CHEMOTHERAPY-INDUCED CARDIOTOXICITY: PATHO-PHYSIOLOGY AND PREVENTION

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Abstract

Along with the remarkable progress registered in oncological treatment that led to increased survival of cancer patients, treatment-related comorbidities have also become an issue for these long-term survivors. Of particular interest is the development of cardiotoxic events, which, even when asymptomatic, not only have a negative impact on the patient`s cardiac prognosis, but also considerably restrict therapeutic opportunities. The pathophysiology of cytostatic-induced cardiotoxicity implies a series of complex and intricate mechanisms, whose understanding enables the development of preventive and therapeutic strategies. Securing cardiac function is an ongoing challenge for the pharmaceutical industry and the physicians who have to deal currently with these adverse reactions. This review focuses on the main mechanism of cardiac toxicity induced by anticancer drugs and especially on the current strategies applied for preventing and minimizing the cardiac side effects.

Keywords: cardiotoxicity, chemotherapy, cardiomyopathy, prevention, cardioprotective drugs.

Background

Chemotherapy has shown great progress over the past two decades, leading to the gradual increase in the survival of cancer patients [1]. However, along with this benefit, the cardiovascular side effects of modern cytostatics have also proven to be an increasing problem, even years after completion of therapy [2,3]. The development of cardiotoxic events, even when they are asymptomatic, not only has a negative impact on the patient's cardiac prognosis, but it also considerably restricts the therapeutic opportunities. The clinical manifestations of cardiotoxicity (CT) cover a broad spectrum of disorders, ranging from mild transient arrhythmias to potentially lethal conditions such as myocardial ischemia or infarction and cardiomyopathy (CMP).

Considering that cardiac damage may limit optimal anticancer treatment and that several pathological myocardial changes can be irreversible, attention was directed towards elucidating the underlying mechanism of cardiotoxicity and the improvement of cardiologic monitoring of neoplastic patients [4-8]. Securing cardiac function is an ongoing challenge for the pharmaceutical industry and the physicians who have to deal currently with these adverse reactions [3,7]. The appropriate management should include better detection of those patients at risk, the development of preventive strategies and the early treatment of cardiotoxicity when it does appear.

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Antineoplastic drugs and cardiotoxicity mechanisms

The most studied chemotherapeutic agents associated with adverse cardiac events are anthracyclines (ANT) (Doxorubicin), used in the treatment of many adult malignancies like breast cancer, sarcoma, lymphoma, or gynecological cancer. They also play an important role in the treatment of childhood cancers, anthracyclines are currently used in more than 50% of regimens contributing to the overall survival rates in excess of 75% [9]. Other cytostatics more frequently correlated with cardiotoxic side effects are taxanes (paclitaxel, docetaxel), alkylating agents (Carboplatin, Cisplatin, Cyclophosphamide), small

molecule tyrosine kinase inhibitors (lapatinib, imatinib, sorafenib, sunitinib) and trastuzumab, a monoclonal antibody directed against the human epidermal growth factor receptor-2 (HER2), used in the treatment of metastatic breast neoplasm.

The mechanisms of doxorubicin cardiotoxicity are necrosis and apoptosis of cardiac myocyte followed by myocardial fibrosis, and, as a result, doxorubicin cardiotoxicity is considered to be irreversible [10-12]. The pathophysiological molecular substrate in CT involves several processes like the formation of iron-dependent oxygen free radicals and subsequent peroxidation of lipids in the membranes of myocardial mitochondria [13], suppression of DNA, RNA and proteins synthesis [4] as well as of important transcription factors that regulate cardiospecific genes [14,15], altering adrenergic and adenylyl cyclase activity [16] and disrupt calcium homeostasis [17]. Recent studies suggest that doxorubicin-induced cardiotoxicity is mediated by topoisomerase-IIβ in cardiomyocytes, a molecule that might represent a target for future cardioprotective drugs [18,19].

Inhibition of HER2 (also known as ErbB2) by trastuzumab modifies mitochondrial integrity via the BCL-X (B-cell CLL/lymphoma-X) protein family, depleting ATP and leading to contractile dysfunction [20,21]. HER2 conjugates with HER4/neureguline1 complex forming heterodimers that promote the activation of several signaling pathways, such as Src–FAK (sarcoma-focal adhesion kinase complex), which increases intercellular contact and mechanical junction [22], or phosphatidylinositol 3-kinase and mitogen-activated protein kinase (MAPK), which stimulate the proliferation, survival and contractile function of cardiac myocytes [23]. Experimental studies have shown that HER2, HER4 and neuregulin1 play an essential role in heart development, considering the fact that the development of mouse embryos is impossible if one of them is absent [24].

Prevention

Identifying patients at risk

The first step in developing preventive strategies is identifying various contributing risk factors for the occurrence of adverse cardiac events. The incidence of chemotherapy-induced cardiotoxicity is variable and the patient-related risk factors so far described are: age, female gender, history of or pre-existing cardiovascular disorders, electrolyte imbalances such as hypokalemia and hypomagnesemia, concurrent administration of cardiotoxic agents, prior anthracycline chemotherapy or prior mediastinal radiation therapy [25].

All patients undergoing chemotherapy should have prior careful clinical evaluation and assessment of CV risk factors or comorbidities. Schmidinger et al. [26] have shown that the pre-existing cardiac disease is underestimated in patients with cancer, as the incidence reported in the study was 9.3%. Many of the cardiovascular risk factors such as hypertension, diabetes, dyslipidemia or electrolyte disturbances can be treated and corrected before the anticancer treatment is started and thereafter closely monitored during therapy [27,28]. Patients with pre-existing cardiac disease or taking drugs that potentially lead to QT prolongation should be evaluated by an advised cardiologist [27].

Regarding imaging techniques, baseline Doppler echocardiography is used in current clinical practice for the assessment of patients treated with anthracyclines, especially those in the high risk group. Echocardiography is also necessary to assess cardiac function in all patients undergoing therapy with trastuzumab, particularly in patients treated previously with anthracyclines [25]. Patients should be reevaluated every 12 weeks. Considerably studied now is the benefit brought by performing baseline measurement of biomarker concentrations (troponin I, B-type natriuretic peptide), but this approach implies larger costs and is still controversial [29].

Regimens of chemotherapy administration

Therapy-related risk factors for chemotherapy–induced cardiotoxic events include: drug type, total dose administered during a day or a cycle, cumulative dose, administration schedule, route of administration, association with other cardiotoxic drugs or concomitant radiotherapy [25].

Cumulative dose. The risk of anthracycline and other cytostatic induced CT can be decreased by maintaining the cumulative dose below the recommended threshold (Table I).

However, this tactic might result in the discontinuation of anthracycline administration in some patients who might obtain additional benefits from treatment. Furthermore, the use of lower doses is not totally secure for the heart or effective from an oncological point of view. Even patients receiving low-dose anthracycline can show signs of heart disease [30]. This variation in susceptibility may be partly explained by certain genes polymorphism, but only a few studies have examined this issue and the results are still contradictory.

Tabel I. Recommended maximum cumulative doses for Anthracyclines

400-450 mg/m^2 for doxorubicin
900 mg/m^2 for epirubicin
800 mg/m^2 for daunorubicin
160 mg/m^2 for idarubicin

Administration rate. Lowered toxicity can also be obtained by slowing the rate of drug administration. Prolonged infusion over 48 to 96 hours allows higher dosage with lower incidence of cardiac toxicity, secondary to lower peak plasma levels of doxorubicin with continuous infusion [31]. Lower weekly doses instead of conventional

higher 3-week dose schedules also allow higher cumulative doses before the same degree of cardiotoxicity. Regarding pediatric cancers, in a recent study, Lipshultz et al. [30] found that there was no difference in cardiotoxic manifestations in children with acute lymphoblastic leukemia, treated with anthracyclines administer in bolus versus those treated with continuous infusion over 48 hours.

Of current interest are the short-term chemotherapy regimens that correlate with lesser side effects and better cost-efficiency ratio [3]. The Finland Herceptin trial concluded that a nine weeks breast cancer treatment with trastuzumab in combination with docetaxel and vinorelbine was associated with reduced cardiotoxicity while maintaining antineoplastic efficacy [32]. Although the results seem promising, further studies are needed to address all aspects of this therapeutic approach.

Peak dose. Another influential factor in chemotherapy-induced cardiotoxicity is the peak serum concentration reached during administration. However, in a large meta-analysis by van Dalen et al., patients treated with doxorubicin who experienced peak doses of less than 60mg/m^2 were compared to those with higher values of up to 81mg/m^2 [33]. They found no significant difference between the two groups concerning clinically manifested heart failure or in the overall survival of patients. Similarly, Fountzilas et al., reached the same conclusion concerning epirubicin, in a randomized clinical trial on 1086 breast cancer patients treated with epirubicine, administred in two serum peak doses: of 83 mg/m^2 versus 110 mg/m^2 [34].

Synthetic analogues of natural compounds

Anthracycline derivates

In an effort to prevent or reduce CT, extensive research has been dedicated to the identification of anthracycline derivates with less cardiotoxic effects than doxorubicin, such as daunorubicin, epirubicin and idarubicin. Out of these, epirubicin is considered a viable alternative in the treatment of advanced adult breast cancer, associated with decreased risk of clinical and subclinical cardiotoxicity compared with doxorubicin, with no difference in tumor response rate or survival [35,36]. Nevertheless, van Dalen et al. concluded, in the meta-analysis cited above, that they "are not able to favor either epirubicin or doxorubicin when given in the same dose" [33]. Based on the currently available evidence on heart failure, they conclude that, in adults with a solid tumor, pegylated liposomal-encapsulated doxorubicin should be favored over both, doxorubicin and epirubicine. Furthermore, no conclusions can be made about the effects of treatment in children with cancer or in patients diagnosed with leukemia.

Liposomal incapsulated anthracyclines

The liposome-encapsulated anthracyclines were developed to reduce doxorubicin toxicity by modifying its tissue distribution and pharmacokinetics [37]. These are high density molecules that cannot extravasate through tight capillary junctions, characteristic to heart muscle, but easily penetrate areas of immature vascular systems, such as tumoral tissue [38]. Encapsulating anthracyclines into liposomes has an obvious benefit, proven in various meta-analyses, allowing patients to receive much higher doses of cytostatics, delivered preferentially into the tumor tissue with fewer cardio-vascular side effects [39]. Liposomal doxorubicin has proven to be as effective as the original molecule in antitumoral outcome, but associated with considerably less cardiac and gastrointestinal toxicity [40,41].

Pegylated liposome-encapsulated doxorubicin (PLD) is surrounded by a polyethylene glycol (PEG) layer which represents a hydrophilic protective barrier between the liposome and the microenvironment, thus preventing the activation of the host immune system, that targets and destroys the liposomal structure, leading to the release of the free drug. As previously mentioned, most randomized trials and meta-analyses in adults comparing PLD with the standard molecule, concluded that they are about as effective in antitumoral results, but correlated with less cardiotoxicity [42], with the amendment that this therapy cannot be also extrapolated to pediatric neoplasms [43].

Trastuzumab-toxin conjugates

Although trastuzumab represents a successful treatment in HER2-positive breast cancer, most metastatic neoplasms, showing HER2 overexpression, manage to develop resistance to transtuzumab within one year of treatment initiation, becoming thus ineffective [44]. Developing trastuzumab-conjugated immunotoxins and nano-immunoconjugates is a promising approach to increase trastuzumab antitumoral efficacy and optimise its therapeutic window (gap between the effective dose and the toxic dose) [45]. Phillips et al. have demonstrated that DM1 (fungal toxin derived from maytansine)-conjugated trastuzumab, is associated with enhanced antineoplasic cytotoxic effect but reduced cardiotoxicity [46]. The benefits and tolerability of this trastuzumab conjugate in breast cancer treatment have been confirmed several clinical studies [45].

Prodrugs

Prodrugs represent one of the most frequently biochemical strategies used towards improving the therapeutic index of anticancer drugs. They are derivatives of drugs that remain inactive or less active in their original form, but which are metabolize inside the body to generate active drugs at the site of action. Prodrugs are associated with reduced toxicity, improved specificity and decreased rate of gaining tumor resistance to chemotherapy [47,48]. Several prodrugs have been developed by conjugating chemotherapeutical agents with various carbohydrates, antibodies, serum proteins, liposomes and synthetic polymers [49,50]. These conjugates can be specifically activated only by cancer cells and cannot breach normal

cells.

There are certain prodrugs with established clinical success, such as capecitabine, an enzyme activated prodrug, that represents an efficient alternative to 5-fluorouracil for the treatment of early and advanced colorectal cancer, with lesser cardio-vascular side effects [51]. 5 N-(2-hydroxypropyl) methacrylamide (HPMA), is one of the most commonly used molecular carriers due to its non-immunogenic and non-toxic proprieties, and its' prolonged circulating time [52]. Prodrugs including HPMA have been developed and tested in preclinical studies, such as caplostatin [53], P-GDM (polymer-bound geldanamycin), and P-hyd-IgG (IgG-modified HPMA copolymer-bound doxorubicin), and phase I/II clinical studies, such as a copolymer of HPMA-Gly-Phe-Leu-Gly-doxorubicin (PK1), oriented poly-galactosamine (HPMA)-doxorubicin (PK2), AP5346 and AP5280 [54]. Of current interest are the fluorescence-active ligands, that allow tracking drug release *in vivo*, thus "providing significant advances toward deeper understanding and exploration of theranostic drug-delivery systems" [55].

Cardioprotective drugs

Dexrazoxane

Dexrazoxane (ICRF-187) is the only drug approved by the US Food and Drug Administration for the prevention of cardiac toxicity induced by anthracycline treatment in adults. This drug acts by chelation of iron redox-active molecules, thus preventing the formation of anthracycline-iron complex and subsequent development of reactive oxygen species [56]. Although there is some controversy regarding this drug that it may reduce the antitumoral efficacy of chemotherapeutics, in the meta-analysis by van Dalen et al., the use of dexrazoxane during doxorubicin treatment was associated with a low risk of symptomatic heart failure (hazard ratio 0.18, CI 0.1 to 0.32, $P<0.001$), and no significant difference in oncological response; the only adverse effect associated with administration of dexrazoxane was an increased risk of leukopenia at nadir, but not during recovery [33]. The use of dexrazoxane implies additional costs and slight uncertainties, so ASCO guidelines state it can be considered for patients with metastatic neoplasm, already treated with a cumulative doses of doxorubicin >300mg/m^2 and may benefit from further anthracycline treatment [57].

The published clinical experience with dexrazoxane in pediatric cancer is limited, longer follow-up time is needed in children to determine whether dexrazoxane has a protective role against the long-term cardiac toxicity that can manifest years after the therapy finishing point and if it correlates with better quality of life and prolonged survival [58].

Statins

Statins are known to have pleiotropic effects that include an ability to reduce oxidative stress. Pre-clinical experiments using human cell cultures and animal models have showed that lovastatin reduces doxorubicin-induced cell death and Top2β mediated DNA damage in cardiomyocytes [59]. In animal studies, lovastatin attenuated troponin I elevation and cardiac fibrosis after exposure to doxorubicin [60] and mice treated with fluvastatin had an attenuation of left ventricular (LV) dysfunction after doxorubicin exposure, postulated to be due to antioxidant and anti-inflammatory mechanisms [61]. This data was confirmed by several small observational clinical studies, that found that uninterrupted statin (atorvastatin) therapy, initiated before and concurrent with anthracycline therapy, reduced the risk for HF development. In a recent large clinical trial, conducted on 628 breast cancer patients treated with transtuzumab, Seicean S. et al. [62] also concluded that the use of statins prior chemotherapy administration, is associated with lowered risk of left ventricular ejection fraction (LVEF) decrease and heart failure development.

β-blockers

β-adrenergic inhibitors are able to diminish mortality in patients with systolic heart failure, and there is currently an increased use of these agents to decrease the range of cardiotoxic effects induced by chemotherapy [63]. The mechanisms behind the protective effect of these agents, especially carvedilol, against ANT-induced CMP are not fully understood. Carvedilol presents antioxidant effects; it induces NO production, inhibits the mitogenic factor and suppress epidermal growth factor through angiotensin 2 receptor type-1 [64]. Recent studies have shown that certain β-blockers (carvedilol, nebivolol, alprenolol) have biased agonism at β1- and/or β2-adrenoreceptors, inhibiting signaling mediated through the traditional G protein-coupled receptors (Gα and Gβ), while activating the G protein-coupled receptor kinase/β-arrestin pathway and transactivation of epidermal growth factor receptor ErbB1 [65,66]. β-arrestin was proven to have cardioprotective effects under chronic cathecolaminic stimulation, preventing harmful remodeling in HF pathogenesis. Other possible mechanisms include: modifying the activity of the sarcoplasmic reticulum Ca-ATPase (SERCA2) preventing myocardial calcium overload, and the inhibition of the SERCA2 suppressor gene [67,68]. Furthermore, carvedilol treatment was correlated with the inhibition of the apoptotic intracellular signaling pathway [69].

Although physiopathological data suggest the cardioprotective potential of beta-blockers during cytostatic treatment, there are no phase III trials at present, that strongly encourage the routine prophylactic administration of carvedilol for protection against ANT-induced CMP. Limited small randomized placebo-controlled studies concluded that the use of carvedilol or nebivolol at chemotherapy initiation correlates with preserved LVEF and diastolic function [65,66,70,71]. The OVERCOME Trial (preventiOn of left Ventricular dysfunction with Enalapril and caRvedilol in patients

submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies) [72] proved that the combination of enalapril and carvedilol prevented LVEF decrease in patients with various hematological malignancies, undergoing intensive ANT chemotherapy. Although the treatment was well tolerated, doses had to be permanently adapted to the patient's status. There are also scarce non-randomized studies which suggests that this dual therapy is also beneficial for LVEF recovery in patients receiving trastuzumab [73,74]. However, further large randomized placebo-controlled trials are needed to define the benefits and drawbacks of this cardioprotective therapy, the optimal timing of treatment initiation and the selection of patients who will most likely benefit from using them. There are a number of ongoing studies investigating the opportunity of using β-blockers in the prevention of cardiotoxicity induced by transtuzumab including multidisciplinary approach to new therapies in Cardiology Oncology Research Trial and NCT0100818 [75].

Angiotensine converting-enzyme (ACE) Inhibitor Therapy (ACEIs)

The concept that ACE inhibitors may prevent heart failure in patients at risk is not an innovative one. Data resulted from experimental models suggest that the cardiac renin-angiotensin system (RAS) plays an important role in the development of anthracycline-induced cardiomyopathy and that treatment with ACEIs protects against chemotherapy-induced cardiotoxicity [76-78]. ACE inhibitors have antioxidant effects [79,80], attenuate aldosterone-induced cardiac fibrosis and reduce apoptosis of cardiac cells [81], they also mediate changes in gene expression that affect mitochondrial metabolism and cardiac cell functioning [82].

Several clinical studies, although limited, reported favorable results in using ACE inhibitors, like enalapril or captopril, in the prevention and treatment of anthracycline-induced cardiomyopathy. Cardinale et al. [21] conducted a placebo-controlled randomized trial focused on the effect of enalapril in monotherapy, that included 114 patients who experienced early troponin elevation (>0.07 ng/ml) after high-dose chemotherapy. Enalapril was started at a dose of 2.5 mg daily and gradually increased to 20 mg once daily. It managed to significantly reduce cardiomyopathy due to cytostatic treatment, none of the subjects receiving ACEIs, but 43% of the subjects in the control group presenting a decrease in LVEF of >10%. The OVERCOME trial [72] included patients with normal LVEF and normal troponin levels at the time of ANT initiation, the intervention group had a lower incidence of premature interruption study follow-up (6.7% vs. 24.4%, respectively, p=0.02), due to death or heart failure (6.7% vs. 22.2%, respectively, p=0.036), or a final LVEF of <45% (6.7% vs. 24.4%, respectively, p=0.02).

Nakame et al. (2005) [83] meant to characterize acute CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) induced cardiotoxicity in patients with Non-Hodgkins Lymphoma, using echocardiography, ECG and serum cardiac markers, in order to assess if valsartan (an angiotensin II type 1 receptor blocker) can have a preventive role in its' occurrence. They demonstrated that patients treated with valsartan did not present more frequently preserved LVEF, but it significantly inhibited ventricular dilatation, elevation of natriuretic peptides, and prolongation of the QTc interval. Whether angiotensin receptor blockers are useful in preventing trastuzumab cardiotoxicity is debatable, but this is an area of current active investigation [75].

Neuregulin-1 (NRG-1)

Neuregulin-1 is an agonist for tyrosine kinases receptor of the epidermal growth factor receptor family, that plays an important role in cardiac myocytes homeostasis. It has previously been shown that doxorubicin significantly reduces NRG-1 protein expression in the heart [84]. Although human recombined NRG-1 is capable of improving cardiac function in patients suffering from congestive heart failure, demonstrating a beneficial effect on pathological remodeling, and shown to improve cardiac function and survival in animal models of doxorubicin induced cardiomyopathy [85], its' use in oncological pathology is controversial due to NRG-1 capacity of stimulating tumor cell proliferation. Cardioprotective therapy with human recombined NRG-1 is promising and current research studies are focused on the development of molecules with selective tropism for cardiac cells.

Conclusions

The extensive use of chemotherapy in clinical practice has led to considerable controversy because of the potential adverse cardiovascular effects it may involve, even for patients who survived the malignant disease. Chemotherapy-induced cardiotoxicity include a combination of mechanisms which influence several intracellular signaling cascades, critical to both cancer progression and the normal functioning of the heart. Operative therapies aimed at the prevention and treatment of chemotherapy-induced cardiotoxicity are focused on tissue type specific differences, or act on downstream mediators of toxicity. Other current therapies considered for cardioprotection include typical cardio-vascular drugs, which uphold increased cardiac reserve and reverse myocardial remodeling. Larger future studies are necessary to reach a point of secure cytostatic therapy, improved patient survival and quality of life.

References

1. Minami M, Matsumoto S, Horiuchi H. Cardiovascular side-effects of modern cancer therapy. Circ J. 2010;74:1779-1786.
2. Yeh ET, Bickford CL. Cardiovascular complications of cancer therapy: incidence, pathogene-sis, diagnosis, and management. J Am Coll Cardiol. 2009;53:2231-2247.

3. Raschi E, Vasina V, Ursino MG, Boriani G, Martoni A, De Ponti F. Anticancer drugs and cardiotoxicity: insights and perspectives in the era of targeted therapy. Pharmacol Ther. 2010;125:196-218.
4. Lim CC, Zuppinger C, Guo X, Kuster GM, Helmes M, Eppenberger HM, et al. Anthracyclines induce calpain-dependent titin proteolysis and necrosis in cardiomyocytes. J Biol Chem. 2004;279:8290-8299.
5. Albini A, Cesana E, Donatelli F, Cammarota R, Bucci EO, Baravelli M, et al. Cardio-oncology in targeting the HER receptor family: the puzzle of different cardiotoxicities of HER2 inhibitors. Future Cardiol. 2011;7:693-704.
6. Magnano LC, Martínez Cibrian N, Andrade González X, Bosch X. Cardiac complications of chemotherapy: role of prevention. Curr Treat Options Cardiovasc Med. 2014;16(6):312. doi: 10.1007/s11936-014-0312-7.
7. Saif MW, Shah MM, Shah AR. Fluoropyrimidine-associated cardiotoxicity: revisited. Expert Opin Drug Saf. 2009;8:191-202.
8. Altena R, Perik PJ, van Veldhuisen DJ, de Vries EG, Gietema JA. Cardiovascular toxicity caused by cancer treatment: strategies for early detection. Lancet Oncol. 2009;10:391-399.
9. Smith LA, Cornelius VR, Plummer CJ, Levitt G, Verrill M, Canney P, et al. Cardiotoxicity of anthracycline agents for the treatment of cancer: Systematic review and meta-analysis of randomised controlled trials. BMC Cancer. 2010;10:337.
10. Sawyer DB, Peng X, Chen B, Pentassuglia L, Lim CC. Mechanisms of anthracycline cardiac injury: can we identify strategies for cardioprotection? Prog Cardiovasc Dis. 2010;53:105–113.
11. Youn HJ, Kim HS, Jeon MH, Lee JH, Seo YJ, Lee YJ, et al. Induction of caspase-independent apoptosis in H9c2 cardiomyocytes by adriamycin treatment. Mol Cell Biochem. 2005;270:13–19.
12. Chung WB, Youn HJ, Choi YS, Park CS, Oh YS, Chung WS, et al. The expression of cardiac ankyrin repeat protein in an animal model of adriamycin-induced cardiomyopathy. Korean Circ J. 2008;38:455–461.
13. Cvetkovic RS, Scott LJ. Dexrazoxane: A review of its use for cardioprotection during anthracycline chemotherapy. Drugs. 2005;68:1005-1024.
14. Takahashi S, Denvir MA, Harder L, Miller DJ, Cobbe SM, Kawakami M, et al. Effects of in vitro and in vivo exposure to doxorubicin (adriamycin) on caffeine-induced Ca2+ release from sarcoplasmic reticulum and contractile protein function in ''chemically-skinned'' rabbit ventricular trabeculae. Jpn J Pharmacol. 1998;76:405-413.
15. Lebrecht D, Kokkori A, Ketelsen UP, Setzer B, Walker UA. Tissue-specific mtDNA lesions and radical-associated mitochondrial dysfunction in human hearts exposed to doxorubicin. J Pathol. 2005;207:436-444.
16. Mordente A, Meucci E, Silvestrini A, et al. New developments in anthracycline-induced cardiotoxicity. Curr Med Chem. 2009;16:1656-1672.
17. Dodd DA, Atkinson JB, Olson RD, Buck S, Cusack BJ, Fleischer S, et al. Doxorubicin cardiomyopathy is associated with a decrease in calcium release channel of the sarcoplasmic reticulum in a chronic rabbit model. J Clin Invest. 1993;91:1697-1705.
18. Vejpongsa P, Yeh ET. Topoisomerase 2β: a promising molecular target for primary prevention of anthracycline-induced cardiotoxicity. Clin Pharmacol Ther. 2014;95(1):45-52. doi: 10.1038/clpt.2013.201.
19. Zhang S, Liu X, Bawa-Khalfe T, Lu LS, Lyu YL, Liu LF, et al. Identification of the molecular basis of doxorubicin-induced cardiotoxicity. Nat Med. 2012;18:1639-1642.
20. Nakagami H, Takemoto M, Liao JK. NADPH oxidase-derived superoxide anion mediates angiotensin II-induced cardiac hypertrophy. J Mol Cell Cardiol. 2003;35:851-859.
21. Cardinale D, Colombo A, Sandri MT, Lamantia G, Colombo N, Civelli M, et al. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. Circulation. 2006;114:2474-2481.
22. Kuramochi Y, Guo X, Sawyer DB. Neuregulin activates erbB2-dependent src/FAK signalling and cytoskeletal remodelling in isolated adult rat cardiac myocytes. J Mol Cell Cardiol. 2006;41:228-235.
23. Baliga RR, Pimental DR, Zhao YY, Simmons WW, Marchionni MA, Sawyer DB, et al. NRG-1 induced cardiomyocyte hypertrophy. Role of PI-3-kinase, p70(S6K), and MEK-MAPK-RSK. Am J Physiol. 1999;277:H2026-2037.
24. Force T, Krause DS, Van Etten RA. Molecular mechanisms of cardiotoxicity of tyrosine kinase inhibition. Nat Rev Cancer. 2007;7:332-344.
25. Bovelli D, Plataniotis G, Roila F, ESMO Guidelines Working Group. Cardiotoxicity of chemotherapeutic agents and radiotherapy-related heart disease: ESMO Clinical Practice Guidelines. Ann Oncol. 2010;21(suppl 5):277-282.
26. Schmidinger M, Zielinski CC, Vogl UM, Bojic A, Bojic M, Schukro C, et al. Cardiac toxicity of sunitinib and sorafenib in patients with metastatic renal cell carcinoma. J Clin Oncol. 2008;26:5204-5212.
27. Ederhy S, Cohen A, Dufaitre G, Izzedine H, Massard C, Meuleman C, et al. QT interval prolongation among patients treated with angiogenesis inhibitors. Target Oncol. 2009;4:89-97.
28. Altena R, Perik PJ, van Veldhuisen DJ, de Vries EG, Gietema JA. Cardiovascular toxicity caused by cancer treatment: strategies for early detection. Lancet Oncol. 2009;10:391-399.
29. Kang Y, Xu X, Cheng L, Li L, Sun M, Chen H, et al. Two-dimensional speckle tracking echocardiography combined with high-sensitive cardiac troponin T in early detection and prediction of cardiotoxicity during epirubicine-based chemotherapy. Eur J Heart Fail. 2014;16(3):300-308.
30. Lipshultz SE, Lipsitz SR, Sallen SE, Dalton VM, Mone SM, Gelber RD, et al. Chronic progressive cardiac dysfunction years after doxorubicin therapy for childhood acute lymphoblastic leukemia. J Clin Oncol. 2005;23(12):2629–2636.
31. Barrett-Lee PJ, Dixon JM, Farrell C, Jones A, Leonard R, Murray N, et al. Expert opinion on the use of anthracyclines in patients with advanced breast cancer at cardiac risk. Ann Oncol. 2009;20(5):816-827.
32. Villman K, Sjöström J, Heikkilä R, Hultborn R, Malmström P, Bengtsson NO, et al. TOP2A and HER2 gene amplification as predictors of response to anthracycline treatment in breast cancer. Acta Oncol. 2006;45:590-596.
33. Van Dalen EC, Michiels EM, Caron HN, Kremer LC. Different anthracycline derivates for reducing cardiotoxicity in cancer patients. Cochrane Database Syst Rev. 2010;CD005006.
34. Fountzilas G, Dafni U, Gogas H, Linardou H, Kalofonos HP, Briasoulis E, et al. Postoperative dose-dense sequential chemotherapy with epirubicin, paclitaxel and CMF in patients with high-risk breast cancer: safety analysis of the Hellenic Cooperative Oncology Group randomized phase III trial HE 10/00. Ann Oncol. 2008;19(5):853-860.
35. Cortés-Funes H, Coronado C. Role of anthracyclines in the era

of targeted therapy. Cardiovasc Toxicol. 2007;7:56-60.
36. Căinap C, Părău A, Muntean A, Hodorog A, Vlad L. New generation chemotherapy in the treatment of operated gastric cancer--an alternative to traditional chemotherapy. Chirurgia (Bucur). 2010;105(1):31-36.
37. Rafiyath SM, Rasul M, Lee B, Wei G, Lamba G, Liu D. Comparison of safety and toxicity of liposomal doxorubicin vs. conventional anthracyclines: a meta-analysis. Exp Hematol Oncol. 2012;1(1):10. doi: 10.1186/2162-3619-1-10.
38. Wouters KA, Kremer LC, Miller TL, Herman EH, Lipshultz SE. Protecting against anthracycline-induced myocardial damage: a review of the most promising strategies. Br J Haematol. 2005;131:561-578.
39. Safra T: Cardiac safety of liposomal anthracyclines. Oncologist 2003, 8 Suppl 2:17-24.
40. Simunek T, Sterba M, Popelova O, Adamcova M, Hrdina R, Gersl V: Anthracycline-induced cardiotoxicity: overview of studies examining the roles of oxidative stress and free cellular iron. Pharmacol Rep. 2009, 61(1):154-171.
41. Lao J, Madani J, Puértolas T, Alvarez M, Hernández A, Pazo-Cid R, et al. Liposomal Doxorubicin in the Treatment of Breast Cancer Patients: A Review. J Drug Deliv. 2013;2013:456409. doi: 10.1155/2013/456409.
42. Pisano C, Cecere SC, Di Napoli N, Cavaliere C, Tambaro R, Facchini G, et al. Clinical trials with pegylated liposomal Doxorubicin in the treatment of ovarian cancer. J Drug Deliv. 2013;2013:898146. doi: 10.1155/2013/898146.
43. 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(13):2000–2008.
44. Huang Y, Fu P, Fan W. Novel targeted therapies to overcome trastuzumab resistance in HER2-overexpressing metastatic breast cancer. Curr Drug Targets. 2013;14(8):889-898.
45. Pohlmann PR, Mayer IA, Mernaugh R. Resistance to trastuzumab in breast cancer. Clin Cancer Res. 2009;15:7479-7491.
46. Muss HB, Thor AD, Berry DA, Kute T, Liu ET, Koerner F, et al. C-erbB-2 expression and response to adjuvant therapy in women with node-positive early breast cancer. N Engl J Med. 1994;330:1260-1266.
47. Müller MB, Keck ME, Binder EB, Kresse AE, Hagemeyer TP, Landgraf R, et al. ABCB1 (MDR1)-type P-glycoproteins at the blood-brain barrier modulate the activity of the hypothalamic-pituitary-adrenocortical system: implications for affective disorder. Neuropsychopharmacology. 2003;28(11):1991-1999.
48. Gottesman MM, Fojo T, Bates SE. Multidrug resistance in cancer: role of ATP-dependent transporters. Nat Rev Cancer. 2002;2(1):48-58.
49. Duncan R. Polymer conjugates as anticancer nanomedicines. Nat Rev Cancer. 2006;6(9):688-701.
50. Vicent MJ, Dieudonné L, Carbajo RJ, Pineda-Lucena A. Polymer conjugates as therapeutics: future trends, challenges and opportunities. Expert Opin Drug Deliv. 2008;5(5):593-614. doi: 10.1517/17425247.5.5.593.
51. Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, et al Capecitabine and Oxaliplatin for Advanced Esophagogastric Cancer. N Engl J Med. 2008;358:36-46.
52. Shiah JG, Sun Y, Peterson CM, Straight RC, Kopeček J. Antitumor activity of N-(2-Hydroxypropyl) methacrylamide copolymer-Mesochlorin e6 and adriamycin conjugates in combination treatments. Clin Cancer Res. 2000;6(3):1008-1015.
53. Satchi-Fainaro R, Mamluk R, Wang L, Short SM, Nagy JA, Feng D, et al. Inhibition of vessel permeability by TNP-470 and its polymer conjugate, caplostatin. Cancer Cell. 2005;7:251–261.
54. Adão R, de Keulenaer G, Leite-Moreira A, Brás-Silva C. Cardiotoxicity associated with cancer therapy: pathophysiology and prevention strategies. Rev Port Cardiol. 2013;32(5):395-409.
55. Wu X, Sun X, Guo Z, Tang J, Shen Y, James TD, et al. In vivo and in situ tracking cancer chemotherapy by highly photostable NIR fluorescent theranostic prodrug. J Am Chem Soc. 2014;136(9):3579–3588.
56. Ozdoğru I. Anthracycline-induced cardiotoxicity. Turk Kardiyol Dern Ars. 2014;42(3):274-276.
57. Hensley ML, Hagerty KL, Kewalramani T, Green DM, Meropol NJ, Wasserman TH, et al. American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. J Clin Oncol. 2009;27:127-145.
58. Sepe DM, Ginsberg JP, Balis FM. Dexrazoxane as a cardioprotectant in children receiving anthracyclines. Oncologist. 2010;15(11):1220-1226.
59. Damrot J, Nubel T, Epe B, Roos WP, Kaina B, Fritz G. Lovastatin protects human endothelial cells from the genotoxic and cytotoxic effects of the anticancer drugs doxorubicin and etoposide. Br J Pharmacol. 2006;149:988-997.
60. 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.
61. Riad A, Bien S, Westermann D, Becher PM, Loya K, Landmesser U, et al. Pretreatment with statin attenuates the cardiotoxicity of Doxorubicin in mice. Cancer Res. 2009;69:695-699.
62. 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(23):2384-2390.
63. Nohria A. β-Adrenergic blockade for anthracycline- and trastuzumab-induced cardiotoxicity: is prevention better than cure? Circ Heart Fail. 2013;6(3):358-361.
64. Oliveira PJ, Bjork JA, Santos MS, Leino RL, Froberg MK, Moreno AJ, et al. Carvedilol-mediated antioxidant protection against doxorubicin-induced cardiac mitochondrial toxicity. Toxicol Appl Pharmacol. 2004;200:159-168.
65. Erickson CE, Gul R, Blessing CP, Nguyen J, Liu T, Pulakat L, et al. The beta-blocker Nebivolol Is a GRK/beta-arrestin Biased Agonist. PLoS One. 2013;8(8):e71980. doi: 10.1371/journal.pone.0071980.
66. Kim IM, Tilley DG, Chen J, Salazar NC, Whalen EJ, Violin JD, et al. Beta-blockers alprenolol and carvedilol stimulate beta-arrestin-mediated EGFR transactivation. Proc Natl Acad Sci USA. 2008;105:14555-14560.
67. Matsui H, Morishima I, Numaguchi Y, Toki Y, Okumura K, Hayakawa T. Protective effects of carvedilol against doxorubicininduced cardiomyopathy in rats. Life Sci. 1999;65:1265-1274.
68. Jonsson O, Behnam-Motlagh P, Persson M, Henriksson R, Grankvist K. Increase in doxorubiicin cytotoxicity by carvedilol inhibition of P-glycoprotein activity. Biochem Pharmacol. 1999;58:1801-1806.
69. Kalay N, Basar E, Ozdogru I, Er O, Cetinkaya Y, Dogan A, et

al. Protective effects of carvedilol against anthracycline-induced cardiomyopathy. J Am Coll Cardiol. 2006;48(11):2258-2262.
70. Asanuma H, Minamino T, Sanada S, Takashima S, Ogita H, Ogai A, et al. Beta-adrenoceptor blocker carvedilol provides cardioprotection via an adenosine-dependent mechanism in ischemic canine hearts. Circulation. 2004;109:2773-2779.
71. Nakamura K, Kusano K, Nakamura Y, Kakishita M, Ohta K, Nagase S, et al. Carvedilol decreases elevated oxidative stress in human failing myocardium. Circulation. 2002;105:2867-2871.
72. Bosch X, Rovira M, Sitges M, Domènech A, Ortiz-Pérez JT, de Caralt TM, et al. Enalapril and carvedilol for preventing chemotherapy-induced left ventricular systolic dysfunction in patients with malignant hemopathies: the OVERCOME trial (prevention of left Ventricular dysfunction with Enalapril and caRvedilol in patients submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies). J Am Coll Cardiol. 2013;61:2355-2362.
73. Ewer MS, Vooletich MT, Durand JB, Woods ML, Davis JR, Valero V, et al. Reversibility of trastuzumab-related cardiotoxicity: new insights based on clinical course and response to medical treatment. J Clin Oncol. 2005;23:7820-7826.
74. Oliva S, Cioffi G, Frattini S, Simoncini EL, Faggiano P, Boccardi L, et al. Italian Cardio-Oncological Network. Administration of angiotensin-converting enzyme inhibitors and beta-blockers during adjuvant trastuzumab chemotherapy for nonmetastatic breast cancer: marker of risk or cardioprotection in the real world? Oncologist. 2012;17:917-924.
75. http://www.clinicaltrials.gov.
76. Tokudome T, Mizushige K, Noma T, Manabe K, Murakami K, Tsuji T, et al. Prevention of doxorubicin (adriamycin)-induced cardiomyopathy by simultaneous administration of angiotensin-converting enzyme inhibitor assessed by acoustic densitometry. J Cardiovasc Pharmacol. 2000; 36: 361–368.
77. Al-Shabanah O, Mansour M, El-Kashef H, Al-Bekairi A. Captopril ameliorates myocardial and hematological toxicities induced by adriamycin. Biochem Mol Biol Int. 1998;45:419–427.
78. Vaynblat M, Shah HR, Bhaskaran D, Ramdev G, Davis WJ 3rd, Cunningham JN Jr, et al. Simultaneous angiotensin converting enzyme inhibition moderates ventricular dysfunction caused by doxorubicin. Eur J Heart Fail. 2002;4:583–586.
79. Abd El-Aziz MA, Othman AI, Amer M, El-Missiry MA. Potential protective role of angiotensin-converting enzyme inhibitors captopril and enalapril against adriamycin-induced acute cardiac and hepatic toxicity in rats. J Appl Toxicol. 2001;21:469-473.
80. Boucek RJ Jr., Steele A, Miracle A, Atkinson J. Effects of angiotensin-converting enzyme inhibitor on delayed-onset doxorubicin-induced cardiotoxicity. Cardiovasc Toxicol. 2003;3:319-329.
81. Lopez-Sendon J, Swedberg K, McMurray J, Tamargo J, Maggioni AP, Dargie H, et al. Task Force on ACE-inhibitors of the European Society of Cardiology. Expert consensus document on angiotensin converting enzyme inhibitors in cardiovascular disease. The Task Force on ACE-inhibitors of the European Society of Cardiology. Eur Heart J. 2004;25:1454-1470.
82. Cernecka H, Ochodnicka-Mackovicova K, Kucerova D, Kmecova J, Nemcekova V, Doka G, et al. Enalaprilat increases PPARbeta/delta expression, without influence on PPARalpha and PPARgamma, and modulate cardiac function in sub-acute model of daunorubicin-induced cardiomyopathy. Eur J Pharmacol. 2013;714:472-477.
83. Nakamae H1, Tsumura K, Terada Y, Nakane T, Nakamae M, Ohta K, et al.Notable effects of angiotensin II receptor blocker, valsartan, on acute cardiotoxic changes after standard chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone. Cancer. 2005;104(11):2492-2498.
84. Horie T1, Ono K, Nishi H, Nagao K, Kinoshita M, Watanabe S, et al. Acute doxorubicin cardiotoxicity is associated with miR-146a-induced inhibition of the neuregulin-ErbB pathway. Cardiovasc Res. 2010;87(4):656-664. doi: 10.1093/cvr/cvq148.
85. Liu X, Gu X, Li Z, Li H, Chang J, Chen P, et al. Neuregulin-1/erbB-activation improves cardiac function and survival in models of ischemic, dilated, and viral cardiomyopathy. J Am Coll Cardiol. 2006;48(7):1438-1447.