Chapter 18

Cardiac Toxicity of HER2-Directed Therapy in Women with Breast Cancer: Epidemiology, Etiology, Risk Factors, and Management

Shahid Ahmed, Arooba Talat, Nayyer Iqbal,
Mohamed Emara, Duc Le, Amir Sami and Jim Xiang

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/66437

Abstract

The HER2-targeted therapy have profoundly changed the outcomes of women with HER2-positive breast cancers. Trastuzumab and pertuzumab, HER2-targeting monoclonal antibodies, lapatinib and Neratinib, small molecule inhibitors of HER2 and the epidermal growth factor receptor, and ado-trastuzumab emtansine, a HER2-positive directed antibody drug conjugate, are approved for the treatment of HER2-positive breast cancer.

Cardiac toxicity is a known adverse effects of trastuzumab, and other HER2-directed therapy. In most cases it manifests as mild and reversible left ventricle dysfunction. Nevertheless, symptomatic heart failure is not rare. The incidence and severity of cardiac dysfunction is greatest among women who received HER2-directed therapy in combination with anthracycline-based therapy. In addition, a borderline low normal left ventricle ejection fraction; prior treatment with antihypertensive medication; and older age are other risk factors for trastuzumab-related cardiac dysfunction. HER2 signaling plays an important role in modulating myocardial response to treatment-related injury. Management of trastuzumab and the other HER2 targeted treatment-related cardiac dysfunction has two key components: withdrawal of HER2-directed therapy and treatment of underlying cardiac dysfunction. A multidisciplinary approach is recommended for an optimal outcome. This chapter reviews cardiac toxicity of trastuzumab and other HER2-directed therapy including epidemiology and pathophysiology of cardiac dysfunction, cardiac monitoring, treatment and prevention.

Keywords: breast cancer, HER2-directed therapy, cardiac toxicity, trastuzumab, pertuzumab, lapatinib, T-DM1, Neratinib

1. Introduction

Breast cancer is one of the most common cancers in women worldwide [1]. In 2012, nearly 1.7 million women were diagnosed with breast cancer. This represents about 12% of all new cancer cases and 25% of all cancers in women [2]. Approximately 20–25% of all breast cancers overexpressed the human epidermal growth factor receptor-2 (HER2). This protein is a member of the HER family of transmembrane receptor tyrosine kinases and is located at the cell surface. HER2 is involved in cellular growth and differentiation, and its overexpression has been associated with adverse prognosis. Prior to the development of HER2-targeted therapy, women with HER2-positive breast cancer had poor outcomes. However, access to HER2-directed therapy including monoclonal antibodies, small molecule inhibitors, and antibody-drug conjugates in the management of early and advanced breast cancer has transformed the natural history of HER2-positive breast cancer [3, 4]. HER2-targeted therapy alone or in combination with chemotherapy has been associated with improvements in response rate, disease control rates, and overall survival in HER2-positive metastatic breast cancer [3–5]. Combination of HER2-targeted agents including dual HER2 blockade and selected delivery of potent chemotherapeutic agent along with HER2 inhibition are new therapeutic approaches that in many women have transformed metastatic HER2-positive breast cancer into a chronic disease. More importantly, HER2 blockade in early-stage breast cancer has resulted in lower recurrence and mortality [3, 6].

As the outcomes of women with HER2-positive breast cancer have improved, increasingly attention has been directed toward minimizing both acute and chronic treatment-related toxicities. Cardiac toxicity is a known adverse effect of trastuzumab and other HER2-directed therapy [7, 8]. In most cases, it manifests as mild and reversible left ventricle dysfunction. Nevertheless, overt heart failure is not unusual. Serial monitoring of cardiac function is recommended for women treated with HER2-directed therapy. In women with treatment-related cardiac dysfunction, trastuzumab and other HER2-directed therapy interruptions and treatment of cardiac dysfunction are recommended. This chapter provides a summary of efficacy of HER2-directed therapy in breast cancer and reviews the incidence, pathophysiology, risk factors, monitoring, and management and prevention of HER2-targeted treatment-related cardiac dysfunction.

2. Efficacy of HER2-directed therapy

The current HER2-directed treatments for women with HER2-positive breast cancer include monoclonal antibodies, small molecule inhibitors, and antibody-drug conjugates (**Table 1**). Trastuzumab is the prototype humanized monoclonal antibody directed against the extracellular domain of human epidermal growth factor receptor-2 [9]. It was first evaluated in women with HER2-positive metastatic breast cancer. The combination of trastuzumab and chemotherapy resulted in improvement in progression-free and overall survival compared with chemotherapy alone, in women with HER2-positive metastatic breast cancer [5]. A Cochrane review assessed efficacy and safety of trastuzumab in seven trials, involving 1497 women

with advanced breast cancer [10]. The combined hazard ratios (HRs) for overall survival and progression-free survival favored the trastuzumab-containing regimens (HR 0.82, 95% confidence interval (CI) 0.71–0.94, *p*-value = 0.004; and HR 0.61, 95% CI 0.54–0.70, *p*-value < 0.00001, respectively).

Class	Comments
Monoclonal antibodies	
Trastuzumab	A humanized monoclonal antibody directed against the extracellular domain of the HER2 receptor that prevents ligand-independent HER2 signaling. It has demonstrated efficacy in both early and advanced stage breast cancer
Pertuzumab	A humanized monoclonal antibody that binds to the extracellular domain II of HER2 and inhibits ligand-dependent HER2-HER3 dimerization. It has been evaluated in combination with trastuzumab in preoperative setting and advanced breast cancer
Antibody-drug conjugates	
Ado-trastuzumab emtansine	An antibody-drug conjugate consisting of the cytotoxic agent DM1 linked to trastuzumab. It has demonstrated efficacy in advanced breast cancer
Small molecules inhibitors	
Lapatinib	An oral dual EGFR/ErbB2 reversible tyrosine kinase inhibitor blocking both HER1 and HER2 that suppresses the downstream pathways. It has been evaluated in both early and advanced breast cancer.
Afatinib, Neratinib	Irreversible tyrosine kinase inhibitor of EGFR/HER2/HER4

Table 1. List of current HER2-directed targeted drugs that are approved for the management of HER2-positive breast cancer.

Later trastuzumab was evaluated in women with early-stage breast cancer, in both adjuvant and neoadjuvant settings, and demonstrated improvement in disease-free and overall survival. A Cochrane review evaluated efficacy and toxicity of trastuzumab in eight studies involving 11,991 women with early-stage breast cancer [11]. The combined HRs for overall survival and disease-free survival significantly favored the trastuzumab-containing regimens (HR 0.66; 95% CI 0.57–0.77, *p*-value < 0.00001; and HR 0.60; 95% CI 0.50–0.71, *p*-value < 0.00001, respectively). Based on results from five randomized adjuvant trials in women with node-positive or high-risk node-negative breast cancer, 1 year of adjuvant trastuzumab has become the standard therapy for women with HER2-positive breast cancer [6, 12–14].

Lapatinib is a dual EGFR/HER2 reversible tyrosine kinase inhibitor that suppresses the downstream signaling involving MAPK/Erk1/2 and PI3K/Akt pathways by blocking both HER1 and HER2 [15]. Lapatinib has demonstrated efficacy in HER2-positive advanced breast cancer [16]. In addition, it has been assessed in both adjuvant and neoadjuvant settings in women with early-stage breast cancer. However, overall the data suggest that lapatinib in early-stage breast cancer is inferior compared with trastuzumab [3, 17].

Pertuzumab is a humanized monoclonal antibody that binds to the extracellular domain II of HER2. It inhibits ligand-dependent HER2-HER3 dimerization and reduces signaling via intracellular pathways such as PI3K/Akt [18]. Pertuzumab has limited antitumor clinical activity alone, but it is a very good synergistic drug when combined with trastuzumab and has demonstrated benefit in combination with trastuzumab in the treatment of both early (neoadjuvant setting) and advanced HER2-positive breast cancer [3, 19, 20]. In the neoadjuvant setting, the pooled pathological complete response rate in the dual anti-HER2 therapy group was 54.8% compared with 36% in the monotherapy group when used in combination with chemotherapy (relative risk [RR], 1.56; 95% CI 1.23–1.97; p-value < 0.001). In the metastatic setting, dual anti-HER2 therapy demonstrated significant benefits in both progression-free survival (HR, 0.71; 95% CI 0.62–0.81; p-value < 0.001) and overall survival (HR, 0.68; 95% CI 0.57–0.82; p-value < 0.001) [21].

Ado-trastuzumab emtansine (T-DM1) is an antibody-drug conjugate consisting of an anti-microtubule cytotoxic agent DM1 linked to trastuzumab [22]. In women with HER2-positive advanced breast cancer, who were previously treated with trastuzumab and a taxane, it has shown significant improvement in progression-free and overall survival compared with lapatinib plus capecitabine [23].

Neratinib is an irreversible binder of HER1, HER2, and HER3 receptors [22, 24] It has demonstrated efficacy in HER2-positive breast cancer that progress on trastuzumab [3]. In addition, 1 year of neratinib following adjuvant chemotherapy and trastuzumab in women with HER2-positive breast cancer has been associated with modest improvement in disease-free survival [25].

In summary, over the past 15 years, HER2-directed therapy has revolutionized the management of HER2-positive breast cancer. In women with early-stage cancer, neoadjuvant and adjuvant HER2-directed therapies have substantially improved the disease-free and overall survival. Likewise, for many women, HER2-targeted therapy has transformed HER2-positive advanced breast cancer into a chronic disease. For example, median overall survival of women with HER2-positive advanced cancer has improved from 20.3 months reported by Slamon et al. in the first randomized trial using trastuzumab with chemotherapy to 48 months with the use of triple combination of pertuzumab, trastuzumab, and docetaxel [5, 26].

3. Cardiac safety of HER2-directed therapy

3.1. Trastuzumab

Trastuzumab-related cardiac dysfunction incidence varies according to the underlying treated population and the definition of cardiac toxicity used in the clinical trials. In the pivotal clinical trial that evaluated trastuzumab in combination with chemotherapy (anthracycline or taxane) in women with HER2-positive metastatic breast cancer, a high rate of cardiac dysfunction was noted, especially when trastuzumab was given in combination with an anthracycline-based chemotherapy [5]. In this trial, cardiac dysfunction was observed in

27% of the women who received an anthracycline, cyclophosphamide, and trastuzumab; 8% of the women who received an anthracycline and cyclophosphamide alone; 13% of the women who received paclitaxel and trastuzumab; and only 1% of the women who received paclitaxel alone. Among these women, the incidence of cardiac dysfunction of New York Heart Association class III or IV was 16% among women who were treated with an anthracycline, cyclophosphamide, and trastuzumab; 3% among women who received an anthracycline and cyclophosphamide alone; 2% among women who received paclitaxel and trastuzumab; and 1% among those who were treated with paclitaxel alone (**Table 2**). Given a high risk of symptomatic heart failure with the concomitant use of trastuzumab with anthracycline, in all adjuvant breast cancer trials, trastuzumab was only used after anthracyclines or with anthracycline-free chemotherapy. A Cochrane review assessed efficacy and safety of trastuzumab in seven trials, involving 1497 women with advanced breast cancer [10]. Trastuzumab increased the risk of congestive heart failure (CHF) (RR 3.49, 90% CI 1.88–6.47, *p*-value = 0.0009) and left ventricular ejection fraction (LVEF) decline (RR 2.65, 90% CI 1.48–4.74, *p*-value = 0.006).

Class	New York association functional classification	Canadian Cardiovascular Society functional classification
I	Patients with cardiac disease but without resulting limitations of physical activity	Ordinary physical activity, such as walking and climbing stairs, does not cause angina
II	Patients with cardiac disease resulting in slight limitation of physical activity	Slight limitation of ordinary activity
III	Patients with cardiac disease resulting in marked limitation of physical activity	Marked limitation of ordinary physical activity
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort	Inability to carry on any physical activity without discomfort

Table 2. New York association and Canadian Cardiovascular Society functional classifications.

In the major adjuvant trastuzumab clinical trials, the rates of symptomatic CHF varied from 0.6 to 4.1%, whereas the rates of symptomatic or minimally symptomatic reduction in LVEF ranged from 4 to 34% (**Table 3**). The Herceptin Adjuvant (HERA) trial compared 1 or 2 years of trastuzumab given once every 3 weeks with observation in women with HER2-positive breast cancer. The incidence of trastuzumab discontinuation due to cardiac disorders was 4.3% [8]. The incidence of cardiac end points was higher in the trastuzumab group compared with observation: severe CHF, 0.60% compared with 0.06%; symptomatic CHF, 2.15% compared with 0.12%; and confirmed significant LVEF drops, 3.04% compared with 0.53%. Most women with cardiac dysfunction recovered in fewer than 6 months.

The National Surgical Adjuvant Breast and Bowel Project trial B-31 compared doxorubicin and cyclophosphamide (AC) followed by paclitaxel with AC followed by paclitaxel plus 52 weeks of trastuzumab beginning concurrently with paclitaxel in women with node-positive, HER2-positive breast cancer [27]. Among women with normal post-AC LVEF

Trial	N	Design	Definition of severe cardiotoxicity	Frequency of monitoring	Asymptomatic drop in LVEF (≥10% points to <55%)	Severe CHF/cardiac events (NYHA class III/IV CHF or death)	Discontinued for cardiac reasons
FinHer[12, 29]	232	V or T + H versus V or T[a] ≥FEC × 3	Myocardial infarction; HF; or LVEF decrease >15 points	Echo or MUGA before chemotherapy, after FEC, and 12 and 36 months after chemotherapy	3.5 versus 8.6%	0.9 versus 1.7%	n/a
NSABP B-31[27, 14]	2030	AC + TH + H versus AC + T	Grade III/IV HF or cardiac death; or LVEF decrease >15 points[b]	MUGA 3 weeks, 6, and 9 months after end of initial AC, and 3 months after last trastuzumab dose	34 versus 17%	4.1 versus 0.8%	19%[c]
BCIRG 006[6]	3222	AC + T versus AC + TH + H versus TCaH[d]	Grade III/IV HF; cardiac death; grade 3–4 arrhythmias; grade 3–4 ischemia/infarction; or LVEF decrease >10 points[b]	After AC, after second dose of docetaxel, at end of chemotherapy, and 3, 12, and 36 months after randomization	11 versus 19% versus 9%	0.7 versus 2.0% versus 0.4%	n/a
NCCTG N9831[28, 14]	3505	AC + TH + H versus AC + T + H versus AC + T	Grade III/IV HF or cardiac death; or LVEF decrease >15 points[b]	MUGA or echo at entry, after AC, and 6, 9, 18, and 21 months after entry	5.8–10.4 versus 4.0–7.8% versus 4.0–5.1%	3.3 versus 2.8% versus 0.3%	n/a[b]
HERA[8, 13]	5090	Adj chemoc[e] ≥H versus Adj chemo alone	Severe HF; symptomatic HF; or LVEF decrease >10 points	LVEF (echo or MUGA) at baseline, 3, 6, 12, 18, 24, 30, 36, and 60 months	7.1 versus 2.2%	0.6 versus 0.06%	4.3%

A: anthracycline; C: cyclophosphamide; T: taxane; H: trastuzumab; Ca: carboplatin; V: vinorelbine; F: 5-flourouracil; E: epirubicin; n/a: information not available; HF: heart failure; LV0EF: left ventricular heart failure; MUGA: multi-gated acquisition scan.

[a] No prior anthracycline before H exposure; H exposure limited to 9 weeks.

[b] Measured from baseline.

[c] 6.7% did not receive H after A due to unacceptable drops in LVEF.

[d] Included a nonanthracycline arm.

[e] 96% of chemotherapy was A containing.

Table 3. Rates of asymptomatic and symptomatic cardiac dysfunction in various adjuvant trastuzumab phase 3 clinical trials.

who began post-AC treatment, 5 of 814 (0.006%) women in the control group developed a cardiac event compared with 31 of 850 (0.036%) women treated with trastuzumab. The difference in cumulative incidence at 3 years was 3.3% (4.1% for trastuzumab-treated women minus 0.8% for control patients; 95% CI 1.7–4.9%). Twenty-seven of the 31 patients in the trastuzumab arm have been followed for ≥6 months after diagnosis of a CE; 26 were asymptomatic at last assessment; and 18 remained on cardiac medication. Fourteen percent of patients discontinued trastuzumab because of asymptomatic decreases in LVEF; 4% discontinued trastuzumab because of symptomatic cardiotoxicity.

In the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial, women with HER2-positive operable breast cancer were randomly assigned to AC followed by either weekly paclitaxel (arm A); paclitaxel then trastuzumab (arm B); or paclitaxel plus trastuzumab then trastuzumab alone (arm C) [28]. There were 1944 women with satisfactory or no LVEF evaluation who proceeded to post-AC therapy. Cardiac events (CHF or cardiac death) were as followed: arm A, n = 3; arm B, n = 19; and arm C, n = 19 with 3-year cumulative incidences of 0.3, 2.8, and 3.3%, respectively. Incidence of asymptomatic LVEF decreases requiring holding trastuzumab was 8–10%; LVEF recovered and trastuzumab were restarted in approximately 50%.

The Breast Cancer International Research Group randomly assigned 3222 women with HER2-positive early-stage breast cancer to receive doxorubicin and cyclophosphamide followed by docetaxel every 3 weeks (AC-T), the same regimen plus 52 weeks of trastuzumab (AC-T plus trastuzumab), or docetaxel and carboplatin plus 52 weeks of trastuzumab (TCH) [6]. The incidence of congestive heart failure in the two trastuzumab-containing regimens was higher in the group receiving AC-T plus trastuzumab (2.0%) than in the AC-T group (0.7%) or the TCH group (0.4%); the incidence with AC-T plus trastuzumab as compared with TCH was increased by a factor of five. In addition, a significant difference in sustained, subclinical loss of mean LVEF (defined as >10% relative loss), was observed in the group receiving AC-T plus trastuzumab, as compared with the TCH group (18.6 versus 9.4%, p-value < 0.001), with a rate of 11.2% in the AC-T group. Of 194 of the 1042 patients (19%) who had a relative reduction in LVEF of more than 10% in the group receiving AC-T plus trastuzumab, the decrease persisted for at least 4 years after randomization in 33% of the women.

The FinHer investigators randomly assigned 1010 women to receive three cycles of docetaxel or vinorelbine, followed by three cycles of fluorouracil, epirubicin, and cyclophosphamide (FEC). The 232 women with HER2-positive cancer were further assigned to receive or not to receive nine weekly trastuzumab infusions [12]. The incidence of symptomatic heart failure among the HER2-positive women was 0.9% (one patient) with trastuzumab and 1.7% (two patients) without trastuzumab. The incidence of absolute declines in LVEF >20% points from baseline was 6.8% with trastuzumab and 10.5% without trastuzumab [12, 29].

The Cochrane review evaluated toxicity of trastuzumab in eight studies involving 11,991 women with early-stage breast cancer [11]. Trastuzumab significantly increased the risk of CHF (RR 5.11; 90% CI 3.00–8.72, p-value < 0.00001) and LVEF (RR 1.83; 90% CI 1.36–2.47, p-value = 0.0008).

3.2. Lapatinib and other HER2-directed therapies

In the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization trial (ALTTO), 8381 women with HER2-positive early breast cancer were randomly assigned to 1 year of adjuvant therapy with trastuzumab, lapatinib, their sequence (T → L), or their combination (L + T). Overall, incidence of primary or secondary cardiac end points was low in all treatment arms; primary cardiac end points occurred in 0.25–0.97% of women. Three fatal cardiac events occurred in the T → L arm and one in each of the other treatment arms [17].

A comprehensive analysis of 49 clinical trials involving 3689 women treated with lapatinib reported a low rated of cardiac events [30]. For example, asymptomatic cardiac events were reported in 53 women (1.4%), and symptomatic grade III and IV systolic dysfunction was observed only in 7 women (0.2%) treated with lapatinib. Cardiac safety of lapatinib in combination with trastuzumab is reviewed in the section of dual HER2-directed therapy.

Cardiotoxicity of pertuzumab was usually reported with the trastuzumab combination, and no additive cardiotoxicity was reported with addition of pertuzumab to trastuzumab. In phase I–III trials of pertuzumab, cardiac dysfunction was seen in 4.5–14.5% of women with pertuzumab treatment and cardiac dysfunction was usually grade I and II [30]. Cardiac safety of pertuzumab is reviewed in more detail in the section of dual HER2-directed therapy.

T-DM1 had a better safety profile compared to trastuzumab, and no significant cardiotoxicity was observed with T-DM1 in heavily pre-treated women. In the EMILIA study, only in 1.7% of women in the T-DM1 group experienced reduction in LVEF and grade III LVEF reduction developed only in one woman (0.2%) in the T-DM1 group compared to the lapatinib plus capacitabine group [23]. In phase I-II trials with neratinib, no cardiotoxicity was reported, whereas cardiotoxicity was seen between 0 and 5.3% with afatinib treatment [30].

3.3. Dual HER2-directed therapy

Several trials have evaluated dual HER2-directed therapy using trastuzumab in combination with lapatinib or pertuzumab in the neoadjuvant setting and metastatic breast cancer. These trials reported the risk of heart failure with dual HER2-directed therapy [20, 26, 31–34]. A meta-analysis of randomized clinical trials compared the risk of cardiac adverse events with dual HER2-directed therapy to HER2 monotherapy and reported a comparable cardiac toxicity between combination and mono-HER2-directed therapies [35]. Overall incidence results for CHF in dual HER2-directed and monotherapy were 0.88% (95% CI 0.47–1.64%) and 1.49% (95% CI 0.98–2.23%). The incidence of LVEF decline was 3.1% (95% CI 2.2–4.4%) and 2.9% (95% CI 2.1–4.1%), respectively. When stratified by each treatment combination, the incidence of CHF was 0.96% (95% CI 0.40–2.31%) for the trastuzumab plus lapatinib combination and 0.80% (95% CI 0.33–1.93%) for the trastuzumab plus pertuzumab combination, while the LVEF decline was 3.2% (95% CI 1.8–5.7%) and 3.1% (95% CI 1.9–4.8%), respectively. The odd ratio of CHF between dual and monotherapy was 0.58 (95% CI 0.26–1.27, p-value = 0.17), while the odd ratio of LVEF decline was 0.88 (95% CI 0.53–1.48, p-value = 0.64). Among the

two trials in the metastatic setting [19, 31], there was no association between dual anti-HER2 therapy and either CHF (OR: 0.85, 95% CI 0.31–2.37, *p*-value = 0.76) or LVEF decline (OR: 1.11, 95% CI 0.24–5.02, *p*-value = 0.90). Among the four trials in the neoadjuvant setting, there was also no evidence of an association between dual anti-HER2 therapy and CHF (OR: 0.74, 95% CI 0.02–29.54, *p*-value = 0.87) or LVEF decline (OR: 1.52, 95% CI 0.44–5.32, *p*-value = 0.51) [20, 32–34]. For CHF, the pooled ORs for the comparison trastuzumab plus lapatinib versus trastuzumab and trastuzumab plus lapatinib versus lapatinib were 0.33 (95% CI 0.08–1.41, *p*-value = 0.13), and 0.64 (95% CI 0.22–1.88, *p*-value = 0.42), respectively. For LVEF decline, the pooled ORs for the trastuzumab plus lapatinib versus trastuzumab, trastuzumab plus lapatinib versus lapatinib, and trastuzumab plus pertuzumab versus trastuzumab were 0.53 (95% CI 0.07–3.98, *p*-value = 0.54), 2.27 (95% CI 0.69–7.49, *p*-value = 0.18), and 0.66 (95% CI 0.36–1.23, *p*-value = 0.19), respectively. Another systematic review and meta-analysis compared treatment outcomes for women who received single or combined anti-HER2 therapies [21]. Overall, no statistically significant difference in the risk of heart failure between dual anti-HER2 therapy and monotherapy was noted (RR, 0.79; 95% CI 0.23–2.68; *p*-value = 0.71). Likewise, no statistically significant difference in risk of left ventricular ejection fraction decline was noted single versus dual HER2-directed therapy (RR, 1.12; 95% CI 0.51–2.44; *p*-value = 0.77).

Overall, cardiac toxicity is more often noted with the regimens employing sequential anthracycline and taxanes. Nonetheless, the majority of women who received the therapy displayed neither acute nor delayed cardiac toxicity [29]. The rates of cardiac dysfunction with the novel HER2-targeted therapies are significantly lower than the trastuzumab. Furthermore, the combination of anti-HER2 treatment does not increase the cardiac toxicity compared to trastuzumab alone. Longer-term follow-up is required to determine the full effect of adverse cardiac events.

4. Pathophysiology of cardiac dysfunction

Cardiac dysfunction is a potential short- or long-term complication of several anticancer therapies. Although the underlying pathophysiology of trastuzumab and other novel HER2-directed therapy-induced cardiac toxicity is not fully understood, it is different from that of anthracycline-related or type I cardiac dysfunction and has been classified as type II cardiac dysfunction [36]. Whereas anthracycline-associated or type I cardiac dysfunction is dose dependent, cumulative, and potentially irreversible and has been associated with structural myocardial abnormalities, such as vacuolization, myofibrillar disarray and drop-out, and myocyte necrosis, trastuzumab-related or type II cardiac dysfunction is not dose related, does not appear to occur in all individuals, is expressed in a broad range of severity, is not related to identifiable structural changes, and, more importantly, appears to be reversible (**Table 4**) [36, 37].

Trastuzumab-induced cardiac dysfunction is considered to be the result of attenuated HER2-mediated signaling in the heart, culminating in decreased functionality of cardiac myocytes. HER

	Type I cardiac dysfunction (myocardial damage)	Type II cardiac dysfunction (myocardial dysfunction)
Prototype drug	• Doxorubicin	• Trastuzumab
Natural history	• typically permanent and irreversible • recurrence in months or years may be related to sequential cardiac stress	• reversible with high likelihood of recovery to baseline heart function in 2–4 months
Dose relationship	• dose-dependent • cumulative	• dose independent
Pathophysiology	• oxidative stress/damage • free radical formation	• blockade of HER2 signaling in myocardium
Electron microscopic findings	• vacuoles • myofibrillar disarray and dropout • necrosis • changes resolve over time	• no characteristic structural abnormalities
Noninvasive cardiac testing Findings	• decreased ejection fraction • global decrease in wall motion	• decreasedejection fraction • global decrease in wall motion
Effect of rechallenge	• high risk of progressive recurrent dysfunction • may result in intractable heart failure and death	• may be safe and appropriate for some individuals
Effect of late sequential stress	• High likelihood of sequential stress-related cardiac dysfunction	• Low likelihood of sequential stress-related cardiac dysfunction

Table 4. Cancer treatment-related cardiac dysfunction.

signaling plays an important role in modulating myocardial response to chemotherapy-induced injury and inhibition of the HER-2/erbB2 receptor worsens anthracycline-associated cardiotoxicity [38]. HER or ErbB receptors are family of transmembrane tyrosine kinase receptors that bind extracellular ligands and regulate cell growth, differentiation, and survival [39]. HER2 appears to function as a compensatory mechanism acting against cardiac stress, such as anthracycline-induced cardiotoxicity. Subsequent administration of trastuzumab may then lead to an inhibition of this compensation, resulting in heart failure [40]. Trastuzumab induces down-regulation of HER2 receptors which leads to apoptosis by disrupting downstream cytoprotective signaling pathways and by decreasing expression of Bcl-2 anti-apoptotic protein [41]. Discontinuation or trastuzumab withdrawal allows recovery of signaling pathway and reversal of LVEF decline, in contrast to the permanent myocyte dysfunction and damage caused by anthracyclines.

Trastuzumab-induced cardiotoxicity is demonstrated by inhibiting ErbB2 signaling in rat cardiac myocytes with a suitable antibody. This process promotes intrinsic (mitochondrial) apoptotic pathway that involves an increase in Bcl-XS/Bcl-XL ratio [42, 43]. Some studies showed that

http://dx.doi.org/10.5772/66437

trastuzumab down-regulates neuregulin-1 (NRG-1), which is released in endocardium and activates MAPK and the PI3K/AKT cell survival pathways as well as focal adhesion kinases (FAK) in cardiomyocytes which are all important for the function and structure of cardiomyocytes [44].

In general, women who develop cardiotoxicity while receiving trastuzumab therapy improve upon withdrawal of the drug. Evidence suggests that reintroducing trastuzumab may be appropriate for some individuals who previously have experienced trastuzumab-related cardiac dysfunction.

5. Risk factors

The following are the risk factors for trastuzumab-associated cardiotoxicity identified in the adjuvant clinical trials: prior treatment with anthracycline-based chemotherapy; a borderline low normal left ventricle ejection fraction; prior treatment with antihypertensive medication; older age; and a body mass index >25 kg/m^2 [7, 29]. In the HERA trial, the women who had a cardiac end point received a significantly higher dose of epirubicin and doxorubicin than the women without [8]. Furthermore, women with a screening LVEF of <60% had a significantly higher incidence of cardiac end points than women with a higher screening LVEF ≥60% (6.90% versus 2.72%; 95% CI 1.33–7.02%). Women with a risk factor of hypertension, current smoker, diabetes, hypothyroidism, or age ≥60 showed a trend to a higher incidence of cardiac end points that was not significant.

In NSABP B-31 trial, CHFs were more frequent in older women and women with marginal post-AC LVEF [27]. LVEF, assessed either at baseline or after AC, was strongly associated with subsequent CHF ($P < 0.0001$), and age at entry was also predictive ($P = 0.03$). Hypertension was marginally significant ($P = 0.07$). In a multivariate analysis, age and post-AC LVEF remained statistically significant.

The NSABP B31 data about risk factors for a cardiac event are supported by NCCTG N9831 trial [28, 29]. For example, women ≥60 years had a risk of 6.6%, women aged 50–59 years had a 2.8% risk, and women <50 years had a 2.1% risk ($P = 0.003$). Previous or current use of antihypertensive agents increased the risk to 6.0% ($P = 0.005$). Baseline LVEF above the lower limit of normal but <55% increased the risk to 5.6% ($P = 0.033$). BMI ($P = 0.161$) and post-AC LVEF level ($P = 0.134$) were not significantly correlated with LV dysfunction.

6. Monitoring

Women treated with adjuvant trastuzumab and other HER2-directed treatment require appropriate monitoring of LV function. LVEF measurement, obtained by echocardiogram or radionuclide ventriculography (multiple-gated acquisition [MUGA] scans), is currently the generally accepted diagnostic tool to detect cardiotoxicity of antineoplastic agents. It is important to note that the LVEF reflects the functional status of the left ventricle, and until functional impairment occurs, myocardial injury will not be detected by LVEF measurement [40].

With about a decade of follow-up involving women treated in the adjuvant setting with trastuzumab-containing regimens, the optimal surveillance for trastuzumab-related cardiotoxicity is not known. The available evidence does not definitively support a specific schedule of screening or demonstrates improved outcomes for the screened patients [45]. In the adjuvant setting, a baseline evaluation for cardiac function is performed with a repeat testing at 3, 6, 9, and 12 months [46]. In metastatic disease, HER2-directed therapy is continued until disease progression. LVEF is typically monitored at baseline, during the first 3–12 months of therapy and then as clinically indicated such as the presence of symptoms suggestive of cardiac dysfunction.

The optimal cardiac monitoring of women who are receiving novel HER2-directed therapy is not known. The United States Food and Drug Administration (US FDA) prescribing information recommends that all women who are treated with pertuzumab or lapatinib or TDM1 have LVEF assessed at the treatment initiation and subsequently at regular intervals (i.e., every 3 months in the metastatic setting and every 6 weeks in the neoadjuvant setting) [47–49]. Given that cardiac dysfunction rates of novel HER2-targeted therapies are not high and the combination of anti-HER2 treatment does not increase the cardiac toxicity compared with trastuzumab, periodic monitoring of cardiac function in otherwise asymptomatic women with metastatic breast cancer may not be cost effective.

The early detection of injured myocardial cells is required more sensitive diagnostic tools than the use of conventional methods for LVEF measurement. For example, several small studies have evaluated tissue Doppler and strain rate imaging to detect early subclinical changes in cardiac function during and after cancer treatment that preceded a decrease in LVEF [50, 51]. Contrast ECG and real-time 3D ECG are under investigation that may allow improvement in the accuracy of calculating LVEF. In addition, early identification of women at high risk of cardiotoxicity by cardiac biomarkers, in particular, troponin can be more effective for targeted preventive strategies [50].

7. Treatment of cardiac dysfunction

A multidisciplinary approach for the management of treatment-related cardiotoxicity is important for optimal outcomes. Cardio-oncology is a new interdisciplinary field of growing interest focusing on management and prevention of therapy-related cardiac dysfunction in cancer patients [52].

Management of trastuzumab and other HER2-directed treatment-related cardiac dysfunction has two key components: withdrawal of trastuzumab and other HER2-directed therapy and treatment of underlying cardiac dysfunction. Although in the adjuvant clinical trials, various "stopping and restarting" criteria were used for asymptomatic declined in LVEF, the optimal withdrawal and continuation schedule for asymptomatic decline in LVEF in general population are not known.

The NSABP B-31 and the NCCTG N9831 trials used the following dosing guidelines.

- If there is 16% or greater decline in LVEF from the baseline value or 10–15% declined in ejection fraction to below the lower limit of normal of LVEF, trastuzumab is withheld for

4 weeks and reassessment of LVEF at week four. Discontinue trastuzumab if at 4 weeks LVEF remains below that levels.

- Discontinue trastuzumab if a person develop symptomatic heart failure during treatment with trastuzumb, it is discontinued.

Symptomatic heart failure is defined as the presence of:

- dyspnea, pedal edema, and orthopnea;
- the presence of sinus tachycardia, raised jugular venous pressure, tachypnea, crackles, and S3 heart sound;
- radiographic evidence of pulmonary congestion or edema.

One of the algorithms for monitoring of cardiac function for women on adjuvant trastuzumab is described in **Figure 1**.

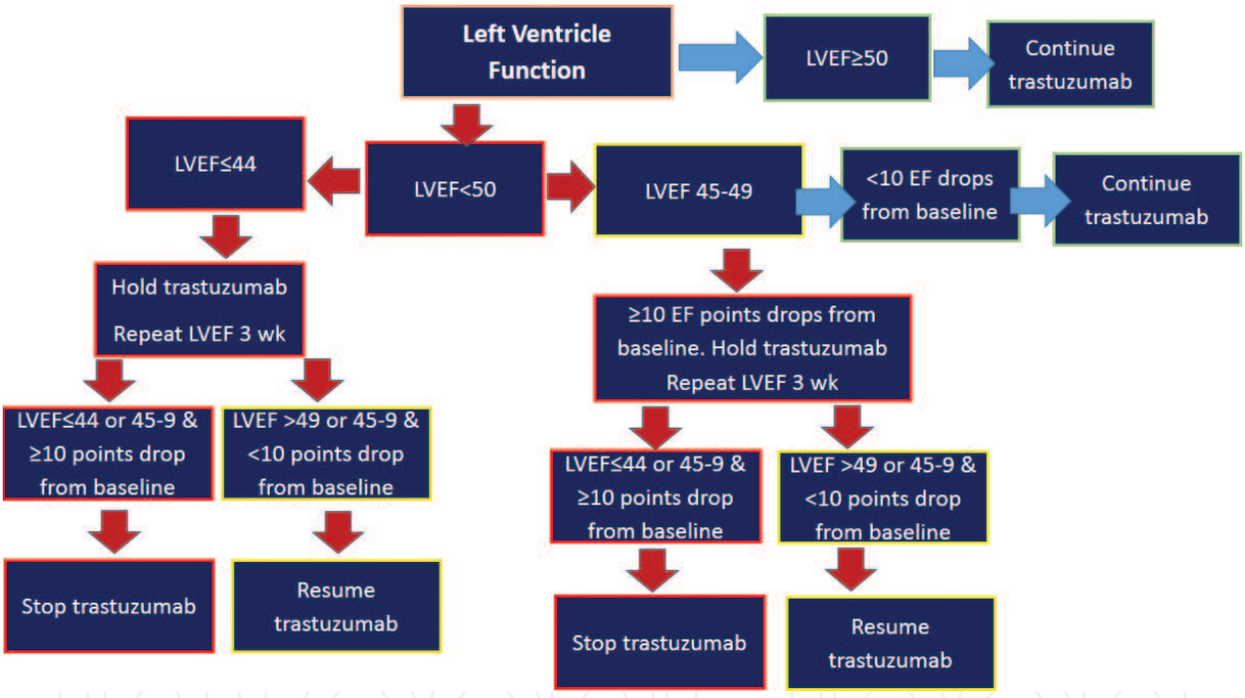

Figure 1. Algorithm for stop and restarting trastuzumab based on LVEF assessments.

Unlike early-stage breast cancer, the dosing criteria for women with metastatic breast cancer are not well defined. In clinical practice, left ventricle function monitoring is infrequently performed in otherwise asymptomatic women with metastatic breast cancer.

Angiotensin-converting enzyme (ACE) inhibitors and beta-blockers have been proven to delay or reverse LV dilation and improve ejection fraction [53–55]. All women with symptomatic heart failure should be treated with an ACE inhibitor in combination with a beta-blocker unless a specific contraindication exists. HER2-directed therapy should be permanently discontinued in such women. ACE inhibitors in combination with a beta-blocker should be used in all asymptomatic

women with LV dysfunction and an ejection fraction below 40% unless a specific contraindication exists. Women with LVEF >40% may also get benefit from pharmacological intervention [56, 57]. The optimal duration of therapy is not known and is determined by several factors such as the degree of LV dysfunction, recovery of LV function, patient symptoms, and preference.

7.1. Lapatinib

The US FDA prescribing information recommends discontinuation of lapatinib for a decline in the LVEF to <50%, for those whose LVEF drops below the institution's lower limit of normal and for any women who develop symptomatic heart failure during therapy [49]. Dose reduction is recommended if the LVEF recovers to normal after a minimum of 2 weeks in otherwise asymptomatic patients.

7.2. Pertuzumab

The US FDA prescribing information recommends to withhold both pertuzumab and trastuzumab if LVEF is <45% or is 45–49% with a ≥10% absolute decrease below the baseline value and suggests discontinuing both pertuzumab and trastuzumab if the LVEF has not improved or has declined further on repeat assessment in 3 weeks [47].

7.3. Ado-trastuzumab emtansine (T-DM1)

For women who are treated with T-DM1, at least temporary discontinuation of therapy is recommended if the LVEF falls to <40% or is 40–45% with a ≥10% absolute decrease below the pretreatment value [48].

8. Preventive strategies

The presence of underlying cardiovascular risk factors can increase the risk of treatment-related cardiac dysfunction. Cardiovascular risk reduction with appropriate control of blood pressure, cholesterol, and blood glucose, as well as positive health-promoting behavior, including healthy diet, smoking cessation, regular exercise, and weight control, is recommended for women with breast cancer to reduce the risk of treatment-related cardiotoxicity [50, 58, 59]. Several strategies have been developed to mitigate the risk of both symptomatic and asymptomatic cardiac dysfunction related to HER2-directed therapy. These interventions include periodic cardiac function monitoring, use of a non-anthracycline-based chemotherapy, stopping and restarting HER2-directed therapy, and early detection of cadiotoxicity by biomarkers, followed by prophylactic intervention in selected high-risk patients.

HER2-directed therapy should be avoided in women with a significant cardiovascular history such as recent myocardial infarction, CHF, unstable angina, significant arrhythmias, uncontrolled hypertension, LV hypertrophy, or significant valvular heart disease. The cardiac toxicity data from the adjuvant trastuzmab trials suggest three approaches which have been

http://dx.doi.org/10.5772/66437

associated with a reduced risk of cardiac toxicity. The first approach employed by the HERA investigators, which is the sequential use of trastuzumab after completion of adjuvant chemotherapy. This approach resulted in very low rates of cardiac toxic effects, despite the fact that 94% of women received an anthracycline-based regimen [29]. However, the direct comparison of concurrent versus sequential administration of trastuzumab in the N9831 trial suggests that even though the sequential approach is effective, concurrent administration provides greater benefit with minimal increased risk for cardiac toxicity [3, 29].

A second approach was employed in FinHer trial which used 9-week duration of adjuvant trastuzumab and showed a very low rate of cardiac dysfunction [29]. However, the non-inferiority of shorter duration of trastuzumab is not confirmed in a randomized clinical trial. In the Protocol for Herceptin as Adjuvant therapy with Reduced Exposure (PHARE) trial, 3380 women were randomly assigned 6 versus 12 months of trastuzumab [60]. The overall incidences of CHF were 0.65 and 0.53% in the 12 and 6 months arms, respectively ($p > 0.05$). Cardiac dysfunction occurred in 5.9 and 3.4% of women in the 12 and 6 months arms, respectively ($p = 0.001$) [61]. However, with a median follow-up of 42.5 months, treatment for 6 months resulted in a shorter 2-year DFS rate compared with 12 months of therapy (91 versus 94%, respectively; HR 1.28, 95% CI 1.05–1.56). In addition, treatment for 6 months resulted inferior overall survival (93 versus 66 events; HR 1.46, 95% CI 1.06–2.01) and more frequent distant recurrences (HR 1.33, 95% CI 1.04–1.71). Hence, the approach of 6 months or shorter duration of adjuvant trastuzumab is not recommended.

The third approach is the use of a non-anthracycline-based chemotherapy regimen such as docetaxel and carboplatin plus 1 year of trastuzumab (TCH → H) that was employed in the BCIRG 006 trial. The rate of symptomatic congestive heart failure was only 0.4% with TCH → H compared with a rate of 2.0% with AC → TH → H [6]. A non-anthracycline-based regimen also eliminates the risk of cardiac dysfunction from anthracycline that may preclude the use of adjuvant trastuzumab. The risk for cardiotoxicity with an anthracycline-based regimen can be reduced by identifying women who are at increased risk for cardiac dysfunction and avoiding such regimen in these women.

The primary prevention using a beta-blocker or an ACE inhibitor has been employed as an approach to reduce cancer therapy-related cardiac toxicity [62–64]. The results of the PRADA (prevention of cardiac dysfunction during adjuvant breast cancer therapy) trial have shown that candesartan—but not metoprolol—concomitantly administrated with adjuvant chemotherapy including epirubicin, with or without trastuzumab, can protect against early decline in LVEF, assessed with cardiac magnetic resonance [62]. MANTICORE 101-Breast (Multidisciplinary Approach to Novel Therapies in Cardiology-Oncology Research) is a randomized trial that evaluated if conventional heart failure pharmacotherapy can prevent trastuzumab-mediated left ventricular remodeling, measured with cardiac MRI. The study randomized 99 women with HER2-positve breast cancer in a 1:1:1 ratio to an ACE inhibitor (perindopril), beta-blocker (bisoprolol), or placebo [63, 64]. The study failed to achieve its primary end point and neither a beta-blocker nor an ACE inhibitor, used as prophylaxis against trastuzumab's adverse cardiac effects, and successfully prevented left ventricle remodeling. The post-treatment LVEF for placebo patients was significantly but not clinically worse than in either of the experimental arms—56% versus 59% for perindopril and 61% for bisoprolol

(down from 61, 62 and 62%, respectively). Although prophylactic beta-blocker or ACE inhibitor is currently not recommended in women with normal baseline LVEF, it may consider in woman at high risk of cardiac dysfunction.

9. Conclusions

The HER2-directed therapy including monoclonal antibodies such as trastuzumab, small molecule inhibitors, and antibody-drug conjugates has revolutionized the management of women with early and advanced HER2-positive breast cancer. Left ventricle dysfunction is a known adverse effect of trastuzumab and other HER-2 directed therapy. In most cases, it is mild and reversible; however, symptomatic heart failure is not a rare complication. The optimal approach to reduce treatment-related LV dysfunction, the best method for its early detection, and the optimal regimen to prevent it remain unknown. Appropriate patient selection for HER2-directed therapy and cardiac monitoring is essential to prevent and manage potential cardiac adverse events. A monitoring schedule that assesses baseline and on-treatment cardiac function but potentially reduces the overall number of assessments is suggested for women on HER2-directed therapy. Intervention strategies with cardiovascular medication such as treatment with ACE inhibitor and beta-blockers and cardiovascular risk reduction to improve cardiac status before, during and after treatment, are important to reduce incidence of heart failure. Simplified rules for starting, interrupting and discontinuing trastuzumab are important for the management of LVEF reduction in women on HER2-directed therapy. We recommend a multidisciplinary approach for the management and prevention of treatment-related cardiac dysfunction for the optimal outcomes.

Author details

Shahid Ahmed[1,2,3]*, Arooba Talat[4], Nayyer Iqbal[1,2], Mohamed Emara[1], Duc Le[1,2], Amir Sami[1,2] and Jim Xiang[1]

*Address all correspondence to: shahid.ahmed@saskcancer.ca

1 Saskatchewan Cancer Agency, University of Saskatchewan, Saskatoon, SK, Canada

2 Department of Oncology, University of Saskatchewan, Saskatoon, SK, Canada

3 Department of Community Health and Epidemiology, University of Saskatchewan, Saskatoon, SK, Canada

4 Department of Medicine, University of Saskatchewan, Saskatoon, SK, Canada

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016; 66:7.

[2] Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.1, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2014. Available from: http://globocan.iarc.fr, accessed on August, 08 2016.

[3] Ahmed S, Sami A, Xiang J. HER2-directed therapy: current treatment options for HER2-positive breast cancer. Breast Cancer. 2015;22:101–116.

[4] Mendes D, Alves C, Afonso N, et al. The benefit of HER2-targeted therapies on overall survival of patients with metastatic HER2-positive breast cancer—a systematic review. Breast Cancer Res. 2015;17:140.

[5] Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001;344:783–792.

[6] Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011;365:1273–1283.

[7] Curigliano G, Cardinale D, Suter T, et al. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. Ann Oncol. 2012;23:vii155–vii166.

[8] Suter TM, Procter M, van Veldhuisen DJ, et al. Trastuzumab-associated cardiac adverse effects in the Herceptin adjuvant trial. J Clin Oncol. 2007;25:3859–3865.

[9] Molina MA, Codony-Servat J, Albanell J, Rojo F, Arribas J, Baselga J. Trastuzumab (herceptin), a humanized anti-HER2 receptor monoclonal antibody, inhibits basal and activated HER2 ectodomain cleavage in breast cancer cells. Cancer Res. 2001;61:4744–4749.

[10] Balduzzi S, Mantarro S, Guarneri V, et al. Trastuzumab-containing regimens for metastatic breast cancer. Cochrane Database Syst Rev. 2014;6:CD006242.

[11] Moja L, Tagliabue L, Balduzzi S, et al. Trastuzumab containing regimens for early breast cancer. Cochrane Database Syst Rev. 2012;4:CD006243.

[12] Joensuu H, Kellokumpu-Lehtinen PL, Bono P, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med. 2006;354:809–820.

[13] Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med. 2005;353:659–1672.

[14] Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med. 2005;353:1673–1684.

[15] Montemurro F, Valabrega G, Aglietta M. Lapatinib: a dual inhibitor of EGFR and HER2 tyrosine kinase activity. Expert Opin Biol Ther. 2007;6:257–268.

[16] Cameron D, Casey M, Oliva C, et al. Lapatinib plus capecitabine in women with HER-2-positive advanced breast cancer: final survival analysis of a phase III randomized trial. Oncologist. 2010;15:924.

[17] Piccart-Gebhart M, Holmes E, Baselga J, et al. Adjuvant lapatinib and trastuzumab for early human epidermal growth factor receptor 2-positive breast cancer: results from the randomized phase III adjuvant lapatinib and/or trastuzumab treatment optimization trial. J Clin Oncol. 2016;34:1034–1042.

[18] Capelan M, Pugliano L, De Azambuja E, et al. Pertuzumab: new hope for patients with HER2-positive breast cancer. Ann Oncol. 2013;24:273–282.

[19] Baselga J, Cortés J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med. 2012;366(2):109–119.

[20] Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol. 2012;13:25.

[21] Zhang X, Zhang XJ, Zhang TY, et al. Effect and safety of dual anti-human epidermal growth factor receptor 2 therapy compared to monotherapy in patients with human epidermal growth factor receptor 2-positive breast cancer: a systematic review. BMC Cancer. 2014;14:625.

[22] Gradishar WJ. HER2 therapy-an abundance of riches. N Engl J Med. 2012;6:176–178.

[23] Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012;367:1783–1791.

[24] Tiwari SR, Mishra P, Abraham J. Neratinib, a novel HER2-targeted tyrosine kinase inhibitor. Clin Breast Cancer. 2016;16(5):344–348.

[25] Chan A, Delaloge S, Holmes FA, Moy B, et al. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2016;17:367.

[26] Swain SM, Kim SB, Cortes J, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol. 2013;14:461–471.

[27] Tan-Chiu E, Yothers G, Romond E, et al. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. J Clin Oncol. 2005;23:7811–7819.

[28] Perez EA, Suman VJ, Davidson NE, et al. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. J Clin Oncol. 2008;26:1231–1238.

[29] Costa RB, Kurra1 G, Greenberg L, et al. Efficacy and cardiac safety of adjuvant trastuzumab-based chemotherapy regimens for HER2-positive early breast cancer. Ann Oncol. 2010;21:2153–2160.

[30] Sendur MA, Aksoy S, Altundag K. Cardiotoxicity of novel HER2-targeted therapies. Curr Med Res Opin. 2013;29:1015–1024.

[31] Blackwell KL, Burstein HJ, Storniolo AM, et al. Overall survival benefit with lapatinib in combination with trastuzumab for patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: final results from the EGF104900 Study. J Clin Oncol. 2012;30:2585.

[32] Baselga J, Bradbury I, Eidtmann H, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. Lancet. 2012;379:633–640.

[33] Robidoux A, Tang G, Rastogi P, et al. Lapatinib as a component of neoadjuvant therapy for HER2-positive operable breast cancer (NSABP protocol B-41): an open-label, randomised phase 3 trial. J Clin Oncol. 2013;14:1183–1192.

[34] Guarneri V, Frassoldati A, Bottini A, et al. Preoperative chemotherapy plus trastuzumab, lapatinib, or both in human epidermal growth factor receptor 2-positive operable breast cancer: results of the randomized phase II CHER-LOB study. J Clin Oncol. 2012;30:1989–1995.

[35] Valachis A, Nearchou A, Polyzos NP, et al. Cardiac toxicity in breast cancer patients treated with dual HER2 blockade. Int J Cancer. 2013;133:2245–2252.

[36] Ewer MS, Lippman SM. Type II chemotherapy-related cardiac dysfunction: time to recognize a new entity. J Clin Oncol. 2005;23:2900–2902.

[37] Ewer MS, Vooletich MT, Durand JB, et al. Reversibility of trastuzumab-related cardiotoxicity: new insights based onw clinical course and response to medical treatment. J Clin Oncol. 2005;23:7820–7826.

[38] Crone SA, Zhao YY, Fan L, et al. ErbB2 is essential in the prevention of dilated cardiomyopathy. Nat Med. 2002;8:459–465.

[39] Yarden Y. The EGFR family and its ligands in human cancer: signalling mechanisms and therapeutic opportunities. Eur J Cancer. 2001;37(Suppl 4):S3–S8.

[40] Perik PJ, de Korte MA, van Veldhuisen DJ, et al. Cardiotoxicity associated with the use of trastuzumab in breast cancer patients. Expert Rev Anticancer Ther. 2007;7:1763–71.

[41] Nagata Y, Lan KH, Zhou X, et al. PTEN activation contributes to tumor inhibition by trastuzumab, and loss of PTEN predicts trastuzumab resistance in patients. Cancer Cell. 2004;6:117–127.

[42] Grazette LP, Boecker W, Matsui T, et al. Inhibition of ErbB2 causes mitochondrial dysfunction in cardiomyocytes: implications for Herceptin-induced cardiomyopathy. J Am Coll Cardiol. 2004;44:2231–2238.

[43] Rohrbach S, Muller U, Werdan K, et al. Apoptosis-modulating interaction of the neuregulin/erbB pathway with anthracyclines in regulating Bcl-xS and Bcl-xL in cardiomyocytes. J Mol Cell Cardiol. 2005;38:485–493.

[44] Zeglinski M, Ludke A, Jassal D, et al. Trastuzumab-induced cardiac dysfunction: a 'dual-hit'. Exp Clin Cardiol. 2011;16:70–74.

[45] Dang CT, Yu AF, Jones LW, et al. Cardiac surveillance guidelines for trastuzumab-containing therapy in early-stage breast cancer: getting to the heart of the matter. J Clin Oncol. 2016;34:1030–1033.

[46] National Comprehensive Cancer Network: NCCN clinical practice guidelines in oncology: Breast cancer, version 3. 2015. http://www.nccn.org.

[47] US Food & Drug Administration (FDA). Pertuzumab (PERJATA) http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125409s051lbl.pdf (Accessed on September 13, 2016).

[48] US Food & Drug Administration (FDA). Ado-Trastuzumab Emtansine (KADCYLA) http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125427lbl.pdf (Accessed on September 13, 2016).

[49] US Food & Drug Administration (FDA). Lapatinib (TYKERB) http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022059s007lbl.pdf (Accessed on September 13, 2016).

[50] Cardinale D, Biasillo G, Cipolla CM. Curing cancer, saving the heart: a challenge that cardioncology should not miss. Curr Cardiol Rep. 2016;18:51.

[51] Thavendiranathan P, Poulin F, Lim KD, Plana JC, Woo A, Marwick TH. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: a systematic review. J Am Coll Cardiol. 2014;63:2751–2768.

[52] Lenihan DJ, Hartlage G, DeCara J, et al. Cardio-oncology training: a proposal from the International Cardioncology Society and Canadian Cardiac Oncology Network for a new multidisciplinary specialty. J Card Fail. 2016. doi:10.1016/j.cardfail.2016.03.012

[53] Bellenger NG, Rajappan K, Rahman SL, Lahiri A, Raval U, Webster J, Murray GD, Coats AJ, Cleland JG, Pennell DJ. Effects of carvedilol on left ventricular remodelling in chronic stable heart failure: a cardiovascular magnetic resonance study. Heart. 2004;90:760–764.

[54] Kalay N, Basar E, Ozdogru I, et al. Protective effects of carvedilol against anthracycline-induced cardiomyopathy. J Am Coll Cardiol. 2006;48:2258–2262.

[55] Abdulla J, Barlera S, Latini R, et al. A systematic review: effect of angiotensin converting enzyme inhibition on left ventricular volumes and ejection fraction in patients with a myocardial infarction and in patients with left ventricular dysfunction. Eur J Heart Fail. 2007;9:129–135.

[56] Mackey JR, Clemons M, Cote MA, et al. Cardiac management during adjuvant trastuzumab therapy: recommendations of the Canadian Trastuzumab Working Group. Curr Oncol. 2008;15:24–35.

[57] Jones AL, Barlow M, Barrett-Lee PJ, et al. Management of cardiac health in trastuzumab-treated patients with breast cancer: updated United Kingdom National Cancer Research Institute recommendations for monitoring. Br J Cancer. 2009;100:684–692.

[58] Albini A, Pennesi G, Donatelli F, et al. Cardiotoxicity of anticancer drugs: the need for cardio-oncology and cardio-oncological prevention. J Natl Cancer Inst. 2010;102:14–25.

[59] Lenihan DJ, Esteva FJ. Multidisciplinary strategy for managing cardiovascular risks when treating patients with early breast cancer. Oncologist. 2008;13:1224–1234.

[60] Pivot X, Romieu G, Debled M, et al. 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial. Lancet Oncol. 2013;14:741.

[61] Pivot X, Suter T, Nabholtz JM, et al. Cardiac toxicity events in the PHARE trial, an adjuvant trastuzumab randomised phase III study. Eur J Cancer. 2015;51:1660–1666.

[62] Gulati G, Heck SL, Ree AH, et al.Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a 2 × 2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol. Eur HeartJ. 2016;37:1671–80.

[63] Pituskin E, Mackey JR, Koshman SR, et al. Prophylactic beta blockade preserves left ventricular ejection fraction in HER2-overexpressing breast cancer patients receiving trastuzumab: Primary results of the MANTICORE randomized controlled trial. Cancer Res 2016;76:S1-5.

[64] Pituskin E, Mackey JR, Koshman SR, et al. Prophylactic beta blockade preserves left ventricular ejection fraction in HER2-overexpressing breast cancer patients receiving trastuzumab: primary results of the MANTICORE randomized controlled trial. SABCS. 2015; Abstract S1-05.

IntechOpen