Research Article
Research progress of cardioprotective agents for prevention of anthracycline cardiotoxicity

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Abstract: Anthracyclines, including doxorubicin, epirubicin, daunorubicin and aclarubicin, are widely used as chemotherapeutic agents in the treatment of hematologic and solid tumor, including acute leukemia, lymphoma, breast cancer, gastric cancer, soft tissue sarcomas and ovarian cancer. In the cancer treatment, anthracyclines also can be combined with other chemotherapies and molecular-targeted drugs. The combination of anthracyclines with other therapies is usually the first-line treatment. Anthracyclines are effective and potent agents with a broad antitumor spectrum, but may cause adverse reactions, including hair loss, myelotoxicity, as well as cardiotoxicity. We used hematopoietic stimulating factors to control the myelotoxicity, such as G-CSF, EPO and TPO. However, the cardiotoxicity is the most serious side effect of anthracyclines. Clinical research and practical observations indicated that the cardiotoxicity of anthracyclines is commonly progressive and irreversible. Especially to those patients who have the first time use of anthracyclines, the damage is common. Therefore, early detection and prevention of anthracyclines induced cardiotoxicity are particularly important and has already aroused more attention in clinic. By literature review, we reviewed the research progress of cardioprotective agents for prevention of anthracycline cardiotoxicity.

Keywords: Anthracycline, cardiotoxicity, prevention, cardioprotective agents

Introduction

Cancer is a major public health problem in the United States and many other parts of the world [1]. The number of cancer survivors continues to increase due to the aging and growth of the population and improvements in early detection and treatment. Nearly 14.5 million Americans with a history of cancer were alive on January 1, 2014, by January 1, 2024, that number will increase to nearly 19 million [2]. Cancer chemotherapy or radiotherapy can cause short- and long-term cardiovascular complications [3]. In a U.S. National Health and Nutrition Examination survey of 1,807 cancer survivors followed for 7 years, 33% died of heart diseases and 51% of cancer [4].

The primary cause of chemotherapy-induced cardiotoxicity is anthracycline compounds, which are used extensively to treat lymphoma, sarcoma, breast cancer, and pediatric leukemia [3]. The prevention of anthracycline-induced cardiotoxicity is an important challenge in cancer survivorship. In this review, we summarized the present effective drugs to prevent and cure anthracycline induced cardiotoxicity (Table 1).

Mechanisms of anthracycline induced cardiotoxicity

Anthracycline, including doxorubicin, daunorubicin, epirubicin, and idarubicin, have been approved and widely used for the treatment of leukemia and many soft tissue tumors [5]. Anthracycline-induced cardiotoxicity is cumulative, dose-dependent, and thought to occur mainly through the generation of reactive oxygen species and the formation of free radical by the electron redox cycling of anthracyclines after binding to DNA [6, 7].

Cardioprotective agents for prevention of anthracycline cardiotoxicity

Dexrazoxane

Dexrazoxane is the only FDA approved cardioprotective agent for anthracycline-induced car-
Cardioprotective in anthracycline cardiotoxicity

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Previously, it was thought that dexrazoxane provides cardiac protection from anthracyclines primarily through the metal-chelating activity of its intracellular hydrolysis products in the myocardium. This activity involves chelation of free iron and iron bound in anthracycline complexes, thereby preventing the formation of cardiotoxic reactive oxygen radicals [8]. It could also act as a catalytic inhibitor of DNA topoisomerase II [9]. Recently, it was suggested that a conceivable explanation is an interaction with topoisomerase IIb isoform [10]. HIF activation is another mechanism contributing to the protective effect of dexrazoxane against anthracycline cardiotoxicity [11].

Randomized controlled trials provided evidence that dexrazoxane prevented anthracycline-induced cardiotoxicity without interfering with its anti-tumor effects. Patients who received dexrazoxane as their anthracycline treatment had about one third of the risk of heart failure compared to patients who with other anthracyclines without dexrazoxane. Dexrazoxane had no significant effect on survival [12]. In doxorubicin-treated children with acute lymphoblastic leukemia, dexrazoxane prevented or reduced cardiac injury without compromising the anti-leukemic efficacy of doxorubicin [13]. Multicenter randomized controlled clinical trials have shown the cardioprotective effect of dexrazoxane in advanced breast cancer patients treated with anthracycline-based chemotherapy [14, 15]. A study from Korean group shown dexrazoxane reduces the incidence and severity of early and late anthracycline cardiotoxicity in childhood solid tumors [16].

The cumulative dose is the most important for anthracycline-associated cardiotoxicity [17].
have received more than 300 mg/m² doxorubicin who may benefit from continued doxorubicin-containing therapy [18].

In 2007 Tebbi et al evaluated dexrazoxane as a cardiopulmonary protectant during treatment for Hodgkin's disease. The results shown that dexrazoxane have increased the incidence of second malignant neoplasms and acute myeloid leukemia/myelodysplastic syndrome [19]. However, a series of studies do not support the result of study did by Tebbi, and that the reason that the previous conclusion is due to the failure to choose the most appropriate statistical method, and some children with basic diseases and chemotherapy drugs is itself carcinogenic [20, 21]. Barry et al assigned 205 children with high-risk acute lymphoblastic leukemia randomly to receive doxorubicin alone (n=100) or doxorubicin with dexrazoxane (n=105) during the induction and intensification phases of multiage chemotherapy, with a media follow-up of 6.2 years, no differences in the incidence of second malignant neoplasms were noted between the two groups [21]. More recently, a study did by Seif et al support dexrazoxane was not associated with an increased risk of secondary AML in a large cohort of pediatric cancer patients receiving anthracyclines in US hospitals [22]. Additional studies are needed to confirm these findings and to quantify dexrazoxane long-term cardioprotective effects.

The adverse reactions of dexrazoxane reported in the current literature including hematological changes, stomatitis, nausea, vomiting, neurotoxicity, pain on injection, anorexia, alopecia, phlebitis, diarrhea, fever [12]. But this may be caused by chemotherapy drugs, a Meta-analysis found the adverse reaction compare with chemotherapy alone, added with dexrazoxane only change blood cell slightly, others were not statistically significant [12].

**Beta-blockers**

**Carvedilol:** Carvedilol blocks beta1, beta2, and 1-adrenoceptors and has potent antioxidant and anti-apoptotic properties [23, 24]. Animal and experimental studies showed that carvedilol prevented anthracycline cardiotoxicity by decreasing free radical release and apoptosis in cardiomyocytes [25-27]. In a placebo-controlled clinical trial, patients in whom anthracycline therapy was planned were randomized to administration of carvedilol, patients were follow-up for 6 months, the results shown carvedilol could protect both systolic and diastolic functions of the left ventricle in patients receiving anthracycline [28]. NCT01110824 evaluate the efficacy of enalapril and carvedilol to prevent chemotherapy-induced left ventricular systolic dysfunction in patients with hematological malignancies, the result shown compared to controls, patients in the intervention group had a lower incidence of the combined event of death or heart failure and of death, heart failure, or a final LVEF<45% [29].

**Nebivolol:** Nebivolol is a β1-selective adrenergic receptor antagonist, with vasodilatory effects mediated by nitric oxide release, a mechanism possibly triggered by activation of β3-receptors [30, 31]. In a randomized, double-blind, placebo-controlled clinical study, effect of prophylactic nebivolol use on prevention of anthracycline induced cardiotoxicity in breast cancer patients were investigated, 45 consecutive patients with breast cancer and planned chemotherapy were randomly assigned to receive nebivolol 5 mg daily (n=27) or placebo (n=18), the result shown prophylactic use of nebivolol treatment could protect the myocardium against anthracycline-induced cardiotoxicity [32].

**Metoprolol:** A prospective, parallel group, randomized, controlled study investigated doxorubicin-induced clinical or subclinical cardiotoxicity in lymphoma patients after concomitant prophylactic therapy with metoprolol or enalapril or no concomitant treatment, the results shown that heart failure was less frequent under concomitant treatment than no treatment, especially in the metoprolol group, but the differences were not significant. No association was found between the presence of cardiotoxicity and concomitant treatment or other variable apart of age that had a significant impact [33].

**ACEIs and angiotensin antagonists**

Angiotensin-converting enzyme inhibitors (ACEIs) have been shown to slow anthracycline-induced cardiomyopathy [34]. Furthermore, data from experimental models shown that the cardiac renin-angiotensin system takes great
part in the development of anthracycline-induced cardiomyopathy and that treatment with ACEIs could prevent anthracycline-induced cardiotoxicity [35-38]. In a prospective, randomized clinical study, patients who showed troponin I increase soon after high-dose chemotherapy were randomized to receive or not to receive enalapril. Untreated patients showed a significant reduction in left ventricular ejection fraction and an increase in end-diastolic and end-systolic volumes, this indicated early treatment with enalapril could prevent the development of late cardiotoxicity [39]. A randomized study also investigated a new class of angiotensin II receptor blocker (ARB) valsartan in acute cardiotoxicity after doxorubicin-based chemotherapy. The result shown that valsartan could significantly prevented doxorubicin induced transient increases in the left ventricular end-diastolic diameter in an echocardiogram, the QTc interval and QTc dispersion in an electrocardiogram, and in the plasma brain natriuretic peptides [40].

**Statins**

Statins could decrease vascular inflammation and oxidative stress [41, 42]. In vitro and animal model experiment studies shown statins could attenuate cardiotoxicity without compromise in treatment efficacy [43, 44]. An observational clinical cohort study retrospectively investigated 628 women with newly diagnosed breast cancer treated with anthracycline, by comparing in propensity-matched patients receiving uninterrupted statin therapy to non-continuous statin therapy. After follow-up period of 2.55±1.68 years, the result shown that uninterrupted statin therapy was associated with a lower risk for incident heart failure [45]. A study shown statin (atorvastatin) could be effective in maintenance of LVEF in patients treated with anthracycline [46].

**Natural antioxidants**

**Dihydromyricetin:** Dihydromyricetin (ampelopsin) is a type of flavonoid extracted from ampelopsis grossedentata. It possesses hepatoprotective effects and antioxidant activity [47, 48]. Recently, in vitro and animal model studies demonstrated dihydromyricetin exerted cardioprotective effect against anthracycline-induced cardiac damage, while potentiated anticancer activities of anthracycline [49].

**Antioxidant compounds from virgin olive oil:** Oleuropein, a hydrophilic phenolic compound belonging to secoiridoid family, is found in virgin olive oil. Their possessive protective effects against anthracycline cardiotoxicity are due to its high antioxidant capacity [50, 51]. Phenolic alcohol hydroxytyrosol is another bioactive molecule found in olive oil also possesses antioxidant properties [52]. Anischemia-reperfusion model indicate hydroxytyrosol could protect rat cardiomyocytes from injury [53]. In rats with breast cancer, hydroxytyrosol could ameliorate oxidative stress and mitochondrial function in doxorubicin-induced cardiotoxicity [54].

**Sesame oil:** Sesame oil is one of the major cooking oils for human diets have antioxidant constituents [55]. Studies from experimental models showed it could protect the heart injury [56, 57]. In male Wistar albino rats, the administering of sesame oil could prevent doxorubicin-induced cardiotoxicity by enhancing cardiac endogenous antioxidants [55].

**Salidroside:** Salidroside is a phenylpropanoid glycoside extracted from Rhodiola rosea L, which grows in regions of high altitude place and mountains [62]. Besides being an adaptogen, salidroside possesses protective effects on cardiovascular tissues against damage and dysfunction induced by different stressors, including ischemia/reperfusion-induced injury [62-64]. In vitro study showed salidroside could effectively protect cardiomyocytes against doxorubicin-induced cardiotoxicity by suppressing the excessive oxidative stress and activating a Bcl2-mediated survival-signaling pathway [65].

**Melatonin:** Melatonin (5-methoxy-N-acetyl-tryptamine) is a pineal hormone, has been demonstrated as a potent scavenge of hydroxyl, peroxyl radicals, and peroxynitrite [66]. It could protect against anthracycline cardiotoxicity in rats [66]. A clinical study investigated the
effects of melatonin administration on clinical outcomes of chemotherapeutic agents in various cancer patients. The melatonin administration could significantly increase survival rate and reduce the frequency of side effects, including cardiotoxicity [67].

**Glutathione**: Glutathione, a tripeptidethiol, is an antioxidant that scavenges free radicals. The supplementation of glutathione may protect the heart from anthracycline-induced cardiomyopathy [68]. The supplementation glutathione could decrease cardiac damage in both in vitro and in vivo studies [69-71]. These results indicate glutathione have the potential in preventing anthracycline-induced cardiac damage.

**Coenzyme Q10**: A control study investigated two groups of children with acute lymphoblastic leukemia or non-Hodgkin lymphoma treated with anthracyclines as two groups with or without coenzyme Q10. The results from this study demonstrated coenzyme Q10 could protect cardiac function during therapy with anthracyclines [72].

**Vitamins**: One study addressed a combination of vitamin E, vitamin C and N-acetyl cysteine to examine the cardioprotective effect in patients with malignancies receiving high dose chemoradio-therapy. The result shown left ventricular ejection fraction fell significantly in patients receiving placebo, but patients on combination showed no significant fall in ejection fraction [73].

**Quercetin**: Quercetin (QRN; 3,3',4',5,7-pentahydroxy flavone) is present in a variety of foods including fruits, vegetables and wine, it is the most abundant of the flavonoid molecules [74]. Due to its antioxidant potential, animal model experiments demonstrate it could protect the heart, brain, and other tissues against ischemia-reperfusion injury, toxic compounds, and other factors related to oxidative stress [75-77]. Quercetin could be a chemosesitizer in the chemotherapy of breast cancer cells to doxorubicin [78]. A quite recent study in rats showed that quercetin could augment the protective effect of losartan against chronic doxorubicin cardiotoxicity [79].

**Isorhamnetin**: Isorhamnetin is an avonol aglycone abundant found in herbal sea buckthorn, Ginkgo biloba L., and such medicinal plants, they could be used in the prevention and treatment of cardiovascular diseases [80, 81]. Studies demonstrated isorhamnetin can alleviate the damages of ischemia-reperfusion to ventricular myocytes and prevent H₂O₂-induced oxidative injury to H9c2 cardiomyocytes [82, 83]. It is also a potent anti-cancer agent on many tumor cell lines [84, 85]. A study by sun et al demonstrated isorhamnetin protect against doxorubicin-induced cardiotoxicity in H9c2 cardiomyocytes and rats model [86].

**Cannabidiol**: Cannabidiol is the major non-psychoactive cannabinoid component. It is derived from the plant Cannabis sativa. Due to its antioxidant and anti-inflammatory activities, studies showed that cannabidiol have therapeutic utility in rheumatoid arthritis, neurodegenerative disorders, diabetes mellitus, and ischemia/reperfusion tissue injury [87-90]. In a rats model study, the results indicated cannabidiol can ameliorate doxorubicin-induced cardiac injury [91].

**Resveratrol**: Resveratrol is a naturally occurring polyphenol, can reduce ROS production in the hearts of several animal models [92, 93]. With the use of a murine model of chronic doxorubicin exposure, a study indicated resveratrol supplementation could attenuate doxorubicin-induced cardiac injury [94].

**Others**

**Mitochondrial division inhibitor (mdivi-1)**: Mitochondrial division inhibitor-1 (mdivi-1), a newly found potential inhibitor of dynamin related protein that has been found to block the mitochondrial fission and confers cardioprotection in experimental cardiac ischemia reperfusion studies in mice [95]. It could also ameliorate pressure overload induced heart failure [96]. The effects of mdivi-1 on anthracyclines-induced cardiac dysfunction was investigated in heart models and a oxidative stress model to assess the effects of mdivi-1 on the mitochondrial depolarization and hypercontracture of cardiac myocytes, the results shown co-treatment of mdivi-1 with doxorubicin attenuated doxorubicin induced impairment of cardiac function and increased the infarct size, it could reverse doxorubicin induced a reduction in the time taken to depolarization and hypercontracture of cardiac myocytes, co-incubation of mdivi-1 with doxorubicin did not reduce the cytotoxicity of doxorubicin against cancer cells [97].
Metformin: Metformin is an oral biguanide antihyperglycemic drug that is widely used for the treatment of type 2 diabetes mellitus. A study found metformin could exert cardioprotective effects by its direct beneficial effects on cellular and mitochondrial function and independent of its insulin-sensitizing effect [98]. Metformin could reduce the generation of ROS in cultured endothelial cells and animal models [99-101]. It could also protect H\textsubscript{2}O\textsubscript{2} or TNF induced oxidative stress of cardiomyocytes [101, 102]. Recently, an in vitro study found metformin could protect against anthracycline-induced cardiotoxicity in the H9c2 cardiomyoblast cell line, the mechanism of low dose metformin’s protective effects against anthracycline is the involvement of AMPK, PKA/CREB1, Src and PDGFR, the mechanism of high dose metformin’s reversion of the effect is the suppression of PDGFR expression [103].

N-acetylcysteine: A randomized controlled trial reported N-acetylcysteine could prevent doxorubicin cardiomyopathy [104].

Phenethylamines: Prenylamine, a calcium antagonistic drug, could partial protect against anthracycline-induced cardiotoxicity in mice and in the rabbit. A pilot double blind study investigated twenty-six patients given ordinary doses of anthracycline, these patients were randomized in two groups, patients in group A received anthracycline plus placebo, patients in group B received anthracycline plus anthracycline, in group A one patient developed a congestive cardiomyopathy while another patient developed a severe supraventricular arrhythmia, in group B no cardiomyopathy was found [105]. The results indicated prenylamine might mitigate anthracycline cardiotoxicity. But preliminary results of a prospective multicenter shown no significant difference in cardiotoxicity has been observed either between the verapamil and nonverapamil group [106].

Amifostine: A prospective comparative randomized trial investigated the cytoprotective effects of amifostine in patients with osteosarcoma receiving cisplatin and doxorubicin, one group patients received amifostine and one group not, the result shown there were not statistical significant differences between the two groups for chemotherapy-related toxicity. But the patients in amifostine group response to chemotherapy were significantly better [107].

Prostacyclin (PGI2) and its analogues: PGI2 possesses important biologic functions, serving as an inhibitor of platelet aggregation, vasodilator, VSMC proliferation, and leukocyte adhesion [108, 109]. Studies indicated that PGI2 and its analogues (Iloprost and 7-oxo-PGI2-Na) could protect the ischemic myocardium after myocardial ischemia [110-112]. PGI2 also has antimitogenic functions and could inhibit DNA synthesis in smooth muscle cells [113]. By literature review, we propose prostacyclin administration could be cardioprotective supplement to attenuate the damaging cardiac effects caused by the traditional cancer chemotherapy regimen [114]. We investigated the effect of Iloprost, a stable synthetic analogue of prostacyclin, on the anthracycline induced human cardiac progenitor cells toxicity, the result indicate lloprost could prevent anthracycline mediated human cardiac progenitor cell depletion [115].

Meloxicam: Meloxicam belongs to enolic acid group of non-steroidal anti-inflammatory drugs, it could selectively inhibit COX2 action [116]. Besides its anti-inflammatory effect, meloxicam has the potential of antioxidant activity [117]. Meloxicam could also enhance tumor suppression and reduce the severity of paclitaxel-induced neuropathy [118]. Mice-bearing solid mammary tumor animal model experiment indicates meloxicam could protect heart against doxorubicin toxicity without affecting its antitumor activity [119].

Diazoxide: Diazoxide has been used in clinical for hypertension and hypoglycaemia. It is a potent opener of mitochondrial KATP, could protect against cardiac ischemia [120, 121]. An in vivo study investigate if opening of mitochondrial KATP-channels by diazoxide could protect against doxorubicin cardiotoxicity, using wistar rats they get the results diazoxide could significantly attenuated the decrease in left ventricular developed pressure and abolished the increased release of H\textsubscript{2}O\textsubscript{2} and TnT induced by doxorubicin treatment [122].

Ferric Carboxymaltose: Ferric Carboxymaltose is a novel iron complex that consists of a ferric hydroxide core stabilized by a carbohydrate shell. It is effective in the treatment of iron-deficiency anemia administered intravenously. In an iron deficiency rat model, ferric carboxymaltose administration could attenuation doxorubicin-induced cardiotoxicity [123].
Lecithinized human recombinant super oxide dismutase: Superoxide dismutase (SOD) is an important scavenger of reactive oxidative species and could prevent organ damage mediated by free radical overload. But the using of exogenous SOD is limited by its short half-life and low affinity for the cell membrane. The lecithinized SOD has a 100-200 fold higher affinity for cell membrane and improved free radical scavenging properties [124]. The studies by several animal models including a doxorubicin-induced cardiotoxicity model showed lecithinized human recombinant super oxide dismutase (PC-SOD) could protect against free radical mediated injuries [125-127]. But in an early phase II study showed PC-SOD at a dose of 80 mg i.v. did not possesses cardioprotective effect in patients with breast carcinoma treated with anthracyclines [128].

Ghrelin: Ghrelin is a stomach hormone consisting of 28 amino acids, it is produced primarily in the stomach and secreted into the systemic circulation [129]. Ghrelin possesses important biologic functions, including dilation in vessels, decrease in blood pressure, reduction in cardiac afterload, and increase in cardiac output [130, 131]. Studies demonstrated ghrelin could significantly attenuate doxorubicin-induced cardiotoxicity, ischemia/reperfusion and heart failure [131-134].

L-carnitine: Carnitine is a compound known for its function on the transport of long-chain FAs into the mitochondrial matrix, where the fatty acyl group is metabolized. A study examined the effects of L-carnitine on anthracycline cytotoxic side-effects in patients with non-Hodgkin lymphoma, but no cardiotoxicity of anthracycline therapy was detected [135].

Molsidomine: Molsidomine belonging to the class of sydnonimines, it is a prodrug has been widely used as an anti-angina agent [136]. An in vivo study showed molsidomine possesses cardioprotective effects on doxorubicin-induced cardiotoxicity [137].

Didox: Didox (3, 4-dihydroxybenzohydroxamic acid) is a synthetic compound, structurally close to resveratrol. It has been found to possess anti-tumor effects and antioxidant properties [138, 139]. In vivo and in vitro studies demonstrated Didox could significantly potentiated the cytotoxicity of doxorubicin in liver cancer cells and protected from its cardiotoxicity [140].

α-Linolenic acid: α-Linolenic acid is one of the precursors of highly unsaturated fatty acids. In vivo studies have demonstrated it could significantly alleviate myocardial ischemia/reperfusion injury in rats through suppression of oxidative stress [141]. The protective effects of α-Linolenic acid on doxorubicin-induced cardiotoxicity and the underlying molecular mechanisms was investigated in rats, the results showed α-Linolenic acid could attenuate doxorubicin-induced cardiotoxicity through suppression of oxidative stress and apoptosis [142].

Nicorandil: Nicorandil is a vasodilatory drug used to treat angina. It has been shown to inhibit oxidative stress induced myocyte apoptosis by the opening of mitochondrial KATP channels or the NO/cGMP-dependent pathway [143]. In a rat model, it has been demonstrated nicorandil could prevent the development of doxorubicin-induced heart failure. The underlying mechanism is the improvement of hemodynamic perturbations, mitochondrial dysfunction and ultrastructural changes without affecting its antitumor activity [144].

Combination therapy: The preliminary report demonstrated the combination therapy with lisinopril, ivabradine and multivitamin supplementation could fully recover left ventricular function with no residual myocardial damage by anthracycline treatment in breast cancer patients [145].

Summary and conclusions

Anthracycline-induced cardiotoxicity is a big problem in clinic. By literature review, we summary the research progress in cardioprotective agents for prevention of anthracycline cardiotoxicity. These cardioprotective agents have been proposed as promising agents of preventing or reducing anthracycline-induced cardiotoxicity, without decreasing the anti-tumor action of anthracycline. But only dexrazoxane is FDA approved by FDA as a cardioprotective agent for anthracycline induced cardiotoxicity. More studies of these cardioprotective agents as cardioprotective agents for anthracycline induced cardiotoxicity at the clinical level are required.
Cardioprotective in anthracycline cardiotoxicity

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None.

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