A Comprehensive Review on Doxorubicin and it's Mechanism of Action

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ABSTRACT

Doxorubicin has been a widely used anti-neoplastic drug for solid and hematogenous cancer since the 1950s, but its use is now restricted because of its toxic effects on various organs. The generation of free radicals is the primary cause of the toxicity. It is evident that the first and foremost organ affected by doxorubicin is the heart, and further, it causes toxic effects in the hepatic, kidney, reproductive organs, adipose tissue, and brain. Through the control of various signaling and biochemical events, this review aims to present recent research on the molecular mechanisms underlying doxorubicin-induced toxicity among various organs.

Keywords: Doxorubicin, Daunorubicin, anthracyclines, topoisomerase II, cardiotoxicity, Brain, Kidney, cancer, Adverse effects, Injection, Novel drug delivery.

1. Introduction

Anthracyclines are the most widely prescribed of the 132 anticancer medications that the US Food and Drug Administration (FDA) has approved (1). Traditional anthracycline-containing regimens, which have been a mainstay of therapy for several decades, demonstrate advantages in terms of response rate, time to disease progression, and overall survival. Early in the 1960s, the pigment-producing Streptomyces peucetius yielded the first two anthracyclines, doxorubicin (DOX) and daunorubicin (DNR), both of which contained aglyconic and sugar moieties. The aglycone is made up of a short side chain with a carbonyl group, a methoxy substituent, and a tetracyclic ring with adjacent quinone-hydroquinone groups. The sugar, known as daunosamine, is joined to one of the rings by a glycosidic bond and is made up of a 3-amino-2,3,6-trideoxyL-fucosyl moiety (2). Chemotherapy medications can be categorised based on many of characteristics, such as their chemical makeup and intended use. Alkylating substances directly damage DNA, preventing the tumour cells from proliferating. Antimetabolites replace the normal building blocks necessary for normal DNA replication and transcription, interfering with the synthesis of DNA and RNA. Antitumor antibiotics (anthracyclines) can act regardless of the cell cycle phase, though mitotic cells are the preferred target because they interfere with the enzymes involved in DNA replication. Topoisomerase inhibitors prevent the enzyme from separating the double strands of DNA, whereas mitotic inhibitors are naturally occurring substances that prevent mitosis by typically interacting with and disrupting the microtubule spindle machinery promoting mitosis(3).Its main effects include inhibiting topoisomerase I and II and intercalating into DNA to prevent it from unwinding properly, which

ultimately results in programmed cell death. DOX is a type of anthracycline antibiotic prototype molecule. While DOX is effective against the majority of solid tumours, including breast, thyroid, ovary, bladder, and lung cancers, sarcomas, and neuroblastoma, it is primarily used to treat acute leukaemias and lymphomas(3).

Doxorubicin-brief background

Doxorubicin is one of the most potent chemotherapeutic medications that the Food and Drug Administration has approved, and it has shown significant therapeutic potential in its unaltered form(4). The only drawback is its toxicity on non-cancerous cells in the human body, but it has been widely acknowledged for decades that it has the ability to oppose rapidly dividing cells and slow the progression of disease. The drug has aglyconic and sugar moieties and is a nonselective class I anthracyline. The aglycone consists of a tetracyclic ring with adjacent quinine-hydroquinone groups, a short side chain with a methoxy substituent, and a carbonyl group. A glycosidic bond holds the sugar component, also known as daunosamine, to one of the rings. A 3-amino-2,3,4-trideoxy-L-fucosyl moiety creates up this(5).

Doxorubicin metabolism

Doxorubicin's pharmacokinetics have been the subject of numerous studies evaluating the effectiveness of single- or multi-agent therapy against a wide range of tumour types. The majority of these studies have demonstrated the multiphasic disposition of doxorubicin following intravenous injection. When administered intravenously, a triphasic plasma clearance is frequently the next step. This results in a doxorubicin distribution half-life of 3-5 min, demonstrating the drug's quick uptake by cells. When administered intravenously, a triphasic plasma clearance is frequently the next step. This results in a doxorubicin distribution half-life of 3-5 min, indicating the drug's quick uptake by cells. The terminal half-life of doxorubicin, which is 24-36 h, indicates that it takes doxorubicin much longer to exit the tissue than it does to enter it(6). To lower the risk of toxicity, the drug must be distributed in a steady state. The range of steady distribution is between 500 and 800 l/m2, allowing for a significant uptake of doxorubicin by body tissues. The rate of systemic clearance is noticeably slower in obese women. The plasma concentration shows levels of doxorubicinol rapidly increasing and depleting parallel to doxorubicin levels after a bolus injection of the drug. Doxorubicinol will eventually surpass doxorubicin in concentration if drug infusion levels are maintained for an extended period of time (6).

Types of cancers that are treated with doxorubicin:

1 Cervical cancer(7)

2. Endometrial cancer(8)

3. Pancreatic cancer(9)

4. Head &neck cancer(10)

5. Adrenal cortex cancer(11)

6. Skin cancer &mucous membrane (usually in patients suffering from AIDS-Kaposi sarcoma(7)

7. Bone cancer-osteosarcoma, Ewings sarcoma (12)

8. Lung cancer (13)

9. Breast cancer (14)

10. Stomach cancer (15)

11. Thyroid cancer (16)

Adverse effects of Doxorubicin:

Cardiotoxicity, Radiosensitive, Bone marrow depression, Nausea, vomiting, ulceration, Hair loss hyperpigmentation of the skin, Nephrotoxicity, Cardiomyopathy leading to congestive heart failure, Tachycardia, low blood pressure (17,18).

Doxorubicin Toxicity:

Doxorubicin-induced cardiotoxicity:

 One of the most crucial and widely acknowledged mechanisms for doxorubicin-induced cardiotoxicity is oxidative stress. The production of ROS and RNS inside the cardiomyocytes, as well as the antioxidant defence system's failure to completely eliminate the oxidative stress that resulted from the administration of doxorubicin, have led to a cytological imbalance(19). It has been determined that doxorubicin dosages greater than 500 mg/m2 also cause oxidative stress on the body's surface area(20). ROS are produced as a result of the non-enzymatic formation of the (Fe2)-doxorubicin complex, which causes lipid peroxidation. The membrane potential is disturbed when lipid peroxidation begins(21). Malondialdehyde (MDA), which is the byproduct of lipid peroxidation, is present in high levels during lipid peroxidation(22). The accumulation of the transition metal iron (Fe) due to the degraded membrane potential leads to an imbalance in cellular homeostasis, and mitochondria play a role in this(23) The concept is that an iron chelator would prevent Fe from building up inside of cells and lessen the chance of doxorubicin cardiotoxicity(24).

Doxorubicin-induced brain:

Brain When investigating doxorubicin-mediated brain toxicity, it's critical to keep in mind that damage to the brain results directly from doxorubicin's inability to cross the blood-brain barrier(25,26). Doxorubicin increases TNF-a production, which causes the brain's microglial cells to release inflammatory cytokines. Reactive nitrogen species (RNS) levels increase when TNF-a is produced in excess because it stimulates the expression of inducible nitric oxide synthase (iNOS)(27). The surrounding proteins, such as manganese superoxide dismutase (MnSOD), go through nitration as RNS levels rise steadily. The protein undergoes nitration, which stimulates the production of ROS and increases the permeability transition pore in the mitochondria. Cell death occurs via apoptosis when the mitochondrial pores release cytochrome c. These behaviours are ultimately responsible for the various brain regions that experience cognitive impairment(28). Patients typically exhibit signs of memory and visuospatial impairment, but after a year without doxorubicin therapy, the majority of cognitive functioning is recovered(29).

Doxorubicin-induced kidney:

Doxorubicin is known to cause proteinuria and nephropathy when kidney toxicity occurs by harming glomerular podocytes(30-35). When the drug disrupts the mitochondria's normal operation by lowering the activity of complexes I and IV, it causes doxorubicin-induced nephropathy. Lipid peroxidation results from this, which raises levels of triglycerides, superoxides, and citrate synthase while lowering levels of vitamin E and antioxidant compounds. When proteins from nearby passages come into contact with exposed renal tissue, the structure of the nephron is changed, ultimately resulting in glomerulosclerosis. The glomeruli-affecting disease is known to result in proteinuria, hypertension, and steroid resistance as well as eventually cause renal failure. The kidney can't regenerate as well as the liver, which limits its capacity to repair itself when the glomeruli are damaged (4). Due to the kidney's crucial function in controlling the chemical composition of blood and preserving fluid balance, this increases the body's susceptibility to damage overall. Damage to the glomeruli prevents it from carrying out its essential functions, leading to glomerular lesions, inflammation, tubular dilation, and changes in capillary permeability.

Doxorubicin as injection

The intravenous route of administration for DOX uses the hydrochloride salt form. The medication is known as DOX hydrochloride injection(36). ABVD (Adriamycin, bleomycin, vinblastine, dacarbazine), BEACOPP, CHOP (cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone), and FAC (5-fluorouracil, adriamycin, cyclophosphamide) are other DOX-containing medications that are frequently used(37). By altering the drug's pharmacological distribution, which lowers the amount of drug in the heart, drug carriers have been used to lessen the toxicity connected with the administration of DOX. A liposomal (lipid-based) formulation is an illustration of such a carrier because it significantly changes the biodistribution of DOX (38).

Novel Drug Delivery of DOX

Liposomal Formulations

Chemotherapy is known chemically as liposomal DOX. Liposomal DOX is available under the trade names Doxil, Caelyx, or Myocet(39). The active ingredient in this medication, DOX (Adriamycin), is encapsulated in a tiny, spherical phospholipid molecule known as a liposome (40). It is used to treat several different types of cancer, including:

Ovarian cancer

Breast cancer

Multiple myelomas

Kaposi's sarcoma is a particular kind of sarcoma.

The development of liposomal DOX was based on the fundamental idea that while liposomes cannot leave the circulation in tissues and organs lined with tightly joined cells, such as heart muscle, they can do so in tissues and organs with loosely joined cells, such as tumor cells(41). In order to deliver more drugs to the cancerous cells, these spheres maintain the level of DOX in the blood for a longer period of time. Therefore, liposomal encapsulation causes anthracyclines to concentrate preferentially in tumor tissue while limiting exposure in areas that are most frequently associated with traditional DOX toxicity, like the myocardium(40).

Due to the negative effects of traditional DOX therapy, it became necessary to create liposomes with comparable efficacy and fewer side effects. Phospholipids are used to create the vesicles that make up liposomes. These phospholipids are isolated from organic materials that are typically safe for human consumption, such as soybeans or egg yolks. Additionally, by adjusting the phospholipid bilayer's degree of saturation, the rate at which liposomes release drugs can be changed. Natural phospholipids mixed with various cholesterol concentrations form liposomes, which are then removed from the bloodstream by the reticuloendothelial system (RES) within a few minutes to several hours after opsonins are captured from plasma. The restricted clinical applications of conventional liposomes are a result of their short circulation half-life (42).

Liposomal DOX is divided into:

1. Pegylated (polyethylene glycol coated) liposomal formulation of DOX.

2. The non-pegylated liposomal formulation of DOX.

LIST OF ABBREVIATIONS

FDA - Food and Drug Administration

DOX-Doxorubicin

MDA- Malondialdehyde

TNF-a- Tumor necrosis factor

RNS - Reactive nitrogen species

iNOS - inducible nitric oxide synthase

 MnSOD-manganese superoxide dismutase

CHOP- Cyclophosphamide, Hydroxy daunorubicin, Vincristine, Prednisone

FAC- 5-fluorouracil, Adriamycin, Cyclophosphamide

RES- Reticuloendothelial System

CONCLUSION:

Doxorubicin or Adriamycin is a multifaceted drug having multiple intracellular targets at low concentrations and can enhance the immunogenicity of infected cells. The time-tested drug is still being preferred as a first-line chemotherapeutic drug in combination or alone, for a large number of cancers to date. Side effects and the development of chemoresistance has become the major undermining factor. Doxorubicin&39's precise methods of action are complex and yet largely unknown, but it is already known that, among other things, this anticancer medication intercalates into DNA, inhibits topoisomerase II, damages mitochondria, and amplifies the production of free radicals and oxidative damage. Several attempts have been made to decrease Doxorubicin side effects, such as the administration of compounds with antioxidant and/or anti-apoptotic activity, the development of efficacious delivery systems, and the production of Doxorubicin analogs. However, some of these strategies failed to alleviate anthracycline toxicity in clinically relevant animal models or clinical trials. Efforts should be employed in the search for more effective strategies against Doxorubicin toxicity while preserving or enhancing its therapeutic effects. A complete understanding of the drug resistance mechanism and factors that could possibly be controlled or manipulated to promote the chemosensitization effect would be vital in combating chemoresistance and improving cancer therapy which provides quality of life for cancer survivors.

AUTHOR CONTRIBUTIONS

Conceptualization, Ramica Sharma, Harkiran Kaur, Diksha Verma; Writing-original draft preparation, Harkiran Kaur; Writing –Review& Editing, Ramica Sharma, Diksha Verma. All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST

There are no conflicts of interest between the authors.

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