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REVIEW

Cardiac toxicity with anti-HER-2 therapies-what have we learned so far?

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Abstract Trastuzumab, a monoclonal antibody that blocks HER-2 receptor, improves the survival of women with HER-2-positive early and advanced breast cancer when given with chemotherapy. Lapatinib, a dual tyrosine kinase inhibitor of EGFR and HER-2, is approved for the treatment of metastatic breast cancer patients after failure of prior anthracycline, taxanes and trastuzumab therapies in combination with capecitabine. Importantly, cardiac toxicity, manifested as symptomatic congestive heart failure or asymptomatic left ventricular ejection fraction decline, has been reported in some of the patients receiving these novel anti-HER-2 therapies, particularly when these drugs are used following anthracyclines, whose cardiotoxic potential has been recognized for decades. This review will focus on the incidence, natural history, underlying mechanisms, management, and areas of uncertainty regarding trastuzumab-and lapatinib-induced cardiotoxicity.

Keywords Breast cancer · Anti-HER-2 therapies · Cardiotoxicity · Trastuzumab · Lapatinib

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Introduction

Since its registration by the Food and Drug Administration (FDA) in 1998, trastuzumab (Herceptin®, Genentech, San Francisco, CA) has been used to treat more than 450,000 women with breast cancer (BC) worldwide [1]. As a monoclonal antibody directed against the human epidermal growth factor receptor-2 (HER-2), trastuzumab was initially shown to prolong the survival of women with HER-2 positive advanced breast cancer [2]. In 2005, landmark adjuvant studies demonstrated that adjuvant trastuzumab either following or in combination with chemotherapy reduced the risk of relapse by approximately 50% and the risk of death by 33% for women with HER-2 positive early BC [3–6].

Cardiac toxicity was recognized as an important side effect at an early stage in the development of trastuzumab [2, 7]. Manifested as symptomatic congestive heart failure (CHF) or asymptomatic left ventricular ejection fraction (LVEF) decline, trastuzumab-induced cardiotoxicity has been attributed to blockade of HER-2 signaling in cardiac myocytes. The cardiac safety of anti-HER-2 therapy is likely to be agent specific, as the early clinical experience with lapatinib (Tykerb®, GlaxoSmithKline, Brentford, UK), a dual tyrosine kinase inhibitor of the EGFR and HER-2 receptors, suggests that it may produces less cardiotoxicity compared with trastuzumab. However, the patient population studied was heterogeneous and highly selected, limiting the conclusions that can be drawn from this early data [8]. Although there are many promising anti-HER-2 agents currently being tested that may further revolutionize the treatment of patients with HER-2 positive BC, this review will focus on the two agents approved for clinical use: trastuzumab and lapatinib. Familiarity with the incidence, natural history, underlying mechanisms, man-

agement, and areas of uncertainty regarding cardiotoxicity induced by trastuzumab and lapatinib is essential, as cardiac concerns are likely to become increasingly relevant for physicians caring for patients with HER-2 positive BC.

Mechanism of trastuzumab-induced cardiotoxicity

Several studies have demonstrated that HER-2 has an essential role in the development of the embryonic heart (Fig. 1) [9, 10]. The embryonic/neonatal myocardium expresses HER-2, HER-3 and HER-4, whereas the adult myocardium expresses HER-2 and HER-4, but not HER-3 [11–13]. Furthermore, neuregulin splice variants are expressed in adult heart by microvascular endothelial cells, but not by cardiac myocytes [12]. HER-2 expression is high in the fetal myocardium and is required for the development of ventricular muscles and valves [14]. Importantly, preclinical experiments demonstrate that activation of the HER-2 receptor, induced by its ligand neuregulin, promotes cardiomyocite survival [12].

HER-2 is a transmembrane protein that contains an immunoglobulin-like domain. Transgenic mice engineered with a cardiac restricted deletion of HER-2 survive embryogenesis; however, they develop a progressive cardiomyopathy in adulthood, which is similar to the type of cardiac dysfunction observed in patients treated with trastuzumab [15]. These HER-2-conditional knockout mice were viable and initially demonstrated no overt phenotypic abnormalities. Nevertheless, they developed progressive features of dilated cardiomyopathy with left ventricular dilation, left ventricular hypertrophy and systolic dysfunction over time, which was likely secondary to myocyte apoptosis and could be rescued with anti-apoptotic therapy (Bcl xl). Also, in the presence of an additional stress, such as aortic banding, these mice developed dilated cardiomyopathy and died more often than the control mice. The activation of cardiac stress pathways by either hemodynamic overload or anthracycline therapy was shown to accelerate the onset of left ventricular dysfunction in genetically engineered mutant HER-2 deficient mouse model [16]. It is important to differentiate between the embryonic/neonatal and adult myocardium. There is only minimal evidence supporting anti-HER-2 induced cell death in the latter, which may explain the high rate of reversibility of trastuzumab-induced cardiac dysfunction [17].

It was recently reported that HER-2 signalling plays an important role in the sympathovagal control systems of the heart [18–20]. In vitro studies showed that the cooperation of neuregulin and the cholinergic system produced potent antiadrenergic effects, resulting in a decrease in cardiac output and blood pressure. These findings suggest that resting sympathetic tone may be increased in patients treated with trastuzumab and in neuregulin-deficient mice [21]. However, the clinical implications of these findings have yet to be elucidated.

Anthracyclines cause type I cardiotoxicity which is dose-dependent, irreversible and normally associated with biopsy

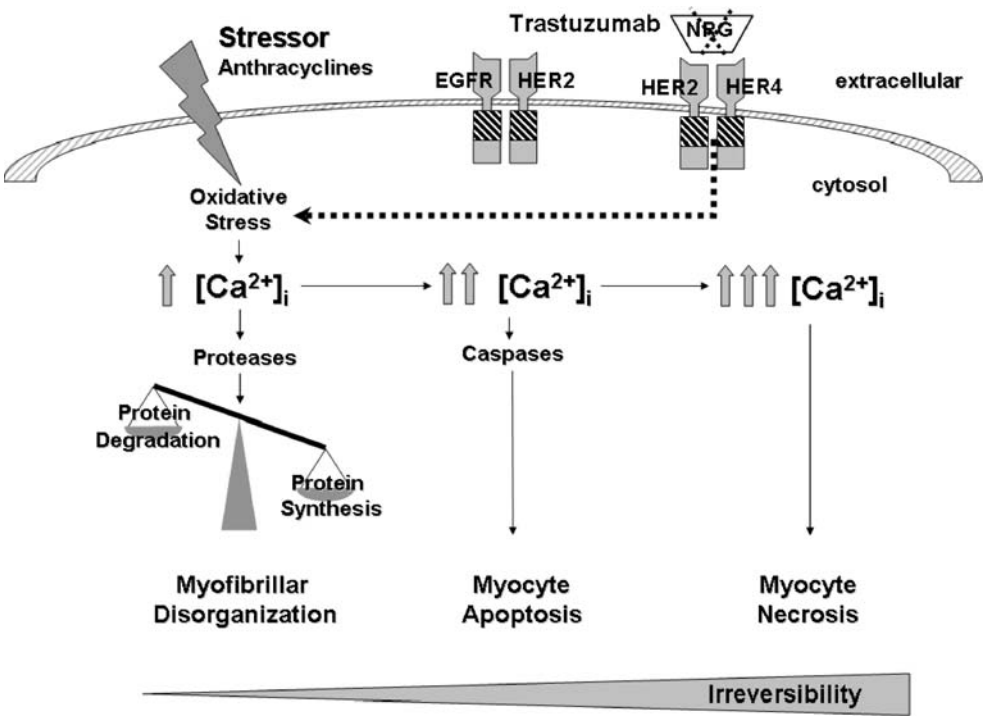

Fig. 1 Anthracyclines induce myocardial oxidative stress by increasing cytosolic calcium concentration that can lead to cardiac dysfunction and at higher concentration to cell death either by apoptosis or necrosis. Stimulation of the HER2/neu receptor can attenuate oxidative stress and is cardioprotective. Conversely, inhibition of HER2/neu can worsen anthracycline-induced cardiac damage through unopposed oxidative stress

changes, whereas trastuzumab causes type II cardiotoxicity, which is not dose-dependent, largely reversible and does not produce ultrastructural changes on histological examination [22]. Several mechanisms have been proposed to explain trastuzumab-induced cardiotoxicity including: a) immune-mediated destruction of cardiomyocytes; b) drug-to-drug interaction with anthracyclines [23]; c) impaired HER-2 signalling required for the maintenance of cardiac contractility [11]; or d) interference with cardiomyocyte survival signals [12].

Therefore, anti-HER-2 therapies should be cautiously used in patients with BC. In the adjuvant setting, the use of trastuzumab following an anthracycline regimen appears to be a good therapeutic option with an acceptable rate of CHF in patients without cardiac disease. Notably, in adult cardiac tissue, the cardiac dysfunction associated with trastuzumab is unlikely to cause cell loss when this drug is not used concomitantly with anthracyclines. Importantly, the results of regimens combining trastuzumab with a non-anthracycline chemotherapy (CT) appear promising. However, the long-term outcome is yet unknown.

The incidence of congestive heart failure with trastuzumab

Metastatic and adjuvant settings

The pivotal metastatic HER-2 positive clinical trial that combined anthracycline— or paclitaxel-based CT with trastuzumab demonstrated an unacceptably high incidence of CHF in the former group [2, 7]. In patients who had received anthracycline-based CT and trastuzumab, 27% developed cardiac dysfunction. In comparison, 8% of patients who received anthracycline-based CT alone, while 13% of patients who received paclitaxel-based CT and trastuzumab and only 1% of patients who received paclitaxel-based CT alone developed cardiac dysfunction (any grade). Among these patients, the incidence of New York Heart Association (NYHA) class III or IV CHF was highest among patients who had received an anthracycline-based CT and trastuzumab (16%) as compared to 3% among patients who had received an anthracycline-based CT alone, 2% among those who had received paclitaxel-based CT and trastuzumab, and 1% among those who had received paclitaxel-based CT alone. In this study, the cumulative dose of anthracycline was not identified as a risk factor. This finding should be interpreted with caution, since there was little variability in cumulative anthracycline dosing, as the majority of patients received all 6 cycles of an anthracycline-based CT as per protocol. Importantly, cardiac assessment was not been prospectively defined and an Independent Cardiac Review Evaluation Committee (CREC) based its assessment on retrospective case report forms analysis. Based upon these data, the concomitant use of trastuzumab and anthracycline-based CT was abandoned in metastatic BC patients.

As a result, all of the adjuvant trastuzumab trials were designed to administer trastuzumab and anthracyclines in a sequential manner and with close monitoring of cardiac safety. A summary of the adjuvant trastuzumab trial designs and their main results is provided in Table 1.

The reported incidence of severe symptomatic CHF (NYHA class III–IV) ranged from 0–3.9% in the adjuvant trastuzumab studies (Table 2 and Fig. 2). Of note, cross-trial comparisons are difficult because of differences in patient characteristics, monitoring schedules, timing of trastuzumab administration and cardiac event definitions. Table 3 summarizes the cardiac event definitions in the adjuvant trastuzumab trials.

The HERceptin Adjuvant (HERA) trial was an international, multicentre, randomised, controlled trial comparing 1 year or 2 years of 3-weekly trastuzumab with observation. To be eligible, patients must have completed locoregional therapy and a minimum of four courses of any acceptable neo- or adjuvant CT. Almost all patients (96%) received anthracycline CT and 26% of patients have received both anthracycline and taxane CT prior to enrolment. No patient died of cardiosvascular disease in the trastuzumab arm and the incidence of severe CHF (NYHA class III–IV) was low (0.6%). Symptomatic CHF (NYHA class II–IV) was seen in 1.7% of the patients in the trastuzumab arm and in 0.06% in the observation arm respectively. A total of 51 patients (3.04%) experienced a significant LVEF drop (defined as an absolute drop of >10% and to below an absolute LVEF of 50%, confirmed after 3 weeks) with trastuzumab, while ten patients (0.53%) in the observation arm had a similar LVEF decrease. Seventy-two patients (4.3%) discontinued trastuzumab because of cardiac problems. No information on cardiac safety or antitumor efficacy has yet been released for the 2-year trastuzumab arm [24, 25]. In the HERA trial, the cardiac function of patients will continue to be monitored up to 10 years after randomisation to determine if trastuzumab increases the risk of long-term anthracycline cardiotoxicity. Preclinical evidence suggests an interaction between the two agents [23] and since anthracycline cardiotoxicity typically manifests years after treatment [26], long-term surveillance of these patients is mandatory.

The National Surgical Adjuvant Breast and Bowel Project (NSABP B-31) trial compared 4 cycles of doxorubicin and cyclophosphamide (AC) followed by 4 cycles of 3-weekly paclitaxel (arm 1) with the same regimen plus 52 weeks of trastuzumab beginning with the first cycle of paclitaxel (arm 2). In this trial, 2,043 patients were enrolled and 66 patients (3.23%) did not meet the post-AC cardiac

Table 1 Main characteristics and results of trastuzumab in HER-2 positive early breast cancer

Trial	Number of HER-2 positive patients	Patient characteristics	Treatment regimens	Primary endpoint	Median follow-up	DFS HR (CI; p value)	OS HR (CI; p value)
NSABP B-31 [51]	2,043	Node-positive	AC×4 → P×4 AC×4 → P×4 +T (P given 3 weekly)	DFS	2.9 years	Pooled analysis: 0.48 (CI 0.41–0.57; $p<0.00001$)	Pooled analysis: 0.65 (CI 0.51–0.84; $p=0.0007$)
Intergroup N9831 [51]	2,766	Node-positive	AC×4 → P×4 AC×4 → P×4 +T starting concurrently with P AC×4 → P×4 +T starting after P (P given weekly)				
HERA [24]	5,102	All except small (<1 cm) node-negative	Any accepted CT alone (observation) T for 1 year after completion of CT T for 2 years after completion of CT	DFS	2 years	0.64 (CI 0.54–0.76; $p<0.0001$)	0.66 (CI 0.47–0.91; $p<0.015$)
BCIRG 006 [5]	3,222	Node-positive or high risk node-negative	AC×4 → D×4 (I) AC×4 → D×4 +T starting concurrently with D (II) D+Cb×6 +T (D given 3 weekly) (III)	DFS	3 years	0.61 (II vs. I) (CI 0.48–0.76; $p<0.0001$) 0.67 (III vs. I) (CI 0.54–0.83; $p=0.0003$)	0.59 (II vs. I) (CI 0.42–0.85; $p=0.004$) 0.66 (III vs. I) (CI 0.47–0.93; $p=0.0017$)
FinHer [6]	232	Node-positive or high risk node-negative	V or D×3 with or without T 9 weeks followed by FEC×3	RFS	38 months	0.42 (CI 0.21–0.83) ($p=0.0078$)	0.41 (CI 0.47–1.08) ($p=0.07$)
PACS-04 [30]	528	Node-positive	FEC×6 or ET×6 → ± T	DFS	48 months	0.86 (0.61–1.22) ($P=0.41$)	1.27 (0.68–2.38) P not provided

AC doxorubicin, cyclophosphamide; *BCIRG* breast cancer international research group; *Cb* carboplatin; *CI* confidence interval; *D* docetaxel; *DFS* disease free survival; *ET* epirubicin, docetaxel; *FEC* 5-fluorouracil, epirubicin, cyclophosphamide; *HERA* HERceptin Adjuvant; *HR* hazard ratio; *NSABP* national surgical adjuvant breast and bowel project; *PACS* protocole adjuvant dans le cancer du sein; *OS* overall survival; *P* paclitaxel; *RFS* relapse free survival; *T* trastuzumab; *V* vinorelbine

Table 2 Cardiac safety results in adjuvant trastuzumab trials

	HERA [25]			NSABP B-31 [28]		N9831 [29]			BCIRG 006 [5]			PACS-04 [30]		
Treatment arms	Obs	1-y H		AC→ P	AC→ PH	AC→ P	AC→ P→ H		AC→ PH	AC→ D	AC→ DH	DCb+H	Obs	1-y H
Women at risk (n)	1,708	1,678		872	932	664	710		570	1,050	1,068	1,056	268	260
Previous Anthracycline		94%			100%		100%				100%	0%		100%
Median time between anthracycline / trastuzumab	NA	12	weeks	NA	4 weeks	NA	12	weeks	4 weeks	NA	4 weeks	0 weeks	NA	8-9 weeks
LVEF at study entry	≥55%			≥50%		≥50%				≥50%			≥50%	
Cardiac deaths	1	0		1	0	1	1		0	0	0	0	0	0
CHF NYHA class 3-4 (%)	0	10 (0.6)		10 (1.3)	35 (3.9)	3 (0.3)	19 (2.8)		19 (3.3)	4 (0.38)	20 (1.87)	4 (0.38)	1 (0.4)	4 (1.7)
Asymptomatic LVEF decrease	2.05%*	7.03%		17%	34%	Not available in the last publication				10%	18%	8.6%	2.2%	4.2%

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. In FinHER, all patients received anthracycline after trastuzumab administration

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

* At least one significant LVEF decline (defined as a decrease in LVEF of ≥10% from baseline and to <50% at any time during the follow up period)

criteria for initiation of trastuzumab (arm 2). One patient died of CHF prior to receiving trastuzumab and the 3-year cumulative incidence of cardiac events (confirmed NYHA class III or IV CHF) for trastuzumab-treated patients was 4.1% compared with 0.8% in the control group. Importantly, 14% of patients discontinued trastuzumab because of asymptomatic LVEF decreases (defined as >10% decline or to below an absolute value of 55%) and 4% of patients because of cardiac events [27]. In a recent update of these data, the 5-year cumulative incidence of cardiac events was similar to the 3-year data (3.9% in the trastuzumab group compared with 1.3% in the control group) suggesting that the majority of cardiac events occur early during trastuzumab treatment. An asymptomatic decline in LVEF occurred in 34% of the patients in the trastuzumab arm and 17% in the control arm with a HR of 2.1 (1.7–2.6; $p<0.0001$) [28].

The Intergroup N9831 trial randomized patients to one of the following regimens: 4 cycles of AC followed by 12 cycles of weekly paclitaxel (arm A); the same regimen followed by 52 weekly doses of trastuzumab (arm B); or the same regimen plus 52 weekly doses of trastuzumab initiated concomitantly with paclitaxel (arm C). Of the 2,992 patients completing AC, 151 patients (5.0%) had significant LVEF decreases (defined as a drop of the LVEF<lower limit of normal or an absolute drop of >15%) that precluded the initiation of adjuvant trastuzumab [3]. In this study two patients died because of CHF (one in arm A and one in arm B) and the 3-year cumulative incidence of cardiac events (CHF or cardiac death) was 0.3% in arm A (AC → T), 2.8% in arm B (AC → T→H), and 3.3% in arm C (AC → TH) [29].

The Breast Cancer International Research Group (BCIRG) 006 trial evaluated the benefit of adding trastuzumab to two CT regimens, one with and one without anthracyclines [5]. Patients were randomized to receive 4 cycles of AC followed by 4 cycles of 3-weekly docetaxel (AC-D); 4 cycles of AC-D combined with 1-year of trastuzumab (AC-DH); or 6 cycles of docetaxel and carboplatin with 1-year of trastuzumab (DCbH). This was the only trial to randomize patients to a non-anthracycline regimen with concomitant with trastuzumab; therefore, the administration of trastuzumab was earlier in these patients than in all other adjuvant trastuzumab trials. No patient died of a cardiac related death. In the second interim analysis, the incidence of symptomatic cardiac events (CHF NYHA class III or IV or cardiac death) was 0.38% in the AC-D arm, 1.87% in the AC-DH arm and 0.38% in the DCbH arm. In addition, the incidence of both asymptomatic LVEF drops and persistent decrease in LVEF in the AC-DH arm was greater than in either the AC-D or DCbH arms ($p<$ 0.001). The incidence of LVEF decrease >10% was 10% in the AC-D arm, 18% in the AC-DH arm, and 8.6% in the DCbH arm. Although controversial, the authors highlight

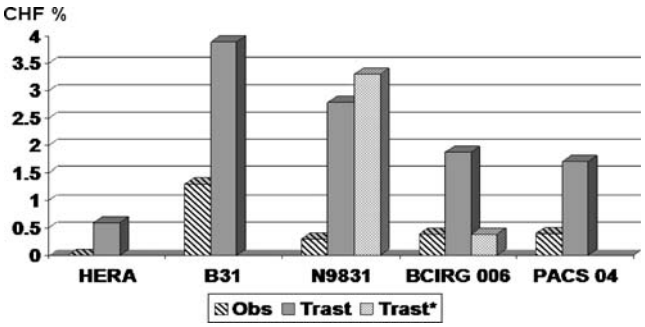

Fig. 2 Incidence of congestive heart failure NYHA class III–IV in the adjuvant trastuzumab trials. BCIRG: Breast Cancer International Research Group; HERA: HERceptin Adjuvant; NSABP B31: National Surgical Adjuvant Breast and Bowel Project; N9831: North Central Cancer Treatment Group; PACS: Protocole Adjuvant dans le cancer du sein; **Note:** Trast*: docetaxel, carboplatin and trastuzumab in BCIRG 006 or doxorubicin, cyclophosphamide followed by paclitaxel and trastuzumab in N9831

an important finding: patients with topoisomerase II alpha and HER-2 gene co-amplification experienced improved DFS with the anthracycline-containing regimen AC→DH than with the non-trastuzumab AC→D or the non-anthracycline DCbH regimen. However, with greater follow-up to 36 months, there was no longer a difference in DFS between the AC→DH and DCbH arms [5]. These findings suggest that the non-anthracycline DCbH regimen may be as effective as anthracycline/trastuzumab-containing regimen, with a lower rate of cardiac toxicity and may be a reasonable alternative for those patients at a higher risk of treatment-induced cardiac dysfunction.

The Finnish Herceptin (FinHer) trial was the smallest of the adjuvant trials (252 HER-2 positive patients) and involved the shortest duration of trastuzumab administration (9 weeks only). In this trial, patients were randomized to receive 3 cycles of vinorelbine or docetaxel with or without 9 weeks of trastuzumab followed by 3 cycles of fluorouracil, epirubicin and cyclophosphamide (FEC). None of the patients experienced clinically significant CHF. Four patients treated with trastuzumab (3.5%) and seven patients who did not receive trastuzumab (6.0%) had one or more LVEF drops greater than 15% compared with the pre-treatment value. However, women treated with trastuzumab might have had a slightly lower cardiovascular risk since their mean LVEF was somewhat higher than the one in patients not receiving trastuzumab. Of note, this is the only trial where trastuzumab was administered before an anthracycline CT regimen; given the long half life of trastuzumab, the three low dose FEC (5-fluorouracil, epirubicin and cyclosphamide) courses were in fact given with concomitant anti-HER-2 therapy [6].

Table 3 Cardiac events definitions in the adjuvant trastuzumab trials

	Cardiac endpoints
HERA [25]	Cardiac death
	Severe CHF defined as NYHA class III/IV symptoms (functional class confirmed by a cardiologist) and LVEF <50% with an absolute decrease of 10% from baseline
	Significant LVEF decline (defined as a decrease in LVEF of≥10% from baseline and to less than 50%)
NSABP B31 [28]	Cardiac death
	CHF defined as NYHA class III/IV symptoms with either decline in LVEF >10% from baseline to <55%, or decline in LVEF >5% to<LLN
NCCTG N9831 [29]	Cardiac death
	CHF defined as NYHA class III/IV symptoms with either decline in LVEF >10% from baseline to <55%, or decline in LVEF >5% to<LLN
BCIRG 006 [5]	Cardiac death
	Symptomatic grade 3/4 CHF
	Asymptomatic decrease in LVEF of more than 15% from baseline or of more than 10% from baseline resulting in an LVEF of less than 50%
FinHer [6]	Cardiac death
	Symptomatic CHF
PACS 04 [30]	Cardiac death
	CHF
	Asymptomatic decline in LVEF to <45%

NSABP national surgical adjuvant breast and bowel project; *NCCTG* North Central cancer treatment group; *HERA* herceptin adjuvant trial; *BCIRG* breast cancer international research group; *FinHer* Finland herceptin trial; *NYHA* New York heart association; *LVEF* left ventricular ejection fraction; *LLN* lower limit of normal; *CHF* congestive heart failure

The Protocole Adjuvant dans le Cancer du Sein (PACS) 04 involving 528 HER-2 positive patients was the only trial that failed to show a statistically significant benefit of adding trastuzumab to the adjuvant treatment of node-positive early BC. In this trial, patients were randomised to receive 6 cycles of FEC or docetaxel plus epirubicin and, in the subset with HER-2 positive disease, randomization to receive either 1 year of adjuvant trastuzumab (260 patients) or no further treatment (268 patients) occurred. No cardiac deaths have been reported in this trial and symptomatic CHF was seen in 1.7% of patients receiving trastuzumab versus 0.4% of patients in the observation arm. In the trastuzumab arm, 16.2% of patients (42 out 260 patients) discontinued trastuzumab due to cardiac toxicity. Asymptomatic decline of LVEF to <45% was observed in 4.2% of patients in the trastuzumab arm and in 2.2% of patients in the observation arm [30].

It is difficult to compare trastuzumab-associated cardiovascular side effects in the adjuvant breast cancer trials since patients, treatment, definitions and stopping rules were different in the trials. However, overall cardiac toxicity appears lowest when chemotherapeutic pretreatment did not include anthracyclines or when trastuzumab was given prior to chemotherapy. When anthracyclines were used prior to trastuzumab, the HERA treatment scheme appears least cardiotoxic, possibly because a) the minimal pre-trastuzumab LVEF (≥55%) was higher than in the other trials, b) the time between anthracycline and trastruzumab treatment was longer than in the other trials, and c) a confirmatory LVEF assessment was required after an initial detection of cardiac dysfunction [25].

Recent reports suggest that the incidence of trastuzumab-induced cardiotoxicity outside of clinical trials setting may be higher than expected. For example, McArthur and Chia described a cohort of 155 women treated with adjuvant trastuzumab given either sequentially or concurrently with CT. There were no significant differences in the mean LVEF at 3, 6 and 9 months in either cohort. However, 21.6% (22 women) treated in the sequential cohort had a cardiac event requiring temporary or permanent trastuzumab discontinuation [31]. It is difficult to analyze the difference in cardiotoxicity between clinical trials and practice; however, inclusion criteria and follow up might be less stringent in clinical practice, possibly accounting for this discrepancy [32].

Neoadjuvant setting

The principle of avoiding concurrent anthracyclines and trastuzumab has recently been challenged by neoadjuvant studies. Buzdar et al. randomized patients to receive either chemotherapy alone (paclitaxel followed by FEC therapy) or the same regimen with concurrent weekly trastuzumab for 24 weeks. Patients with a history of heart failure or with a LVEF <45% were excluded [33]. After 6 months of CT, similar median LVEF values were observed in 66 patients and remained largely unchanged through the course of the study. No patient experienced symptomatic heart failure or cardiac death.

In the neoadjuvant trastuzumab in locally advanced breast cancer (NOAH) trial, 228 HER-2 positive patients were randomized to receive 3 cycles of doxorubicin/paclitaxel (AT), followed by 4 cycles of T, and then 3 cycles of cyclophosphamide, methotrexate, 5-fluorouracil (CMF) on days 1 and 8, with (n=115) or without (n=113) concomitant trastuzumab before surgery. Trastuzumab was given after surgery for up to 1 year of therapy following the previous randomization. HER2- negative patients (n=99) were treated in parallel with AT→T→CMF. LVEF at baseline was similar in all three groups. An LVEF decrease of at least 10% was seen in ten patients receiving trastuzumab after AT, in eight patients after T alone, and in 11 patients after CMF. Only one patient treated with trastuzumab experienced a cardiac event with an LVEF value of <45% and was withdrawn from the study [34]. A recent update presented at the San Antonio Breast Cancer Symposium 2008, showed Grade 3–4 LVEF decline in 2 (1.8%) HER-2 positive patients treated with concomitant trastuzumab [35].

The GeparQuattro is the largest randomized neoadjuvant trastuzumab trial (453 HER-2 positive patients). In this study, patients were randomized to receive 4 cycles of epirubicin/cyclophosphamide (EC) and were then randomized to either 4 cycles of docetaxel (D) or 4 cycles of D-capecitabine (DX, combination arm) or 4 cycles of D followed by 4 cycles of X (D→X, sequential arm). Patients with HER-2 positive disease received trastuzumab every 3 weeks concomitantly with all neoadjuvant CT before surgery and for up to 1 year after surgery. In the HER-2 positive cohort, 147 patients were randomized to D, 144 patients to DX, and 136 patients to D→X. LVEF at baseline was >55% in 97% of patients included in this cohort. The interim safety interim analysis showed no increase in toxicity for neoadjuvant CT and trastuzumab compared to CT alone. None of the patients experienced an LVEF decrease to below 45% and no episodes of CHF or cardiac death were observed [36].

Despite these observations, there are concerns regarding cardiac toxicity with the concomitant use of trastuzumab and anthracycline CT and further follow up of these studies is needed. The use of concomitant trastuzumab and antracyclines is not presently recommended outside the context of a clinical trial.

Risk factors for trastuzumab-related cardiac toxicity

All of the adjuvant trastuzumab trials have carefully evaluated cardiac function in a prospective manner and

only included patients with normal or near normal cardiac function. The inclusion criteria usually included an LVEF of≥50% or≥55% and no pre-existing cardiac disease such as heart failure, ischemic and valvular heart disease, arrhythmia (except controlled atrial arrhythmia) or poorly controlled hypertension [25, 27, 37]. The risk factors for trastuzumab-associated cardiotoxicity were analyzed based on the occurrence of heart failure or systolic dysfunction. In most trials a lower pre-trastuzumab LVEF was associated with the onset of a cardiac event.

For example in the HERA trial, patients with a screening LVEF≥65% had a lower risk for a cardiac event than patients with an LVEF <65% (1.88% versus 3.89%) and patients with a screening LVEF of ≥60% had a lower risk than patients with an LVEF between 55% and 60% (2.72% versus 6.90%) [25]. Similarly, in the NSABP B31 trial a lower LVEF (50%–54%) at baseline or after AC was associated with a higher incidence of cardiac dysfunction [27] and in the N9831 trial, an LVEF higher than the lower limit of normal but lower than 55% was a risk factor for cardiac dysfunction [29].

Another important risk factor for trastuzumab-associated cardiac dysfunction in the HERA trial was the dose of anthracyclines used prior to trastuzumab. A higher cumulative dose of doxorubicin (287 mg/m^2 versus 257 mg/m^2) or epirubicin (480 mg/m^2 versus 422 mg/m^2) was associated with a cardiac event [25].

Other risk factors included a higher age of the patients (both in N9831 and B31) and prior or current use of antihypertensive medication in the N9831 trial [27, 37]. These data indicate that increased cardiac stress (i.e., lower LVEF, preexisting exposure to anthracyclines, older patients) might be a risk factor for trastuzumab-associated cardiac side effects and might explain why trastuzumab-associated cardiac dysfunction appears more frequent in clinical practice than in controlled trials [31, 38]. Another risk factor whose pathophysiology is poorly understood is an elevated BMI (>25 kg/m²) compared to a normal BMI (≥20 and <25) in the HERA trial [25]. In contrast, radiation therapy was not associated with an increased risk of cardiac side effects [25, 27, 37]. A definitive conclusion regarding the lack of an interaction between radiotherapy and trastuzumab, as far as cardiac morbidity is concerned, will require a much more prolonged follow-up.

Reversibility of trastuzumab-induced cardiac toxicity in the adjuvant trials

Contrary to anthracycline-induced cardiotoxicity, trastuzumab alone does not seem to cause myocyte cell death, but might induce changes in the geometrical structure of contractile proteins [11, 22]. This might explain the data from 38 MBC patients treated with trastuzumab who experienced cardiotoxicity with most of patients demonstrating an improvement of cardiac dysfunction when trastuzumab was held or continued in combination with CHF medications [22]. It should be pointed out, however, that there is an interaction between anthracycline and trastuzumab cardiotoxicity and the concomitant use of both therapies might increase the rate of anthracycline-induced myocardial cell death due to worsening cellular oxidative stress [39]. This also explains the high rate of cardiotoxicity when the two drugs were combined in the metastatic trials [2].

In the adjuvant trials patients with cardiac dysfunction had a high rate of reversibility. In the HERA trial, 8 out 10 patients with severe CHF were asymptomatic at the last scheduled assessment. Recovery of LVEF from a cardiac endpoint was defined as an LVEF ≥ 55% at any time after the date of onset until the last scheduled assessment. Six of ten patients with severe CHF recovered their LVEF in a median of 124 days (36–409 days). Among the 36 patients with symptomatic CHF (NYHA class III or IV), 24 patients recovered their LVEF by a median of 151 days (26–831 days) and among the 51 patients with a confirmed significant LVEF drop, 35 patients recovered by a median of 191 days (13–831 days) [25]. However, this may be an underestimation of the true rate of reversibility because of limited follow-up at the time of reporting.

In the N9831 trial, trastuzumab-induced LVEF decrease requiring re-evaluation was observed in 4.0% at 6 months, 7.8% at 9 months, and 5.4% at the final evaluation (month 18) in the sequential trastuzumab arm. Recovery of LVEF at re-evaluation was observed in 1.9%, 3.0%, and 0.4% respectively. Failure to recover was observed 1.7%, 3.3%, and 0.2% respectively. However, a significant fraction of these symptomatic patients did not undergo re-evaluation at these specified time points: 0.4% at 6 months, 1.5% at 9 months, and 4.8% at 18 months. In the concomitant trastuzumab arm, LVEF decrease requiring re-evaluation was observed in 14.0% at 6 months, 9.4% at 9 months, and 5.8% at 18 months. Recovery of LVEF at re-evaluation was observed in 5.1%, 4.9%, and 0.3% respectively, while failure to recover LVEF occurred in 3.8%, 2.8%, and 0.5% respectively. Of note, a significant proportion of patients did not undergo re-evaluation: 1.5% at 6 months, 1.7% at 9 months, and 5.0% at 18 months. This high rate of non-re-evaluation at month 18 limits any definitive conclusions that can be drawn regarding the reversibility of trastuzumab-associated cardiac dysfunction. For all 39 patients experiencing CHF (arm A=2; Arm B=18; arm C=19), trastuzumab was discontinued and the majority received cardiac medication including diuretics, beta-blockers, and antiarrhytmic agents. Improvement in cardiac function was observed in the majority of these patients [29].

In the BCIRG 006 trial, the mean LVEF decreased during trastuzumab administration but appeared to recover after discontinuation of trastuzumab. Unfortunately, detailed reporting of cardiac toxicity is not available since this trial has only been published in abstract form [5]. Similarly, detailed cardiac safety data is not available from the PACS 04 study [30]. Since none of the trastuzumab-treated patients experienced CHF or LVEF decreases in the FinHer trial, no further information on recovery is possible in this trial [6].

Screening, monitoring and management of trastuzumab-associated cardiac dysfunction

Assessment of the risk factors for trastuzumab-associated cardiac side effects and a thorough cardiac examination before treatment is as important as careful monitoring during treatment. Almost all trials excluded patients with pre-existing cardiac diseases such as prior myocardial infarction, angina pectoris requiring medication, cardiac dysfunction, heart failure and arrhythmias (except rate-controlled supraventricular arrhythmias) and uncontrolled hypertension (usually defined as systolic blood pressure >160 mmHg despite antihypertensive therapy). Consequently, patients who do not meet these inclusion criteria should not be considered for trastuzumab treatment, except under special circumstances. Similarly, an abnormally low LVEF prior to initiation of trastuzumab is associated with an increased risk of cardiotoxicity [25, 28, 37].

Although it is difficult to compare the different adjuvant trastuzumab breast cancer trials it appears that HERA which used an inclusion LVEF >55% had a lower rate of cardiotoxicity, despite the fact that most of the patients had received prior anthracyclines [25].

The appropriate schedule of LVEF monitoring in asymptomatic patients during trastuzumab treatment remains controversial. Most of the adjuvant trials have assessed LVEF either by echocardiography or MUGA scan every 3 months up to the 9th month of treatment, and a new assessment 6 months after cessation of treatment. Based on these criteria, it was recommended to monitor cardiac function at 3-month intervals during trastuzumab treatment and every 6 months for at least 2 years after completion of treatment [22]. Others have recommended less frequent surveillance, provided that the patient remains asymptomatic [40]. The preferred method of LVEF monitoring is somewhat arbitrary; however, it is generally recommended that the same imaging modality be used for each assessment.

The monitoring of patients with asymptomatic LVEF drops was also different in the adjuvant breast cancer trials. For example, in HERA, patients were required to have a confirmatory LVEF assessment 3 weeks after an initial LVEF drop [25]. This may, in part, explain the lower incidence of cardiac dysfunction in HERA compared to the other adjuvant trials.

The management of trastuzumab-related asymptomatic or symptomatic cardiac dysfunction also varied across the adjuvant trastuzumab trials. In general, holding or definitive cessation of trastuzumab, with treatment of cardiac dysfunction should be considered when a cardiac event occurs. Several trials held trastuzumab treatment, if the LVEF dropped more than 10% to 15% from baseline and below 45% to 40% [25, 28, 37]. Most of the trials allowed restarting treatment when the LVEF recovered. In patients with severe symptomatic CHF, trastuzumab treatment was discontinued in all trials and patients were primarily treated according to local guidelines. The appropriate cardiac management of patients with asymptomatic LVEF drop is more controversial. In general, trastuzumab treatment was stopped according to the same rules used for symptomatic patients. Of note, it remains unclear whether these patients benefit from cardiac therapeutics such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers or beta-blockers.

In patients with risk factors for trastuzumab-associated cardiotoxicity, the early initiation of trastuzumab therapy may be important to prevent early recurrence. However, while several strategies may reduce the risk of anthracycline-induced cardiotoxicity, these strategies have not been properly studied in trials testing trastuzumab or other anti-HER2 therapies. It is believed that the mechanisms of trastuzumab-and anthracycline-induced cardiotoxicity are different, but prior anthracycline administration appears to increase the risk of trastuzumab-associated cardiac dysfunction [5, 23, 41]. Therefore, the best option to protect trastuzumab-induced cardiotoxicity may be to protect the heart from initial anthracycline damage.

Cardiotoxicity of lapatinib

Two early phase I dose-finding studies with lapatinib involving 67 [42] and 81 [43] patients respectively with advanced refractory solid malignancies reported minimal cardiotoxicity, with only one patient experiencing an asymptomatic grade 2 LVEF decline [43]. A pooled analysis of the GlaxoSmithKline safety database involving 4,990 patients enrolled in 49 (n=25 phase I, n=13 phase II, and n=6 phase III) clinical trials with lapatinib reported a similarly low incidence of cardiotoxicity [8]. This review included 3,689 lapatinib treated patients, with lapatinib administered as monotherapy in 1,991 (54%), combined with chemotherapy or endocrine therapy in 1,502 (41%),

and concomitant administration with trastuzumab in 196 (5%). A baseline LVEF≥40% was required for phase I trials and above the institutional LLN in phase II and III studies. Patients with a history of cardiac disease were excluded. Cardiac monitoring was undertaken every 8 weeks for the phase II and III studies and was not specified for phase I trials. Asymptomatic cardiac events, defined as an LVEF decrease≥20% relative to baseline, were reported in 53 patients (1.4%), and symptomatic events, defined as NCIC-CTCAE Grade 3 or 4 systolic dysfunction, occurred in 7 patients (0.2%) treated with lapatinib. The incidence of lapatinib-associated cardiac dysfunction appeared similar, regardless of whether the patients were pre-pretreated with anthracyclines or with a non-anthracycline containing chemotherapy. Data regarding LVEF recovery was only available for 40 patients. Thirty-five of the 40 patients (88%) had a partial or complete recovery, irrespective of whether lapatinib was continued or stopped. No predictive risk factors for an LVEF dysfunction could be identified.

Although patients included in this cohort were heterogeneous, these data suggest that lapatinib may be less cardiotoxic than trastuzumab. However, it should be noted that due to the inclusion criteria for most of the patients in these trials, the time between anthracyclines and lapatinib was longer than in any trastuzumab trials, which may explain the low rate of observed cardiotoxicity. In addition, many patients were pretreated with trastuzumab, potentially leading to a selection bias. Nevertheless, an underlying molecular mechanism for the observed differences in cardiotoxicity between lapatinib and trastuzumab has recently been proposed by Spector et al. [44]. These investigators demonstrated that lapatinib protects against TNFα-induced cardiomyocyte cell death through induction of AMP-activated protein kinase (AMPK) signalling [44]. This protective effect was not seen when human cardiomyocyte cells were treated with trastuzumab.

The ongoing four-arm phase III Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTTO) trial will directly compare the cardiac safety of lapatinib and trastuzumab used alone, in sequential or in combination [45, 46]. One of the experimental arms in ALTTO is combined lapatinib and trastuzumab therapy, supported by preclinical studies indicating that this combination may have synergistic anti-tumour activity [47]. The addition of trastuzumab to lapatinib prolonged progression free survival in a randomized phase III study involving 295 heavily pre-treated patients with advanced HER-2 positive disease [48]. Although prior anthracycline therapy was mandatory and patients included in this study had received a median of 3 prior lines of trastuzumab-containing therapy, only two patients experienced symptomatic cardiac events (1.3%), including one cardiac death (0.7%), occurred in the combination arm as compared with one symptomatic cardiac event (0.7%) in the lapatinib monotherapy arm. Similarly, there were six asymptomatic cardiac events (4.1%) in the combination arm versus four asymptomatic cardiac events (2.7%) in the lapatinib monotherapy arm. Recovery was seen in 11 of 13 patients (85%) who experienced a cardiac event. These preliminary findings are encouraging, but further data from ongoing studies, including ALTTO and a number of small neoadjuvant trials involving the combined HER-2 blockade, are eagerly awaited.

Conclusion

Over the last decade, the HER-2 protein has been validated as an important therapeutic target in BC. Early studies with anthracyclines in combination with trastuzumab demonstrated that cardiomyopathy was an important side effect that might limit the development of future anti-HER-2 targeted approaches. Since then, researchers have elucidated the critical role of the HER-2 signaling pathway in mediating the response of cardiac myocytes to environmental stresses. Further experience with trastuzumab has shown that this agent can safely be delivered as monotherapy or in combination with non-anthracycline cytotoxic chemotherapy. Clinicians are now acutely aware of the importance of serial cardiac monitoring and temporarily discontinuing trastuzumab in the face of symptomatic CHF or asymptomatic LVEF decline. While the cardiac safety data from the large adjuvant trastuzumab studies continue to be collected, it is already apparent that “low-normal” baseline cardiac contractile function prior to or following anthracycline therapy, along with obesity, age, and concomitant anti-hypertensive medication use, may predispose patients to developing trastuzumab-associated cardiac dysfunction. Established trastuzumab-associated cardiomyopathy appears to be largely reversible in the short-term, with suspension of trastuzumab and the inititation of appropriate heart failure therapy, although selected patients may not recover their contractile function. The long-term outcome of patients with trastuzumab-associated cardiac dysfunction is largely unknown.

Indirect evidence suggests that anti-HER-2-associated cardiotoxicity may be agent specific, as blockade of the intracellular HER-2 tyrosine kinase domain by lapatinib is associated with less clinical cardiac dysfunction than trastuzumab. This favorable cardiac safety profile of lapatinib may be due activation of the AMPK pro-survival pathway cardiac myocytes in response to metabolic stress. Ongoing studies will directly compare these two agents, providing an opportunity to further elucidate the biological mechanisms underlying anti-HER-2-associated cardiotoxicity.

In the future, oncologic decision-making will increasingly take into account the cardiac side effects of biological anti-cancer therapy. There have been recent reports of cardiomyopathy with non-HER-2 multi-targeted tyrosine kinase inhitors, such as imatinib, sunitinib, and sorafenib [49]. The combination of biological agents that do not directly target the HER-2 receptor, such as bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF), may also potentiate trastuzumab-associated cardiac dysfunction [50]. Recognition of the fundamental role of oncogenic signaling pathways in cardiomyocyte maintenance and survival will mandate close collaboration between oncologists and cardiologists to better improve the outcome of patients diagnosed with HER-2 positive BC.

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