

Review Article

Heart Failure Due to Doxorubicin

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ABSTRACT

Doxorubicin (adriamycin) is a potent chemotherapeutic agent for the treatment of a variety of human malignancies. The side effect of the development of a dose-dependent cardiomyopathy and congestive heart failure has limited the use of this drug. Once diagnosed, the prognosis for these patients is very poor. Among several different mechanisms proposed for explaining the pathogenesis, increased oxidative stress appears to play a major role. Adriamycin has been shown to increase free radical production and decrease activities of endogenous antioxidant enzymes. There is an early depression in glutathione peroxidase activity. Cardiomyopathy is also associated with apoptosis.

These changes precede the development of cardiomyopathy and congestive heart failure. Many different approaches have been used to minimize the incidence of adriamycin-induced heart failure but only with limited success. In the rat model, the development of heart failure was prevented by reducing oxidative stress using probucol, a lipid lowering drug with known antioxidant properties. Adjunct therapy with probucol did not interfere with the antitumor effect of adriamycin. Based on these animal studies, it is suggested that a carefully planned combination therapy with adriamycin and probucol should be clinically investigated to prevent the cardiotoxic effects of this useful drug.

KEYWORDS: antioxidants; apoptosis; congestive heart failure; doxorubicin-cardiomyopathy

INTRODUCTION

Doxorubicin (adriamycin) has been used as a single agent as well as in combination with other chemotherapeutic agents to control and regress a variety of neoplastic conditions. However, the beneficial effects of this drug are complicated by the acute as well as serious chronic side effects. Most of the acute side effects such as myelosuppression, nausea, vomiting and arrhythmias are not life threatening and are reversible as well as clinically manageable^[1]. It is the chronic side effects of the development of cardiomyopathy and ultimately congestive heart failure which are critical and life-threatening and thus limit the clinical usefulness of adriamycin^[1-3]. These cardiotoxic effects in patients have been found to correlate with the cumulative dose of the drug administered^[1,4,5]. Consequently, the administration of a cumulative dose of 500 mg/m² body surface area has been advised. Beyond this dose adriamycin therapy is generally excluded from the patient's chemotherapeutic regimen. Such an empirical approach may preclude those patients who can tolerate and can benefit from a higher dose and conversely patients with other concurrent risk factors may not tolerate even this dose. It is, therefore, imperative that we

unravel the mechanisms underlying this condition if we are to optimize the safe usage of this drug.

Clinical and laboratory findings:

Patients treated for advanced carcinoma by repeated injections of adriamycin (cumulative dose range 500 to 1000 mg/m² body surface) over several months showed marked hypotension (blood pressure 70/50 mmHg), tachycardia (150 beats/min) with a significant decrease in the QRS voltage, cardiac dilatation, and ventricular failure. These life-threatening, chronic effects often develop in several weeks or months after the treatment. The most characteristic feature of this condition is the relative refractoriness of these patients to the administration of inotropic drugs and mechanical circulatory assistance^[1]. Serum enzymes, such as SGOT, LDH, and CPK, increase significantly, particularly in the late stages of failure^[1]. A delayed cardiomyopathy, several years (6-19 years) after treatment, attributed to chronic side-effects of adriamycin has also been reported^[6]. Thus, the risk of developing heart failure remains a life-long threat^[3,7].

Other characteristic features of adriamycin-induced cardiomyopathy are in the ultrastructural

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pathology. In adriamycin-induced cardiomyopathy in the patients, myocardial biopsy samples show the loss of myofibrils, dilation of the sarcoplasmic reticulum and cytoplasmic vacuolization, swelling of mitochondria and increased number of lysosomes^[1,8,9]. These ultrastructural changes have also been confirmed in a variety of animal models such as: rabbits,^[10,11] mice,^[12,13] and rats^[14-16]. Among different animal models, the rat seem to mimic most of the clinical, hemodynamic and myocardial structural changes seen in patients^[17]. In this regard, the functional refractoriness of adriamycin-induced heart failure to inotropic support in humans has also been observed in rats^[18,19]. Thus, the information obtained from the rat as a model bears resemblance and has provided valuable information in understanding the pathogenesis of this form of cardiomyopathy^[17,20,21].

Adriamycin and apoptosis:

Apoptosis is an energy dependent process for programmed cell death. As neighbouring cells are unaffected by apoptosis this mechanism of cell death can be considered as evolutionary conserved process of a selective cell elimination. There are specific morphological changes in the nuclear material of cells undergoing apoptosis. It is possible to differentiate apoptotic and necrotic cells both morphologically and biochemically. Apoptosis has been shown to occur in cardiomyopathy, congestive heart failure and myocardial ischemia^[22-24]. Adriamycin has been shown to induce apoptosis in the myocardium, although there is some controversy about the type of cells being affected^[25,26].

Some reports suggest that only interstitial dendritic cells and macrophages showed the signs of apoptosis due to adriamycin in cardiac myocytes^[27]. In this study, only one time point was examined and it is likely that the window of apoptosis may have been missed. In this regard, we have shown a biphasic increase in apoptosis in the heart subsequent to adriamycin treatment^[26]. Myocardial Bax and caspase activities were found to be increased by adriamycin^[26]. An increase in the caspase-8 activity and the Fas/FasL signaling pathway, following adriamycin treatment of cardiac myocytes also suggests the existence of adriamycin-induced apoptosis in cardiomyocytes^[28]. The protective role of nitrogen spin trap, ebselen and MT overexpression in heart against adriamycin-induced apoptosis in cardiac myocytes may initiate a role for free radical-induced apoptosis^[29,30]. Recent work done in our lab has provided evidence to support this hypothesis because probucol, an antioxidant, resulted in a significant reduction in adriamycin-induced apoptosis^[26]. However, more

research is required in order to provide conclusive evidence for a role for apoptosis in adriamycin-induced cardiomyopathy.

PATHOPHYSIOLOGY OF HEART FAILURE

Extensive clinical as well as basic research efforts have been focused on understanding the pathogenesis of this cardiomyopathy and a number of mechanisms have been put forward to explain the development of adriamycin-induced cardiomyopathy^[3,16,31]. Although the cause of adriamycin-induced cardiomyopathy is multifactorial and complex, most of the myocardial changes seen in this condition could be explained on the basis of the increased oxidative stress^[3,32]. An imbalance between free radical production and endogenous myocardial antioxidants has been suggested to play a major role in the pathogenesis of this heart failure^[31]. Thus, recent research efforts have been focused on maintaining this balance by scavenging free radicals or upregulating endogenous antioxidants^[3,32].

OXIDATIVE STRESS DUE TO ADRIAMYCIN

Redox cycling of adriamycin-derived quinone-semiquinone, in the presence of oxygen, and transition metals, yields superoxide radicals. The latter is dismutated by the antioxidant enzyme superoxide dismutase which catalyzes the conversion of superoxide radicals to hydrogen peroxide^[33]. These two species, subsequently, through a Haber-Weiss reaction, lead to the formation of hydroxyl radicals. The latter can react with polyunsaturated fatty acids, initiating a lipid-radical chain reaction and oxidative damage to cell membranes. Increased levels of oxygen species due to adriamycin have been detected directly by electron spin resonance spectroscopy^[34-37] and indirectly by an increase in tissue malondialdehyde (MDA) which is a breakdown product of lipid peroxidation^[31,33,38]. In the presence of transition metal ions, the chain reaction continues and free iron appears to play a particularly important role in adriamycin-induced lipid peroxidation. Without free iron, MDA formation is minimal and even a low concentration of free iron can lead to a substantial MDA production^[39]. Adriamycin may act by transferring an electron directly to Fe³⁺ and the produced Fe²⁺ can reduce oxygen to hydrogen peroxide. Redox cycling of adriamycin in this manner also generates free radical metabolites and active oxygen species^[32,40,41].

Antioxidant changes and a precise molecular defect:

Three antioxidant enzymes, superoxide dismutase (SOD), glutathione peroxidase (GSHPx)

and catalase play an important role in mitigating free radical-induced cell injury. In heart, GSHPx is extremely important because of its ability to use and remove organic and inorganic peroxides^[33]. A number of studies reported diverse results in the changes of these antioxidant enzyme activities in different animal species, treated with different doses and administration schedules of adriamycin^[42-47]. Administration of adriamycin resulted in a dose- and time-dependent decrease in myocardial GSHPx activity in rabbits and mice^[42,43]. The decreased GSHPx activity has also been observed in rats^[45,46]. More recently, we have shown that the GSHPx enzyme system is adversely affected very early on and a repeat administration of the drug causes a more sustained defect in this enzyme system^[48].

Adriamycin effects the gene expression of different antioxidant enzymes^[49]. Adriamycin decreased the activity and protein levels of GSHPx as early as at two hours. The changes in activity and levels of this protein were exaggerated by multiple treatments with the drug. Although there was a decrease in level and activity of MnSOD at two hours after the treatment, these changes were transitory and the activity returned to normal in about 24 hours. Probucol pretreatment prevented the occurrence of these changes in GSHPx and MnSOD activities^[48]. It is, therefore, proposed that a decrease in GSHPx and SOD may play a role in the initiation of cardiomyopathy, but it is the persistent decrease in GSHPx that may be responsible for the progression of cardiomyopathic changes.

DISSOCIATION BETWEEN ANTITUMOR AND ANTICARDIAC ACTION

It is imperative that any methods designed to minimize the cardiotoxic effects of adriamycin must preserve its antineoplastic efficacy, and a great deal of efforts has been expended in preventing or mitigating the cardiotoxic side effects of adriamycin. Strategies in prevention of adriamycin-induced cardiotoxicity have focussed on the optimization of the dose, synthesis of non-toxic analogues and combination therapy. Although no ideal solution has been found, recent laboratory data with combination therapy have raised a new hope.

Some of the earlier reports suggested that the antitumor action of adriamycin may be mediated by an increase in oxidative stress^[50-52]. However, more recent data suggest that the antitumor action of adriamycin may be explained by non-free radical dependent mechanisms including inhibition of the topoisomerase II, adriamycin-iron complex binding to DNA and intercalation of the drug between DNA base pairs^[32]. Cardiotoxic effects of the drug, on the other hand, have been demonstrated to be due to

increased oxidative stress caused by free radical overproduction and decrease in endogenous antioxidant reserve^[53]. The latter understanding has been used to reduce adriamycin cardiotoxicity without interfering with its antitumor property.

The effects of probucol on adriamycin-induced cardiomyopathy were examined in the rat model and it has been reported that treatment with probucol offers complete protection against adriamycin-induced mortality, alterations in the hemodynamic function, endogenous antioxidant changes and myocardial ultrastructural damage^[46]. The mortality in these animals due to adriamycin treatment (cumulative dose 15 mg/kg) is generally 30% in three weeks after the last injection and animals develop extensive (>100 ml) ascites. In hemodynamic study of adriamycin group, peak left ventricular systolic pressure (LVSP) was depressed and left ventricular end-diastolic pressure (LVEDP) was elevated. All these abnormalities were completely prevented by probucol.

Lipid peroxidation measured by thiobarbituric acid reactive substances has been generally accepted as an indicator of oxidative stress resulting from free radical overproduction and reduced antioxidant reserve. Adriamycin treatment causes a significant increase in myocardial lipid peroxidation which was completely prevented by probucol^[37]. While the adriamycin-induced cardiotoxicity was completely prevented by probucol, the anti-tumor property of the adriamycin remained unchanged^[16]. Using tumor-bearing mouse model, we showed that tumor size was significantly decreased after treatment with adriamycin alone as well as in combination with probucol^[46].

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