induced cardiomyopathy was found to have a poor outcome (up to 61% mortality rate), recent studies show a clear survival benefit associated with proper medical management. There is no specific treatment for cancer therapy-related cardiomyopathy. Symptomatic patients receive standard treatments for congestive heart failure, such as angiotensin-converting enzyme inhibitors, beta-blockers, diuretic, digoxin and spironolactone [14]. The pathway of how anthracyclines are responsible for heart failure is Shown in fig no 2.

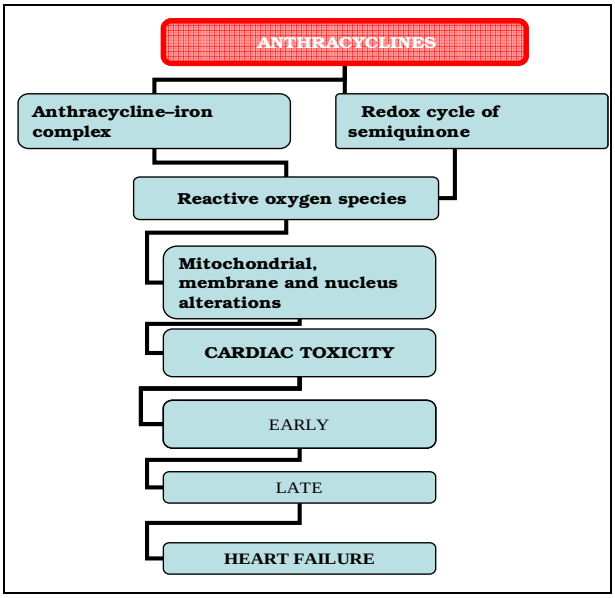

Fig No. 2: Pathway of Anthracyclines leading to Heart Failure [15].

Recent experimental evidence supports the preventive effects of erythropoietin on cardiac dysfunction in Dox induced cardiomyopathy. Attempts to reduce Dox toxicity were directed towards schedule modifications, developing less cardiotoxic analogs, or concurrent administration of cardio protective agents like dexrazoxane, an iron chelator. However, these strategies were of limited effect [16].

Dox cardiotoxicity has been termed type I chemotherapy related cardiac dysfunction, which in contrast to type II is characterized by ultrastructural changes and has a greater tendency to become irreversible. The major morphological changes in myocardium of patients treated with Dox were described as myofibrillar loss, dilatation of sarcoplasmic reticulum and swollen mitochondria. The severity of these changes can be assessed semiquantitatively according to the score [17], but these histopathological features are not specific for Dox toxicity.

ANIMAL MODEL

A powerful tool to study different aspects of Doxorubicin cardiotoxicity and its prevention was made available by the development of different small animal models. Doxorubicin-induced cardiac changes in rats closely mimic several features of the cardiomyopathy seen in humans [18]. The rat model is considered suitable because it emulates structural as well as functional changes observed in patients and is highly reproducible [19].

MECHANISMS:

Antitumor action and Cardiotoxicity:

The subcellular basis for Doxorubicin-induced cardiomyopathy as well as its antitumor action were earlier thought to involve a common pathway. However, more recently it has become possible to distinguish the mechanisms underlying these dual effects of Dox, as discussed here:-

Antitumor action:

Because Doxorubicin has been shown to produce free radicals, it was suggested earlier that free radical injury might be a mechanism of Doxorubicin antitumor action [20]. The formation of free radicals in breast cancer

cells as well as in some other cell types exposed to high concentrations of Dox was established [21] and the possible mechanism of ROS production by Dox is shown in Fig No 3.

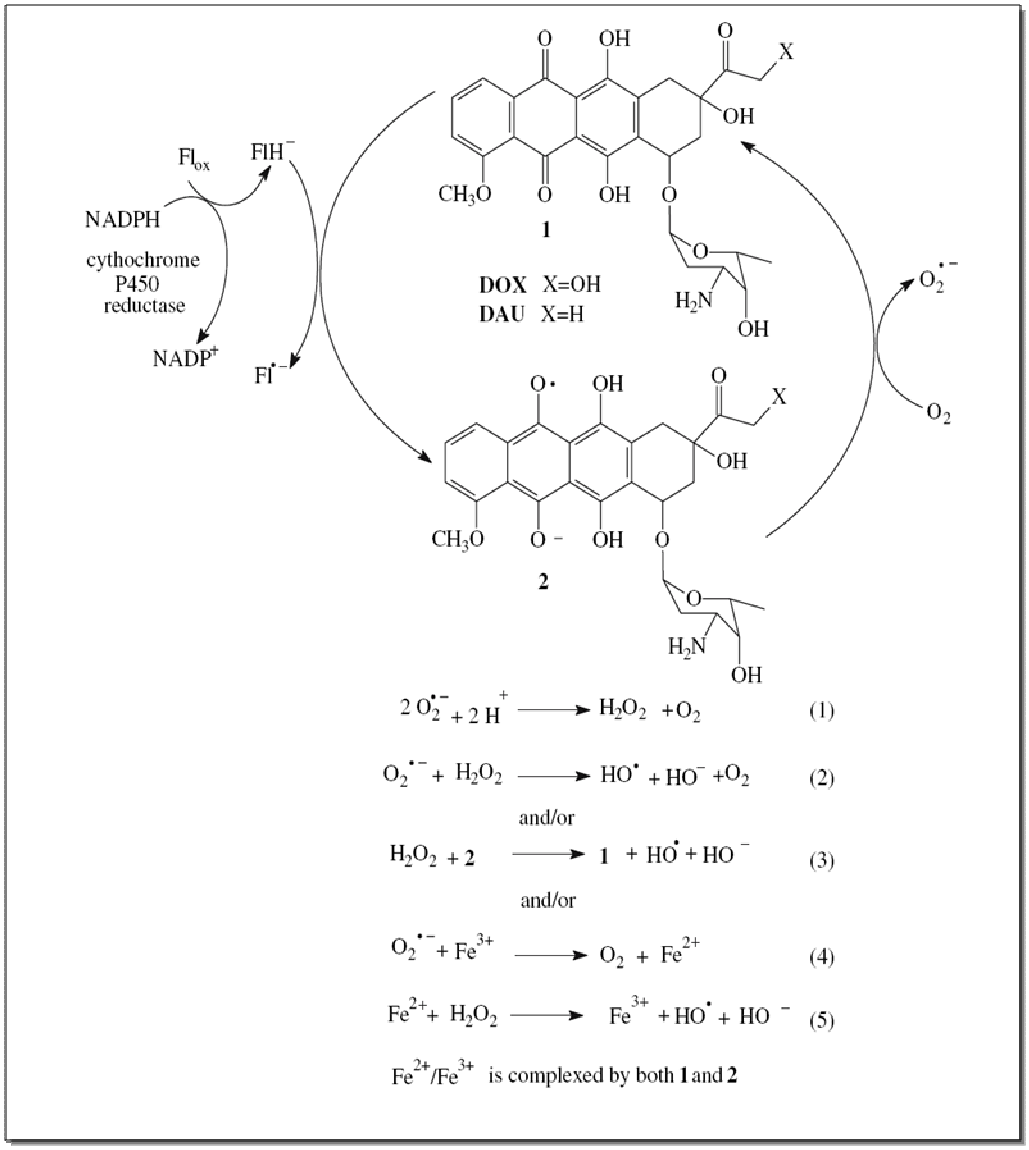

Fig No. 3:- Possible mechanism of ROS production during oxygen dependent metabolism of anthracycline antibiotics (Doxorubicin) [22].

Another important point supporting the concept of free radical-mediated antitumor action is that Doxorubicin easily binds with iron, forming an adriamycin-iron complex. Doxorubicin bound to iron can also complex with DNA. These complexes can stimulate the production of partially reduced forms of oxygen [23].

These radicals are formed in the neighborhood of DNA strands, and free radical-induced DNA damage as well as strand breaks are extensively described in literature [24].

A careful review of the available literature reveals that relatively high in vitro concentrations of Doxorubicin were used to demonstrate the free radical-mediated DNA damage in tumor cells [25]. Doses used in in-vivo conditions are much lower, suggesting that a free radical mechanism might not be the primary cause of the antitumor activity of Doxorubicin. This point is supported by a multitude of studies in which the addition of different antioxidants did not compromise Dox cytotoxicity in a variety of tumor cells [26]. Fig No 4 shows the source of generation of free radicals.

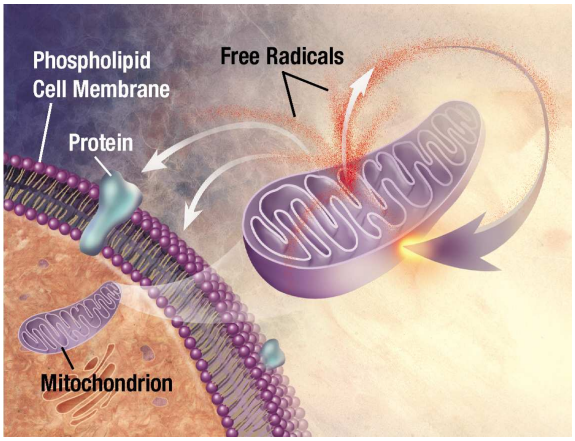

Fig No. 4:- Liberation of Free radicals from Mitochondria [27].

However, other mechanisms explain inhibition of DNA replication by Doxorubicin, and thus its cytotoxicity and antitumor action, without the involvement of free radicals. A direct intercalation of Doxorubicin between DNA base pairs interferes with DNA replication; this is a cooperative interaction between Dox and DNA [28]. Doxorubicin-mediated inhibition of DNA topoisomerase II has also been shown to inhibit DNA replication. Adriamycin-topoisomerase Il-DNA complex prevents repairing of the broken DNA strands.

At lower Dox concentrations similar to that observed in clinical situations, L1210 cells had only DNA topoisomerase II mediated, protein-associated strand breaks [29], whereas with increased adriamycin concentrations, cells died mainly due to direct strand breaks, not the protein-associated ones. Thus, Doxorubicin can exert an antitumor effect without involving free radical production.

Antitumor action at low concentrations of Dox independent of free radical mediation has been reconciled with the free radical mediated cardiotoxic effect of the drug seen at higher cumulative doses in a scheme shown in Fig. No.5.

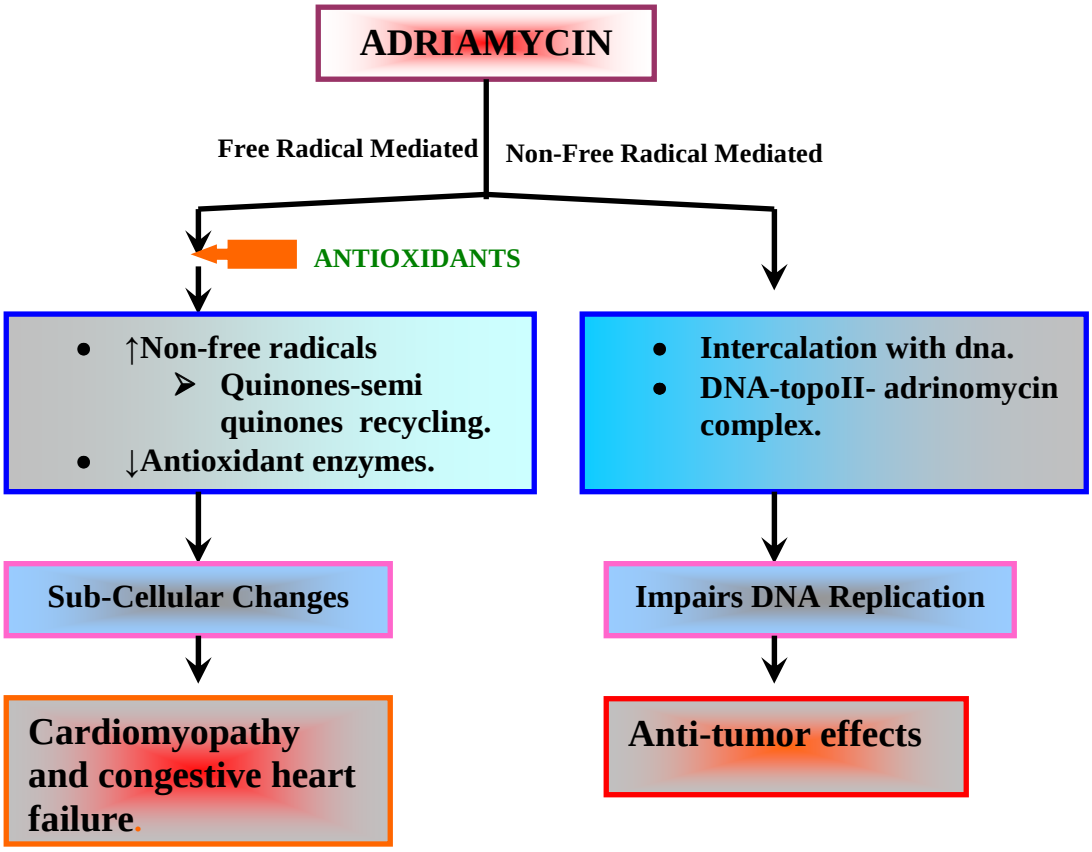

Fig. No. 05:- Distinction between the cardiotoxic and antitumor mechanisms of action of Doxorubicin [30].

MOLECULAR MECHANISMS:

Existing evidence points to a complex situation with a multitude of molecular mechanisms involved in Dox - induced impairment of cardiac energetics and other cellular targets, finally leading to cardiac dysfunction. The details of mechanisms and targets of Dox cardiotoxic action is shown in Fig No 6.

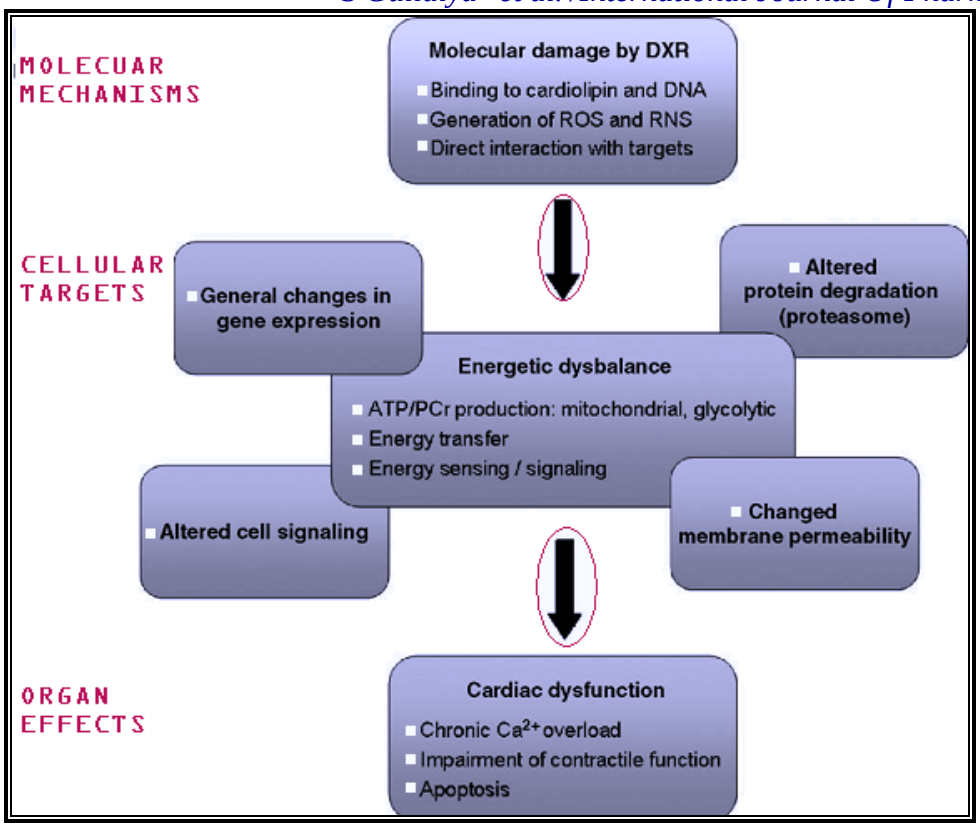

Fig. No. 6: Mechanisms and targets of doxorubicin cardiotoxic action. The schematic diagram summarizes multiple molecular mechanisms and intracellular targets, including cellular energetic network, implicated in development of doxorubicin-induced cardiac dysfunction [31].

An important factor, which can mediate the toxic action of Dox, especially in mitochondria, is high affinity binding of Dox to cardiolipin, an anionic phospholipid specific for the inner mitochondrial membrane, which has been recognized as an essential phospholipid in eukaryotic energy metabolism [32]. Cardiolipin with its particular ability to interact more or less specifically with many proteins, is very important not only for mitochondrial structure and function, but also for overall cardiac energy metabolism as well as for cell survival [33].

Binding of Dox would modify membrane properties and thus change phospholipid environment and function of numerous crucial mitochondrial integral membrane proteins, which depend on cardiolipin in their function.

Cardiolipin-bound Dox would also induce dissociation of cardiolipin-associated peripheral proteins from the inner mitochondrial membrane, like e.g. cytochrome c and MtCK [34]. This could affect electron transport chain and energy channeling, as well as favor initiation of programmed cell death. Toxicity of mitochondrial, mostly cardiolipin-bound Dox is mediated by oxidative stress, which represents a particular threat to cellular energetics in the myocardium and is considered as the main mediator of Dox cardiotoxic action.

Heart tissue is rich in mitochondria, since it heavily relies on oxidative metabolism, and thus produces significant amounts of free radicals. Accumulation of redox active Dox in these organelles would enhance mitochondrial production of reactive oxygen (ROS), and–as more recently evidenced–also of nitrogen species (RNS) [35].

Dox generates free radicals and other related reactive oxygen and nitrogen species both through an enzymatic mechanism utilizing cellular oxidoreductases (NADH dehydrogenase of complex I, cytochrome P-450 reductase, xanthine oxidase) and through nonenzymatic pathways involving complexation with iron (Fe^{3+}) [36]. The redox cycling of Dox catalysed by oxidoreductive enzymes is shown in Fig No 7.

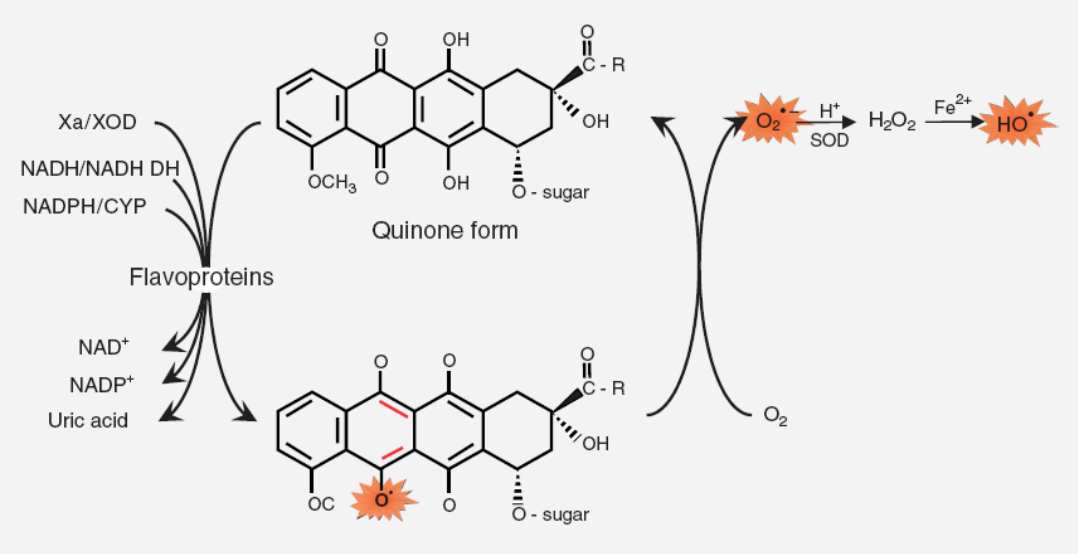

Fig No. 7: Chemical structure of doxorubicin and related redox cycling by enzymatic mechanism. One-electron reduction of the quinone moiety mediated by the cellular oxidoreductases results in formation of a semiquinone radical that regenerates the parent quinone by reducing oxygen molecule (O_2) to superoxide radical (O_2 S−). This

initiates a reaction cascade leading to the formation of other reactive oxygen and nitrogen species (ROS, RNS) [37].

Dox, a quinone containing drug, can be converted to the semiquinone form by one electron reduction. The Dox semiquinone can subsequently transfer an electron to the oxygen molecule (O_2) to form superoxide anion radical (O_2-) [38]. The latter can dismutate to form hydrogen peroxide (H_2O_2) and further hydroxyl radical (HOS) or may react with nitric oxide to form peroxynitrite (ONOO−). The noxious action of these reactive compounds includes the peroxidation of lipids and oxidative damage to proteins and DNA.

Peroxidation of membrane phospholipids associated with a decrease in membrane fluidity, as well as oxidation or nitration of proteins have been reported after Dox treatment [39]. Oxidative and nitrosative stress interfere with many aspects of cardiac function, inducing among others energetic imbalance, mitochondrial permeability transition and apoptosis, as well as activation of various related signaling pathways. In particular the response of cardiac Ca^{2+} to Dox can be closely related with the perturbation of heart energy homeostasis. Dox induced alterations in Ca^{2+} handling and their possible consequences are already reported [40].

It is to note, that the actual extent and impact of oxidative and nitrosative stress produced by Dox in different toxicity models, as well as in patients, are a matter of discussion. Interestingly, quinone-containing molecules can exert their effect independently of free radicals by directly affecting some sensible protein residues [41], as e.g. reactive sulfhydryl groups. Finally, Dox can interfere with cardiac gene expression [42], in particular by down-regulating genes of several enzymes implicated in energy metabolism.

Although such interference with DNA is considered important for the anticancer action of the drug, it may also affect macromolecular biosynthesis in the heart. In addition, oxidative stress has been implicated in Dox-impaired gene expression [43].

Fragmentation and proteolysis of Dox modified proteins were shown to occur in Dox-treated mitochondrial preparations [44]. In addition to lower biosynthetic rate and enhanced degradation rate, reduced cellular levels of soluble proteins and metabolites in Dox-challenged cells can occur through leakage. This is well known for

cytosolic MBCK, the plasma level of which serves as clinical marker of different cardiac pathologies, including Dox toxicity [45].

However, it should be noted that certain genes encoding proteins implicated in energy metabolism have been found upregulated in a mice model of chronic Dox-cardiotoxicity. This may reflect induction of a protective or compensatory response. Further mechanisms contributing to the toxic effect of Dox in cardiac tissue can be mediated by iron or Dox metabolites, as well as by an important damage of endothelial origin [46].

Collectively, the response of cardiac energetics to Dox involves a complex cross-talk between different pathways and mechanisms. Fig No 8 shows how Adriamycin redox cycling generates ROS.

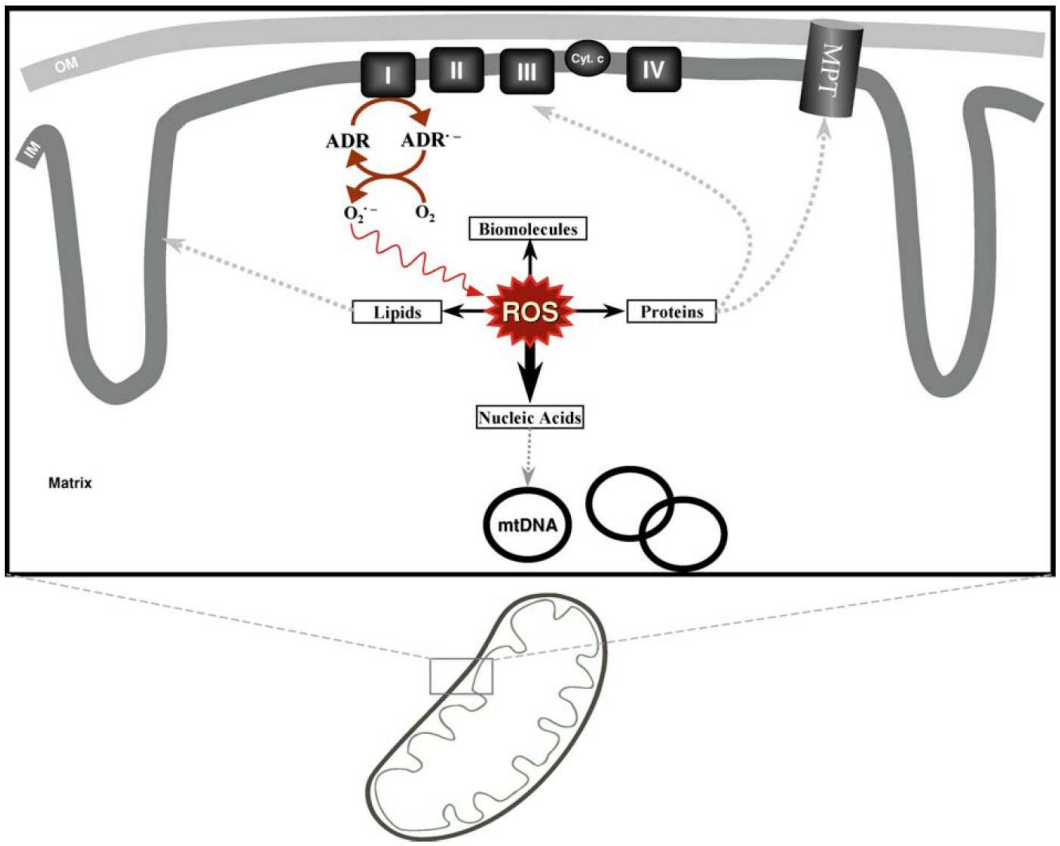

Fig. No. 08: Adriamycin (ADR) redox cycling at complex I of the electron transport chain results in the generation of reactive oxygen species (ROS) that may interact with a number of mitochondrial components in close proximity. This oxidative burden leads to increased damage to the mitochondrial genome (mtDNA),

proteins, lipids and other biomolecules. In particular, damage to the mtDNA could account for the persistent mitochondrial dysfunction and cardiotoxicity of ADR [47].

PREVENTION OF CARDIOTOXICITY

A number of approaches have been used for minimizing doxorubicin cardiotoxicity:

(1) Tailoring the maximum dose of doxorubicin for each patient to a threshold of earliest signs of cardiotoxicity.

(2) Dividing the dose of doxorubicin into small bolus injections or continuous slow infusion of doxorubicin,

(3) Modification of the doxorubicin formulation to reduce myocardial concentration,

(4) Coadministration of cardioprotective agents, and

(5) Development of newer, less cardiotoxic doxorubicin analogues.

Fig no 9: depicts the strategies to reduce the cardiotoxicity

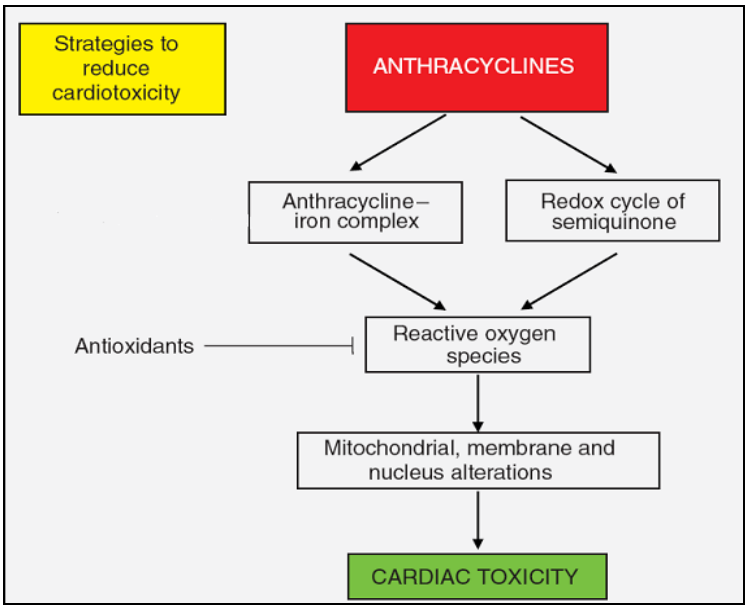

Fig. No. 09: General scheme explaining the cardiac toxicity of anthracyclines that is driven by ROS, and strategies to reduce the cardiotoxicity [48].

Tailoring the dose of doxorubicin:

Marked differences in the susceptibility to the cardiotoxic effects of Doxorubicin make it difficult to fix arbitrarily a ceiling for the cumulative dose limit of Doxorubicin. A lower dose limit would reduce the incidence

of serious cardiotoxicity, but this strategy would deny treatment with a potent and effective agent to many who would tolerate much higher doses and potentially benefit from its maximum antineoplastic therapeutic effects.

The current strategy is to administer Doxorubicin up to a point beyond which further therapy would result in cardiotoxicity. This requires an ability to monitor for cardiotoxicity and safely titrate the cumulative dose of Doxorubicin accordingly [49]. A significant reduction in the incidence of severe Doxorubicin cardiotoxicity has been achieved with the use of this approach.

A recent study has reaffirmed the validity and cost effectiveness of serial equilibrium radionuclide angiocardiography in the current context [50]. Elderly patients, patients with preexisting cardiac disease, those with hepatic dysfunction, and those with prior mediastinal irradiation are more prone to the development of Doxorubicin cardiotoxicity; however, there are no specific biochemical markers to predict individual predisposition to Doxorubicin cardiotoxicity.

Dividing the dose of doxorubicin:

In experimental studies with rabbits and rats, it was observed that cardiomyopathy was more severe when Doxorubicin was given in larger individual doses than when the same cumulative dose was given in smaller, more closely spaced doses [51]. Less concentration of Doxorubicin occurred with the latter regimen. These observations indicate that cardiotoxicity is related to peak blood levels of doxorubicin. This principle was subsequently used for reducing doxorubicin cardiotoxicity by slow, continuous intravenous infusion over a period of 24 to 72 hours. However, this is a relatively cumbersome approach and any accidental tissue infiltration of Doxorubicin results in marked tissue necrosis. Moreover, the frequency and intensity of some other side effects such as mucositis are increased with continuous infusion.

Modification of doxorubicin formulation:

Complexes of anthracyclines with several different substances such as liposomes, DNA, dextran, and albumin microspheres have been developed in an attempt to ameliorate cardiotoxicity. These complexes tend to

act as slow-release formulations that prevent the high peak plasma levels. Of these, liposomal incorporation of Doxorubicin has been consistently effective in experimental studies.

Experimental studies in mice and dogs have shown a decrease in cardiotoxicity of Doxorubicin and Daunorubicin administered in liposomes compared with the cardiotoxicity of these drugs administered as free agents [52]. Because myocytes have limited capacity for endocytic uptake of liposomes, the cardiac concentration of agents given in liposomal concentration is low. Liposomes tend to be taken up preferentially by the reticuloendothelial system and do not localize in extravascular compartments of skeletal or cardiac muscles. These factors possibly contribute to reduced cardiotoxicity of liposomal Doxorubicin. Interestingly, some other side effects of Doxorubicin such as alopecia and weight loss were also reduced with the liposomal formulation in the animal studies.

Studies done in tumor-bearing rats have shown no change in antitumor efficacy, whereas overall survival was better, with reduced severity of myocardial lesions and nephrotoxicity in rats treated with liposomal doxorubicin compared with these effects in the rats treated with standard Doxorubicin.

An experimental approach of administering Doxorubicin coupled to peptides that home specifically in tumor endothelial cells has been evaluated in a mouse model of human breast cancer xenograft. This approach resulted in a high concentration of Doxorubicin in tumors, associated with an enhanced antitumor effect and reduced cardiotoxicity. This approach has potential for reducing Doxorubicin cardiotoxicity in human studies [53].

Cardioprotective agents:

An extensive array of compounds has been evaluated in various experimental models for their potential to reduce Doxorubicin cardiotoxicity, on the basis of a perceived ability to modulate some of the biochemical alterations that accompany Doxorubicin administration. The list of such compounds includes adenosine, Doxorubicin-specific antibody, antihistamine agents (both H1 and H2 blockers), amrinone, dextran, salts of bismuth, polyethylene glycol, tetracycline antibiotics, a number of antioxidants, and venoruten. However, none of

these compounds resulted in a consistent and impressive reduction in doxorubicin cardiotoxicity so as to warrant large-scale clinical studies [54].

Cardioactive glycosides and calcium channel blockers have also been tried in small human studies without success. Conversely, the combination of verapamil with doxorubicin has been found to enhance the cardiotoxicity of doxorubicin [55]. This is possibly related to the inhibition of P-glycoprotein by verapamil, which increases the intracellular concentration of doxorubicin both in tumor cells and in cardiomyocytes.

In rats, concomitant administration of superoxide dismutase, catalase, or a combination of the two resulted in reduced toxicity of doxorubicin. Coenzyme Q10, high doses of vitamin E, and N-acetylcysteine have also been found to offer some cardioprotection in rat models of doxorubicin cardiotoxicity.

Another group of agents that are found to be effective in preventing doxorubicin cardiotoxicity is the dioxopiperazine derivatives [56]. Use of dexrazoxane permitted higher cumulative doses of Doxorubicin, and the incidence of congestive heart failure was 3% in the patients treated with dexrazoxane compared with 22% in the control patients [57]. There is some evidence that dexrazoxane administration, when started early in the course of doxorubicin therapy, might decrease the antitumor effect of the chemotherapy.

Cardiotoxic analogues:

Considerable efforts have been made to develop anthracycline analogues with higher therapeutic/toxicity ratios. Despite some promising data in animal models, no single analogue has been found to be consistently free of cardiotoxicity at equivalent antitumor doses. Quelamycin (triferric Doxorubicin) resulted in acute iron toxicity and acute cardiotoxicity. Smaller trials have shown less cardiotoxicity compared with Doxorubicin for the treatment of leukemias. Mitoxantrone is an aminoanthraquinone and is effective against leukemia, lymphomas, and breast cancer. The cardiotoxic potential of mitoxantrone is not fully resolved, although the degree of such toxicity appears to be less than that of Doxorubicin [58]. The search for an anthracycline agent free of cardiotoxicity continues.

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