Cardiotoxicity of anthracycline therapy: current perspectives

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Submitted: 1 August 2014
Accepted: 7 October 2014

Arch Med Sci 2016; 12, 2: 428–435
DOI: 10.5114/aoms.2016.59270
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Abstract
Anthracyclines, especially doxorubicin and daunorubicin, are the drugs of first choice in the treatment of patients with hematologic malignancies, soft-tissue sarcomas, and solid tumors. Unfortunately, the use of anthracyclines is limited by their dose-dependent and cumulative cardiotoxicity. The molecular mechanism responsible for anthracycline-induced cardiotoxicity remains poorly understood, although experimental and clinical studies have shown that oxidative stress plays the main role. Hence, antioxidant agents, especially dexrazoxane, and also other drug classes (statins, β-blockers) proved to have a beneficial effect in protecting against anthracycline-induced cardiotoxicity. According to previous clinical trials, the major high-risk factors for anthracycline-induced cardiotoxicity are age, body weight, female gender, radiotherapy, and other diseases such as Down syndrome, familial dilated cardiomyopathy, diabetes and hypertension. Consequently, further studies are needed to elucidate the molecular pathogenesis of anthracycline-induced cardiotoxicity and also to discover new cardioprotective agents against anthracycline-induced cardiotoxicity.

Key words: cardiotoxicity, anthracycline, doxorubicin, breast cancer.

Introduction
Anthracyclines (ANT) are cytostatic antibiotics that were discovered almost half a century ago [1]. For example, in the 1960s, daunorubicin was the first ANT isolated from the bacterium Streptomyces peucetius [2]. Nowadays, doxorubicin (DOX), epirubicin and idarubicin are widely recommended both in children and adult patients with hematologic malignancies, soft-tissue sarcomas and solid tumors [3].

Unfortunately, the use of ANT is limited by their dose-dependent and cumulative cardiotoxicity [4], manifested as dilated cardiomyopathy with or without symptoms of heart failure (HF) [5]. Consequently, ANT-induced cardiotoxicity (AIC) may be classified as acute/subacute or chronic/late toxicity [6], being a devastating side effect resulting in morbidity, poor quality of life, and premature mortality [7]. Furthermore,
many children treated with less than 300 mg/m² doses of ANT have manifested cardiac dysfunction [8]. Asymptomatic AIC is a serious problem in childhood cancer patients [9]. Moreover, HF may appear even after a long time in cancer survivors [10]. For example, in the United States more than 50% of > 270 000 childhood cancer survivors developed AIC [11], HF being a major consequence of exposure to ANT in children [12]. Anthracyclines agents, especially dexrazoxane (DEX), are widely used for treating pediatric malignancies, increasing the number of childhood cancer survivors [13]. In this regard, development of new cardioprotective therapies for prevention of cardiac dysfunction in children after ANT is required [14].

According to statistics, the incidence and prevalence of cancers is rising; therefore decreasing AIC is crucial [15]. In this regard, experimental and clinical studies have focused on one hand on reducing the toxicity of classic ANT, using drug carriers such as liposomes, and on the other hand on discovering new ANT derivatives, such as amrubicin and pixantrone [16]. Consequently, available clinical evidence on DOX-induced HF supports the use of liposomal-encapsulated DOX over DOX in adult patients with solid tumors [17]. Moreover, serious allergic reactions, mucositis, infections, hematoxotincities and/or hepatotoxicity were observed after a single dose of liposomal ANT in children with cancer [18].

Regarding the novel third generation of ANT, amrubicin is a potent topoisomerase II inhibitor with less cardiotoxicity. Therefore, the main clinical indications of amrubicin are to treat ANT-refractory or ANT-resistant tumors [19]. Over the last decades, new ANT have been discovered, although doxorubicin and daunorubicin continue to be the drugs of first choice in the treatment of many types of cancer [20].

This review analyzes the most prescribed ANT, their various mechanisms of inducing cardiotoxicity in patients with malignant diseases, and also the newest strategies for reducing their toxicity [21].

### Risk factors

Early detection of high-risk patients is considered to be the main way to reduce the ANT cardiotoxicity [22]. According to several clinical trials, African-American ethnicity, age, body weight, female gender [13], radiotherapy, use of other chemotherapeutics, Down syndrome [23], familial dilated cardiomyopathy [24] or other severe co-morbidities, especially diabetes and hypertension [25], increased the risk of AIC [26].

Cumulative doses of ANT were mostly incriminated as causes of cardiotoxicity [25], being associated with early development of subclinical abnormalities of cardiac and vascular function [27]. For example, according to a clinical trial in 72 patients treated with a cumulative ANT dose < 120 mg/m, abnormalities in right ventricular diastolic function (RVDF) and in left ventricular systolic function (LVSF) were observed by tissue Doppler imaging (TDI) [28].

Another risk factor in ANT-treated childhood cancer survivors seemed to be cranial irradiation because of its association with decrease of insulin-like growth factor-1 (IGF-1), a marker of growth hormone (GH). Therefore, GH therapy may prevent AIC [29]. Protein malnutrition is also a risk factor for development of ANT cardiotoxicity, being frequently found in cancer patients [30]. Furthermore, cigarette smoking was found to have a negative effect on longitudinal strain in asymptomatic breast cancer survivors [31].

### Mechanism of toxicity

The molecular mechanisms responsible for ANT cardiotoxicity remain poorly understood [32]. In the last 40 years, many experimental and clinical studies have tried to explain the molecular mechanisms of ANT cardiotoxicity, but the results have been inconclusive, further studies being necessary [33].

One possible mechanism responsible for ANT toxicity refers to reactive oxygen species (ROS) formation and site-specific DNA damage [34]. Oxidative stress induction is widely believed to play the main role in AIC [35] by inducing DNA damage, sarcemere damage, mitochondrial dysfunction and loss of pro-survival signaling [36], mediating both death and survival of cardiomyocytes [37]. For example, increase of oxidative stress was observed in patients with solid tumors even after cessation of ANT therapy [38]. Consequently, AIC may appear any time in cancer survivors [39].

Another mechanism of AIC consists in the chelation reaction between iron (III) and the α-ketol group of DOX and epirubicin anticancer drugs [40]. Moreover, the preventive efficacy of DEX, which is an iron chelator, also supports the hypothesis of iron involvement in ANT cardiotoxicity [41].

A recent clinical study demonstrated that other factors such as sarcomeric structure disruption, toxic accumulation of metabolites, energetic alterations and inflammation may be responsible for ANT cardiotoxicity [1]. Furthermore, according to an in vitro study, depletion of GATA4 and cardiac ankyrin repeat protein (CARP) in cardiomyocytes contributes to the sarcomere disarray and loss of myofilaments in AIC [42].

Nevertheless, the genetic variants of the ABCC1 (ATP-binding cassette, sub-family C, member 1; also denoted as MRPI (multidrug resistance-associated protein 1)) gene seemed to have a role in ANT-induced LV dysfunction, as demonstrated by a clinical trial in pediatric patients with acute lymphoblastic leukemia [43].
Diagnosis

The early detection of AIC is made by biomarker detection, echocardiographic follow-up of LV systolic and diastolic function, and cardiac enzymes [44].

Biomarkers

A biomarker is defined as an indicator of objective measurement that can be used to detect various diseases, or to evaluate treatment risks, or effectiveness [45] (Table I). According to several clinical studies in asymptomatic survivors of acute leukemia, the N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) is a sensitive cardiac biomarker [22], which proved to be more useful than cardiac troponin I (cTnI) in the early identification of high-risk patients with AIC [46, 47]. Furthermore, in childhood cancer survivors, growth-differentiation factor-15 level may be used as a biomarker of AIC [48].

CBR1, AKR1A1, and AKR7A2 protein levels proved to be important determinants for predicting the synthesis of cardiotoxic ANT alcohol metabolites (e.g. daunorubicinol) in cancer patients with Down syndrome [23].

A powerful method to detect the effects of ANT on cardiac function in patients with surgically treated early breast cancer consisted in measuring the rate of change in hemoglobin concentration during ANT treatment and left ventricular ejection fraction (LVEF) at the end of cytostatic therapy [49, 50].

Experimental and clinical evidence showed that topoisomerase II α gene alterations may be responsible for ANT-induced sensitivity in breast cancer patients [51, 52]. For example, a clinical trial in 71 breast cancer patients proved that topoisomerase II α expression can be considered a proliferation marker and a prognostic factor in estrogen receptor (ER)-positive, human epidermal growth factor type-2 (HER2)-negative breast cancer [53, 54]. Moreover, topoisomerases 2β may also be responsible for AIC, being the only Top2 present in the cardiac tissue [2].

Echocardiography, dobutamine stress echocardiography, radionuclide ventriculography, cardiac magnetic resonance imaging

Clinical evidence proved that echocardiography (ECHO), radionuclide ventriculography (multigated acquisition (MUGA) scan) and cardiac magnetic resonance imaging (MRI) are important strategies for analyzing subclinical late AIC in pediatric patients [55]. For example, MRI can be used to detect diffuse interstitial fibrosis and regional myocardial dysfunction [11]. Magnetic resonance imaging is an accurate means for assessing tumor size on the surgical specimen in patients after chemothera-apy [56]. Magnetic resonance imaging can also be used to calculate myocardial extracellular volume fraction (ECV), which is elevated in patients treated with ANT. Extracellular volume fraction is correlated with diastolic dysfunction and increased atrial volumes [57].

ECHO is a non-invasive investigative method commonly used for monitoring AIC [58]. Ejection fraction (EF) and fractional shortening (FS) are common ECHO parameters of cardiac function, but newer imaging techniques proved to be more useful in detection of preclinical AIC [59].

Reduced LV systolic strain after ANT treatment may indicate early impairment of myocardial function, before any detectable change in LVEF [60]. A recent clinical study in patients before chemotherapy showed that LV torsion analysis might be useful for early detection of subclinical AIC [61]. Furthermore, it was demonstrated that left ventricular diastolic function (LVF) deteriorates earlier than LVSF in patients treated with ANT [62]. In breast cancer patients treated with ANT who developed LVSF subclinical activation of the neuro-hormonal profile was also observed [63]. According to another clinical study in patients with acute promyelocytic leukemia in long-term remission, changes in diastolic function seemed to be useful in the detection of subclinical AIC [64].

Myocardial strain imaging proved to be more sensitive than LVEF for early detection and inter-

Table I. Biomarkers used to detect AIC

| Biomarkers                                      | Study population                          | References |
|------------------------------------------------|------------------------------------------|------------|
| Prohormone brain natriuretic peptide (NT-proBNP) | High-risk patients with AIC              | [22]       |
| Cardiac troponin I (cTnI)                       | Early identification of high-risk patients with AIC | [46]       |
| Growth-differentiation factor-15                | AIC in childhood cancer survivors        | [48]       |
| CBR1, AKR1A1, and AKR7A2 protein                | Cancer patients with Down syndrome       | [23]       |
| Rate of change in hemoglobin concentration      | Early breast cancer surgically treated   | [49]       |
| TOP2A (topoisomerase II α) expression           | ER (estrogen receptor-positive), HER2 (human epidermal growth factor type-2-negative breast cancer) | [53]       |
mediate monitoring of LVSF in breast cancer patients treated with ANT [65].

Dobutamine stress echocardiography (DSE) is an effective and safe method for evaluation of late subclinical AIC, using a dobutamine dose of 20 μg/kg/min [66]. Moreover, according to another clinical trial, dobutamine-stress QT dispersion and heart-rate corrected QT dispersion are also helpful for detecting AIC and subclinical cardiac abnormality at low cumulative ANT doses [67].

Another clinical study revealed that combined real-time continuous-wave-Doppler ultrasound cardiac output monitoring and serum biomarkers is useful for evaluating the acute and chronic hemodynamic changes induced by ANT [68].

According to another clinical study, radionuclide ventriculography was more sensitive than ECHO in identifying early impairment of LV function in children with Hodgkin disease treated with DOX [69].

Treatment

There is no clinical evidence to demonstrate that the same drug therapies used in adults with other than AIC-induced causes of cardiac dysfunction may also be useful in childhood cancer patients and survivors treated with ANT [70]. It is generally known that different mechanisms of action are responsible for antitumoral cytotoxicity and for AIC.

Therefore, the main challenge of pharmaceutical research is to discover less cardiotoxic drugs able to maintain their chemotherapeutic effect [71].

Common strategies for preventing cardiotoxic effects consist in modifying the chemical structure and dosages of ANT and in using cardioprotective agents [14] (Table II). For example, N-benzyladriamycin-14-valerate (AD 198) is a less cardiotoxic ANT with a modified chemical structure, but with the same antitumor efficacy as DOX [72].

Antioxidant agents – dexrazoxane

It is known that AIC is partly caused by production of free radicals [73]. Therefore, DEX has been approved as a cardioprotective agent, being considered the treatment of first choice for AIC [74]. Also, clinical research in breast cancer patients after an operation [75] and pediatric cancer patients [76] proved that DEX protects against the development of AIC, without increasing non-cardiac and non-hematologic toxicity [75]. Dexrazoxane was, generally, well tolerated, although the most commonly reported side effects of DEX seemed to be leukopenia, thrombocytopenia and local reactions at the infusion site [74]. Dexrazoxane combined with ANT has been shown to increase the risk of bone marrow suppression; therefore, peripheral blood morphology should be monitored and routine bone marrow support might be needed [75].

Most of the studies have been done in experimental animal models. For example, N-acetylcysteine and selenium (Se) did not significantly reduce the activity of xanthine oxidase (XOD) in a mouse model [77], although, according to a small clinical study in nine children with a high pro-BNP level and/or cardiac failure, Se supplementation proved to prevent AIC [78].

Moreover, a meta-analysis of 15 published randomized controlled trials showed that sequential ANT and taxane schedules are less toxic than ANT alone [79]. Moreover, another clinical trial showed a significant increase in the cancer recurrence rate in patients treated with ANT compared to those treated with ANT and taxane [80].

According to an experimental study in a large-animal model of ANT-induced nonischemic cardiomyopathy, dietary intake of omega-3 polyunsaturated fatty acids failed to prevent and on the contrary exacerbated DOX-induced cardiotoxicity [81]. In a clinical trial in children with acute promyelocytic leukemia, the combination of all-trans-retinoic acid and a reduced cumulative dose of 350 mg/m² ANT reduced acute and long-term cardiotoxicity [82].

Moreover, prophylactic administration of probucol, another antioxidant agent, demonstrated preservation of cardiac function and decreased mortality in mice treated with DOX+Trz [83, 84].

Table II. Cardioprotective agents used in AIC

| Drug       | Actions                                                                 | References |
|------------|-------------------------------------------------------------------------|------------|
| Dexrazoxane| Antioxidant agent against development of AIC, without increasing non-cardiac and non-hematologic toxicity | [75]       |
| Selenium   | Antioxidant agent                                                       | [78]       |
| Probucol   | Antioxidant agent preserves cardiac function                             | [83]       |
| Ranolazine | Selective inhibitor of the cardiomyocyte late inward sodium current (INaL), with anti-ischemic, antiarrhythmic and ATP-sparing actions | [85]       |
| Statins    | Inhibition of the Ras-homologous GTPase Rac1                             | [86]       |
| β-blockers | Antioxidant and anti-apoptotic effects                                   | [88]       |
Ranolazine

Ranolazine, the most powerful and selective clinical inhibitor of the cardiomyocyte late inward sodium current (INaL) [71], might also be effective in patients with AIC [85].

Statins

Lovastatin, a HMG-CoA reductase inhibitor (statin), protects against AIC by inhibition of the Ras-homologous GTPase Rac1 in rat H9c2 cardiomyoblasts [86]. Moreover, pre-clinical experiments using cell cultures and animal models and also a small randomized clinical study in female patients with breast cancer treated with ANT showed that statin use was associated with a lower risk of HF [87].

β-blockers

ANT-induced cardiovascular complications have been treated with angiotensin-converting enzyme inhibitors, β-blockers, and growth hormone replacement therapy [14]. Carvedilol, a non-selective, adrenergic blocker may be useful in the prevention of AIC because of its added antioxidant and anti-apoptotic effects [88]. Moreover, another clinical trial showed that oral administration of carvedilol 2.5 mg to 5 mg bid combined with candesartan 2.5 mg once a day could reduce acute and chronic AIC [89]. Furthermore, another small, prospective, double-blind study in 45 patients with breast cancer revealed that nebivolol (5 mg daily) can be used in the prevention of ANT cardiotoxicity [90].

Angiotensin-converting enzyme inhibitors

Both chronic AIC and ischemic cardiomyopathies are treated with β-blockade and angiotensin-converting enzyme (ACE) inhibition [91]. The ACE inhibitors transiently improved left ventricular structure and function in patients with congestive heart failure [92]. Renin-angiotensin-aldosterone gene polymorphisms were not significantly associated with AIC in early breast cancer patients [4]. Further clinical trials are necessary to establish the effects of ACE inhibitors in cancer patients with left ventricular dysfunction after ANT therapy [93].

Other therapies

A recent therapeutic strategy for prevention and/or management of HF induced by ANT was tested in rats with DOX-induced cardiomyopathy and consisted in the administration of previously harvested functionally competent cardiac progenitor cells to individuals who manifested cardiotoxicity [94].

Non-pharmacological therapies

Non-pharmacological interventions to prevent and/or treat AIC consisted in exercise training initiated at the same time as the cytostatic treatment [95] and music therapy that improved autonomic function in ANT-treated breast cancer survivors [96].

Further investigations are required to explain the cardioprotective mechanisms of exercises before, during, and after ANT treatment. Alternative therapies should be used with caution in cancer patients [7]. The discovery of less toxic, targeted therapies represents a new option for older patients with acute myeloid leukemia [97].

Conclusions

Further prospective and multicenter randomized clinical trials are needed to elucidate the molecular pathogenesis of AIC, to identify new strategies of managing the risk factors and to evaluate new methods for early AIC detection. Furthermore, the discovery of new ANT characterized by less cardiotoxicity for improving the life quality and expectancy of cancer survivors should also be a major target for pharmaceutical research.

Conflict of interest

The authors declare no conflict of interest.

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Cardiotoxicity of anthracycline therapy: current perspectives

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