

REVIEW

Targeted therapies in breast cancer: are heart and vessels also being targeted?

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Abstract

The concept of 'targeted' therapies implies that such drugs only act on cells that specifically express the particular target, therefore giving rise to a low incidence of side effects. However, targeted therapies currently approved for the treatment of breast cancer have demonstrated a relatively high incidence of cardiovascular events. The anti-HER2 agents trastuzumab and lapatinib may cause left ventricular dysfunction or even congestive heart failure. Bevacizumab, an antiangiogenic drug, has been shown to increase the risk of hypertension, cardiovascular dysfunction and thromboembolic events. In addition, several anti-human epidermal growth factor receptor 2 (HER2) and antiangiogenic agents plus their combinations are currently being developed and evaluated for the treatment of breast cancer. In this review, we aim to assess the incidence of cardiac adverse events associated with targeted therapies designed to block HER2 and angiogenic pathways.

Introduction

Cardiovascular toxicity following breast cancer (BC) treatments may manifest as hypertension, ischemic heart disease, rhythm disturbances, thromboembolic events, or congestive heart failure (CHF). The Common Terminology Criteria for Adverse Events (CTCAE; version 4.03, June 2010) encompasses 36 distinct cardiac disorders and 17 vascular disorders. Classic risk factors for cardiac disease, such as diabetes, dyslipidemia, obesity, hypertension and smoking, are frequent among BC patients, adding detrimental effects to cardiotoxic drugs used in conventional therapy. When assessing the cardiotoxicity

associated with the targeted therapies now available for BC, one needs to take into account several variables (Figure 1). Considerable data are available regarding trastuzumab-associated cardiotoxicity, but knowledge about other targeted therapies is more limited.

Search criteria

This review aims to describe the cardiotoxicity of targeted therapies designed to block the epidermal growth factor (EGF) family of receptors and antiangiogenic therapies currently under investigation for the treatment of BC. We conducted English-language MEDLINE searches, giving priority to phase III studies when those were available. The search terms included the targeted therapies described in Table 1 and 'breast cancer'. The last search was updated on 28 June 2011. Considering the likelihood of unpublished data, we also performed an electronic search of the proceedings of major conferences. Finally, we checked the Clinicaltrials.gov website for ongoing adjuvant studies involving the selected targeted therapies. The authors briefly discuss management strategies in patients with new-onset heart failure or decreased left ventricular ejection fraction (LVEF) as well as the role of cardiac markers in identifying sub-clinical myocardial damage associated with oncologic therapies.

Anti-HER2 therapy

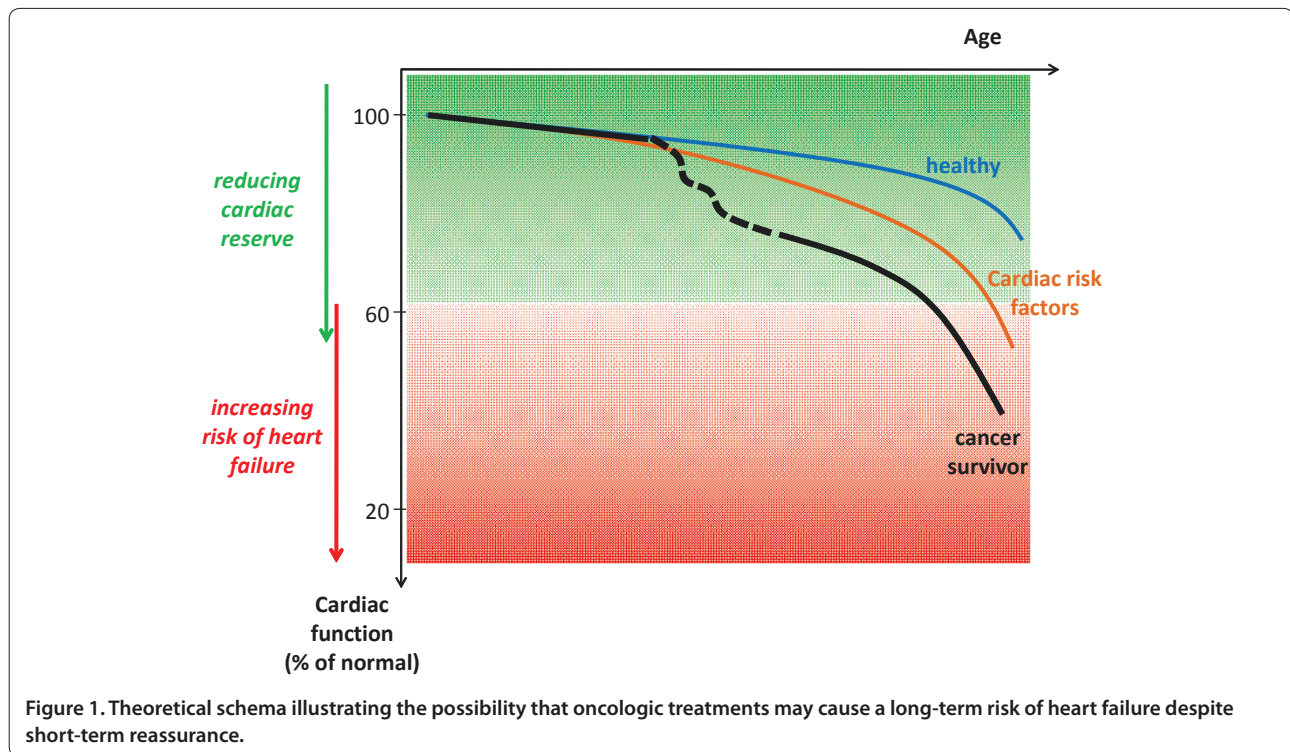
Human epidermal growth factor receptor (HER)2 belongs to a family of EGF receptors (EGFRs; HER1, HER2/neu, HER3 and HER4), and is overexpressed in about 15 to 20% of all BCs [1]. Trastuzumab, a monoclonal antibody designed to block HER2, was first approved for the treatment of metastatic BC (MBC) in 1998, and since 2006 its indication has been broadened to early-stage BC (EBC) as part of adjuvant treatment [2]. In EBC, the addition of trastuzumab to chemotherapy has been shown to reduce BC recurrence by 50% and mortality by 33% [2]. Unexpectedly, however, severe cardiac toxicity was observed when trastuzumab was added to classic chemotherapy regimens [2]. Following the identification of trastuzumab-mediated cardiotoxicity, comprehensive

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research programs were started to clarify the role of HER receptors in heart physiology.

The HER family members and their ligands are important for fetal cardiac development. Deletion of HER2, HER3, HER4 or its ligand neuregulin-1 (NRG-1) is known to cause embryonic lethality [3]. The deletion of EGFR is also associated with embryonic or early post-natal lethality, although it is probably not related to cardiac effects [4].

In the adult heart, HER3 expression is no longer detectable, but HER1, HER2, HER4, and NRG-1 do remain detectable and are thus important components in myocardial physiology [5]. NRG-1 is considered to be an important cardioprotective mediator because it induces antiapoptotic pathways, hypertrophic and mitotic myocardial growth, and angiogenesis, and it also reduces myocardial sensitivity to adrenergic stress [5]. The exact role of HER1 expression in myocardial physiology remains to be defined. Ligands such as heparin-binding EGF and EGF are known to activate EGFR, leading to its dimerization. The HER2 pathway in the heart is involved in the regulation of cellular metabolism, growth and survival upon activation of important signaling pathways, such as phosphoinositide 3-kinase/AKT signaling. In contrast to cancer cells, HER2 is not overexpressed in cardiomyocytes, and it is activated exclusively upon heterodimerization with ligand-activated receptors (EGFR or HER4) [4]. Recent research raises doubt regarding the

hypothesis that HER2 blockade causes trastuzumab-mediated cardiotoxicity [4].

The availability of novel anti-HER2 drugs with different mechanisms of action will shed light on the role played by EGFR family members in cardiac physiology. Lapatinib, an oral tyrosine kinase inhibitor (TKI) of EGFR and HER2, is approved in combination with chemotherapy for the treatment of MBC. The ability of lapatinib to block ligand-induced and ligand-independent activation makes the blockade of the HER2 receptor in the heart more likely than with trastuzumab. Nevertheless, despite its different mechanism of action, lapatinib has not been associated with high rates of cardiotoxicity (described below in the 'Lapatinib' section). A possible explanation for the restrained incidence of cardiotoxicity with lapatinib therapy could be the induction of protective pathways mediated by the mitochondrial production of energy [6]. However, direct comparisons in prospective large trials are not available yet and are eagerly waited.

Pertuzumab, a monoclonal antibody designed to block domain II of HER2 receptors, blocks the dimerization of HER2 with ligand-dependent EGFR members [7]. As a result, blockade of the HER2 receptor in the heart is expected. Due to its mechanism of action, pertuzumab can also interfere with cardioprotective pathways mediated by NRG-1, increasing the risk of cardiotoxicity. Safety data from phase II and ongoing/planned phase III studies are described below in the 'Pertuzumab' section.

Table 1. Targeted therapies and their main targets

Drug	Targets
Trastuzumab	HER2 (epitope IV)
Lapatinib	EGFR and HER2
Pertuzumab	HER2 (epitope II)
Neratinib	EGFR, HER2, HER4 (irreversible)
T-DM1	HER2
Tanespimycin	HSP-90
BIBW 2992	EGFR, HER2
Gefitinib	EGFR
Erlotinib	EGFR
Cetuximab	EGFR
Bevacizumab	VEGF-A
Sunitinib ^a	VEGFR2, PDGFR-beta, c-kit, FLT3
Sorafenib ^a	VEGFR-2/PDGFR-beta, RAF kinase
Pazopanib	VEGFR-1, VEGFR-2, VEGFR-3, cKIT, PDGFR
Vandetanib	VEGFR2, EGFR, RET

^aTargeted therapies with low specificity and blockade of additional targets. EGFR, epidermal growth factor receptor; HER, human epidermal growth factor receptor; PDGFR, platelet-derived growth factor receptor; T-DM1, trastuzumab-DM1; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

The body of safety information for novel anti-HER2 antibodies and TKIs is growing, but the precise relationship between their mechanisms of action and heart physiology remains to be elucidated.

Trastuzumab

Contrary to the irreversible cardiomyocyte damage caused by anthracyclines, trastuzumab-mediated toxicity seems to be reversible [2]. The observation of cardiac functional recovery after exposure to trastuzumab led to the description of 'chemotherapy-related cardiac dysfunction' (CRCD) [8].

Type I CRCD related to anthracyclines is initiated just after the earliest exposure to these drugs and, once a threshold level of damage takes place, cell death ensues [9]. Anthracyclines lead to structural cardiomyocyte alterations and cell death, which is probably mediated by reactive oxygen species (ROS) generated in iron-dependent chemical reactions. Type I damage diagnosed by reduced LVEF increases the heart's vulnerability to a later cardiac stress [10].

Type II CRCD, such as that caused by trastuzumab, can be differentiated from type I CRCD by its reversibility [2]. Patients treated with trastuzumab frequently experience asymptomatic drops in LVEF with subsequent recovery after drug withdrawal [11], although in some cases the LVEF decline persists after completion of therapy [12]. In a milestone trial (NSABP B31), asymptomatic decrease in LVEF occurred in 14% of patients, requiring discontinuation

of trastuzumab [13]. Endomyocardial biopsy, the most reliable method to evaluate myocardial damage, was performed in a limited number of patients exposed to trastuzumab and demonstrated no significant abnormalities [8,14]. However, longer follow-up of patients participating in adjuvant studies is needed to better characterize type II CRCD. At this moment, the data available regarding long-term trastuzumab cardiotoxicity cover a limited period of five years only. Prospective collection of these data for adjuvant trastuzumab up to year 10 will help better our understanding of this toxicity.

Consistent information about trastuzumab cardiac safety is available [2]. The incidence of severe CHF in the trastuzumab adjuvant studies is in the range of 1% to 4% (Table 2). In the Herceptin Adjuvant trial (HERA), with 3.6 years of median follow-up, all cases of severe CHF occurred during trastuzumab treatment; however, the cardiac condition of the majority of affected patients improved when trastuzumab was withdrawn [15]. Importantly, patients with cardiac risks were not included in the adjuvant studies of trastuzumab [2]. Subgroup analysis identified subpopulations most likely to experience cardiac damage upon trastuzumab exposure [11,13,16,17].

Though there is a risk of cardiac toxicity with adjuvant trastuzumab in general, the improvement of outcomes in patients treated with this drug outweighs that risk. It is essential, therefore, to properly assess cardiac function prior to, during, and after trastuzumab therapy in all patients. Additionally, longer follow-up is recommended in order to verify whether cardiac reversibility remains and, accordingly, whether the short-term risk is exaggerated or understated. It must be noted, however, that the incidence of CHF in older patients treated with trastuzumab is expected to be higher than in the overall population evaluated in large clinical trials [18,19]. Hence, cardiac risk assessment, BC recurrence risk, and discussion between cardiologists and oncologists should take place prior to deciding which adjuvant treatment is appropriate for a woman with EBC.

Lapatinib

In a pooled analysis of 3,689 patients treated with lapatinib (15% of them anthracycline pre-treated), asymptomatic cardiac events were reported in 1.6% of patients, and symptomatic events in 0.2% [20]. The results of three phase III studies evaluating the addition of lapatinib to either chemotherapy or hormonal therapy did not show any significant increase of cardiac adverse events (AEs) [21-23]. In the Lapatinib Expanded Access Program (LEAP) [24], 4,283 patients previously treated with anthracyclines, taxanes and trastuzumab were treated with capecitabine plus lapatinib. The median duration of treatment was 24.7 weeks, and the incidence of LVEF decrease was 0.5%.

Table 2. Rates of severe congestive heart failure in trastuzumab adjuvant trials

Treatment arms	HERA [15]		NSABP B-31 [111]		N9831 [16]			BCIRG 006 [112]			PACS-04 [113]	
	Obs	1-year H	AC→P	AC→PH	AC→P	AC→P→H	AC→PH	AC→D	AC→DH	DCb+H	Obs	1-year H
Women at risk (n)	1,698	1,703	872	932	767	718	875	1,050	1,068	1,056	268	260
Cardiac deaths	1	0	1	0	1	1	0	0	0	0	0	0
CHF NYHA class 3-4 (%)	0	13 (0.8)	9 (1.3)	35 (3.9)	2 (0.3)	18 (2.8)	19 (3.3)	4 (0.38)	20 (1.87)	4 (0.38)	1 (0.4)	4 (1.7)

NSABP B-31, cumulative incidence at 5 years; N9831, cumulative incidence at 3 years; no CHF class 3-4 and no cardiac death reported in the FinHer trial. AC, doxorubicin and cyclophosphamide; BCIRG, Breast Cancer International Research Group; Cb, carboplatin; CHF, congestive heart failure; D, docetaxel; H, Herceptin® (trastuzumab); HERA, HERceptin Adjuvant; NSABP, National Surgical Adjuvant Breast and Bowel Project; NYHA, New York Heart Association; Obs, observation; P, paclitaxel; PACS, Protocole Adjuvant dans le cancer du sein.

Due to their synergistic antitumor activity, the combination of lapatinib and trastuzumab was evaluated in MBC studies and is being investigated across adjuvant and neoadjuvant studies [25,26]. In a randomized phase III study, lapatinib combined with trastuzumab resulted in an increased number of LVEF drops compared to lapatinib alone [27].

The ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization) study recently completed enrolment of nearly 8,400 patients randomized to one of the following study arms: trastuzumab for 1 year, lapatinib for 1 year, trastuzumab followed by lapatinib for a total duration of 1 year, and lapatinib in combination with trastuzumab for 1 year, either after completion of anthracycline-based chemotherapy or concomitantly with chemotherapy. ALTTO is expected to help settle the controversy around sequential versus combination treatment approaches with respect to cardiotoxicity.

In contrast to ALTTO, the TEACH (Tykerb Evaluation After Chemotherapy) study aims to evaluate the benefit of lapatinib in EBC for patients with HER2-positive BC who have not received trastuzumab, even if introduced several years after diagnosis. This study did not show a significant improvement in disease-free survival, while the incidence of cardiac events were similar between lapatinib and placebo arms (3% versus 3%); no cardiac deaths were associated with lapatinib [28].

An open-label, randomized phase II study evaluating the efficacy and safety of neoadjuvant docetaxel and carboplatin plus trastuzumab and/or lapatinib in HER2-positive BC assigned the first 20 patients to receive all four drugs in order to assess the safety of this regimen. No CHF or decline in LVEF >10% was observed [29]. Similarly, neither major cardiac dysfunctions nor any toxic deaths occurred in the NeoALTTO trial, a phase III, randomized, open label study comparing the efficacy of lapatinib, trastuzumab or their combination together with paclitaxel when given as neoadjuvant treatment for HER2-positive primary BC [30]. In this trial, no anthracycline chemotherapy was given prior to surgery. Finally, the Geparquinto trial did not show increased cardiotoxicity of either lapatinib or trastuzumab in combination with neoadjuvant anthracycline-taxane-based

chemotherapy in patients with early HER2-positive BC [31].

Pertuzumab

Pertuzumab is a humanized monoclonal antibody that binds to domain II (dimerization domain) of the HER2 receptor [7]. In a phase II study of MBC, pertuzumab monotherapy was associated with LVEF reduction in 7.6% of 78 patients [32]. A phase II study designed to evaluate tumor response and cardiac safety when trastuzumab and pertuzumab are combined was limited to 11 patients (37 planned) due to an excessive rate of cardiotoxicity [33]. All patients had previously been treated with anthracyclines and trastuzumab, and 54% of them experienced a decrease in LVEF (one patient had symptomatic CHF) with the pertuzumab-trastuzumab combination.

A subsequent phase II study evaluated the safety and efficacy of combined trastuzumab-pertuzumab treatment in 66 patients previously exposed to trastuzumab [25]. Asymptomatic LVEF reduction was observed in three patients and CHF in none. An extension of the study was performed with 29 patients (who had previously received trastuzumab) to be treated with pertuzumab monotherapy, followed by the combination of pertuzumab/trastuzumab upon progression [34]. Three patients experienced an asymptomatic LVEF decrease, but no CHF was reported. In a pooled analysis of 569 patients treated with pertuzumab across different disease subsets, 5.7% of patients experienced a decrease in LVEF and 0.7% developed symptomatic CHF [35].

Recently, the NeoSphere trial, in which patients with HER2-positive BC were randomized to receive trastuzumab-docetaxel (TH), trastuzumab-docetaxel-pertuzumab (THP), trastuzumab-pertuzumab (HP) or docetaxel-pertuzumab (TP) as neoadjuvant therapy, showed only one case of CHF (HP arm). Asymptomatic decline in LVEF was observed in five more patients with TH (one patient), THP (three patients) and TP (one patient), but the LVEF drop was resolved in all cases at the subsequent evaluation [36]. Results from TRYPHAENA, a randomized phase II neoadjuvant trial investigating the combination of pertuzumab and trastuzumab with or

without an anthracycline-based chemotherapy regimen, indicate a low incidence of symptomatic and asymptomatic LVEF drop across all arms [37].

Neratinib

Neratinib (HKI-272) is an oral irreversible pan-ErbB TKI that blocks downstream signaling of HER1, HER2, and HER4 by binding to the intracellular ATP binding sites of these receptors. Neratinib may have advantages over other inhibitors because of its pan-ErbB inhibition and ability to irreversibly inhibit intracellular tyrosine kinase domains. In one study, no indication of LVEF impairment was observed in patients with advanced HER2-positive BC treated with neratinib, with or without previous exposure to trastuzumab [38]. Also, the combination of neratinib with trastuzumab does not seem to increase the risk of cardiac toxicity [39]. Similar findings were observed when neratinib was combined with different chemotherapy regimens [40-42]. However, clinical experience with neratinib is scantier than that with previously reported drugs and longer follow-up and data from a greater number of patients treated with this drug are required before its level of cardiac safety can be confidently assessed.

Trastuzumab-DM1

Trastuzumab-DM1 (T-DM1), an antibody drug conjugate of maytansine and trastuzumab, was developed to deliver the potent microtubule inhibitor maytansine to HER2-overexpressing cells by attaching it to trastuzumab [43]. In a phase II study including 112 patients with MBC previously treated with trastuzumab and/or lapatinib, no severe cardiotoxicity was reported [44]. A subsequent phase II study evaluated T-DM1 in 107 patients pretreated with anthracyclines, trastuzumab, taxanes, capecitabine, and lapatinib. Reduction in LVEF was observed in two patients [45]. This drug is currently being tested for its cardiac safety in EBC.

Tanespimycin and HSP90 inhibitors

HSP90 is a chaperone protein that stabilizes proteins such as HER2, AKT, EGFR and platelet-derived growth factor. Blocking HSP90 leads to the degradation of its targets [46]. In a phase II trial of tanespimycin given in combination with trastuzumab involving 29 patients, no evidence of cardiotoxicity was observed [47].

Afatinib

Afatinib (BIBW 2292) is an oral, irreversible EGFR and HER2 TKI. This agent has been evaluated in 28 patients with estrogen receptor-positive BC previously treated with letrozole [48], in 41 patients previously exposed to trastuzumab [49], and in 50 patients with HER2-negative disease [50], with no serious cardiac AEs. However,

additional clinical data are required to better evaluate the cardiac safety of afatinib.

Anti-HER1 (EGFR) therapy

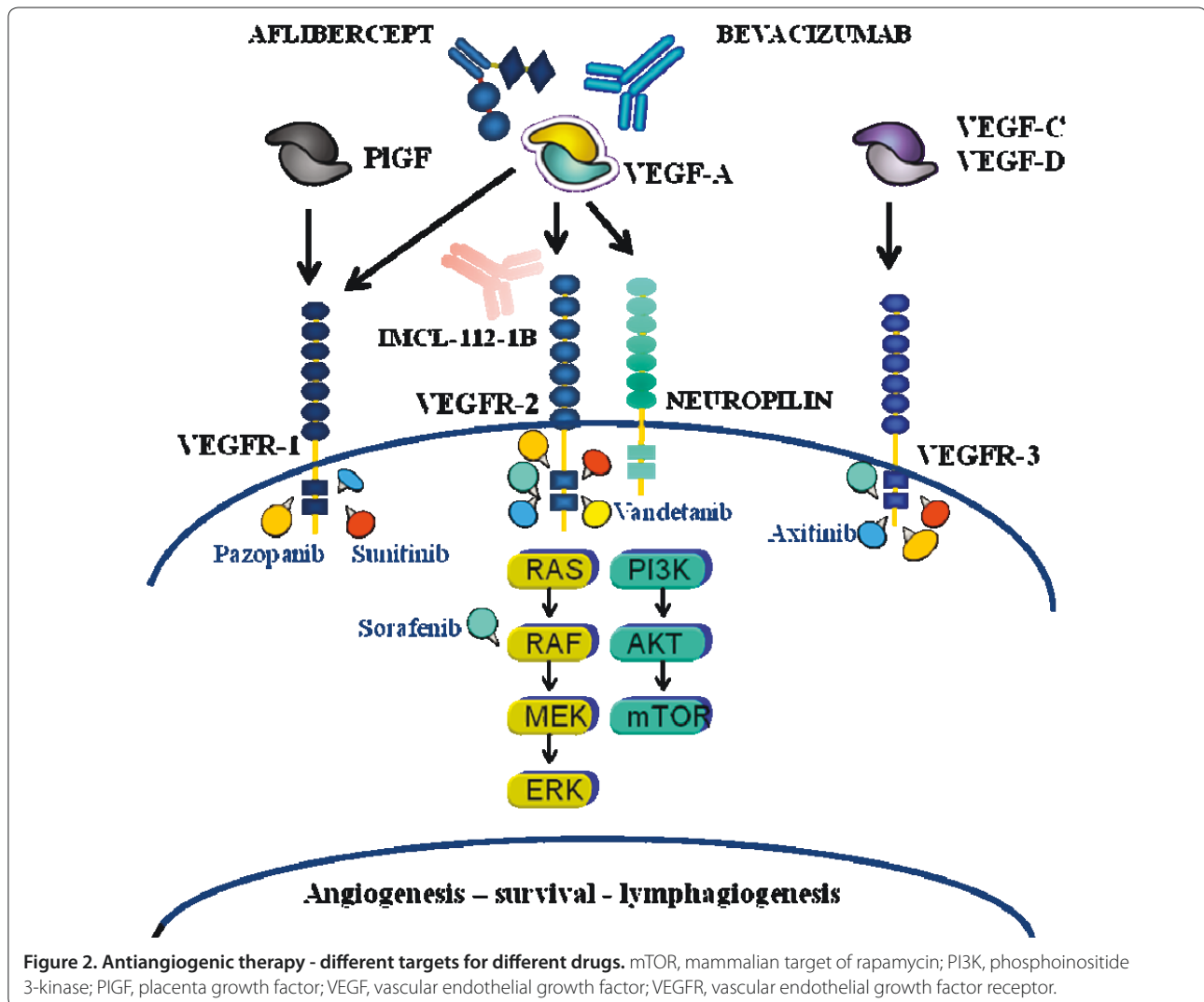
Erlotinib and gefitinib are TKIs designed to block EGFRs. In a multicenter phase II study of erlotinib monotherapy in MBC, no serious cardiac events were reported among 68 patients treated, but the intervention was associated with limited efficacy (complete or partial response sustained for ≥ 4 weeks according to World Health Organization criteria assessed by the investigator (ORR) = 3%) [51]. Gefitinib was evaluated in combination with hormonal therapy in four randomized phase II studies, which resulted in no gefitinib-related serious cardiotoxic events [52-55]. Cetuximab is a chimeric monoclonal antibody designed to block EGFR. No serious cardiac events were reported when cetuximab was combined with chemotherapy in two randomized phase II trials for the treatment of MBC [56,57]. In brief, until now anti-EGFR therapies seem not to be associated with an increased risk of cardiovascular events in BC patients; however, the use of anti-EGFR in BC remains low.

Antiangiogenic therapy

Targeting angiogenesis has emerged as another potential therapeutic approach for BC. Numerous targeted therapies with variable mechanisms of action to block the vascular endothelial growth factor (VEGF) pathway are in clinical development (Figure 2). Following the promising improvement in proliferation-free survival reported in the ECOG-E2100 study, bevacizumab, a monoclonal antibody against vascular VEGF-A, was approved for the first-line treatment of MBC in 2008 [58]. Nevertheless, two subsequent trials were unable to confirm the magnitude of this benefit [59,60]. Ultimately, considering the modest clinical benefit on the one hand, and the increase in toxicity on the other, the US Food and Drug Administration withdrew its approval of the BC indication for bevacizumab [61].

Serious cardiovascular AEs, such as hypertension, CHF and thromboembolic events, have been reported with antiangiogenic therapies. Preclinical models have demonstrated the importance of angiogenesis to the maintenance of cardiac homeostasis [62,63], which in part explains the cardiac AEs reported with such therapies.

Inhibitors of VEGF receptors, such as sunitinib and sorafenib, are able to block a large number of tyrosine kinase receptors, making it difficult to identify the target(s) mediating cardiotoxicity [64]. Overlapping mechanisms have been proposed to explain the increased incidence of thromboembolic events with antiangiogenic targeted therapies. VEGF inhibition leads to a blockade of the capability of endothelial cells to regenerate, causing endothelial dysfunction [65]. VEGF blockade decreases



the production of vasodilators, activates pro-coagulant pathways, and increases hematocrit and blood viscosity due to overproduction of erythropoetin [65,66]. The ensemble of pro-thrombotic factors mediated by antiangiogenic therapy, coupled with cancer patients' predisposition to thrombosis, explains the increased incidence of thrombotic events observed with targeted antiangiogenic therapies.

Newly developed or worsened hypertension is the most common cardiovascular AE observed with antiangiogenic therapy. Antiangiogenesis-induced hypertension is thought to be related to a reduction of nitric oxide production in the wall of arterioles and resistance vessels. However, no correlation between the deregulation of the renin-angiotensin system and hypertension was observed in a study of 20 patients treated with sorafenib [67].

Bevacizumab

A significant incidence of cardiotoxicity has been identified in early experience with bevacizumab, and cardiac

events are being carefully monitored in current phase III trials. Recently, a meta-analysis of five randomized trials involving a total of 3,784 MBC patients investigated the incidence of CHF when using chemotherapy with or without bevacizumab. The incidence of high-grade CHF was 1.6% in patients treated with bevacizumab and 0.4% in patients who did not receive this drug. Also, patients treated with bevacizumab showed a higher relative risk (4.74, $P = 0.001$) of developing CHF than patients in the control/placebo group [68].

In another recent meta-analysis of bevacizumab in the first-line treatment of MBC, bevacizumab was associated with a five-fold increased chance of hypertension (odds ratio = 5.17, 95% confidence interval (CI) 1.35 to 19.78) and a three-fold increased chance of cardiovascular dysfunction (odds ratio = 3.04, 95% CI 1.27 to 7.31) [69]. In a pooled analysis of 1,745 patients, of whom 963 were treated with bevacizumab (24% BC), the incidence of thromboembolic events was 4% in patients treated with

bevacizumab plus chemotherapy, and 2% in those treated with chemotherapy alone. Mortality-associated thromboembolic events was 0.8% in patients treated with bevacizumab plus chemotherapy, and 0.4% in those receiving chemotherapy alone [70].

Bevacizumab in combination with chemotherapy was evaluated in five phase III randomized clinical studies for the treatment of MBC [58-60,71,72]. Serious cardiovascular AEs were reported with variable frequency across the studies (Table 3). A direct relationship between bevacizumab dose and hypertension was observed in the AVADO trial, in which a higher dose of bevacizumab was associated with a higher incidence of cardiotoxicity [73].

The ECOG-2104 study is a non-randomized phase II trial designed to evaluate the safety of incorporating bevacizumab into an anthracycline-containing adjuvant therapy (dose-dense doxorubicin plus cyclophosphamide (ddAC)) followed by paclitaxel [74]. A total of 226 patients were enrolled, and all received bevacizumab, initiated either concurrently with ddAC (n = 104 patients) or sequentially after ddAC (n = 122 patients). Grade 3 hypertension and thrombosis were reported in 11% and 2% of patients, respectively. CHF was diagnosed in four patients (two in each study arm).

In a phase II study including 80 patients receiving ddAC followed by nab-paclitaxel, 13.6% of patients reported grade 3 hypertension [75]. No patients developed symptomatic LVEF dysfunction, but asymptomatic and temporary LVEF decline was observed in 1.2% and 5%, respectively [76].

CHF was diagnosed in 3 out of 138 patients treated with the combination of bevacizumab with three docetaxel-containing chemotherapy regimens [77].

Bevacizumab is being evaluated across different studies in the adjuvant setting. One of these trials, ECOG-5103, was temporarily halted according to a pre-planned cardiotoxicity analysis of the first 200 patients enrolled when 6 patients developed CHF after taking bevacizumab. However, none of the patients enrolled in the trial died from cardiac problems. After a thorough independent review of the safety data, no concern about the cardiac safety of bevacizumab was identified, and the ECOG-5103 study was re-opened for accrual.

In summary, bevacizumab has been associated with hypertension, reductions in LVEF and an increase in heart failure. Its cardiac safety is being carefully assessed in ongoing trials.

Sunitinib

Sunitinib has been associated with a moderate rate of cardiovascular events, although hypertension constitutes the majority of cases. A study in imatinib-resistant gastrointestinal stromal tumor patients was the first to demonstrate that sunitinib was associated with heart

failure, LVEF decline, and hypertension [78]. In a phase II study involving 64 patients with MBC treated with sunitinib monotherapy, no cases of CHF were reported, but 6% experienced grade 3 hypertension [79].

Subsequent phase III studies of sunitinib in MBC failed to improve patient outcomes, and the cardiac data were mixed [80-82]. When compared to capecitabine in the second-line treatment of MBC, sunitinib was associated with 3% of grade 3 hypertension [80]. In that study, five treatment-related mortalities were reported, including one case due to CHF and one due to pulmonary embolism [80]. In contrast, the preliminary reports of two studies evaluating sunitinib plus capecitabine versus capecitabine and sunitinib plus docetaxel versus docetaxel did not report excessive cardiotoxicity related to sunitinib [81,82]. In another study, sunitinib plus paclitaxel did not show any benefits when compared to bevacizumab plus paclitaxel in the first-line treatment of MBC, and was associated with 3% of grade 3-4 hypertension. Toxicity clearly increases, however, when sunitinib is combined with standard doses of bevacizumab and paclitaxel, as seen by 39 patients in the sunitinib-containing arm requiring antihypertensive therapy compared to only 26 patients in the arm without sunitinib. Nonetheless, this was not tightly related to the rates of hypertension, which were 4% in the experimental arm and 9% in the standard arm [83].

Recently, a combined analysis of 6,935 patients treated with sunitinib in several clinical trials showed a relative risk of high-grade CHF in sunitinib-treated patients compared with placebo-treated patients of 3.30 (95% CI 1.29 to 8.45; $P = 0.01$), demonstrating that sunitinib is associated with increased risk of heart failure in cancer patients [84].

Sorafenib

Serious cardiac AEs have been reported with sorafenib in patients with solid tumors [85]. In a systematic review and meta-analysis of 4,599 patients treated with sorafenib, but not including BC patients, grade 3-4 hypertension occurred in 5.7% of the patients, and sorafenib was associated with a six-fold higher chance of all-grade hypertension [85]. However, for BC patients treated with sorafenib across different phase II studies (Table 4), no cases of severe cardiac dysfunction were reported [86-88].

Other antiangiogenic targeted drugs

Several other antiangiogenic drugs - vandetanib, axitinib and pazopanib - have been evaluated in phase II studies of MBC [89-92] (Table 4). Overall, due to the limited number of patients who have been treated, no detailed cardiac safety evaluation of the individual drugs is possible. However, vandetanib monotherapy in particular

Table 3. Bevacizumab plus chemotherapy versus chemotherapy

Study	Treatment	Line of therapy	Number of patients	Hypertension (grade 3 or 4) (%)	CHF NYHA class III or IV (%)	Thrombotic events (grade 3 or 4) (%)
Miller et al. [110]	Capecitabine + bevacizumab versus capecitabine	1, 2, 3	462	G3: 17.9 versus 0.5 G4: 0 versus 0	G3: 2.2 versus 0 G4: 0.5 versus 0	Thrombotic event - general G3: 2.2 versus 0 G4: 0.5 versus 0
Miller et al. [58]	Paclitaxel + bevacizumab versus paclitaxel	1	722	G3: 14.5 versus 0 G4: 0.3 versus 0 P = 0.001	LV dysfunction G3: 0.8 versus 0 G4: 0 versus 0.3 P = NS	Cerebrovascular ischemia G3: 0.8 versus 0 G4: 1.1 versus 0 P = 0.02
Miles et al. (AVADO) [73]	Docetaxel + bevacizumab (7.5 mg/kg) versus docetaxel + placebo	1	736	Grade 3 to 4: 0.8 versus 1.3	Grade 3 to 4: 1.2 versus 0	No G3-4 arterial events
Robert et al. (RIBBON-1) [60]	Docetaxel + bevacizumab (15 mg/kg) versus docetaxel + placebo	1	605	Grade 3 to 4: 4.5 versus 1.3	Grade 3 to 4: 0 versus 0	Arterial events G3: 0 versus 0 G4: 0.8 versus 0
	Capecitabine plus bevacizumab versus capecitabine	1	605	Grade 3 to 4: 9.4 versus 1.0	LV dysfunction Grade 3 to 4: 1.0 versus 0.5	Venous events 4.8 versus 3.5
	Taxane + bvacizumab versus taxane		405	Grade 3 to 4: 8.9 versus 2.0	LV dysfunction Grade 3 to 4: 2.0 versus 0	Venous events 2.0 versus 4.9
	Anthracycline + bevacizumab versus anthracycline		310	Grade 3 to 4: 10 versus 0	LV dysfunction Grade 3 to 4: 2.9 versus 0	Venous events 2.9 versus 1.0
Brufsky et al. (RIBBON-2) [72]	Chemotherapy ^a + bevacizumab versus bevacizumab	2	684	Grade 3 to 4: 9 versus 0.5	LV dysfunction Grade 3 to 4: 0.9 versus 0	Arterial events Grade 3 to 4: 0.7 versus 1.4

^aPrior to randomization, the investigators could choose among one of the following chemotherapy regimens: paclitaxel, nab-paclitaxel, gemcitabine, capecitabine and vinorelbine. CHF, congestive heart failure; G, grade; NS, not significant; NYHA, New York Heart Association.

Table 4. Phase II studies of antiangiogenic therapy

Study	Treatment	Line of therapy	Number of patients	Hypertension (grade 3 or 4) (%)	CHF NYHA class III or IV (%)	Thrombotic events (grade 3 or 4) (%)
Miller <i>et al.</i> [89]	Vandetanib monotherapy	2, 3	46	0	0	0
Boer <i>et al.</i> [90]	Vandetanib + docetaxel versus vandetanib	1	64	0	0	0
Rugo <i>et al.</i> [91]	Axitinib + docetaxel versus docetaxel	1	168	5	0	0
Taylor <i>et al.</i> [92]	Pazopanib monotherapy ^a	1, 2, 3	18	14	0	0
Moreno-Aspitia <i>et al.</i> [111]	Sorafenib monotherapy	1, 2	23	0	0	0
Baselga <i>et al.</i> [86]	Sorafenib + capecitabine versus capecitabine	1, 2	229	0	0	0
Isaacs <i>et al.</i> [87]	Sorafenib + anastrozole versus anastrozole ^a	1, 2	35	11	0	0
Gradishar <i>et al.</i> [88]	Sorafenib + paclitaxel versus paclitaxel	1	237	0	0	0

^aPreliminary results. CHF, congestive heart failure; NYHA, New York Heart Association.

was associated with asymptomatic prolongation of the QTc interval in 29% of the 46 patients enrolled in a phase II study [89]. Also, it seems that while antiangiogenics do not increase the risk of CHF, they are associated with a non-negligible risk of hypertension, making prompt identification and treatment crucial.

Antiangiogenic plus anti-HER2 targeted therapy

The activation of angiogenic signaling pathways has been associated with trastuzumab resistance [93]. The combination of bevacizumab plus trastuzumab demonstrated synergistic activity in preclinical models [94]. Combining anti-HER2 and anti-VEGF drugs has consequently emerged as an important strategy to optimize the targeted treatment of BC.

Several studies have started to investigate this approach. For example, the bevacizumab plus trastuzumab combination was evaluated in 50 heavily pretreated MBC patients [95]. This combination was associated with a 30% incidence of asymptomatic LVEF decrease, 2% grade 4 LVEF decrease, and 36% incidence of grade 3 hypertension. Similarly, in another study, 50 heavily pretreated MBC patients received the combination of bevacizumab plus lapatinib. In that study, two grade 2 asymptomatic LVEF decreases were reported [96]. Lapatinib has also been combined with pazopanib in a randomized phase II study, and has not been associated with any serious cardiac AEs to date [97]. The results of future studies evaluating anti-HER2 and antiangiogenic therapies are awaited, and should give oncologists and cardiologists a more precise estimation of the real risk of cardiotoxicity.

Cardiac biomarkers

The challenge in assessing cardiotoxicity in novel 'targeted' agents is that there is considerable reserve in the heart function of a healthy adult (Figure 1). Thus, significant cardiac damage may occur prior to the onset

of symptoms, at which stage cardiac function may be irreversibly impaired. The goal is to define those patients at risk from repeated injury that may, in its own right, be too insignificant to cause a perturbation in measures such as ejection fraction that have been the mainstay of surveillance over past decades. In this regard, there has been great interest in cardiac biomarkers that appear to be more sensitive in detecting cardiac damage. However, there is much speculation as to whether biomarkers such as troponin and B-type natriuretic peptide are too sensitive and raise undue alarm in patients in whom long-term cardiac sequelae are unlikely.

Several studies have been looking at the role of cardiac biomarker changes in oncologic therapies. Two biomarkers (troponin and B-type natriuretic peptide) have been most frequently assessed and will be briefly described.

Cardiac troponin is a medium-sized protein that regulates the cardiac contractile elements actin and myosin. Modern assays are entirely specific for detecting troponin of cardiac, rather than peripheral muscle, origin and cardiac troponin is normally undetectable in the bloodstream. As assays have become more sensitive, however, debate exists regarding the significance of small but detectable increases in troponin. For example, troponin may be detectable following episodes of increased cardiac stress such as a rapid heart rate, bleeding, sepsis or even exercise [98]. In such circumstances, it has been argued that troponin may 'leak' from the myocyte cytosol into the bloodstream without causing significant damage or that these small troponin elevations represent an amount of myocyte necrosis/apoptosis from which complete recovery may be expected [99]. On the other hand, there is some evidence that even small increases in troponin may predict those at greater cumulative risk of cardiac events following cancer treatment [100].

B-type natriuretic peptide (BNP) is a hormone released from the cardiac ventricles at times of increased load or

stress. It and the amino-terminal fragment (NT pro-BNP) are useful for diagnosing cardiac failure in breathless patients but its utility for identifying subclinical cardiac pathology is unclear. It has proven to lack sensitivity and specificity in large community-based studies [101] and further investigation is required to assess the significance of increases in BNP on repeated measures. At present, BNP does not replace cardiac imaging but may prove a useful adjunct.

Overall, the use of cardiac biomarkers such as troponin or BNP in clinical practice is not standard and they should be tested in prospective trials. One seminar paper evaluated the role of troponin I (TNI) in 251 women with breast cancer receiving trastuzumab therapy [102]. TNI was measured before and after each trastuzumab cycle. Trastuzumab-induced cardiotoxicity (TIC) occurred in 42 patients (17%) and was more frequent in patients with TNI elevation ($P < 0.01$). The vast majority of patients (60%) recovered from TIC, with patients who were TNI-positive experiencing less recovery compared to those who were TNI-negative ($P < 0.01$). In multivariate analysis, TNI was the only predictor of TIC (hazard ratio 22.9, 95% CI 11.6 to 45.5; $P < 0.001$) and of lack of LVEF recovery (hazard ratio 2.88; 95% CI 1.78 to 4.65; $P < 0.001$). Therefore, TNI may be used as a marker to identify patients who are at risk of developing TIC and are unlikely to recover from cardiac dysfunction [103]. The roles of cardiac biomarkers and other targeted agents are less understood.

Several prospective trials are ongoing to try to better establish the role of cardiac markers in patients receiving targeted therapies and their results are eagerly awaited.

Management

Of the targeted breast cancer therapies, the most experience with cardiac dysfunction diagnosis and management comes from the trastuzumab trials. Low baseline LVEF values, increased body mass index, older age, and hypertension are associated with increased incidence of cardiac dysfunction in patients receiving trastuzumab [2]. LVEF assessment during trastuzumab is recommended and should be done at 3-month intervals during therapy and every 6 months for at least 2 years after completion of treatment [8]. The use of a non-anthracycline regimen in patients at high risk of developing cardiac dysfunction during chemotherapy is a plausible option. Guidelines from the European Society of Cardiology have been published and nicely represent the joint effort of cardiologists and oncologists in trying to better understand cardiac dysfunction due to anti-cancer drugs [103].

Importantly, cardiac dysfunction related to anticancer treatments should be managed irrespectively of its oncological genesis. For instance, in patients experiencing

a decrease in LVEF while on targeted therapies, the drug(s) should be at least temporarily stopped and anti-hypertensive medications (especially angiotensin converting enzyme (ACE) inhibitors) should be used until LVEF recovery. Afterwards, if the drop is reversible, reintroduction of the targeted therapy agent can be evaluated and its use should be weighed against the risk of cancer progression. There is great interest in whether heart failure agents may be used as prophylaxis in those at high risk of cardiac dysfunction during cancer treatment. Such strategies have been tried with some success in other patient groups [104], but further evidence will be needed prior to considering such treatments in the routine care of cancer patients. Also, the side effect profile of some heart failure therapies (such as hypotension, bradycardia, fatigue) may be expected to be particularly poorly tolerated amongst breast cancer patients.

For patients who develop heart failure, treatment with standard guideline-based heart failure therapy as in any other heart failure patients is recommended. Of utmost importance, multidisciplinary work among cardiologists, oncologists, pharmacologists, biochemists and cell biologists should be encouraged [103].

Conclusion

The increasing number of targeted therapies is broadening the therapeutic options available to patients with cancer, and survival from cancer has been improving overall. Nevertheless, targeted agents are associated with an increased incidence of different cardiovascular AEs. This being the case, and with targeted agents being increasingly used to treat EBC in the adjuvant setting with cure as the main objective, special attention to the short- and long-term toxicities to the heart and cardiovascular system is essential.

Previous clinical trials suggest that the combined use of trastuzumab and anthracyclines should be avoided due to the high incidence of LVEF drop and CHF [105]. Some investigators challenge this concept and have included this type of combination (low cumulative dose of anthracycline and trastuzumab) in neoadjuvant trials with the intention of obtaining a high rate of pathological complete response and, ultimately, improving patient prognosis [106-108]. Though these studies did not show significant cardiotoxicity at the time of reporting, a recent meta-analysis suggests that they may be individually underpowered to show any cardiac risk and that when the data are combined, there is indeed an increase in the risk of CHF for patients with EBC. This approach should therefore remain investigational: only patients included in clinical trials with close cardiac assessment and long follow-up should receive treatment combining trastuzumab and anthracyclines [109].

It is a challenge to provide the maximum therapeutic benefit to a patient while minimizing the risk of cardiotoxicity. To enable physicians to avoid using drugs most likely to cause cardiotoxicity in patients with previous cardiovascular comorbidities, it is paramount to determine the exact cardiac risk associated with each targeted therapy and to balance decision-making between risks and benefits. Importantly, for patients with early HER2-positive BC who have cardiac risks prior to chemotherapy, the use of non-anthracycline-based regimens, such as docetaxel, carboplatin and trastuzumab, may be an option. Close cardiac assessment in all patients receiving targeted therapies should take place before, during and after treatment with such drugs.

In large phase III studies, strategies to manage and prevent cardiac toxicities should be implemented so physicians will be better informed about how to optimally manage such complications when they occur. In the adjuvant trastuzumab trials, echocardiogram, cardiac scintigraphy and magnetic resonance imaging were used, with LVEF readings as the main tool to define cardiotoxicity. A drawback of LVEF, however, is that it lacks sensitivity: a reduction in LVEF does not necessarily mean myocardial damage, and an unchanged LVEF does not mean that significant myocardial damage has not occurred. LVEF is a blunt tool being used for increasingly heterogeneous patterns of myocardial injury. Therefore, efforts to better characterize the underlying mechanisms of cardiotoxicity induced by targeted therapy are ongoing, and we believe that in the near future a detailed understanding of these mechanisms will be possible. This in turn will lead to the development of even more 'intelligent' targeted drugs, those that spare the cardiovascular system from damage while offering patients maximum benefits and chances for cure.

New generation studies incorporating BNP and TNI as markers of cardiac toxicity as well as cardiac imaging (such as cardiac magnetic resonance imaging) are very much needed to establish their definitive role in the assessment of patients treated with targeted agents. Importantly, the management of cancer patients experiencing cardiac dysfunction is similar to traditional approaches used in non-cancer patients. As previously mentioned, only the continuous collaboration between different disciplines, in particular cardiologists and oncologists, will make cardio-oncology a well-defined area where patients will benefit the most.

Abbreviations

AE, adverse event; BC, breast cancer; BNP, B-type natriuretic peptide; CHF, congestive heart failure; CI, confidence interval; CRCD, chemotherapy-related cardiac dysfunction; ddAC, dose-dense doxorubicin plus cyclophosphamide; EBC, early-stage breast cancer; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; HER, human epidermal growth factor receptor; LVEF, left ventricular ejection fraction; MBC, metastatic breast cancer; NRG, neuroregulin; T-DM1, T-DM1, trastuzumab-DM1; TIC, trastuzumab-induced

cardiotoxicity; TKI, tyrosine kinase inhibitor; TNI, troponin I; VEGF, vascular endothelial growth factor.

Competing interests

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