

Review Article

Pharmacological Study and Overcome the Cardiotoxicity Associated with Anticancer Drug Doxorubicin

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ABSTRACT

Doxorubicin, also known as Adriamycin, is an anthracycline drug commonly used in cancer chemotherapy. Adriamycin is being used clinically for solid tumours, e.g. adenocarcinoma of breast, malignant sarcomas, neuroblastoma, ovarian cancer, small lung cancer as well as hematologic malignancies including lymphomas and leukaemias. In this review we can answer different questions from which mainly we focus on that how we can prevent its toxicity and interactions with other agents and which parameters we use for to overcome this. Unfortunately, its therapeutic potential can be limited to cardiotoxicity so for to overcome this liposomal encapsulation of doxorubicin done for to overcome toxicity problems.

However its use has been limited by its major clinical side effect, cardiotoxicity. Toxic effect of Adriamycin can be prevented by using different pharmacologic substances like antioxidants. Adriamycin produces its antineoplastic effect by multiple mechanisms and the exact mechanism of action of Adriamycin is still unknown. The proposed mechanism of the antineoplastic effect of Adriamycin at the cellular level is drug binding to DNA by intercalation between base pairs and inhibition of RNA synthesis by template disordering and steric obstruction.

Keywords: Doxorubicin; Anti-cancer drug; Electron spin resonance; Liposomal encapsulation

Introduction

Adriamycin (Doxorubicin Hydrochloride) is an anthracycline antibiotic which belongs to “duanomycin” family and is produced by fungus *Streptomyces paucities* var. *caecius*. Adriamycin is used against many tumors including solid tumors, some leukaemia's and Hodgkin's lymphoma. Adriamycin act by binding with DNA and inhibits DNA replication and RNA transcription. It has wide spectrum of activity and is being used as standard chemotherapeutic agent against solid tumors including breast cancer, hepatocellular carcinoma, advanced urinary tract cancer ovarian cancer, small lung cancer and hematopoietic malignancies [1].

Adriamycin is actually a naturally occurring substance containing Quinone that is used as antineoplastic drug. Adriamycin precise mechanism of action is not completely described. Some suggested mechanisms for Adriamycin activity include DNA synthesis inhibition, free radical formation, DNA binding and alkylation, DNA crosslinking, interference with DNA strand separation, inhibition of topoisomerase II leading to DNA damage and direct membrane effect [2].

Adriamycin has been administered as frequent low doses (weekly), single high dose, and as a continuous infusion. The optimal schedule with respect to tumour cytotoxicity and dose limiting side effects such as cardiotoxicity has never been investigated in a prospective manner. Clinical trials are large enough to study optimal and possibly individualized doxorubicin chemotherapy need to be performed [3].

Wide interpatient variations in plasma pharmacokinetics have been noted but no firm relation to clinical outcome was observed. An apparent volume of distribution of approximately 25 L/Kg points to extensive uptake by tissues. Several weeks after administration, significant concentrations of doxorubicin in hematopoietic and other tissues have been found. The maximum cellular doxorubicin concentration reached *in vivo* remains significantly below those at which all clonogenic leukemic cells are killed *in vitro* [2,4].

Despite its broad spectrum of activity its use is limited by dose dependent cardiomyopathy. Many recent studies suggest that this cardiac toxicity of Adriamycin is due to cardiac reactive oxygen metabolism which leads to formation of drug induced free radicals (may also explain lipid peroxidation of cardiac membrane) and also the Adriamycin has inhibitory effect on cardiac enzymes to detoxify reactive oxygen metabolites. Sign and symptoms of Adriamycin toxicity are tachycardia, shortness of breath, ankle edema, hepatomegaly, cardiomegaly, neck vein distention and pleural effusion.

Adverse effect can be prevented by using different pharmacologic substances, e.g. vitamin E, a-tocopherol. Ascorbate, Qishenyiqi pills, N-acetylcystein. Vitamin E and ascorbate are antioxidants and inhibit formation of free radicals. Qishenyiqi pills improve cardiac function through inhibition of apoptosis of myocardial cells while N-acetyl cysteine increases non-protein sulfhydryl contents of heart and prevent drug induced cardiomyopathy.

Doxorubicin's Evaluation Several Aspects

Pharmacological observations

To study the relation between clinical and pharmacologic observations, 96 patients treated with Adriamycin were taken (with dosage schedule of 60 mg/m² I.V. for 3 weeks) has found that pharmacokinetics of Adriamycin showed a prolong plasma half-life, low urinary excretion and undetectable levels in CSF. Patients with significant liver impairment showed elevated plasma level of Adriamycin, associated with severe toxicity, so dose reduction is necessary in such patients. Of the 82 evaluable patients, 10/25 with sarcomas, 15/26 with hematologic malignancies, 9/31 with carcinomas achieved complete or partial remission. An additional 22/48 has improved while 6 patients with solid tumours had progressive CNS disease when responding systemically. So Adriamycin can be used with relative safety and high efficacy in a dosage schedule that resulted from pharmacologic studies [5].

Pharmacokinetics and pharmacodynamics study

Studied the pharmacokinetics and pharmacodynamics of Adriamycin in normal healthy patient, plasma extraction technique utilizing Chloroform: isopropyl (1:1) and ammonium sulphate saturation has been used to isolate Adriamycin and its metabolites from human plasma. Adriamycin was the most prominent species in plasma and sex metabolites were isolated from Adriamycin by thin-layer chromatography. Three were aglycones and three were polar metabolites, one of which was identified as Adriamycinol. All metabolites appeared rapidly and disappeared according to biphasic or triphasic pattern. The most prominent metabolite was a less polar aglycon is deoxy Adriamycin aglycon and the least prominent metabolite was Adriamycin aglycon. While demethyl deoxy Adriamycinolaglycon showed variable pharmacokinetics in different patients. The polar metabolites were found in similar relative concentration to those in urine while aglycone metabolites were found to be in significant concentration in plasma and only small amount was present in urine.

Toxicity parameters

Role of oxidative stress: To assess the role of oxidative stress in Adriamycin toxicity, checked lipid metabolites in urinary excretion at 0, 6, 12, 24, 48, 72 h after administration of Adriamycin (single oral administration and IV doses of 10mg/Kg). Urine excretion of malonaldehyde (MDA), formaldehyde (FA), acetaldehyde (ACT) and acetone (ACON) was significantly increased at all-time points examined after administration of Adriamycin. Following oral and IV administration, a significant increase was observed in myocardial and hepatic lipid peroxidation in mitochondrial and microsomal membranes and hepatic and myocardial nuclei DNA single strand break 24 h after administration.

Electron spin resonance: To checked degree of resistance to Adriamycin electron spin resonance spectroscopy was used to analyse the changes in membrane order parameter in sarcoma 180 cells under condition in which an alteration in cellular susceptibility to the chemotherapeutic agent Adriamycin is

demonstrable. While para-magnetic probe 5-doxy1 stearic acid was used to analyse changes in membrane fluidity and was associated with two phenomena which result in changed cellular response to Adriamycin: (1) the presence of oxygen deficient environment and (2) the expression of drug resistance. In hypoxic conditions, susceptibility to Adriamycin is increased and decrease in bulk membrane parameter was observed. Upon reoxygenation, the membrane fluidity and increased susceptibility to Adriamycin reverted to control conditions with the same time course. In drug resistant cells, a progressive decrease in membrane fluidity was observed correlated with the degree of resistance to Adriamycin.

Vitamin E study

Here we discuss the study of the protective effect of Vitamin E, Adult male Sprague-Dawley rats received seven weekly subcutaneous injection of 2 mg/Kg of doxorubicin and fed either standard diet or diet supplemented with alpha-tocopherol succinate. Treatment with accumulated dose of 14 mg/Kg of doxorubicin caused mitochondrial cardiomyopathy as evidenced by histology, accumulation of oxidized proteins and significant decrease in mitochondrial calcium loading capacity. When rat is maintained on this alpha-tocopherol supplemented diet, it resulted in increased level of alpha-tocopherol in cardiac mitochondrial membrane and contents of oxidized cardiac proteins associated with doxorubicin treatment were diminished. However it failed to protect against mitochondrial dysfunction and cardiac histopathology [6].

Salvianolic acid study

Here we studied the protection of Adriamycin toxicity by salvianolic acid A (Sai A), formation of Malonaldehyde and rigidification of membrane were significantly reduced by the use of electron spin resonance it was found that Sai A has no significant effect on formation of Adriamycin semi Quinone radicals (AQ) while hydroxyl radicals generated by electron transfer from AQ to H₂O₂ was scavenged by Sai A dose dependently. And has no effect on antitumor activity of Adriamycin in L1210 ascetic tumour cells and in mice with p388 ascetic tumor.

Adriamycin and its standard preparation's doses

Adriamycin produce antineoplastic effect at frequent low doses (weekly), single high dose, and as a continuous infusion. It is supplied in hydrochloride form as a sterile red-orange lyophilized powder containing lactose and as a sterile parenteral, isotonic solution with sodium chloride for IV use only [7].

Adriamycin (doxorubicin HCL) for injection, USP:

- Each 10mg lyophilized vial contains 10 mg of doxorubicin hydrochloride, USP and 50 mg of lactose monohydrate, NF.
- Each 20 mg lyophilized vial contains 20 mg of doxorubicin hydrochloride, USP and 100 mg of lactose monohydrate, NF.
- Each 50 mg lyophilized vial contains 50 mg of doxorubicin hydrochloride, USP and 250 mg of lactose monohydrate, NF.

Adriamycin (doxorubicin) injection, USP:

- Each 2 mg/ml, 5 ml (10 mg) vial contain 10 mg doxorubicin hydrochloride, USP; sodium chloride 0.9% (to adjust tonicity) and water for injection q.s; pH adjusted to 3 using hydrochloric acid.
- Each 2 mg/ml, 10 ml (20 mg) vial contain 20 mg doxorubicin hydrochloride, USP; sodium chloride 0.9% (to adjust tonicity) and water for injection q.s; pH adjusted to 3 using hydrochloric acid.
- Each 2 mg/ml, 25 ml (50 mg) vial contains 50 mg doxorubicin hydrochloride, USP; sodium chloride 0.9% (to adjust tonicity) and water for injection q.s; pH adjusted to 3 using hydrochloric acid.
- Each 2 mg/ml, 100 ml (200 mg) multiple dose vial contain 200 mg doxorubicin hydrochloride, USP; sodium chloride 0.9% (to adjust tonicity) and water for injection q.s; pH adjusted to 3 using hydrochloric acid.

Preventions

The concentration of doxorubicin decrease exponentially with distance from tumor blood vessels, decreasing to half its perivascular concentration at a distance of about 40 to 50 μm . The mean distance from blood vessels to region of hypoxia is 90 to 140 μm in these tumors. Many viable tumor cells are not exposed to detectable concentration of drug following a single injection. Unfortunately the long term use of this drug is limited due to cardiac toxicity, especially drug-induced congestive heart failure.

Cardiotoxicity Caused by Adriamycin and How to Prevent This???

Doxorubicin cardiotoxicity can be characterized as either type 1 or type 2 cardiotoxicity based on the effect of the agent on cardiomyocytes. Type 1 cardiotoxicity is caused by cardiomyocytes death, either through necrosis or apoptosis, and as a result is not reversible. Type 2 cardiotoxicity is caused by cardiomyocytes dysfunction rather than cell death, and therefore may be reversible. The long term cardiotoxicity caused by the anthracyclines includes cardiomyocyte death and therefore represent a type 1 toxicity Doxorubicin cardiotoxicity can be prevented by liposomal encapsulation, by using different pharmacological substances like, antioxidant, and by limiting the total dose of drug.

As result, Anthracyclines (doxorubicin) remain an important class of drugs in treatment of cancer, but also remain a problematic chemotherapeutic agent given their cardio toxic effects. Close monitoring of patients is essential to decrease the risk of anthracycline-induced cardiotoxicity as is the early implementation of cardio protective therapies, especially in those individuals at increased risk of developing left ventricular dysfunction in response to anthracyclines. The likelihood of avoiding or reducing the cardio toxic effects of these agents while improving the oncological benefits of the therapy can be increased by close collaboration, between the oncologist and cardiologist.

Liposomal Encapsulation

Cardiotoxicity can be prevented by liposomal encapsulation,

There is PEGylated (polyethylene glycol coated) liposomal-encapsulated form of doxorubicin, solid as Doxil. It was developed to treat Kaposi's sarcoma, an AIDS-related cancer that causes lesions to grow under the skin, in the lining of the mouth, nose and throat, or in other organs. The polyethylene glycol coating results in preferential concentration of doxorubicin in the skin. However, this also results in side effects called palmar plantar erythrodysesthesia (PPE), more commonly known as hand-foot syndrome. Following administration of this form of doxorubicin, small amounts of the drug can leak from capillaries in the palms of the hands and soles of feet. The result of the leakage is redness, tenderness, and peeling of the skin that can be uncomfortable and even painful. In clinical testing at 50mg/m² dosing every 4 weeks, half of people developed hand-foot syndrome. The rate of this side effect limits the dose of this formulation that can be given as compared with plain doxorubicin in the same treatment regimen, thereby limiting potential substitution. Substitution would be desirable. Because liposomal encapsulated doxorubicin is less cardio toxic then encapsulated doxorubicin. This form is also approved by FDA for treatment of ovarian cancer & multiple myeloma.

Non-PEGylated Liposomal Doxorubicin

A non-PEGylated liposomal doxorubicin, called myocet, is approved in Europe and Canada for treatment of metastatic breast cancer in combination with cyclophosphamide but has not been approved by the FDA for use in the United States. Unlike Doxil, the myocet liposome does not have a polyethylene glycol coating, and therefore does not result in the same rate of hand-foot syndrome. The minimization of this side effect may allow for one substitution with doxorubicin in the same treatment regimen, thereby improving safety with no loss of efficacy. Like Doxil, the liposomal encapsulation of the doxorubicin limits the cardiotoxicity. In theory, by limiting the cardiotoxicity of doxorubicin through liposomal encapsulation it can be used safely in concurrent combination with other cardiotoxicity chemotherapy drugs, such as trastuzumab.

Combination Therapy

There is an FDA black box warning that trastuzumab cannot be used in concurrent combination with doxorubicin, only in sequential combination. Though concurrent combination of doxorubicin and trastuzumab in clinical study found superior tumor response, the combination resulted in unacceptable cardiotoxicity, including the risk of cardiac failure manifesting as congestive heart failure (CHF). Published phase II study results have shown that myocet, trastuzumab, and paclitaxel can safely be used concurrently without the cardiac risk, as measured by reduction in LVEF function, while still achieving superior tumor response. The finding is the basis for the ongoing phase III trial for FDA approval.

As doxorubicin cardiotoxicity is due to generation of large part of free radicals through mitochondrial redox cycling of doxorubicin in the cardiomyocytes, which ultimately result in left ventricular dysfunction, and in most severe case congestive heart failure (CHF), as a result, effort aimed at decreasing this exogenous oxidant stress may decrease the cardiotoxicity.

Reduction of this oxidative stress from circulating anthracyclines can be achieved through variety of mechanism. THE antioxidant, probucol, has been shown to prevent the decrease in LVEF in animal model of doxorubicin cardiotoxicity. The beta-adrenergic blockers, carvedilol, doxorubicin-induced left ventricular dysfunction through its anti-oxidant properties. Interestingly, the anti-oxidant properties of vitamin E have been shown too ineffective in preventing the left ventricular dysfunction in animals treated doxorubicin. And the third one by limiting the dose of drug, for patients with previous cardiac radiation therapy, a limited dose of 400 mg/m² is suggested.

For patients without other significant risks factors, such as advanced age (more than 70 years old) or previous left ventricular dysfunction, a limited dose of 500 to 550 mg/m² is suggested.

Conclusion

Doxorubicin (Adriamycin) produces antineoplastic effects at a low dose, single high dose or continued infusion; it has better activity, especially in solid tumor. It also showed a higher therapeutic index, as compare to some other anticancer drug like daunorubicin, with minor change in its structure, yet the cardiotoxicity remained.

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