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REVIEW

Cancer drug related cardiotoxicity during breast cancer treatment

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ABSTRACT

Introduction: Breast cancer (BC) is the most common cancer in women. Although therapeutic armamentarium like chemotherapy, endocrine and target agents have increased survival, cardiovascular side effects have been observed. A comprehensive risk assessment, early detection and management of cardiac adverse events is therefore needed.

Areas covered: In this review we focus on cardiotoxicity data deriving from Phase III randomized trials, systematic reviews and meta-analysis in BC patients. We provide insight into advances that have been made in the molecular mechanisms, clinical presentation and management of such adverse event.

Expert opinion: Despite the large number of data from Phase III trials about cardiac events incidence, there are poor evidences for detection, monitoring and management of cardiotoxicity during BC treatment. Future cardiotoxicity-oriented clinical cancer research can help to predict the risk of cardiac adverse events and improve patients' outcome. Multidisciplinary approach as well as integration of blood biomarkers with imaging will be desirable.

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1. Introduction

Breast cancer (BC) is the most common neoplasm and the second leading cause of cancer-related death in women.[1] Incidence rates are increasing and expected to continue to grow over the next 20 years in several of the world's countries, due to earlier detection through screening programs.[2] In 2015, BC survival rates are at their highest ever. Indeed, BCs are now treated with combination of surgery, chemotherapy, and radiation, making treatments more precise and minimizing side effects.[2] Despite this, an important issue is represented by cardiac adverse events. Anticancer treatments including (1) anthracyclines, taxanes, fluoropyrimidines, or alkylating agents; (2) targeted agents anti-HER2 and anti-vascular endothelial growth factor (VEGF) drugs; (3) endocrine therapies; (4) radiotherapy have been, directly or indirectly, implicated as risk factors for cardiac complications.[3] Studies continue to be performed to better understand, prevent, and mitigate against cancer drug-associated cardiovascular disease.[4] Clinically, cardiotoxicity has been classified as acute 'during treatment' or chronic 'months after treatment completion,' potentially resulting in symptomatic congestive heart failure (CHF).[5] Left ventricular ejection fraction (LVEF) reduction is commonly used to detect cardiac stress or impairment in clinical setting.[6] Unfortunately, there is a lack of univocal strategy for detection, monitoring, and management of BC therapy-associated cardiovascular disease.[3,7] This review summarizes the incidence, risks, and effects of treatment-induced cardiovascular disease in patients with BC, highlighting cardio-safety data from phase III clinical trials, large systematic reviews, and meta-analysis. Moreover, the molecular mechanisms, clinical implication, detection, and management of such adverse events are also described.

2. Anthracyclines

Anthracyclines, doxorubicin (DOX) and epidoxorubicin (EPI), represent a cornerstone in BC treatment, both in adjuvant and metastatic settings.[8] DNA damage induced by anthracyclines includes a wealth of different mechanisms: (1) topoisomerase II inhibition with consequent induction of apoptosis; (2) intercalation into DNA-blocking protein synthesis; (3) lipid peroxidation due to reactive oxygen species (ROS); (4) DNA cross-linking; (5) interference with helicase activity determining DNA unwinding problems; (6) DNA binding and alkylation; (7) direct membrane effects.[9] Unfortunately, despite proved efficacy, anthracyclines are characterized by a wide spectrum of adverse events making cardiotoxicity one of the most common.[10] Most studies in this area suggested two anthracycline-induced toxicity mechanisms: (1) oxidative stress; (2) topoisomerase IIb inhibition (Figure 1(a, b)).[9,11,12] In fact, it is well established that antioxidative activity is inefficient in cardiomyocytes as a consequence of the reduced catalase and GSH-peroxidase-1 activities (Figure 1(a)).[9,12]

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Article highlights

- Breast Cancer incidence is rising in the last decades and higher number of patients to treat is expected in the next few years
- Cytotoxic agents (Anthracyclines, Fluoropyrimidines, Taxanes, Alkylating agents), Target Agents (anti-HER2 and anti-VEGF drugs) and Endocrine therapies (Aromatase Inhibitors) have intrinsic cardiotoxicity
- It is possible to distinguish a Type I and a Type II cardiotoxicity different in physiopathology and clinical presentation that ranges from rhythm disorders to ischemia, hypertension and CHF
- There is no consensus about early detection and management of cardiac events and Echocardiography is the useful imaging technique
- Blood biomarkers of early cardiac injury (Troponines I and T and BNP) are under investigation
- A toxicity oriented, specific, multidisciplinary approach is needed

This box summarizes key points contained in the article.

Mitochondrial enzymes such as NADPH oxidase, cytochrome P450 reductase, and xanthine oxidase transform DOX in semiquinone.[13] DOX-semiquinone forms a complex with iron free radicals, generating superoxide anion, magnifying ROS production and resulting in apoptosis (Figure 1(b)).[9,13–15] More recent evidences show that iron accumulation within mitochondria following DOX exposure might lead to cell death, [15] DNA double-stranded breaks, and cell death through topoisomerase II inhibition might represent an alternative mechanism. Two classes of topoisomerase II (IIα, IIβ) have been identified in mammalian cells. Notably, topoisomerase IIα is overexpressed in normally dividing, and cancer cells, it is required for DNA replication as being considered the main target of anthracyclines' anticancer activity. By contrast, topoisomerase IIβ is overexpressed in quiescent and cardiomyocytes cells whereby it acts as a key mediator of anthracycline-induced toxicity through three proposed mechanisms: (1) DNA-repair activity defects via *TP53* inactivation; (2) ROS overproduction interfering with antioxidant enzymes; (3) reduction of peroxisome proliferator-activated receptor-γ coactivator 1-α/1-β activities essential to maintain mitochondrial biogenesis.[12] Accordingly, Billingham et al. and Mackay et al. have evidenced myofibrillar disarray, vacuoles, and myocyte necrosis in ultrastructure upon cardiac biopsies in anthracyclines-treated patients.[16,17] Clinical data from two large retrospective studies have shown a dose-dependent relationship between DOX and cardiotoxicity. Von Hoff et al. described across different tumors an increase of CHF incidence ranging from 3%, 7%, and 18% at DOX cumulative dose of 400, 550, and 700 mg/m^2, respectively. [18] A retrospective study from 630 patients, including metastatic BC, reported 5% CHF incidence at DOX cumulative dose of 400 mg/m^2 and 16%, 26%, 48% at cumulative dose of 500, 550, 700 mg/m^2, respectively.[19] EPI has demonstrated lower risk of cardiac toxicity profile than DOX, despite similar mechanism of action.[20] Similarly, a meta-analysis of 13 randomized trials, showed a reduced risk of subclinical and clinical cardiotoxicity in advanced BC patients receiving EPI compared to DOX.[21] Based on these studies, it should be widely recommended not to exceed a cumulative dose of 400–450 and 900 mg/m^2 for DOX and EPI, respectively. A large meta-analysis conducted by Early Breast Cancer Trialists' Collaborative Group consisting of 123 trials in adjuvant setting, confirmed an increased anthracycline-induced cardiac mortality.[22] Anthracyclines have also been investigated in combination with other cytotoxic agents like taxanes; cardiotoxicity data regarding these studies are reported in Table 1.[23–35]

2.1. Liposomal anthracyclines

Recently, to minimize anthracycline-related deleterious cardiovascular effects, novel anthracycline formulations based on liposomes have been developed. Given their size, liposomes-encapsulated DOX do not pass through capillaries reducing drug accumulation in cardiomyocytes and promoting their elimination by the lymphatic system. Notably, the occurrence of damaged capillaries in the neoplastic tissue increases the concentration of active drug.[36] In a consistent manner, addition of polyethylene glycol on the liposomal membrane named pegylated liposomal DOX (PLD) reflects improvements in cardio-safety profile. Such formulation is not recognized by immune system resulting in increased half-life and reduced systemic toxicity.[37]

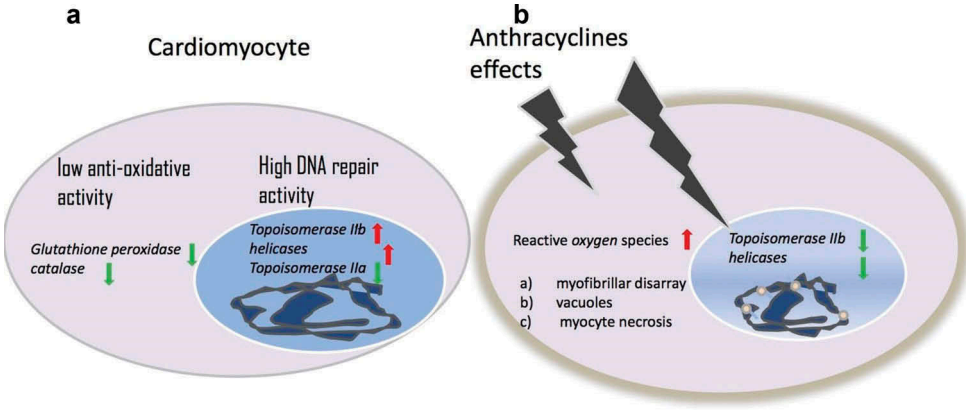

Figure 1. Role of ROS and DNA repair activity in cardiomyocyte apoptosis induced by anthracyclines.
(a) Defenses against reactive oxygen species (ROS) are inefficient in the cells that constitute cardiac muscle, cardiomyocytes as a consequence of low activity (red arrows) of enzymes such as glutathione peroxidase and catalase that eliminate ROS from the cell. Similarly, key enzymes involved in DNA repair activity such Topoisomerase IIb and helicase are highly efficient (red arrows) in mediating DNA double strand-break repair. (b) Anthracyclines generating superoxide anion, can magnify ROS production in cardiomyocyte. Similarly they might increase DNA-repair activity defects by interfering with Topoisomerase IIb and helicase causing a wide spectrum of adverse cardiomyocyte events. (Full color available online).

Table 1. Cardiac events in metastatic BC phase III trials including anthracyclines and taxanes.

Study	Patients	Arms	Cardiac events	Cardiac event definition
Pluzzanska et al. [23]	267	AP	15%	LVEF drop ≥ 20%
		FAC	10%	
Biganzoli et al. [24]	275	AP	29%	Cardiac toxicities[a]
		AC	15%	
Luck et al. [25]	560	EP	2 pts	NYHA class III/IV CHF or cardiac death
		EC	0 pts	
TAX 306 [26]	429	AT	3%	Grade 3/4 CHF
		AC	4%	
TAX 307 [27]	484	TAC	2.4%	CHF
		FAC	0.4%	
Jassem et al. [28]	267	A→P	3%	CHF
		FAC	6%	
Bontenbal et al. [29]	216	AT	3%	CHF
		FAC	6%	
Chan et al. [30]	326	T	0%	CHF[d]
		A	3.7%	
Sledge et al. E1193 trial [31]	739	A	8.7%	Moderate and severe cardiac complications[c]
		P	3.7%	
		AP	8.6%	
Bonneterre et al. [32]	142	ET	1.4%	G3/4 Cardiotoxocity[e]
		FEC	0%	
Langley et al. trial AB01 [33]	705	EP	11%	Moderate or severe cardiac toxicity[b]
		EC	4%	
GEICAM-9903 [34]	144	A→T	0%	CHF (according to the National Cancer Institute Common Toxicity Criteria [December 1994 version])
		AT	3%	
Italian GONO trial [35]	202	EP	6.8%	G3/4 CHF
		E→P	0%	

A: Doxorubicin; P: paclitaxel; F: 5-fluorouracil; C: cyclophosphamide; E: epidoxorubicin; T: docetaxel;
→: followed by;
NYHA: New York Heart Association; G3/4: grading of common toxicity criteria for adverse events of the National Cancer Institute; CHF: congestive heart failure; LVEF: left ventricular ejection fraction.
[a]CHF or Absolute LVEF drop of ≥5% below the normal limit or relative drop of ≥10% from baseline and to below the normal limit. There were 122 assessable patients in the AT arm and 118 assessable patients in the AC arm.
[b]Defined as clinical congestive cardiac failure or a decrease of more than 15% in left ventricular ejection fraction.
[c]The common toxicity criteria of the National Cancer Institute were used to define moderate (grade 3), average (grade 4).
[d]Also a decrease in LVEF of 10% (absolute units) in association with a decline below 50% (Schwartz criteria[1]) was specified as the criterion for treatment discontinuation based on LVEF assessment (discontinuation rate: 0% in T and 9.2% in A). [1]Schwartz RG, McKenzie WB, Alexander J, et al: Congestiveheart failure and left ventricular dysfunction complicating doxorubicin therapy: Seven-year experience using serial radionuclide angiocardiography. Am J Med 82:1109–1118, 1987.
[e]CHF or reductions of at least 10 or 20% in LVEF.

PLD is approved as monotherapy for the treatment of metastatic BC patients with increased risks of cardiovascular adverse events.

In randomized trials, liposomal DOX showed a lower risk of cardiac toxicity when compared to non-liposomal anthracyclines in metastatic BC patients.[38–40] Similarly, in a meta-analysis, liposomal DOX had lower risk of clinical and subclinical cardiotoxicity than non-liposomal formulations.[41] Cardiotoxicity data from randomized phase III trials with liposomal anthracyclines are reported in Table 2.[38–40,42,43]

Table 2. Conventional DOX versus encapsulated doxorubicin phase III trials.

Study	Patients	Arms	Cardiac events (%)	CHF (*n* patients)
Batist et al. [38]	142	MC	6	0
	155	AC	21	5
Harris et al. [39]	108	M	13	2
	116	A	29	9
Chan et al. [40]	80	MC	12	0
	80	EC	10	0
O'Brien et al. [42]	254	PLD	10	2
	255	A	48	10
Keller et al. [43]	150	PLD	0	0
	151	VNR or MIT C	0	0

M: Liposome-encapsulated doxorubicin citrate complex; A: doxorubicin; C: cyclophosphamide; E: epidoxorubicin; PLD: pegylated liposomal DOX; VNR: vinorelbine; MIT C: mitomycin C; CHF: congestive heart failure.

3. Other cytotoxic agents

Fluoropyrimidines, like 5-fluorouracil (5FU) and capecitabine (CAP), despite their potential risk of cardiac toxicity, are widely used in BC treatment. 5FU acts as a pyrimidine analogous inhibiting thymidylate synthase and interfering with DNA synthesis. CAP is converted to 5FU by enzymes during its hepatic metabolism.[44] Although the molecular basis underlying 5FU-associated cardiac damage remains unclear, multiple proposed mechanisms of 5FU-induced cardiotoxicity exist: (1) Endothelial dysfunction and altered coagulation; (2) coronary artery spasm followed by ischemia; (3) thrombotic events and direct cardiac toxicity.[45,46] Incidence of 5FU-induced symptomatic cardiotoxicity, across cancer types ranges 0–20% depending on multiple factors such as dose, cardiac comorbidities, and concomitant cytotoxic drugs. Noteworthy, CAP-related symptomatic cardiotoxicity ranges 3–35%.[46] Taxanes like paclitaxel (PAC) and docetaxel (DOC) are anti-microtubule agents used either alone or in combination, in adjuvant and metastatic setting.[47] Addition of taxanes to anthracyclines, in concomitant schedules, is associated with increased risks of cardiovascular complications. Molecular findings indicate that PAC interferes with the excretion of anthracycline metabolites increasing anthracycline-related cardiac toxicity.[48] A systematic review taking into account 27,039 BC patients from 15 adjuvant randomized trials, compared

DOX alone versus DOX plus taxanes. Interestingly, combination schedules were associated with decreased risk of cardiac toxicity due to lower cumulative anthracyclines doses than control arms.[49] Nab-paclitaxel, an encapsulated PAC in nanometer particles of albumin has been approved as single agent in metastatic setting. Interestingly, such drug showed no risk of developing an adverse cardiovascular event.[47] Cyclophosphamide, an alkylating agent might be associated with a low rate of cardiac disease through oxidative stress mechanisms.[50] Accordingly, data on murine models showed that administration of antioxidants such as alpha-lipoic acid and probucol-reduced cyclophosphamide-associated cardiotoxicity.[51,52] Oxidative stress appears to be also relevant in the cisplatin-associated cardiovascular toxicity.[50] Similarly, also Gemcitabine, a nucleoside analog that blocks DNA replication, showed less than 0.5% of BC-associated cardiac injury in a large, drug-specific, safety review of 22 phase II clinical trials.[53] No risk of cardiotoxicity has been associated to carboplatin, vinorelbine (VIN) and eribulin, cytotoxic agents employed in BC treatment.

4. Anti-HER2 agents

Human Epidermal Growth Factor Receptor family includes four tyrosine-kinase isoforms known as ErbB1 (HER1), ErbB2 (HER2), ErbB3 (HER3), ErbB4 (HER4) involved in cell–cell interactions, cell proliferation, and differentiation.[54] HER2 is overexpressed in approximately 30% of cases and it plays a crucial role in BC aggressiveness.[55,56] BC patients with HER2 overexpression may benefit from anti-HER2 agents.[56] Nowadays, four anti-HER2 drugs have proven efficacy in HER2 positive BC therapy: trastuzumab (TRZ), lapatinib (LPT), pertuzumab (PTZ), and trastuzumab–emtansine (T-DM1). Although such drugs are widely used for their safety profile, unfortunately they show an increased risk of adverse cardiac events (Figure 2).[3,56,57]

4.1. TRZ

TRZ is a recombinant humanized monoclonal antibody binding HER2 extracellular domain IV, thus preventing receptor homodimerization and blocking cancer cell proliferation and survival.[58] HER2, signaling through Neuregulin-1 (NRG-1), activates mitogen-activated protein kinase/extracellular signal regulated kinases (MAPK/ERK 1/2), phosphatidyl inositide 3 kinase PI3K/AkT, and focal adhesion kinases (FAK)/Src pathways (Figure 2).[59,60] ERK 1/2 activates downstream transcription factors, stabilizes myofibril structure, and inhibits apoptosis. In addition, the cross-talk between NRG-1 and PI3K/AkT decreases ROS production resulting in cell survival.[61] Finally, FAK/Src promotes sarcomeres structure and function as well as cardiomyocytes survival by recruiting other adhesion molecules.[62] Thus, blocking MAPK/ERK 1/2, PI3K/AkT, and FAK/Src dependent pathways through HER2 might cause ROS overproduction (Figure 2). Cardiomyocytes are then unable to face up ROS accumulation leading to cell impairment and organ dysfunction (Figures 1(a) and 2).[57,63,64] Recent data suggest that TRZ may obstacle cardiac stem cells differentiation interfering with their ability to forming microvascular networks.[65] TRZ-induced

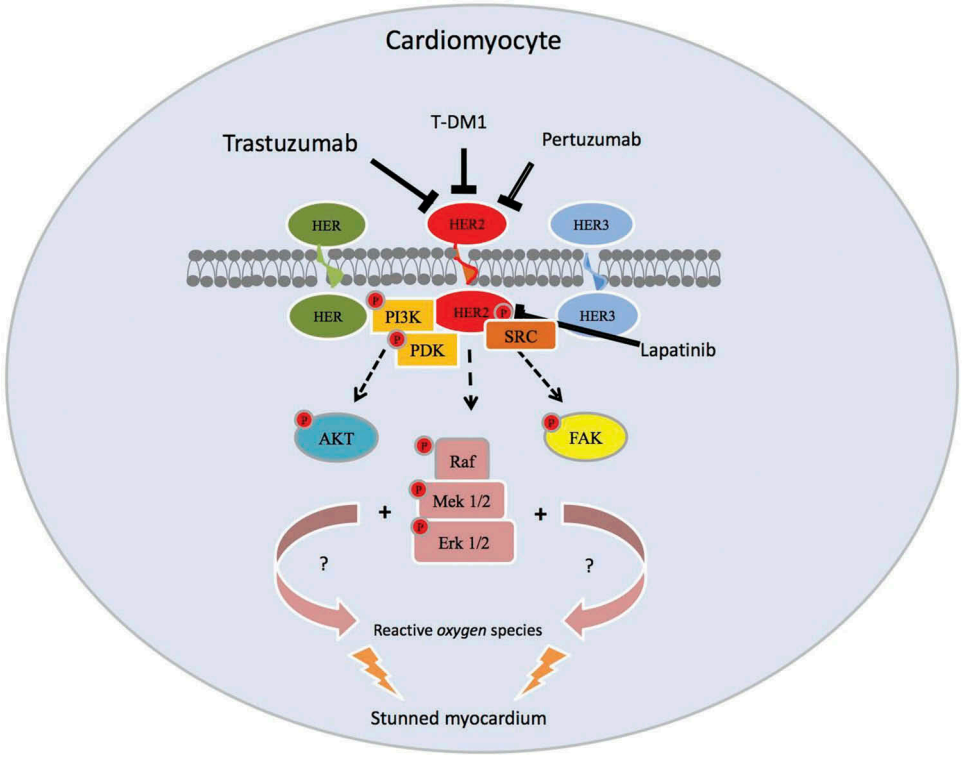

Figure 2. anti-HER2-associated cardiovascular disease is mediated by ROS overproduction in cardiomyocyte.
Proposed molecular mechanism of anti-HER2-associated cardiovascular disease. Four anti-HER2 drugs are used into clinical practice: Trastuzumab (TRZ), Lapatinib (LPT), Pertuzumab (PTZ) and Trastuzumab-Emtansine (T-DM1). These targeting molecules blocking HER2 activity cause ROS overproduction resulting in stunned myocardium and cardiotoxicity.

cardiac event occurs regardless of dose or duration.[66] TRZ has been largely investigated in phase III randomized trials showing treatment efficacy in adjuvant and metastatic setting. In the first phase III trial, 469 women with HER2 positive metastatic BC were randomized to standard chemotherapy (anthracyclines + cyclophosphamide or PAC) versus chemotherapy plus TRZ. In TRZ containing arms, the most relevant non-hematological adverse event included cardiotoxicity in patients receiving TRZ and anthracyclines combination. The incidence of New York Heart Association (NYHA) class III or IV heart failure was 16%, 3%, 2%, 1% among patients receiving anthracyclines plus TRZ, anthracyclines alone, PAC plus TRZ, and PAC alone, respectively.[67] Another phase III randomized trial in metastatic BC patients receiving TRZ in combination with DOC or VIN showed similar efficacy for both schedules. VIN plus TRZ was better tolerated than DOC plus TRZ but cardiac toxicity profile was slightly worsened in terms of LVEF decrease in VIN arm.[68] A Cochrane review including 7 phase II/III randomized trials for a total of 1497 women with HER2 positive metastatic BC receiving TRZ plus chemotherapy, endocrine therapy or other anti-HER2 agents, showed an increased risk of CHF in patients treated with TRZ containing regimens (risk ratio 3.48, confidence interval [CI] 90% 1.88–6.47).[69] Five large phase III randomized trials with TRZ in adjuvant setting have been published in which sequential schedules containing anthracyclines and TRZ were performed. All patients had normal cardiac function and the cumulative DOX dose was limited to 300 mg/m^2. NYHA class III/IV cardiotoxicity rate in these trials ranged 0–4.1% in TRZ-treated patients versus 0–1.3% in the non-TRZ regimens.[70–74] To improve patients' compliance and quality of life, a new subcutaneous formulation of TRZ has been introduced into clinical practice following the results of a large phase III randomized trial.[75] Cardio-safety data from the major TRZ adjuvant randomized trials are reported in Table 3.[70–75]

4.2. Other anti-HER2 agents (LPT, PTZ, T-DM1)

LPT is an oral, dual, small molecule tyrosine kinase inhibitor blocking HER1–2 isoforms.[56] In the pivotal phase III trial with HER2 positive advanced BC patients who had already received TRZ, were randomized with LPT plus CAP or CAP alone. Combination treatment LPT plus CAP, did not increase the risk of cardiac-related events.[76] PTZ is a fully humanized monoclonal antibody binding extracellular subdomain II of HER2, inhibiting its dimerization with other HER family receptors (EGFR, HER3, and HER4).[56] In the CLEOPATRA phase III trial, 808 metastatic BC positive for HER2, untreated for metastatic disease, were randomized to receiving TRZ plus DOC with PTZ or placebo as first-line therapy. PTZ was generally well tolerated, showing no significant difference in left ventricular systolic dysfunction (2.8% DOC plus TRZ vs. 1.2% DOC + TRZ + PTZ).[77] T-DM1 is an innovative molecule, TRZ conjugate to Emtansine (DM1), a potent anti-microtubule cytotoxic agent, via nonreducible thioether linkage. T-DM1 allows a selective TRZ intracellular delivery to cancer cells by reducing the contact of normal tissues with the cytotoxic agent.[56] In a phase III study, 'EMILIA' of 991 metastatic BC patients positive for HER2 treated with TRZ plus taxane, were randomized to receive T-DM1 versus LPT plus CAP. Among the patients receiving treatment, 1.7% of T-DM1 and 1.6% of LPT plus CAP patients had adverse cardiovascular events as revealed by LVEF less than 50% or 15% below the baseline value, respectively.[78] Furthermore, findings from safety analysis showed low rates of cardiotoxicity in 884T-DM1-treated patients. On a macrovascular level, LVEF declined to less than 40% in 0.5% of patients, whereas, ≥15% from baseline to below 50% was reported in 1.8% of patients. Cardiac toxicity resulted in discontinuation of T-DM1 in 0.45% of patients.[79]

5. Bevacizumab

Bevacizumab (BEV) is a humanized monoclonal antibody binding to VEGF-A, preventing its interaction with VEGF Receptor-2 and inhibiting endothelial proliferation and neo-angiogenesis. BEV causes a broad spectrum of cardiovascular toxicities such as arterial hypertension (HTN), CHF, venous and arterial thromboembolic events.[80] Uncontrolled HTN might result in left ventricular hypertrophy and as a consequence of CHF.[81] HTN is caused by imbalance between vasodilator and

Table 3. Cardiotoxicity in adjuvant trastuzumab phase III trials.

Study	*N* patients	Arm	Cardiac event (%)	Cardiac event definition
BIRCG 006 [70]	1073	AC–T	0.7	NYHA class III/IV CHF
	1074	AC–TH	2	
	1075	TCH	0.4	
FinHer [71]	116	Chemotherapy	1.7	Symptomatic CHF[a]
	115	Chemotherapy + H	0.9	
HERA [72]	1698	Chemotherapy	0.1	Primary cardiac endpoint[b]
	1703	Chemotherapy + 1 y H	0.8	
	1701	Chemotherapy + 2 y H	1	
NSAPB-31 [73]	814	AC–P	0.8	NYHA class III/IV CHF or cardiac death
	850	AC–PH	4.1	
N9831 [74]	664	AC–P	0.3	Symptomatic CHF or cardiac death
	710	AC–P–H	2.8	
	570	AC–PH	3.3	
HannaH Study [75]	299	H	0	NYHA Class III/IV CHF
	297	Subcutaneous H	0	

A: Doxorubicin; C: cyclophosphamide; H: trastuzumab; P: paclitaxel; T: docetaxel; y: years of administration; CHF: congestive heart failure; NYHA: New York Heart Association.

[a]Common toxicity criteria of the National Cancer Institute v 2.0.

[b]NYHA class III or IV, confirmed by a cardiologist, and a significant left ventricular ejection fraction (LVEF) drop of at least 10 percentage points from baseline and to an absolute LVEF below 50%, or cardiac death.

Table 4. Cardiotoxicity in BEV phase III trials.

Study	*N* patients	Arm	Hypertension G3/4 (%)	CHF NYHA class III or IV (%)
E2100 [86]	365	P + BEV	14.8	0.8
	346	P	0	0.3
AVADO [87]	247	T + BEV 15 mg/mq	4.5	0
	248	T + BEV 7.5 mg/mq	0.8	1.2
	241	T	1.3	0
RIBBON-1[88]	404	CAP + BEV	10.1	1.5
	201	CAP	1.0	0.5
	203	TAX + BEV	10.5	6.2
	102	TAX	0	6.0
	210	ANTHRA + BEV	8.9	2.5
	100	ANTHRA	2.0	2.0
TURANDOT [89]	284	P + BEV	4	NR
	277	CAP + BEV	6	

P: Paclitaxel; BEV: bevacizumab; CAP: capecitabine; TAX: taxanes; ANTHRA: anthracycline; NYHA: New York Heart Association; CHF: congestive heart failure.

vasoconstrictor factors; in fact nitric oxide reduction in endothelial cells and expression of plasminogen-activator inhibitor 1 (PAI-1) is observed upon BEV exposure. These events result in vasoconscriction, high peripheral vascular resistance, and increased blood pressure.[82] Anti-VEGF-associated HTN may also be caused by cholesterol embolization syndrome.[83] Finally, BEV-induced CHF may also be induced by direct disruption of cardiac tissue growth, contributing to the progression from adaptive cardiac hypertrophy to heart failure.[84] Indeed, a meta-analysis of metastatic BC negative for HER2, demonstrated that the treatment of BEV plus chemotherapy increased risk of cardiac events, left ventricular dysfunction, and CHF as well as probability of G3-4 HTN (odds ratio 5.56; 95% CI 1.66–18.62).[85] Similarly, four phase III randomized trial investigating efficacy of BEV plus chemotherapy (taxanes or CAP) versus chemotherapy alone in metastatic BC first-line therapy confirmed BEV-induced cardiotoxicity. The cardiosafety of combining BEV plus chemotherapy are reported in Table 4.[86–89]

6. Endocrine therapy

Currently, endocrine therapy is recognized as major therapeutic value demonstrating reduced risk of recurrence and improved survival in patients with estrogen-receptor positive tumors. [90] Luteinizing hormone releasing hormone (LH-RH) agonists, tamoxifen (TAM), and aromatase inhibitors (AI) are recommended both in premenopausal and postmenopausal BC patients in adjuvant and metastatic setting. TAM is a selective estrogen receptor modulator with both antagonistic and agonistic estrogenic properties. TAM reduces plasma levels of low-density lipoprotein cholesterol and decreases the risk of cardiovascular events.[91] Differently, AI (anastrozole [ANZ], letrozole [LTZ], exemestane [EXE]) block the conversion of androgens to estrogens by increasing levels of cholesterol and consequently the risk of developing cardiovascular events.[92] However, TAM has demonstrated no significant impact on the incidence of myocardial infarction as well as the risk of cardiac death.[93] Whereas combination of ANZ and TAM increased from mild–to-moderate angina and hypertension incidence versus TAM alone in ATAC phase III trial taking into account adjuvant setting.[94] In BIG-1 trial, 5-year-LTZ treatment revealed a higher G 3–5 cardiac failure/peripheral atherosclerotic events than TAM alone or LTZ and TAM in sequence.[95] Coherently, TAM followed by EXE, correlated with higher number of ischemic cardiac adverse events than TAM alone with 91 months median follow-up in a phase III randomized trial.[96] Prolonged treatment with LTZ or TAM after 5-year-TAM therapy did not reveal increased risk of cardiovascular adverse events.[97] Similarly, no significant cardiac events have been related to LH-RH agonists in premenopausal early BC patients.[98] Few data are available regarding the risk of cardiac events in metastatic BC treatment following endocrine therapy.[99] A major risk of cardiac dysfunction in EXE arm, in a metastatic BC trial comparing EXE versus TAM was reported.[100] A phase III randomized trial in first-line metastatic BC treatment showed an incidence of 0.6% and 2.2% in coronary thrombosis for ANZ and TAM, respectively.[101] Fulvestrant, a selective estrogen receptor degrader molecule for metastatic BC, did not show cardiac events in phase III trials versus TAM, ANZ, and EXE as first-line therapy.[102–104] Notably, the CONFIRM phase III randomized study with two different doses of Fulvestrant (250 vs. 500 mg) demonstrated an incidence of cardiovascular disorders shifting from 1.4% to 1.9% in metastatic BC.[105] In BOLERO-2 phase III randomized trial, combination of Everolimus (selective mammalian target of rapamycin inhibitor) and EXE significantly prolonged progression free survival versus EXE alone in hormone receptor-positive BC patients without increasing cardiac events.[106] Similarly, in PALOMA-3 phase III study, addition of Palbociclib (selective cyclin-dependent kinases 4 and 6 inhibitor), to fulvestrant in estrogen receptor-positive, HER2 negative, and advanced BC did not show any increase risk of cardiotoxicity.[107]

7. Clinical presentation

BC therapy-associated cardiovascular disease may have a broad spectrum of subclinical and clinical events like LVEF, asymptomatic decrease, symptomatic CHF, and cardiovascular related-deaths.[108] Despite lack of consensus on drug-induced cardiotoxicity, type I and II classifications have been proposed.[109] Type I is anthracycline-associated, primarily dose-dependent and estimated to occur in about 10% of patients.[9,110] It causes cardiac cell damaging, leading to apoptosis during drug exposure, regardless of clinical signs

appearance.[9] Many risk factors may increase anthracyclines-related cardiotoxicity: (1) preexisting cardiac disease, (2) diabetes mellitus, (3) hypertension, (4) very young or old age, (5) concurrent mediastinal radio-therapy.[3,111] This suggests the contribution of putative genetic factors and candidate gene variants to drug-related cardiotoxicity. For example, dystrophin genetic variants might determine a different sensitivity to anthracycline-induced cardiotoxicity in murine models.[112] Retrospective clinical studies also suggested a correlation between cardiotoxicity gene variants involved in oxidative stress, metabolism, and transport of anthracyclines.[113] Clinically, anthracyclines-related cardiotoxicity can be classified into acute or chronic. Acute presentation occurs after initiation of an anthtracycline regimen within a week, consisting of rhythm disorders, hypotension or contractile function depression (LVEF decrease).[9] Acute toxicity is mostly a reversible condition. Chronic toxicity arising months or years after anthracyclines exposure is characterized by loss of cardiomyocytes. Major clinical evidences include asymptomatic heart dysfunction, cardiomyopathy, or irreversible CHF.[5] The cardiac subclinical damage and subsequent clinical presentation could be explained by two mechanisms: activation of pro-survival pathways or through myocardial functional reserve of cardiomiocytes.[11] Type II cardiotoxicity, has been related to anti-HER2 and anti-VEGF drugs and it is estimated to occur in 2–10% of patients.[108,114] Differently from type I, type II is neither dose-related, nor characterized by ultra-structural abnormalities. Lastly, type II toxicity does not cause cardiac cell loss and histological changes, often resulting in reversible (a) symptomatic LVEF reduction or symptomatic CHF.[110] Notably, the majority of patients who developed TRZ-related CHF, might benefit from drug discontinuation leading to spontaneous or treated cardiac functional recovering.[110] Anthracycline-pretreated patients receiving subsequent anti-HER2 therapy might develop coexisting type I and II toxicity. A comparison between type I and II cardiotoxicity is reported in Table 5. Additional cardiac disorders have been linked to other drugs employed in BC management. Consistently, fluoropyrimidines such as 5FU and CAP may induce chest pain, dyspnea, hypotension, myocardial infarction, angina, and arrhythmias.[46] Taxanes can cause few cardiac events including, rhythm disturbance consisting in asymptomatic sinus bradycardia, conduction block, or cardiac ischemia.[49] Although endocrine therapy is better tolerated than chemotherapy, may lead to ischemic events as major cardiac toxicity.[99] Finally, BEV-cardiovascular toxicity is represented by HTN, arterial and venous thromboembolic events, and cardiomyopathy mostly described as type II toxicity.[85]

8. Detection and management

Despite the publication of numerous guidelines and recommendations about cardiotoxicity management and monitoring, only few evidences are available so far. Adequate clinical examination and potential, drug-related cardiovascular risk evaluation are mandatory. According with this, recent recommendations by American Heart Association suggest to consider patients on anticancer treatment at high risk of developing heart failure.[115] Comorbidities such as HTN, diabetes, previous ischemic or thromboembolic events, CHF, rhythm disorders as well as other conditions like age, previous cytotoxic treatments, or radiotherapy should be taken into account for a correct risk-assessment. Blood pressure measurement and ECG should be performed at baseline for screening and early detection of rhythm alterations, ischemic conditions, and indirect signs of cardiac overload. Next, to evaluate baseline and on-treatment LVEF, non-invasive imaging techniques, echocardiography or Multiple Gated Acquisition (MUGA), also known as radionuclide ventriculography, represent the most commonly used ones.[116] However, echocardiography and MUGA might have limited clinical utility despite their wide use to monitor cardiac function following chemotherapy. (1) They do not differentiate between irreversible and reversible forms of cardiotoxicity; (2) MUGA may suffer from excessive radiation exposure; (3) echocardiography may not be enough sensitive in LVEF measurement.[117] Tissue Doppler and Speckle Tracking echocardiography have been introduced into clinical practice for early detection of both subclinical and irreversible anthracyclines-related damage. However, these two techniques do not distinguish between Type I and II cardiotoxicity.[3] Additionally, Echo-stress seems to be sensitive in the detection of undiagnosed functional changes; however, limited data are available in Oncology.[118] Although limited by cost-effectiveness, cardiac magnetic

Table 5. Different types of BC drug-related cardiotoxicity.

Drug	Cardiotoxicity	Mechanism	Detriment	Dose	Clinical event
Anthracyclines	Type I	Redox cycling and produce ROS	Cardiomyocyte damage	Dose related	Overt heart failure, atrial and/or ventricular arrhythmias, pericarditis/ myocarditis
Anti-Her2	Type II	Oxidative stress	Cardiomyocyte dysfunction	Not dose related	Left ventricular dysfunction, myocardial infarction
Anti-VEGF	Type II	Oxidative stress	Cardiomyocyte dysfunction	Not dose related	Left ventricular dysfunction, thromboembolism, hypertension, heart failure
Taxanes	Other cardiac disorders	Conversion of DOX to doxorubicinol	Rhythm disturbances	Not dose related	Bradycardia, atrio-ventricular block, atrial and/or ventricular arrhythmias
Pyrimidine analogs	Other cardiac disorders	Unknown	Ischemia	Not dose related	Coronary spasm
Endocrine therapy	Other cardiac disorders	Unknown	Embolism	Not dose related	Thromboembolic events, hypertension
Alkylating	Other cardiac disorders	ROS production?	Cardiomyocite dysfunction	Not dose related	Left ventricular dysfunction
Cisplatin	Other cardiac disorders	Unknown	Cardiomyocite dysfunction	Not dose related	Left ventricular dysfunction

? indicates that ROS production is not a well-established mechanism of damage.

resonance provides accurate images of inflammation, edema, and strain of myocardial tissue.[119] Integration of cardiac biomarkers with imaging techniques might improve diagnosis of cardiac events. Accordingly, Troponins have been shown to be easily detectable, reproducible, specific, and sensitive biomarkers of myocardial damage.[120] Increased serum troponin levels may predict cardiac impairment earlier than LVEF reduction. Some authors confirmed the role of Troponin I associated with Left Ventricular dysfunction when BC patients underwent sequential therapy with DOX and TRZ.[114] Interestingly, although high-sensitivity Troponin might predict for which individuals are at increased risk of heart failure, few studies in BC patients are available so far.[121] Brain Natriuretic Peptide (BNP), a blood marker that increases during anthracyclines-treatment, has no predictive value regarding long-term cardiotoxicity.[122] Unfortunately, no universally accepted BC cardiotoxicity management algorithms are available. Some authors have proposed a LVEF-based flow chart. Accordingly, 15% or 10% LVEF decrease from baseline to 50% or less should suggest cardiac dysfunction.[3] European Society of Medical Oncology guidelines recommend to monitor cardiac function at 3, 6, and 9 months by echocardiography or MUGA if there are no variations in LVEF during anthracyclines and/or TRZ treatment. These techniques should also be used 12 and 18 months after treatment initiation.[123] Anthracyclines or TRZ treatment should be held or stopped whereby a clinical relevant LVEF decrease has been diagnosed. In such condition, systolic function monitoring at 3 weeks along with medical treatment for heart failure should be considered. In case of type II toxicity, TRZ treatment could be reintroduced if cardiac function has been recovered.[110] Long-term cardiotoxicity follow-up should include LVEF evaluation 6 months after treatment conclusion, yearly for 2–3 years and then every 3–5 years.[123] In this scenario, an important concern might be represented by cardio-prevention. A number of molecules, Dexrazoxane, ACE-inhibitors, statins, beta-blockers, and recently visnagin, have been proposed and investigated as cardio-protective agents.[3] In particular, iron-chelating agent Dexrazoxane reduces anthracycline-related cardiotoxicity by decreasing ROS overproduction.[124] Preclinical studies have indicated that Visnagin modulates malate-dehydrogenase enzyme activity leading to electrons intake within mitochondria. By this way, Visnagin limits ROS over-production in cardiomyocites acting as promising cardio-protective agent.[125]

9. Conclusions

In 2015, BC survival rates are at their highest ever. BCs are now treated with tailored combinations of surgery, chemotherapy and radiation. Last decades have seen greatly improved BC prognosis and research is making treatments more precise and minimizing side effects. Although treatments such as anthracyclines, which are a mainstay of chemotherapy, have prolonged survival, cardiotoxicity represents an important issue in BC management. In line with this, endocrine agents, AIs (ANZ, LTZ, EXE) and newer targeted agents such as anti-HER2 molecules TRZ, LPT, PTZ, and T-DM1 together with anti-VEGF agent BEV both have established risks of cardiotoxicity, which can limit their effectiveness and result in increased morbidity and/or mortality. Therefore, sensitive and cost-effective biomarkers of cardiotoxicity might offer a tool to diagnose early drug-induced cardiac injury. Despite this, there is a paucity of data that might be used to guide treatment recommendations. Moreover, screening programs for overt heart failure do not adequately address the needs of the majority of patients with BC. Recent but still limited studies indicate that drugs that inhibit production of ROS seem to prevent the development of early myocardial impairment. As a result of this lack of evidence-based recommendations, clinical approaches for patients with asymptomatic decrease in LVEF are variable and inconsistent. Future directions in clinical management should provide integration of novel, more sensitive, blood biomarkers with imaging methods to improve cardiotoxicity early detection. Introduction of new molecules requires further investigation to fully understanding the molecular basis of cardiac damage. Cooperation among clinicians such as Oncologists, Cardiologists, Radiologists, Pathologists, Radiotherapists, and Molecular Biologists is needed to provide higher evidence-based knowledge as well as a larger consensus about drug-related cardiotoxicity management in BC patients.

10. Expert opinion

Over the last decade, BC incidence rates are rising in several countries, therefore, an even higher number of patients will need care. Drugs employed in BC treatment both in adjuvant and metastatic setting have a range of adverse events, therefore, an important issue is represented by detection and management of cardiotoxicity. Anthracyclines and anti-HER2 agents represent the major cardiotoxic drugs but also endocrine-therapy and anti-VEGF molecules should be taken into account. Interestingly, a spectrum of newer drugs such as Phosphoinositide 3-Kinase (Buparlisib) or Cyclin Dependent Kinase inhibitors (Palbociclib and Ribociclib) are under phase III trials evaluation in BC treatment. These innovative molecules have been tested in combination schedules with endocrine-therapy (AIs or Fulvestrant) mostly in metastatic setting. Even if they are not related to an intrinsic cardiotoxicity the question whether they may worsen cardiac safety profile of endocrine therapy has still to be established. Molecular basis of BC drug-related toxicity partially explain the broad spectrum of clinical presentations including arrhythmias, ischemia, CHF, or patient death. Until now, it is possible to distinguish between type I and II cardiotoxicity with deep differences in physiopathology and clinical presentation. Although large amount of data from literature are available, low evidences and no guidelines for detection, monitoring, and management of drug-related cardiotoxicity have been suggested. Clinical evaluation and risk assessment are mandatory for treatment choice. In clinical practice, a parameter to monitor cardiac events occurrence is represented by LVEF. Several imaging methods are available to measure LVEF with different outcomes in terms of sensitivity and specificity. Nevertheless echocardiography remains the routinely accepted technique with several limitations. Although cardiac magnetic resonance is accurate in determining cardiac volumes and LVEF its clinical use is limited by cost and access issues. An important

contribution to cardiotoxicity detection and management could result from the introduction of blood biomarkers in the context of a comprehensive patient evaluation. Both Troponin I and T and BNP, easily and quickly available biomarkers, have been studied as potential indicators of cardiac injury. Interestingly, high sensitivity Troponin should be further investigated to improve early cardiotoxicty. In the future, integration of such biomarkers with imaging techniques could allow a more precise baseline risk assessment and cardio-safety monitoring during treatment. In order to validate the use of cardiotoxicity predictive biomarkers, prospective and randomized clinical trials are needed. Actually, there is no consensus about the timing of safety follow-up after a potentially cardiotoxic treatment and daily practice is not based on validated algorithms. The absence of univocal guidelines about detection, monitoring, and follow-up of BC drug-related cardiac events may also reflect a lack of cooperation between Oncologists, Cardiologists, and other clinicians. Future clinical studies by integrating clinical parameters, predictive biomarkers with imaging techniques could provide new insight into drug-related cardiotoxicity assessment and tailored algorithms aiming to improve BC patients' management.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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