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Review article

Doxorubicin Side Effects and Its Uses a new update: A narrative review

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Abstract

Background: Doxorubicin is considered one of the best drugs used to treat leukemia, but it has many other uses such as Antimalarial effect and anticancer in general. In this research, we will talk about Doxorubicin, its uses, and treatment methods, in addition to its side effects, especially the cardiotoxicity side effect, and related effects on the heart.

Object: To summarize the uses and side effects of new dosage forms of doxorubicin

Materials and Method: We searched by using Google Scholar and PubMed sites and used several Keywords such as Doxorubicin is a mechanism of action, Doxorubicin toxicity and side effects, and new uses of doxorubicin and from a total of 180 studies, we got 40 articles that included side effects and problems that could result from it. We excluded the use of doxorubicin cardiotoxicity in heart patients, pregnant women, and other uses.

Results: Adriamycin or Doxorubicin this medication is categorized as an antimetabolite or anti-tumor medication. By interfering with DNA, act by inserting and preventing the formation of macromolecules, doxorubicin interacts with DNA, doxorubicin used for the treatment of leukemia, and antimalaria drug, with several side effects such as hair loss.

Conclusion: We concluded that Doxorubicin, despite its side effects, is still used in the treatment of many Diseases, as it has been proven to be effective up to 90% for treating leukemia and some other diseases. As you know, leukemia is a type of cancer.

Keywords: Doxorubicin; Neoplasms; Antimetabolites; Leukemia.

INTRODUCTION

Cancer continues to be the leading cause of death worldwide, taking the lives of over 6 million people annually. [1] Because the medications have adverse effects on healthy tissues, it has been determined that cancer chemotherapy is not safe. Doxorubicin, often known as Adriamycin, is a common form of chemotherapy medication that belongs to the anthracycline group of antibiotics. Originating from the bacteria Streptomyces paucities. [2] Anthracyclines, such as Doxorubicin (DOX), which was discovered about fifty years ago, are regarded as the mainstay of chemotherapy regimens that can save lives. [2]. Heart-related harm was noted and documented shortly after its debut [3]. The pathophysiology of cardiotoxicity remains unclear despite decades of usage and research on this family of medications. Doxorubicin is mostly used to treat lymphomas, leukemias, and other solid tumors like lung, breast, and ovarian cancer. It is quite successful against a variety of cancers. Thyroid gland, among other things. [4] Doxorubicin has its own dose-dependent cytotoxicity on the heart and other organs, which is comparable to the side effects of other anticancer medications. [5] Both therapeutic benefits and hazards may result from doxorubicin-induced apoptosis [6]. Doxorubicin has a good effectiveness rate; however, a major negative effect of treatment is cardiotoxicity. Furthermore, anthracyclines may result in myelosuppression, mouth ulcers, and hair loss [7,8]. One of the most popular anticancer medications is Doxorubicin [9]. The main thing stopping this medication from being used is the development of cardiotoxicity. For instance, congestive heart failure was more common in patients receiving high doses of Doxorubicin in a trial involving 399 patients (>18%). Although the exact processes underlying doxorubicin-induced cardiomyopathy remain unclear, a substantial amount of evidence points to the involvement of heart inflammation and oxidative stress [10].

MATERIALS AND METHOD

We searched by using Google Scholar and PubMed sites and used several Keywords such as Doxorubicin is a mechanism of action, Doxorubicin toxicity and side effects, new uses of Doxorubicin and from a total of 180 studies; we got 40 articles that included side effects and problems that could result from it. We excluded the use of doxorubicin cardiotoxicity in heart patients, pregnant women, and other uses.

RESULT

Adriamycin or Doxorubicin this medication is categorized as an anthracycline drug , an antitumor medication. By interfering with DNA, the genetic material found in cells, it stops the growth of tumor cells. This could result in the emergence of some negative effects because it might also have an impact on the formation of healthy body cells. Even yet, most of the time, some adverse effects do not manifest. However, when it manifests, a medical follow-up can be necessary [11]. The Doxorubicin is called the anthracycline group because Doxorubicin contains an anthracycline nucleus . The picture 1 shows the structure of Doxorubicin.

Mechanism of action

Act by inserting and preventing the formation of macromolecules, Doxorubicin interacts with DNA [12]. Topoisomerase II, which unravels DNA supercoils, is inhibited by this activity. Doxorubicin stabilizes topoisomerase II and stops the DNA double helices from rejoining, which stops the replication process after topoisomerase II unwinds the DNA strands for replication [13-15]. The six-carbon amino sugar resides in the minor groove and interacts as numerous crystal structures with the base pairs right next to the insertion site of the planar aromatic molecule's chromophore, which is placed between two DNA base pairs. evidence [16,17]

Anticancer Effect

Doxorubicin is one of the best chemotherapies used in the treatment of Leukemia, especially Acute lymphoblastic Leukemia, and it's effective to induce complete remission in about 90-95 percent of leukemic patients with ALL. Moreover, Doxorubicin shows effects against different types of cancer, such as Breast cancer and bone and many others [20].

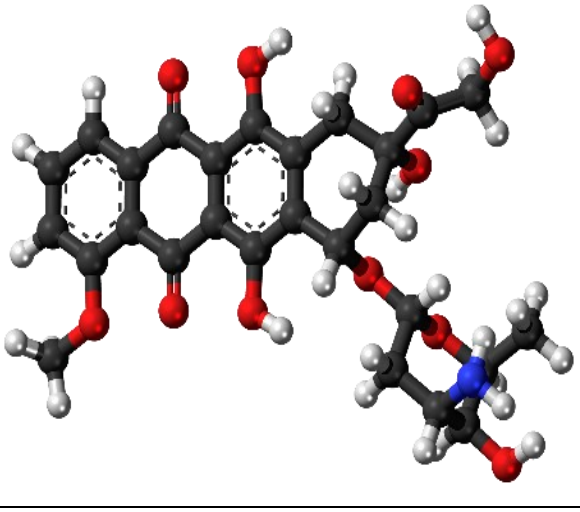

Figure 1 structure of Doxorubicin

Antimalarial effect

There is evidence that doxorubicin and related substances have antimalarial properties. Compounds resembling Doxorubicin in structure were discovered in 2009 to block plasmepsin II, an enzyme exclusive to the malaria parasite Plasmodium falciparum [18]. Subsequently, the pharmaceutical company GlaxoSmithKline (GSK) discovered that substances resembling Doxorubicin can stop parasite growth [19].

Side effects

Acute side effects of Doxorubicin include nausea, vomiting, and cardiac arrhythmias. It can also cause neutropenia and complete hair loss [20]. Another milder side effect is urine discoloration - urine will turn bright red 48 hours after dosing. When the cumulative dose of Doxorubicin reaches 500-550 mg/m², the risk of side effects, including congestive heart failure (CHF), dilated cardiomyopathy, and even death, increases significantly [20]. The cardiotoxicity of Doxorubicin is characterized by a dose-dependent decrease in mitochondrial oxidative phosphorylation [21,22]. The reactive oxygen species generated by the interaction between Doxorubicin and iron can damage the myocardium, causing the loss of myofibrils and vacuolization of the cytoplasm. In addition, some patients may develop PPE, which is characterized by skin rash, swelling, pain, and erythema on the palms or soles of the feet [20] Due to these side effects and red color of doxorubicin solution that reflect red color of urine and other physiological fluid such as due to these symptoms, Doxorubicin has the title of "Red Devil" [23] or "Red Death" as shown in figure 2 [24]. Chemotherapy can trigger hepatitis B, and regimens containing Doxorubicin are no exception. [22].

Figure 2 show doxorubicin (red color)

doxorubicin and some chemotherapy drugs can cause pigmentation abnormalities, including cyclophosphamide, antimalarial drugs, amiodarone, heavy metals (except iron), tetracyclines, and antipsychotic drugs.

Liposome dosage forms

Doxil is polyethylene glycol (polyethylene glycol-coated)liposome-encapsulated form of Doxorubicin that was developed to treat Kaposi's sarcoma, AIDS-related cancer that causes tumors in the mouth and nose. The lining of the throat, subcutaneous, or other organs develop lesions and grow. The polyethylene glycol coating causes Doxil to preferentially accumulate in the skin. However, this also comes with the side effect of erythrodysesthesia (PPE), or Hand-Foot Syndrome. The following is how to use Doxil: A small amount of the drug can leak from the capillaries into the palms and soles of the hands, causing redness, swelling, pain, discomfort and even pain caused by skin peeling. In clinical trials, 50.6% of patients developed hand-foot syndrome if a dose of 50 mg/m2 was given every 4 weeks. This side effect limits the combination therapy of Doxil with Doxorubicin, thereby limiting the substitution possibilities of Doxil. The

replacement of Doxil is worth looking forward to because the cardiotoxicity of liposome-encapsulated Doxorubicin is lower than that of unencapsulated Doxorubicin. Doxil is also approved by the FDA to treat ovarian cancer and multiple myeloma. [25]

Myocet is a non-pegylated liposomal doxorubicin that is approved in Europe and Canada in combination with cyclophosphamide for the treatment of metastatic breast cancer but has not yet been approved by the FDA for use in the United States [26]. Sopherion Therapeutics' development of it is currently entering a critical global Phase III, using both trastuzumab and Paclitaxel to treat HER2-positive metastatic breast cancer [27]. Unlike Doxil, Myocet liposomes are not coated with polyethylene glycol and, therefore, do not cause hand-foot syndrome. Reducing this side effect allows it to be used to provide an alternative to Doxorubicin in the same therapy, thereby increasing safety without reducing efficacy like Doxil, liposome encapsulation of doxorubicin limits cardiotoxicity. In theory, using liposomes to encapsulate Doxorubicin to limit its cardiotoxicity can be safely treated simultaneously with other cardiotoxic chemotherapy drugs, such as trastuzumab. However, the FDA issued a black box warning stating that trastuzumab cannot be used with Doxorubicin for simultaneous treatment and can only be used for continuous treatment. Although concomitant treatment with trastuzumab and Doxorubicin produced superior antitumor responses in clinical studies, it was associated with unacceptable cardiotoxicity, including the risk of heart failure leading to congestive heart failure (CHF). According to the published results of the second phase of the study, Myocet, trastuzumab, and Paclitaxel can be safely used for simultaneous treatment without the risk of cardiac side effects and can take advantage of thein left ventricular ejection fraction (LVEF) function. This discovery is the basis for the FDA to approve the Phase III trial [28].

Doxorubicin cardiotoxicity

Since DOX was discovered in 1969 and its therapeutic use started in the early 1970s, DOX-induced cardiotoxicity has drawn more and more attention [23]. Even though DOX is one of the most potent anticancer medications on the market and has been used in clinical trials for over 40 years, its use is severely limited due to its irreversible cardiotoxicity [20] and potential for clinical manifestations of cardiotoxicity. Acute and chronic cardiac damage caused by DOX. The frequency of doxorubicin-induced cardiotoxicity varies greatly. Acute cardiac effects include arrhythmia, hypotension, and several ECG abnormalities [20], which go away when medication is stopped [22]. Acute cardiac effects are clinically manageable and frequently reversible, occurring in 11% of patients shortly after starting treatment. Just 1.7% of individuals receiving DOX treatment experience chronic side effects, and the death percentage is 50%. Congestive heart failure is the eventual result of dose-dependent chronic cardiac damage caused by DOX [15].

Mice given chronic DOX for seven weeks were shown to have hypertrophied hearts [16]. According to multiple additional significant investigations, these conclusions were validated by in vitro experiments that demonstrated DOX induces cardiomyocyte enlargement in primary cardiomyocytes of neonates [29]. Doxorubicin produces reactive oxygen species (ROS) such as hydroxyl radicals, superoxide, and hydrogen peroxide, which disrupt mitochondrial activity and cause damage to cardiomyocytes [22].

Because cardiomyocytes contain free radicals, they are more susceptible to the harm that Doxorubicin causes to cardiac cells. Antioxidant enzymes like catalase and superoxide dismutase (SOD) are present in comparatively modest amounts in it [22]. These enzymes offer protection by breaking down hydrogen peroxide into oxygen and water. Thus, doxorubicin-induced ROS in cardiac muscles can be avoided by smothering doxorubicin-induced cardiotoxicity [30].

Research

Combination therapy trials with sirolimus (rapamycin) and Doxorubicin show promise in treating Akt-positive lymphoma in mice [31]. Furthermore, the release of photoactivated Doxorubicin with the help of nanoporous optical antennas produced significant anticancer effects in MCF-7 breasts. Cancer cell. In 2006, animal studies combined mouse monoclonal antibodies with Doxorubicin to create an immune complex that eliminated HIV-1 infection in mice.

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Author contribution

All Authors contribute equally to this article

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Conflict of interest

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