Cardiotoxicity of anthracycline therapy: current perspectives

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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/m^2 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, hematotoxicities 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, sarcomere 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 MRP1 (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].

Mihaela Valcovici, Florina Andrica, Corina Serban, Simona Dragan

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 chemotherapy [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/m^2 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]

Mihaela Valcovici, Florina Andrica, Corina Serban, Simona Dragan

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 nonselective, 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.

References

1. Salazar-Mendiguchia J, Gonzalez-Costello J, Roca J, Ariza-Sole A, Manito N, Cequier A. Anthracycline-mediated cardiomyopathy: basic molecular knowledge for the cardiologist. Arch Cardiol Mex 2014; 84: 218-23.
2. Vejpongsa P, Yeh ET. Topoisomerase 2beta: a promising molecular target for primary prevention of anthracycline-induced cardiotoxicity. Clin Pharmacol Ther 2014; 95: 45-52.
3. Raj S, Franco VI, Lipshultz SE. Anthracycline-induced cardiotoxicity: a review of pathophysiology, diagnosis, and treatment. Curr Treat Options Cardiovasc Med 2014; 16: 315.
4. Vivenza D, Feola M, Garrone O, Monteverde M, Merlano M, Lo Nigro C. Role of the renin-angiotensin-aldosterone system and the glutathione S-transferase Mu, Pi and Theta gene polymorphisms in cardiotoxicity after anthracycline chemotherapy for breast carcinoma. Int J Biol Markers 2013; 28: e336-47.
5. Chatterjee K, Zhang J, Honbo N, Karliner JS. Doxorubicin cardiomyopathy. Cardiology 2010; 115: 155-62.
6. Appel JM, Sander K, Hansen PB, Moller JE, Krarup-Hansen A, Gustafsson F. Left ventricular assist device as bridge to recovery for anthracycline-induced terminal heart failure. Congest Heart Fail 2012; 18: 291-4.
7. Scott JM, Khakoo A, Mackey JR, Haykowsky MJ, Douglas PS, Jones LW. Modulation of anthracycline-induced cardiotoxicity by aerobic exercise in breast cancer: current evidence and underlying mechanisms. Circulation 2011; 124: 642-50.

8. Choi HS, Park ES, Kang HJ, et al. Dexrazoxane for preventing anthracycline cardiotoxicity in children with solid tumors. J Korean Med Sci 2010; 25: 1336-42.

9. van Dalen EC, van der Pal HJ, Reitsma JB, et al. Management of asymptomatic anthracycline-induced cardiac damage after treatment for childhood cancer: a postal survey among Dutch adult and pediatric cardiologists. J Pediatr Hematol Oncol 2005; 27: 319-22.

10. Iarussi D, Martino V, Iacono C, Indolfi P, Muto R, Calabro R. [Biventricular heart failure in patient treated with anthracycline in childhood: myocardial dysfunction is not always the cause]. Ital Heart J Suppl 2004; 5: 294-7.

11. Toro-Salazar OH, Gillan E, O'Loughlin MT, et al. Occult cardiotoxicity in childhood cancer survivors exposed to anthracycline therapy. Circ Cardiovasc Imaging 2013; 6: 873-80.

12. Zhu W, Zhang W, Shou W, Field LJ. P53 inhibition exacerbates late-stage anthracycline cardiotoxicity. Cardiovasc Res 2014; 103: 81-9.

13. Trachtenberg BH, Landy DC, Franco VI, et al. Anthracycline-associated cardiotoxicity in survivors of childhood cancer. Pediatr Cardiol 2011; 32: 342-53.

14. Lipshultz SE, Karnik R, Sambatakos P, Franco VI, Ross SW, Miller TL. Anthracycline-related cardiotoxicity in childhood cancer survivors. Curr Opin Cardiol 2014; 29: 103-12.

15. Ky B, Carver JR. Biomarker approach to the detection and cardioprotective strategies during anthracycline chemotherapy. Heart Fail Clin 2011; 7: 323-31.

16. Fulbright JM, Huh W, Anderson P, Chandra J. Can anthracycline therapy for pediatric malignancies be less cardiotoxic? Curr Oncol Rep 2010; 12: 411-9.

17. van Dalen EC, Michiels EM, Caron HN, Kremer LC. Different anthracycline derivates for reducing cardiotoxicity in cancer patients. Cochrane Database Syst Rev 2010; 5: CD005006.

18. Sieswerda E, Kremer LC, Caron HN, van Dalen EC. The use of liposomal anthracycline analogues for childhood malignancies: a systematic review. Eur J Cancer 2011; 47: 2000-8.

19. Mamidipudi V, Shi T, Brady H, et al. Increased cellular accumulation and distribution of amrubicin contribute to its activity in anthracycline-resistant cancer cells. Cancer Chemother Pharmacol 2012; 69: 965-76.

20. Carvalho H, Garrido LM, Furlan RL, et al. DNA damage induced by the anthracycline cosmomycin D in DNA repair-deficient cells. Cancer Chemother Pharmacol 2010; 65: 989-94.

21. Ewer MS, Von Hoff DD, Benjamin RS. A historical perspective of anthracycline cardiotoxicity. Heart Fail Clin 2011; 7: 363-72.

22. Sherief LM, Kamal AG, Khalek EA, Kamal NM, Soliman AA, Esh AM. Biomarkers and early detection of late onset anthracycline-induced cardiotoxicity in children. Hematology 2012; 17: 151-6.

23. Quinones-Lombrana A, Ferguson D, Hageman Blair R, Kalabus JL, Redzematovic A, Blanco JG. Interindividual variability in the cardiac expression of anthracycline reductases in donors with and without Down syndrome. Pharmaceut Res 2014; 31: 1644-55.

24. van den Berg MP, van Spaendonck-Zwarts KY, van Veldhuisen DJ, Gietema JA, Postma A, van Tintelen JP. Familial dilated cardiomyopathy: another risk factor for anthracycline-induced cardiotoxicity? Eur J Heart Fail 2010; 12: 1297-9.

25. Lotrionte M, Biondi-Zoccai G, Abbate A, et al. Review and meta-analysis of incidence and clinical predictors of anthracycline cardiotoxicity. Am J Cardiol 2013; 112: 1980-4.

26. Ali AA, Al-Mudhafar AM. Prediction of anthracycline induced cardiotoxicity: study of thirty-one Iraqi adult patients. Gulf J Oncol 2011; 10: 33-9.

27. Drafts BC, Twomley KM, D'Agostino R Jr, et al. Low to moderate dose anthracycline-based chemotherapy is associated with early noninvasive imaging evidence of subclinical cardiovascular disease. JACC Cardiovasc Imag 2013; 6: 877-85.

28. Kocabas A, Kardelen F, Ertug H, et al. Assessment of early-onset chronic progressive anthracycline cardiotoxicity in children: different response patterns of right and left ventricles. Pediatr Cardiol 2014; 35: 82-8.

29. Landy DC, Miller TL, Lipsitz SR, et al. Cranial irradiation as an additional risk factor for anthracycline cardiotoxicity in childhood cancer survivors: an analysis from the cardiac risk factors in childhood cancer survivors study. Pediatr Cardiol 2013; 34: 826-34.

30. El-Demerdash E, Ali AA, El-Taher DE, Hamada FM. Effect of low-protein diet on anthracycline pharmacokinetics and cardiotoxicity. J Pharm Pharmacol 2012; 64: 344-52.

31. Ho E, Brown A, Barrett P, et al. Subclinical anthracycline- and trastuzumab-induced cardiotoxicity in the long-term follow-up of asymptomatic breast cancer survivors: a speckle tracking echocardiographic study. Heart 2010; 96: 701-7.

32. Sterba M, Popelova O, Lenco J, et al. Proteomic insights into chronic anthracycline cardiotoxicity. J Mol Cell Cardiol 2011; 50: 849-62.

33. Jirkovsky E, Popelova O, Krivakova-Stankova P, et al. Chronic anthracycline cardiotoxicity: molecular and functional analysis with focus on nuclear factor erythroid 2-related factor 2 and mitochondrial biogenesis pathways. J Pharmacol Exp Therap 2012; 343: 468-78.

34. Sterba M, Popelova O, Vavrova A, et al. Oxidative stress, redox signaling, and metal chelation in anthracycline cardiotoxicity and pharmacological cardioprotection. Antioxid Redox Signal 2013; 18: 899-929.

35. Vavrova A, Popelova O, Sterba M, et al. In vivo and in vitro assessment of the role of glutathione antioxidant system in anthracycline-induced cardiotoxicity. Arch Toxicol 2011; 85: 525-35.

36. Force T, Wang Y. Mechanism-based engineering against anthracycline cardiotoxicity. Circulation 2013; 128: 98-100.

37. Menna P, Salvatorelli E, Minotti G. Anthracycline degradation in cardiomyocytes: a journey to oxidative survival. Chem Res Toxicol 2010; 23: 6-10.

38. Kocik M, Zimovjanova M, Petruzelka L, Kodydkova J, Vavrova L, Zak A. Oxidative stress after anthracycline therapy in patients with solid tumors. Casopis Lekaru Ceskych 2012; 151: 463-7.

39. Menna P, Paz OG, Chello M, Covino E, Salvatorelli E, Minotti G. Anthracycline cardiotoxicity. Expert Opin Drug Safety 2012; 11 Suppl 1: S21-36.

40. Eizaguirre A, Yanez M, Eriksson LA. Stability and iron coordination in DNA adducts of anthracycline based anti-cancer drugs. Phys Chem Chem Phys 2012; 14: 12505-14.

41. Cascales A, Sanchez-Vega B, Navarro N, et al. Clinical and genetic determinants of anthracycline-induced cardiac iron accumulation. Int J Cardiol 2012; 154: 282-6.

42. Chen B, Zhong L, Roush SF, et al. Disruption of a GATA4/Ankrd1 signaling axis in cardiomyocytes leads to sarcomere disarray: implications for anthracycline cardiomyopathy. PloS One 2012; 7: e35743.

43. Semsei AF, Erdelyi DJ, Ungvari I, et al. ABCC1 polymorphisms in anthracycline-induced cardiotoxicity in childhood acute lymphoblastic leukaemia. Cell Biol Intern 2012; 36: 79-86.

44. Oztarhan K, Guler S, Aktas B, Arslan M, Salcioglu Z, Aydogan G. The value of echocardiography versus cardiac troponin I levels in the early detection of anthracycline cardiotoxicity in childhood acute leukemia: prospective evaluation of a 7-year-long clinical follow-up. Pediatr Hematol Oncol 2011; 28: 380-94.

45. Dickey JS, Rao VA. Current and proposed biomarkers of anthracycline cardiotoxicity in cancer: emerging opportunities in oxidative damage and autophagy. Curr Mol Med 2012; 12: 763-71.

46. Romano S, Fratini S, Ricevuto E, et al. Serial measurements of NT-proBNP are predictive of not-high-dose anthracycline cardiotoxicity in breast cancer patients. Br J Cancer 2011; 105: 1663-8.

47. Stachowiak P, Kornacewicz-Jach Z, Safranow K. Prognostic role of troponin and natriuretic peptides as biomarkers for deterioration of left ventricular ejection fraction after chemotherapy, Arch Med Sci 2014; 10: 1007-18.

48. Arslan D, Cihan T, Kose D, et al. Growth-differentiation factor-15 and tissue Doppler imaging in detection of asymptomatic anthracycline cardiomyopathy in childhood cancer survivors. Clin Biochem 2013; 46: 1239-43.

49. Garrone O, Crosetto N, Lo Nigro C, et al. Prediction of anthracycline cardiotoxicity after chemotherapy by biomarkers kinetic analysis. Cardiovasc Toxicol 2012; 12: 135-42.

50. Huszno J, Badora A, Nowara E. The influence of steroid receptor status on the cardiotoxicity risk in HER2-positive breast cancer patients receiving trastuzumab. Arch Med Sci 2015; 11: 371-7.

51. Almeida D, Gerhard R, Leitao D, Davilla C, Damasceno M, Schmitt F. Topoisomerase II-alfa gene as a predictive marker of response to anthracyclines in breast cancer. Pathol Res Pract 2014; 210: 675-9.

52. Trinh BQ, Ko SY, Barengo N, Lin SY, Naora H. Dual functions of the homeoprotein DLX4 in modulating responsiveness of tumor cells to topoisomerase II-targeting drugs. Cancer Res 2013; 73: 1000-10.

53. Tokiniwa H, Horiguchi J, Takata D, et al. Topoisomerase II alpha expression and the Ki-67 labeling index correlate with prognostic factors in estrogen receptor-positive and human epidermal growth factor type-2-negative breast cancer. Breast Cancer 2012; 19: 309-14.

54. Piotrowski G, Gawor R, Stasiak A, Gawor Z, Potemski P, Banach M. Cardiac complications associated with trastuzumab in the setting of adjuvant chemotherapy for breast cancer overexpressing human epidermal growth factor receptor type 2 – a prospective study. Arch Med Sci 2012; 8: 227-35.

55. Basar EZ, Corapcioglu F, Babaoglu K, Anik Y, Gorur Daglioz G, Dedeoglu R. Are cardiac magnetic resonance imaging and radionuclide ventriculography good options against echocardiography for evaluation of anthracycline induced chronic cardiotoxicity in childhood cancer survivors? Pediatr Hematol Oncol 2014; 31: 237-52.

56. Charehbili A, Wasser MN, Smit VT, et al. Accuracy of MRI for treatment response assessment after taxane- and anthracycline-based neoadjuvant chemotherapy in HER2-negative breast cancer. Eur J Surg Oncol 2014; 23: 344-352.

57. Neilan TG, Coelho-Filho OR, Shah RV, et al. Myocardial extracellular volume by cardiac magnetic resonance imaging in patients treated with anthracycline-based chemotherapy. Am J Cardiol 2013; 111: 717-22.

58. Erdogan D, Yucel H, Alanoglu EG, et al. Can comprehensive echocardiographic evaluation provide an advantage to predict anthracycline-induced cardiomyopathy? Turk Kardiyoloji Dernegi Arsivi 2011; 39: 646-53.

59. Dietz AC, Sivanandam S, Konety S, et al. Evaluation of traditional and novel measures of cardiac function to detect anthracycline-induced cardiotoxicity in survivors of childhood cancer. J Cancer Surviv 2014; 8: 183-9.

60. Stoodley PW, Richards DA, Hui R, et al. Two-dimensional myocardial strain imaging detects changes in left ventricular systolic function immediately after anthracycline chemotherapy. Eur J Echocardiogr 2011; 12: 945-52.

61. Motoki H, Koyama J, Nakazawa H, et al. Torsion analysis in the early detection of anthracycline-mediated cardiomyopathy. Eur Heart J Cardiovasc Imag 2012; 13: 95-103.

62. Patel CD, Balakrishnan VB, Kumar L, Naswa N, Malhotra A. Does left ventricular diastolic function deteriorate earlier than left ventricular systolic function in anthracycline cardiotoxicity? Hell J Nucl Med 2010; 13: 233-7.

63. Feola M, Garrone O, Occelli M, et al. Cardiotoxicity after anthracycline chemotherapy in breast carcinoma: effects on left ventricular ejection fraction, troponin I and brain natriuretic peptide. Int J Cardiol 2011; 148: 194-8.

64. Pellicori P, Calicchia A, Lococo F, Cimino G, Torromeo C. Subclinical anthracycline cardiotoxicity in patients with acute promyelocytic leukemia in long-term remission after the AIDA protocol. Congest Heart Fail 2012; 18: 217-21.

65. Stoodley PW, Richards DA, Boyd A, et al. Left ventricular systolic function in HER2/neu negative breast cancer patients treated with anthracycline chemotherapy: a comparative analysis of left ventricular ejection fraction and myocardial strain imaging over 12 months. Eur J Cancer 2013; 49: 3396-403.

66. Yildirim A, Tunaoglu FS, Pinarli FG, et al. The role of dobutamine stress echocardiography in early diagnosis of cardiac toxicity in long-term survivors of asymptomatic children treated with anthracycline. Anatol J Cardiol 2010; 10: 154-62.

67. Uchikoba Y, Fukazawa R, Ohkubo T, Maeda M, Ogawa S. Early detection of subclinical anthracycline cardiotoxicity on the basis of QT dispersion. J Nippon Med School 2010; 77: 234-43.

68. Geiger S, Stemmler HJ, Suhl P, et al. Anthracycline-induced cardiotoxicity: cardiac monitoring by continuous wave-Doppler ultrasound cardiac output monitoring and correlation to echocardiography. Onkologie 2012; 35: 241-6.

69. Tantawy AA, Elmasry OA, Shaaban M, Toaima DN, El Shahat AM. Radionuclide ventriculography detects early anthracycline cardiotoxicity in children with Hodgkin lymphoma. J Pediatr Hematol Oncol 2011; 33: e132-7.

70. Sieswerda E, van Dalen EC, Postma A, Cheuk DK, Caron HN, Kremer LC. Medical interventions for treating anthracycline-induced symptomatic and asymptomatic cardiotoxicity during and after treatment for childhood cancer. Cochrane Database Syst Rev 2011; 9: CD008011.

71. Corradi F, Paolini L, De Caterina R. Ranolazine in the prevention of anthracycline-related cardiotoxicity. G Ital Cardiol 2013; 14: 424-37.

72. Cai C, Lothstein L, Morrison RR, Hofmann PA. Protection from doxorubicin-induced cardiomyopathy using the modified anthracycline N-benzyladriamycin-14-valerate (AD 198). J Pharmacol Exp Therap 2010; 335: 223-30.

73. Broeyer FJ, Osanto S, Suzuki J, et al. Evaluation of lecithinized human recombinant super oxide dismutase as

cardioprotectant in anthracycline-treated breast cancer patients. Br J Clin Pharmacol 2014; 78: 950-60.

74. Goey AK, Schellens JH, Beijnen JH, Huitema AD. [Dexrazoxane in anthracycline induced cardiotoxicity and extravasation]. Nederlands Tijdschrift Voor Geneeskunde 2010; 154: A1155.

75. Wang P, Zhang S, Zhang XB, Li WJ, Hao XM, Zhang J. [Protective effect of dexrazoxane on cardiotoxicity in breast cancer patients who received anthracycline-containing chemotherapy]. Zhonghua Zhong Liu Za Zhi 2013; 35: 135-9.

76. Kang M, Kim KI, Song YC, Shin WG, Oh JM. Cardioprotective effect of early dexrazoxane use in anthracycline treated pediatric patients. J Chemother 2012; 24: 292-6.

77. Popovic M, Kolarovic J, Mikov M, Trivic S, Kaurinovic B. Anthracycline-based combined chemotherapy in the mouse model. Eur J Drug Metabol Pharmacokinet 2007; 32: 101-8.

78. Tacyildiz N, Ozyoruk D, Ozelci Kavas G, et al. Selenium in the prevention of anthracycline-induced cardiac toxicity in children with cancer. J Oncol 2012; 2012: 651630.

79. Petrelli F, Borgonovo K, Cabiddu M, Lonati V, Barni S. Mortality, leukemic risk, and cardiovascular toxicity of adjuvant anthracycline and taxane chemotherapy in breast cancer: a meta-analysis. Breast Cancer Res Treat 2012; 135: 335-46.

80. Feng QJ, Zhang F, Huang XY, Wu ZX. Effectiveness and complications of anthracycline and taxane in the therapy of breast cancer: a meta-analysis. Pathol Oncol Res 2014; 20: 179-84.

81. Carbone A, Psaltis PJ, Nelson AJ, et al. Dietary omega-3 supplementation exacerbates left ventricular dysfunction in an ovine model of anthracycline-induced cardiotoxicity. J Card Fail 2012; 18: 502-11.

82. Creutzig U, Zimmermann M, Dworzak M, et al. Favourable outcome of patients with childhood acute promyelocytic leukaemia after treatment with reduced cumulative anthracycline doses. Br J Haematol 2010; 149: 399-409.

83. Walker JR, Sharma A, Lytwyn M, et al. The cardioprotective role of probucol against anthracycline and trastuzumab-mediated cardiotoxicity. J Am Soc Echocardiogr 2011; 24: 699-705.

84. Piotrowski G, Gawor R, Bourge RC, et al. Heart remodeling induced by adjuvant trastuzumab-containing chemotherapy for breast cancer overexpressing human epidermal growth factor receptor type 2: a prospective study. Pharmacol Res 2013; 78: 41-8.

85. Corradi F, Paolini L, De Caterina R. Ranolazine in the prevention of anthracycline cardiotoxicity. Pharmacol Res 2014; 79: 88-102.

86. Huelsenbeck J, Henninger C, Schad A, Lackner KJ, Kaina B, Fritz G. Inhibition of Rac1 signaling by lovastatin protects against anthracycline-induced cardiac toxicity. Cell Death Dis 2011; 2: e190.

87. Seicean S, Seicean A, Plana JC, Budd GT, Marwick TH. Effect of statin therapy on the risk for incident heart failure in patients with breast cancer receiving anthracycline chemotherapy: an observational clinical cohort study. J Am Coll Cardiol 2012; 60: 2384-90.

88. Elitok A, Oz F, Cizgici AY, et al. Effect of carvedilol on silent anthracycline-induced cardiotoxicity assessed by strain imaging: a prospective randomized controlled study with 6-month follow-up. Cardiol J 2014; 21: 509-15.

89. Liu L, Liu ZZ, Liu YY, et al. Preventive effect of low-dose carvedilol combined with candesartan on the cardiotoxicity of anthracycline drugs in the adjuvant chemother-apy of breast cancer. Zhonghua Zhong Liu Za Zhi 2013; 35: 936-40.

90. Kaya MG, Ozkan M, Gunebakmaz O, et al. Protective effects of nebivolol against anthracycline-induced cardiomyopathy: a randomized control study. Int J Cardiol 2013; 167: 2306-10.

91. Simmons A, Vacek JL, Meyers D. Anthracycline-induced cardiomyopathy. Postgrad Med 2008; 120: 67-72.

92. Iarussi D, Indolfi P, Casale F, Martino V, Di Tullio MT, Calabro R. Anthracycline-induced cardiotoxicity in children with cancer: strategies for prevention and management. Paediatr Drugs 2005; 7: 67-76.

93. Silber JH. Role of afterload reduction in the prevention of late anthracycline cardiomyopathy. Pediatr Blood Cancer 2005; 44: 607-13.

94. De Angelis A, Piegari E, Cappetta D, et al. Anthracycline cardiomyopathy is mediated by depletion of the cardiac stem cell pool and is rescued by restoration of progenitor cell function. Circulation 2010; 121: 276-92.

95. Hayward R, Lien CY, Jensen BT, Hydock DS, Schneider CM. Exercise training mitigates anthracycline-induced chronic cardiotoxicity in a juvenile rat model. Pediatr Blood Cancer 2012; 59: 149-54.

96. Chuang CY, Han WR, Li PC, Song MY, Young ST. Effect of long-term music therapy intervention on autonomic function in anthracycline-treated breast cancer patients. Integrat Cancer Therap 2011; 10: 312-6.

97. Isidori A, Venditti A, Maurillo L, et al. Alternative novel therapies for the treatment of elderly acute myeloid leukemia patients. Exp Rev Hematol 2013; 6: 767-84.