Anthracycline-Related Heart Failure: Certain Knowledge and Open Questions

Where Do we Stand with Chemotherapy-induced Cardiotoxicity?

Emma Louise Robinson 1, Maral Azodi 2, Stephane Heymans 1, Ward Heggermont 1,3

Accepted: 8 September 2020 / Published online: 23 September 2020
© The Author(s) 2020

Abstract
In the last decade, cardio-oncology has become a discipline on its own, with tremendous research going on to unravel the mechanisms underpinning different manifestations of cardiotoxicity caused by anticancer drugs. Although this domain is much broader than the effect of chemotherapy alone, a lot of questions about anthracycline-induced cardiotoxicity remain unknown. In this invited review, we provide insights in molecular mechanisms behind anthracycline-induced cardiotoxicity and put it in a clinical framework emphasizing the need for patients to understand, detect, and treat this detrimental condition.

Keywords Cardio-oncology · Anthracyclines · Cardiotoxicity · Chemotherapy-induced heart failure · Doxorubicin · Reactive oxygen species

Introduction
Anticancer therapy-associated cardiotoxicity, in particular chemotherapy-induced heart failure, is increasing as a clinical entity [1, 2]. Explanations for this phenomenon are an increased awareness of cardiotoxicity in patients receiving chemotherapy, a prolonged survival for young cancer patients exposing them to long-term cardiotoxicity risks, and an explosive growth of alternative anticancer drugs based on small molecules (e.g., tyrosine kinase inhibitors, proteasome inhibitors, etc.) [3, 4]. There is increased awareness that cardiotoxicity might even lead to premature morbidity and death in young cancer survivors. On the other hand, due to the fact that side effects of chemotherapy are often unpredictable, fear of cardiotoxicity sometimes leads to unnecessary and certainly inappropriate interruptions or restriction of potentially lifesaving cancer treatments. The different nature of the available anticancer drugs accounts for different cardiotoxicity risks, different times of onset, and subsequently different follow-up regimens. Moreover, it is also extremely challenging and hardly possible for the oncologist and cardiologist to be aware of all these specific side effects, sometimes even dependent on single molecule properties, not even class effects [5, 6].

Anthracycline-induced cardiotoxicity and subsequent heart failure is the best known clinical entity, especially in breast cancer patients and patients suffering from hematopoietic cancer such as lymphoma [7]. For anthracyclines, e.g., epirubicin and doxorubicin, cardiotoxicity is observed in up to 48% of patients following high-dose regimens, and on average, 1 in 5 anthracycline patients are affected [5]. However, these high doses are very rarely used—certainly in breast cancer—so the real-life risk of cardiotoxicity is lower than the aforementioned numbers, albeit that the risk of cardiotoxicity...
increas...ly increases when different cardiotoxic products are combined [8, 9]. The difficulty of cardiotoxicity is that there are no specific risk factors or predictors to adequately and timely assess cardiotoxicity risk in patients, and a late diagnosis confers a dismal prognosis, at least in anthracycline cardiotoxicity [10]. Furthermore, the detailed mechanisms behind this clinical entity vary dramatically and are as yet incompletely understood. In this review, we elaborate on what is known about anthracycline-related heart failure and we shed light on some interesting research avenues to pursue.

**Anthracycline-Related Heart Failure**

**Past and Current Understandings**

As early as 1967, about a decade after their use began, the first report for anthracycline-induced cardiotoxicity was observed in children receiving doxorubicin. The first thorough analysis of cases of anthracycline-associated cardiotoxicity (in casu adriamycin, or toxic cardiomyopathy) was described in 1973 by Lefrak and co-authors [11]. Since then, multiple reports of anthracycline-induced heart failure—cardiomyopathy—have been published. In the slipstream of research investigating the possible mechanisms behind cardiotoxicity, a classification into different types of cardiotoxicity was suggested in 2005. Type I cardiotoxicity (e.g., anthracycline cardiotoxicity) was related to myocardial apoptosis and necrosis in a dose-dependent manner, with a cumulative effect, causing permanent damage at the cellular level [12]. The reversibility of the disease is considered rather limited and the prognosis dismal. Type II cardiotoxicity (e.g., trastuzumab, bevacizumab) is related to interference with angiogenesis and is reversible if the causative therapy is interrupted [13]. However, there is now an overall consensus that this binary classification should be abolished. The detrimental effect of the so-called type II cardiotoxicity (exemplified with trastuzumab) was wrongly underestimated because it was always compared with the irreversible damage caused by anthracyclines, whereas, in fact, with the new and emerging anticancer therapies, multiple toxicities do exist, shedding light on the ever more complex pathophysiology of anticancer therapy-induced cardiotoxicity.

**Diagnostic Challenges in Detecting Anthracycline Cardiotoxicity**

There are two major concerns hampering effective detection of anthracycline-induced cardiotoxicity. The first is that the disease starts with subtle and subclinical changes that can hardly be detected by means of classical techniques, e.g., transthoracic echocardiography, although progress has been made in the field [14, 15]. The second problem is that anthracycline-related cardiotoxicity can occur much later, i.e., months or years after cessation of chemotherapy [5, 8].

Two distinct cardiotoxic effects of anthracyclines can be classified by the time of onset post cessation of treatment, as depicted in Fig. 1 [10]. Acute cardiotoxicity is apparent from immediately to within 1 year of treatment, whereas chronic late-onset cardiomyopathy can occur many years after cessation of the chemotherapy. Late-onset cardiotoxicity—often only discovered up to 15 years, sometimes longer, after treatment—is the one leading to chronic heart failure in cancer survivors and, therefore, represents a major clinical problem [16, 17].

The present understanding of the mechanisms behind the cardiotoxic effects of neoplastic treatment is remarkably limited. The suitability of classic circulating diagnostic biomarkers for heart failure is inadequate. Prospective tools to identify patients that will develop acute and delayed cardiomyopathy following anticancer therapy are currently nonexistent. Early diagnostic of the patients prone or subjected to develop an (acute or late) anthracycline-induced cardiotoxic event would allow adapting the cancer treatment immediately and managing cardiotoxicity with cardioprotective drugs.

The in-depth assessment of diagnostic challenges is however beyond the scope of this review. A detailed flowchart on the diagnosis of anthracycline-related cardiotoxicity is available in the position paper of the European Society of Cardiology, 2016 [5].

**Prevention of Cardiotoxicity: Dexrazoxane**

Given the reasonably irreversible nature of late-onset anthracycline-induced cardiotoxicity, a strategy aiming at preventing the disease is paramount. Randomized trials have been performed to explore primary prevention in patients undergoing anthracycline chemotherapy. One of the best studied molecules is dexrazoxane. This molecule, which is a derivative of ethylenediaminetetraacetic acid (EDTA), has been licensed in several countries for the prevention of cardiotoxicity due to anthracycline-based chemotherapy as well as for the treatment of accidental extravasation of anthracyclines. A thorough review on different aspects of this molecule has been published in the past [18]. In general, it can be stated that indeed, dexrazoxane prevents—at least in part—cardiotoxicity caused by anthracyclines. Furthermore, in large meta-analyses, the administration of dexrazoxane does not significantly reduce overall survival or progression-free survival from the cancer for which the anthracyclines were initially administered [19]. Other options to prevent anthracycline-induced cardiotoxicity are the administration of a liposomal form or a less toxic form of anthracycline [20–23]. Prevention of cardiotoxicity is nevertheless much broader than the administration of dexrazoxane, which is grossly only effective in anthracycline-related cardiotoxicity. Numerous trials with classical heart failure therapies (beta
blockers, angiotensin-converting enzyme (ACE) inhibitors, ARBs) have been undertaken to prevent cardiotoxicity. However, until recently, no unequivocal clinical benefit of these molecules was observed, except maybe for patients with asymptomatic troponin elevation [24].

**Treatment Options for Anthracycline-Induced Cardiotoxicity**

So far, no clear guidance exists on the treatment of patients with symptomatic heart failure due to anthracycline-induced cardiotoxicity. In the detailed position paper of the European Society of Cardiology, it is advised that patients be treated according to the most recent guidelines for the treatment of heart failure [5, 25]. In circumstances of severe instability, chemotherapy should also be interrupted. In the case of a recuperated LV function and a rechallenge with the same or similar chemotherapy, the initiation or continuation of ACE inhibitors and beta blockers is recommended.

**Molecular Basis of Anthracycline-Related Heart Failure**

**Overview**

The molecular mechanisms for cardiotoxicity induced by anthracyclines include disruption of transcription by topoisomerase II, mitochondrial iron accumulation, oxidative stress such as lipid peroxidation and protein nitrosylation, mitochondrial dysfunction, and Ca²⁺ handling abnormality [26]. Generation of reactive oxygen species (ROS) is considered the most significant mechanism of chemotherapy-induced cardiotoxicity. One of the mechanisms of action for doxorubicin-induced...
cardiotoxicity is related to the excessive generation of ROS followed by oxidative stress [27]. Thus, it is obligatory to keep the proper level of ROS because of its significant role in hemo-
stasis, cell proliferation, and cell death and its direct effects on DNA, RNA, proteins, and lipids [28]. Mitochondrial perme-
ability transition, outer membrane rupture, release of apoptotic
signaling molecules, and irreversible injury to the mitochondria
are the other implications of excess ROS production [29].
Although the mechanism of action of anthracycline


cardiotoxicity is not completely clarified, the most widely ac-
cepted hypothesis for the mechanisms of anthracycline-induced

cardiotoxicity is mediated by topoisomerase IIβ (Top2b) spe-
cifically in cardiomyocytes. Deletion of Top2b protects
cardiomyocytes from doxorubicin-induced DNA double-
strand modifications [30].

Crucial Role for ROS Formation in Mitochondria

In anticancer therapy, the mitochondria are a preferential place
for doxorubicin-induced ROS overproduction mediated by the
activity of mitochondrial NADPH oxidase (mitoNOX).

Essentially, nitric oxide synthase (NOS) converts L-arginine to
nitric oxide (NO) in the presence of molecular oxygen while

using NADPH as reductant. Under the circumstance of lower
levels of L-arginine or cofactor (6R)-5,6,7,8-tetrahydrobiopterin
(BH4), formation of superoxide instead of NO may occur [31].

Vásquez-Vivar et al. have shown that doxorubicin binds to en-

dothelial NOS, increasing superoxide formation and reducing

nitric oxide production [32]. In the oxido-reductive reaction,
a single electron is transferred from NADPH to doxorubicin.

This forms a semiquinone radical which, when complexed with
iron, is responsible for oxygen reduction, producing a superoxide
ion. In addition, the interaction between doxorubicin and
cardiolin forms a drug–phospholipid complex that, in turn,
can inhibit mitochondrial enzymes involved in oxidative phos-
phorylation. Mitochondrial membrane damage can also cause
the inactivation of sodium and calcium transporters. These trans-
porters are involved in ion homeostasis. Cardiolipin is rich in
polyunsaturated fatty acids, which is located in the inner mito-

chondrial membrane and is required for the activity of the respir-
atory chain [33]. Cardiac tissue is rich in mitochondria and its
cytotoxic potential of anthracyclines may be magnified by a high
density of mitochondria and lower levels of enzymatic capacity
to detoxify ROS [34].

Animal and Cellular Models
of Anthracycline-Related Heart Failure

Animal Models of Anthracycline Cardiotoxicity

Mouse, rat, rabbit, pig, and dog are the common experimental
models for in vivo studies. The advantage of using animal

studies is due to being able to perform repeated administration
of chemotherapeutic agents, thereby mimicking chronic
cardiotoxicity in clinical practice [35]. A comprehensive over-
view of in vivo experimental studies into the cardiotoxicity of
anthracyclines, along with the advantages and disadvantages
of each experimental model, is presented in Table 1. Rabbits
were the first long-term animal for anthracycline-induced
cardiotoxicity by demonstrating myocardial damage and fi-
brosis [44]. Richard et al. showed that doxorubicin-treated rats
have increased oxidative stress and pathological remodeling
with lower left ventricular contractility, higher levels of thio-
obarbituric acid or dihydroethidium fluorescence—which are
plasma and myocardial oxidative stress markers—and mark-
edly altered transcript levels for all measured markers of car-
diac remodeling, except VEGF-A [41]. Expression of induc-
able NOS at the RNA and protein levels was significantly
increased in male Wistar rats following 8 weeks of Adriamycin
treatment, which continued to increase up to 10 weeks of
treatment [42]. Also, human-induced pluripotent stem cell
(iPSC)-derived cardiomyocytes generated from patients with
depressed left ventricular ejection fraction (LVEF) demon-
strate increased cell death and ROS production following
in vitro doxorubicin treatment [45].

Juvenile mice were treated with doxorubicin for a period of
5 weeks (25 mg/kg cumulative dose) from 2 weeks of age. A
reduction of cardiac systolic function due to atrophy of the
heart, low levels of cardiomyocyte apoptosis, and decreased
growth velocity were observed. However, most adult murine
models still require acute drug administration which might
skew the observations [46]. Rea et al. generated a mouse
model of cardiotoxicity induced by doxorubicin showing ear-
ly remodeling of the left ventricle. In addition, histological
analysis revealed increased fibrosis, increased cardiomyocyte
diameter, and apoptosis [36].

Overexpression of eIF5A induced by doxorubicin in H9c2
cardiomyocyte leads to a gradual increase in ROS generation,
growth perturbation, and initiation of apoptosis. Mitochondrial
dysfunction becomes prominent after a gradual increase in ROS
generation. In addition, increased Ca2+ influx in the mitochondria
leads to loss of the mitochondrial transmembrane potential,
release of cytochrome c, and caspase activation [47]. Intrinsic ap-
optosis pathway or mitochondrial apoptosis pathway is initiated
by intracellular stress such as oxidative stress, calcium overload,
and DNA damage, leading to Bax/Bak-dependent mitochondrial
outer membrane permeabilization (MOMP) and release of cyto-
chrome c from the mitochondria into the cytosol. Cytosolic cy-
tochrome c and apoptotic protease-activating factor 1 (Apaf-1)
result in activation of caspase 9 [48].

Due to the time, costs, and differential long-term effects of
anthracycline treatment in small experimental animal models,
studies into the late-onset cardiotoxic effects and, therefore,
understanding of underlying molecular mechanisms are lack-
ing (Fig. 1).
| Animal models | Mechanism of action |
|---------------|---------------------|
| **Mice** | Inhibit with topoisomerase IIβ and induce apoptosis [30] |
| **Rats** | The upregulation of inducible NOS (iNOS) gene and protein [41] |
| **Rabbits** | Leads to Ca\(^{2+}\) overload [43] |

**Advantages:**
- Low purchase and maintenance costs
- More suitable for "high-throughput" studies than large animal models
- Up to 99% genetic similarity between human and murine genes
- Relatively short breeding time and high breeding rate—suitable for generation of genetically modified mouse lines
- Short gestation time (21 days)
- Ideal for rapid establishment of proof-of-principle, discovery, and functional data, which can then be applied to other experimental models and, eventually, into humans

**Disadvantages:**
- Typically do not recapitulate all aspects of human cardiovascular disease (e.g., mice rarely develop atherosclerosis of the coronary arteries)
- Murine cardiac physiology poorly replicates that of humans, including cellular electrophysiology and Ca\(^{2+}\) transport and predominant myosin heavy chain (MHC) α expression in the adult heart over β-MHC, as compared with other small animal models mentioned here
- They are phylogenetically far from humans and some pathophysiological features of disease and their response may not be reliable predictors
- Translational aspects and the value of genetic mouse models must be interpreted with caution
- Mice have a differential response than humans to anthracyclines, an exacerbated acute cardiac response. Protocols for anthracycline treatment in mice that mimic the human phenotypic response are yet to be established

**Advantages:**
- Easy to handle—some strains more docile than mice and experimental interventions easier on a slightly larger animal than mice
- Short gestation period (21–23 days), high breeding rate, and litters of up to 15 pups
- Rats treated with adriamycin are usually used to investigate the mechanisms of cardiotoxicity and ways of preventing it

**Disadvantages:**
- Few genetically modified rat lines, making experimental cardiology using genetic interventions difficult
- Not useful in investigating mechanisms of stroke

**Advantages:**
- Rats have similar cardiomyocyte cellular electrophysiology properties and Ca\(^{2+}\) transport system to humans or larger animals (e.g., dogs and pigs) as well as predominant expression of myosin β-MHC over α-MHC, as for humans
- Most studies using rabbit models of anthracycline-induced cardiomyopathy have concentrated on the evaluation of potential cardioprotective agents
- Can develop atherosclerosis with high fat feeding, for example

**Disadvantages:**
- Higher maintenance costs than rats and mice
- Harder to handle
- Few transgenic rabbit lines. Genetic intervention for functional experiments uncommon in rabbits
Cell Culture Models of Anthracycline Cardiotoxicity

In in vitro cell culture models, including isolated cardiac myocytes (particularly primary neonatal rat cardiomyocytes or less often adult cardiomyocytes), cardiomyocyte-derived cell lines (e.g., H9c2 rat embryonic cardiomyoblasts) are the most straightforward approach due to their ease of use to investigate gene function in a high-throughput manner and lower cost [49]. Merten et al. reported doxorubicin as a potent inducer of apoptosis in H9c2 cardiomyocytes by activation of PI3K/Akt and, to a lesser extent, calcineurin [50]. MicroRNA-21 expression significantly increases in both mouse heart tissue and H9C2 cells after treatment by doxorubicin. The mechanism of action for this microRNA is related to the modulation of the antiproliferative factor, B cell translocation gene 2 [51].

Tumor necrosis factor-α (TNF-α), Fas ligand (FasL), and TNF-related apoptosis-inducing ligand (TRAIL) are extracellular stress signals. By binding to their individual death receptors—TNF-α receptor 1 (TNFR1), Fas, and TRAIL receptor 1/2 (TRAILR1/2), extrinsic apoptosis will take place. Fas-associated death domain (FADD) is recruited by death receptors. Finally, caspase activation causes apoptotic death of the cell [48]. Doxorubicin induces cardiotoxicity through upregulation of death receptors (DRs) (TNFR1, Fas, DR4, and DR5) in iPSC-derived cardiomyocytes at both the protein and mRNA levels. Spontaneous apoptosis is enhanced by physiologically relevant death ligands including TRAIL. Induced death receptors in cardiomyocytes could be a critical mechanism by which doxorubicin causes cardiotoxicity [52].

Increased MMP1, IL-6, TGF-β, and collagen expression in human cardiac fibroblasts (HCFs) is followed by doxorubicin treatment. This suggests a new—or additive—mechanism of doxorubicin-induced cardiotoxicity [53]. Treatment of the murine HL-1 cardiomyocyte cell line or isolated adult rat ventricular myocytes with doxorubicin decreased GATA-4 protein and mRNA levels. Prevention of GATA-4 DNA-binding activity by adenoviral-mediated expression of dominant negative mutant of GATA-4 induced apoptosis. Downregulation of GATA-4 inciting cardiomyocyte apoptosis could be a mechanism of anthracycline-induced cardiotoxicity [54]. A complete reference table of in vitro functional experiments can be found in Table 2.

Conclusions

Cardiotoxicity in general and anthracycline-induced heart failure in particular are fast evolving scientific research avenues. Despite increasing knowledge on the mechanisms of cardiotoxicity, timely diagnosis of subclinical cardiac dysfunction remains a difficult item. Furthermore, there is no curative treatment for the disease—except for general heart failure medications. Further mechanistic research is warranted in order to discover a disease-specific treatment.
Author Contributions All authors wrote substantial parts of the manuscript, performed literature search, designed the central figure and tables, and critically assessed the complete manuscript before submission.

Funding E.L.R. and S.H. were supported by the CardioVascular Onderzoek Nederland (CVON) EARLY-HFPEF consortium grant (Dutch Heart Foundation).

Compliance with Ethical Standards

Conflict of Interest All authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent As a review article, this manuscript does not contain any studies with human or animal subjects performed by the authors.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

1. Grumbach IM. Cardio-oncology at the beginning of a new decade. J Am Heart Assoc. 2019;9(2):e015890.
2. Herrmann J. From trends to transformation: where cardio-oncology is to make a difference. Eur Heart J. 2019;40(48):3898–900.
3. Anker MS, Hazdhibougovic S, Lena A, Belenkoy Y, Bergerl-Klein J, de Boer RA, et al. Recent advances in cardiac oncology: a report from the ‘Heart Failure Association 2019 and World Congress on Acute Heart Failure 2019’. ESC Heart Fail. 2019;6(6):1140–8.
4. Kim G, Cogswell R. Editorial: Highlights from the emerging field of cardio-oncology. Curr Opin Cardiol. 2019;34(3):282.
5. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggianno R, Galdersi M, et al. 2016 ESC position paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: the Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur J Heart Fail. 2017;19(1):9–42.
6. Lancellotti P, Suter TM, López-Fernández T, Galdersi M, Lyon AR, Van der Meer P, et al. Cardio-oncology services: rationale, organization, and implementation. Eur Heart J. 2019;40(22):1756–63.
7. Sawyer DB. Anthracyclines and heart failure. N Engl J Med. 2013;368(12):1154–6.
8. Dent SF, Suter TM, López-Fernández T, Opolski G, Menna P, Minotti G. Cardio-oncology in clinical studies and real life. Semin Oncol. 2019;46(6):421–5.
9. Rosa GM, Gigli L, Tagliasacchi MI, Di Iorio C, Carbone F, Nencioni A, et al. Update on cardiotoxicity of anti-cancer treatments. Eur J Clin Investig. 2016;46(3):264–84.
10. Volkova M, Russell R. Anthracycline cardiotoxicity: prevalence, pathogenesis and treatment. Curr Cardiol Rev. 2011;7(4):214–20.
11. Lefrak EA, Pitha J, Rosenheim S, Gottlieb JA. A clinicopathologic analysis of adriamycin cardiotoxicity. Cancer. 1973;32(2):302–14.
12. Daher IN, Daigle TR, Bhatia N, Durand J-B. The prevention of cardiovascular disease in cancer survivors. Tex Heart Inst J. 2012;39(2):190–8.
13. Ewer MS, Lippman SM. Type II chemotherapy-related cardiac dysfunction: time to recognize a new entity. J Clin Oncol. 2005;23(13):2900–2.
14. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2014;15(10):1063–93.
15. Liu J, Bansch J, Mousavi N, Plana JC, Scherrer-Crosbie M, Thavendiranathan P, et al. Contemporary role of echocardiography for clinical decision making in patients during and after cancer therapy. JACC Cardiovasc Imaging. 2018;11(8):1122–31.
16. Shan K, Lincoff AM, Young JB. Anthracycline-induced cardiotoxicity. Ann Intern Med. 1996;125(1):47–58.
17. Kumar S, Marfatia R, Tannenbaum S, Yang C, Avelar E. Doxorubicin-induced cardiomyopathy 17 years after chemotherapy. Tex Heart Inst J. 2012;39(3):424–7.
18. Langer SW. Dextrazoxane for the treatment of chemotherapy-related side effects. Cancer Manag Res. 2014;6:357–63.
19. Speyer JL, Green MD, Kramer E, Rey M, Sanger J, Ward C, et al. Protective effect of the bispiperazinedione ICRF-187 against doxorubicin-induced cardiac toxicity in women with advanced breast cancer. N Engl J Med. 1988;319(12):745–52.
20. Holbein R-D, Gnad-Vogt SU, Beyer U, Hochhaus A. Liposomal encapsulated anti-cancer drugs. Anti-Cancer Drugs. 2005;16(7):691–707.
21. Olivier J, Pema GP, Bocci C, Montevecchi C, Olivier A, Leoni P, et al. Modern management of anthracycline-induced cardiotoxicity in lymphoma patients: low occurrence of cardiotoxicity with comprehensive assessment and tailored substitution by nonpegylated liposomal doxorubicin. Oncologist. 2017;22(4):422–31.
22. Robert J. Clinical pharmacokinetics of epirubicin. Clin Pharmacokinet. 1994;26(6):428–38.
23. Yang F, Lei Q, Li L, He JC, Zeng J, Luo C, et al. Delivery of epirubicin via slow infusion as a strategy to mitigate chemotherapy-induced cardiotoxicity. PLoS One. 2017;12(11):e0188025.
24. 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(23):2474–81.
25. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129–200.
26. Zhang Y-W, Shi J, Li Y-J, Wei L. Cardiomyocyte death in doxorubicin-induced cardiotoxicity. Arch Immunol Ther Exp. 2009;57(6):435–45.
27. Kim SH, Kim K-J, Kim J-H, Kwak J-H, Song H, Cho J-Y, et al. Comparison of doxorubicin-induced cardiotoxicity in the ICR mice of different sources. Lab Anim Res. 2017;33(2):165–70.
28. Devasagayam TPA, Tilak JC, Boloor KK, Sane KS, Ghaskadbi SS, Lele RD. Free radicals and antioxidants in human health: current status and future prospects. J Assoc Physicians India. 2004;52:794–804.
29. Moris D, Spartalis M, Tzatzaki E, Spartalis E, Karachaliou G-S, Triantafyllyis AS, et al. The role of reactive oxygen species in myocardial redox signaling and regulation. Ann Transl Med. 2017;5(16):324.
30. Zhang S, Liu X, Bawa-Khalfe T, Lu L-S, Lyu YL, Liu LF, et al. Identification of the molecular basis of doxorubicin-induced cardiotoxicity. Nat Med. 2012;18(11):1639–42.

31. Asensio-López MC, Soler F, Pascual-Figal D, Fernández-Belda F, Lax A. Doxorubicin-induced oxidative stress: the protective effect of nicorandil on HL-1 cardiomyocytes. PLoS One. 2017;12(2):e0172803.

32. Vásquez-Vivar J, Martasek P, Hogg N, Masters BS, Pritchard KA, Kalyanaraman B. Endothelial nitric oxide synthase-dependent superoxide generation from adriamycin. Biochemistry. 1997;36(38):11293–7.

33. Doroshow JH. Mechanisms of anthracycline-enhanced reactive oxygen metabolism in tumor cells. Oxidative Med Cell Longev. 2019;2019:9474823.

34. Angusutarax P, Luanpitpong S, Issaragrisil S. Chemotherapy-induced cardiotoxicity: overview of the roles of oxidative stress. Oxidative Med Cell Longev. 2015;2015:795602.

35. Gamberti M, Giovane G, Garzillo EM, Avino F, Feola A, Porto S, et al. Animal models in studies of cardiotoxicity side effects from antiblastic drugs in patients and occupational exposed workers. Biomed Res Int. 2014;2014:240642.

36. Rea D, Coppola C, Barbieri A, Monti MG, Misso G, Palmi G, et al. Strain analysis in the assessment of a mouse model of cardiotoxicity due to chemotherapy: sample for preclinical research. In Vivo. 2016;30(3):279–90.

37. Amgalan D, Garner TP, Pekson R, Jia XF, Yanamandala P, Paulino V, et al. A small-molecule allosteric inhibitor of BAX protects against doxorubicin-induced cardiomyopathy. Nat Can. 2020;1(3):315–28.

38. Lin J, Fang L, Li H, Li Z, Lyu L, Wang H, et al. Astragaloside IV alleviates doxorubicin induced cardiomyopathy by inhibiting NADPH oxidase derived oxidative stress. Eur J Pharmacol. 2019;859:172490.

39. Zhang Y-J, Huang H, Liu Y, Kong B, Wang G. MD-1 deficiency accelerates myocardial inflammation and apoptosis in doxorubicin-induced cardiotoxicity by activating the TLR4/MAPKs/nuclear factor kappa B (NF-kB) signaling pathway. Med Sci Monit. 2019;25:7898–907.

40. Hu C, Zhang X, Wei W, Zhang N, Wu H, Ma Z, et al. Matrine attenuates oxidative stress and cardiomyocyte apoptosis in doxorubicin-induced cardiotoxicity via maintaining AMPK/UCP2 pathway. Acta Pharm Sin B. 2019;9(4):690–701.

41. Richard C, Ghibu S, Delmasure-Chalameau S, Guillard JC, Des Rosiers C, Zeller M, et al. Oxidative stress and myocardial gene alterations associated with doxorubicin-induced cardiotoxicity in rats persist for 2 months after treatment cessation. J Pharmacol Exp Ther. 2011;339(3):807–14.

42. Liu B, Li H, Qu H, Sun B. Nitric oxide synthase expressions in ADR-induced cardiomyopathy in rats. J Biochem Mol Biol. 2006;39(6):759–65.

43. Takahashi S, Denvir MA, Harder LD, 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(4):405–13.

44. Talavera J, Giraldo A, Fernández-Del-Palacio MJ, García-Nicolás O, Seva J, Brooks G, et al. An upgrade on the rabbit model of anthracycline-induced cardiomyopathy: shorter protocol, reduced mortality, and higher incidence of overt dilated cardiomyopathy. Biomed Res Int. 2015;2015:465342.

45. Henriksen PA. Anthracycline cardiotoxicity: an update on mechanisms, monitoring and prevention. Heart. 2018;104(12):971–7.

46. Zhu W, Shou W, Payne RM, Caldwell R, Field LJ. A mouse model for juvenile doxorubicin-induced cardiac dysfunction. Pediatr Res. 2008;64(5):488–94.

47. Tan X, Wang D-B, Lu X, Wei H, Zhu R, Zhu S-S, et al. Doxorubicin induces apoptosis in H9c2 cardiomyocytes: role of overexpressed eukaryotic translation initiation factor 5A. Biol Pharm Bull. 2010;33(10):1666–72.

48. Xia P, Liu Y, Cheng Z. Signaling pathways in cardiac myocyte apoptosis. Biomed Res Int. 2016;2016:9583268.

49. Simcinek T, Stéba M, Popelová O, Adamcová M, Hrdina R, Gersl V. Anthracycline- induced cardiotoxicity: overview of studies examining the roles of oxidative stress and free cellular iron. Pharmaco Rep. 2009;61(1):154–71.

50. Merten KE, Jiang Y, Feng W, Kang YJ. Calcineurin activation is not necessary for doxorubicin-induced hypertrophy in H9c2 embryonic rat cardiac cells: involvement of the phosphoinositide 3-kinase-Akt pathway. J Pharmacol Exp Ther. 2006;319(2):934–40.

51. Sala V, Dela Sala A, Hölsch E, Ghigo A. Signaling pathways underlying anthracycline cardiotoxicity. Antioxid Redox Signal. 2020;32(15):1096–114.

52. Zhao L-M, Li L, Huang Y, Han L-J, Li D, Hua B-J, et al. Antitumor effect of periplocin in TRAIL-resistant gastric cancer cells via up-regulation of death receptor through activating ERK1/2-ERK1 pathway. Mol Carcinog. 2019;58(6):1033–45.

53. Nairakawa M, Uememura M, Tanaka R, Hikichi M, Nagasako A, Fujita T, et al. Doxorubicin induces trans-differentiation and MMP1 expression in cardiac fibroblasts via cell death-independent pathways. PLoS One. 2019;14(9):e0221940.

54. Kim Y, Ma A-G, Kitta K, Fitch SN, Ikeda T, Ihara Y, et al. Anthracycline-induced suppression of GATA-4 transcription factor: implication in the regulation of cardiac myocyte apoptosis. Mol Pharmacol. 2003;63(2):368–77.

55. Moreira AC, Branco AF, Sampaio SF, Cunha-Oliveira T, Martins TR, Holy J, et al. Mitochondrial apoptosis-inducing factor is involved in doxorubicin-induced toxicity on H9c2 cardiomyoblasts. Biochim Biophys Acta. 2014;1842(12 Pt A):2468–78.

56. Zhang X, Hu C, Kong C-Y, Song P, Wu H-M, Xu S-C, et al. FNDC5 alleviates oxidative stress and cardiomyocyte apoptosis in doxorubicin-induced cardiotoxicity via activating AKT. Cell Death Differ. 2020;27(2):540–55.

57. Chen L, Xia W, Hou M. Mesenchymal stem cells attenuate doxorubicin-induced cellular senescence through the VEGF/Notch/TGf-β signaling pathway in H9c2 cardiomyocytes. Int J Mol Med. 2018;42(1):674–84.

58. Maillet A, Tan K, Chai X, Sadananda SN, Mehta A, Ooi J, et al. Modeling doxorubicin-induced cardiotoxicity in human pluripotent stem cell derived-cardiomyocytes. Sci Rep. 2016;6:25333.

59. Burtidge PW, Li YF, Matsa E, Wu H, Ong S-G, Sharma A, et al. Human induced pluripotent stem cell-derived cardiomyocytes recapitulate the predilection of breast cancer patients to doxorubicin-induced cardiotoxicity. Nat Med. 2016;22(5):547–56.

60. McSweeney KM, Bozza WP, Alterovitz W-L, Zhang B. Transcriptomic profiling reveals p53 as a key regulator of doxorubicin-induced cardiotoxicity. Cell Death Dis. 2019;5:102.

61. Zhao L, Zhang B. Doxorubicin induces cardiotoxicity through up-regulation of death receptors mediated apoptosis in cardiomyocytes. Sci Rep. 2017;7:44735.

62. Ikeda S, Matsushima S, Okabe K, Ikeda M, Ishikita A, Tadokoro T, et al. Blockade of L-type Ca2+ channel attenuates doxorubicin-induced cardiomyopathy: overview of published maps and institutional affiliations.