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Doxorubicin: Insights into Dynamics, Clinical Uses and Adverse Effects

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Abstract Doxorubicin (DOX) is one of the anthracycline antibiotics that is used frequently for treatment of various types of malignancies including lung, breast and testicular cancers. DOX reacts with DNA by intercalation and inhibits the synthesis of DNA macromolecular components. Also, it may increase the production of free radicals which may contribute to its cytotoxicity. DOX may cause serious adverse effects including cardiotoxicity, hepatotoxicity and testicular toxicity. So, it has become increasingly important to find pharmacological remedies to protect against these serious adverse effects. This mini-review sheds light on DOX including its history, dynamics, clinical uses and adverse effects.

Keywords: *doxorubicin, dynamics, uses, toxicity*

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1. Introduction

Cancer is a group of diseases characterized by unregulated growth of the body cells. The use of the traditional anticancer agents such as 5-fluorouracil, methotrexate, adriamycin and cisplatin was faced by their harmful adverse effects [1]. Doxorubicin (DOX), also known as adriamycin, is a medication used for cancer chemotherapy. It is derived by chemical semisynthesis from bacteria. It is an anthracycline antitumor antibiotic closely related to the natural product daunomycin [2]. Like all anthracyclines, it works by intercalating DNA which inhibits the synthesis of DNA macromolecular components. This inhibits the progression of topoisomerase II, an enzyme which is vitally important for DNA transcription. Moreover, DOX may increase the production of free radicals and reactive oxygen species, which in turn will contribute to its cytotoxicity [3]. Also, it was suggested that DOX increases the production of ceramide which might be specifically involved in sensitizing cancer cells to the cytotoxic effects of DOX [4,5]. The most serious adverse effects of DOX include life-threatening cardiotoxicity, hepatotoxicity and nephrotoxicity [6]. It is commonly used in the treatment of a wide range of cancers, including hematological malignancies, solid tumors and soft tissue sarcomas. It is often used in combination chemotherapy as a component of various chemotherapy regimens [7,8].

2. History of DOX

In the 1950s, an Italian research company, Farmitalia Research Laboratories, began an organized effort to find anticancer compounds from soil-based microbes. A soil sample was isolated from the area surrounding the Castel del Monte. A new strain of Streptomyces peucetius, which produced a red pigment, was isolated and an antibiotic from this bacterium was effective against tumors in mice. Since a group of French researchers discovered the same compound at about the same time, the two teams named the compound daunorubicin, combining the name Dauni, a pre-Roman tribe that occupied the area of Italy where the compound was isolated, with the French word for ruby, rubis, describing the color. Clinical trials began in the 1960s, and the drug was successful in treating acute leukemia and lymphoma. However, by 1967, it was recognized that daunorubicin could produce fatal cardiac toxicity [9].

Researchers soon discovered that changes in biological activity could be made by minor changes in the structure of the compound. A strain of Streptomyces was mutated producing a different, red-colored antibiotic. They named this new compound Adriamycin and the name was later changed to doxorubicin to conform to the established name. Doxorubicin showed better activity than daunorubicin against mouse tumors, and especially solid tumors. It also showed a higher therapeutic index, yet the cardiotoxicity remained [10].

3. Chemical Structure of DOX

(7S,9S)-7-[(2R,4S,5S,6S)-4-amino-5-hydroxy-6-methyloxan-2-yl]oxy-6,9,11 trihydroxy-9-(2-hydroxyacetyl) -4-methoxy-8,10-dihydro-7H-tetracene-5,12-dione.

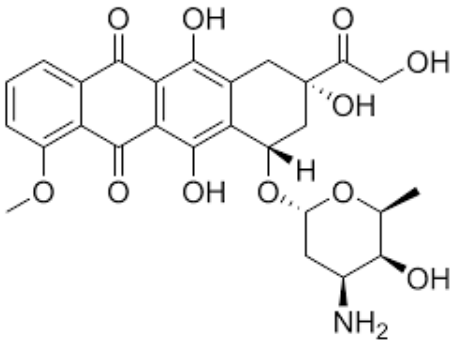

Figure 1. Chemical structure of doxorubicin [11]

4. Pharmacokinetics of DOX

DOX has an oral bioavailability of 5%. Its plasma protein binding is 75 %. It is metabolized mainly in the liver. After intravenous administration, it has a triphasic biological half-life at 12 minutes, 3.3 hours, 30 hours. Its mean plasma half-life is 1-3 hours. It is excreted in urine (5-12%) and faeces (40-50%) [12].

5. Mechanisms of Action of DOX

DOX interacts with DNA by intercalation and inhibition of macromolecular biosynthesis. This inhibits the progression of the enzyme topoisomerase II, which relaxes supercoils in DNA for transcription. DOX stabilizes the topoisomerase II complex after it has broken the DNA chain for replication, preventing the DNA double helix from being resealed and thereby stopping replication [13]. It may also increase quinone type free radical production, hence contributing to its cytotoxicity. By intercalation, DOX can also induce histone separation from the transcriptionally active chromatin leading to deregulation of DNA damage response, epigenome and transcriptome in DOX-exposed cells [14].

6. Medical Uses of DOX

DOX is commonly used to treat some leukemias and Hodgkin's lymphoma, as well as cancers of the bladder, breast, stomach, lung, ovaries, thyroid, soft tissue sarcoma, multiple myeloma, and other malignant tumors [8]. Commonly used doxorubicin-containing regimens are AC (Adriamycin, cyclophosphamide), TAC (Taxotere), ABVD (Adriamycin, bleomycin, vinblastine, dacarbazine), CHOP (cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone) and FAC (5-fluorouracil, adriamycin, cyclophosphamide). There is some evidence for antimalarial activity for doxorubicin and similar compounds. In 2009, a compound similar in structure to doxorubicin was found to inhibit plasmepsin II, an enzyme unique to the malarial parasite Plasmodium falciparum [15].

7. Adverse Effects of DOX

The most dangerous side effect of DOX is cardiomyopathy leading to congestive heart failure. The rate of cardiomyopathy is dependent on its cumulative dose. There are several mechanisms by which DOX is believed to cause cardiomyopathy, including oxidative stress, downregulation of genes for contractile proteins, and p53 mediated apoptosis [16]. Shi et al. [17] attributed DOX-induced cardiotoxicity to abnormal protein processing, hyperactivated innate immune responses, inhibition of neuregulin-1/ErbBsignalling, impaired progenitor cell renewal/cardiac repair, and decreased vasculogenesis.

Another common and fatal complication of DOX is typhlitis, an acute life-threatening infection of the bowel [18]. Some patients may develop allergic reactions characterized by skin eruptions on the palms of the hand or soles of the feet, swelling, pain, and erythema. DOX-containing regimens can cause reactivation of hepatitis B infection and dyspigmentation [19].

7.1. Doxorubicin-induced Cardiotoxicity

Induction of production of free radicals is the best described mechanism through which DOX injures the myocardium. The heart's unique vulnerability to oxidative stress has given this aspect of DOX-induced cardiomyopathy an overwhelming prominence in the literature. DOX is retained in the mitochondrial inner membrane by forming a nearly-irreversible complex with cardiolipin which is required for the the functions of the proteins of the electron-transport chain. This leads to disruption of the cardiolipin–protein interface leading to superoxide (O_2−) formation [20]. Other membrane proteins, such as those responsible for the transfer of carnitine, can also be affected by doxorubicin, contributing to the decrease in mitochondrial function. Moreover, it was reported that the binding of DOX to eNOS (nitric oxide synthase) reductase domain results on O_2− generation. Also, DOX has a strong affinity for iron, and that the iron complex could cause lipid peroxidation through its interactions with the negatively-charged membranes. This sets up a cycle for free radical generation and the metabolite doxorubicinol is known to interact with thiol groups on proteins, leading to severe damage to the cardiomyocytes [21].

DOX-induced cardiotoxicity is also accompanied by an increase in intracellular calcium levels. Dysregulation of intracellular calcium concentrations is both a result and a cause of ROS-generation. DOX-mediated ROS generation and apoptosis can be inhibited by using a Ca^{2+} chelator. The ROS can alter normal calcium homeostasis in a variety of muscle cell types via disruption of normal sarcoplasmic reticulum function. This is accomplished by inhibiting the Ca^{2+} ATPase pump resulting in impaired Ca2+ handling and/or by directly activating the ryanodine calcium-release channels themselves [22]. DOX was reported to induce release of calcium from the sarcoplasmic reticulum by increasing the probability that

the channel adopts the open state. H2O2 generated by DOX can modify key thiol groups on the ryanodine Ca^{2+}-release channels in the sarcoplasmic reticulum contributing to DOX-induced cardiomyopathy. Also, DOX increases sensitivity of the mitochondria to intracellular calcium leading to disruption of mitochondrial functions [21].

Both cellular and extracellular factors have an important role in the complex process of myocardial remodeling. DOX was proven to induce significant alterations in the structure and composition of the extracellular matrix contributing to the development of heart failure. It has been shown that DOX enhance the production of matrix metalloproteinases-2 and -9 (MMP-2, MMP-9) in the heart [23]. This is believed to contribute to cardiomyopathy by weakening the collagenous matrix against which the cardiomyocytes work and contributing to pathological remodeling. Both MMP-2 and MMP-9 activities are enhanced by DOX-induced ROS generation. Tissue-inhibitor of metalloproteinase-3 (TIMP, the family which includes MMP-2 and MMP-9) also decreased after DOX administration which is consistent with the apparent increase in MMP-2 and MMP-9 activity in earlier studies [24].

7.2. DOX-induced Hepatotoxicity

The mechanisms underlying DOX-induced hepatic dysfunction are not yet completely elucidated. However, oxidative stress is suggested to be the major cause of DOX-induced hepatotoxicity [4]. Oxygen-free radicals produced during the metabolic activation of DOX may have toxic effects on the hepatocytes, possibly by decreasing the levels of the antioxidant enzymes in the hepatic tissues such as catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) [25]. Also, it was reported that the extrinsic and intrinsic apoptotic responses mediated by Fas and Bax, respectively, were associated with the acute toxic effects of DOX on the hepatic tissues [5]. Moreover, induction of the inflammatory cascade was proven to play a vital role in the pathogenesis of DOX-induced hepatotoxicity [26]. DOX was reported to induce the expression of the acute phase proteins such as C-reactive protein and the proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin 6 in Kupfer cells which in turn may induce severe inflammatory reactions in the parenchyma of the liver leading to significant hepatic dysfunction [27].

8. Conclusion

DOX is one of the most important anticancer drugs that was proven effective for management of breast, head and gastrointestinal malignancies. Its use is limited by its possible cytotoxicity mediated by its effect on oxidative stress and the proinflammatory cytokines. Further studies are needed to develop strategies for prevention of DOX-induced cytotoxicity.

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