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Twenty years of anti-HER2 therapy-associated cardiotoxicity

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ABSTRACT

Over the past 20 years, the prognosis of HER2-positive breast cancer has been transformed by the development of anti-HER2 targeted therapies. In early clinical trials of trastuzumab (ie, the first anti-HER2 agent to be developed) cardiotoxicity became a major concern. In the first published phase 3 trial of trastuzumab, 27% of patients receiving anthracyclines and trastuzumab experienced cardiac events and 16% suffered from severe congestive heart failure. In subsequent trials conducted in advanced and early settings, the incidence of cardiac events was reduced through changes in chemotherapy regimens, more strict patient selection and close cardiac assessment. However, cardiotoxicity remains a significant problem in clinical practice that is likely to increase as new agents are approved and exposure times increase through improved patients' survival. Though numerous trials have led to improved understanding of many aspects of anti-HER2 therapy-related cardiotoxicity, its underlying physiopathology mechanisms are not well understood. The purpose of this article is to provide an in-depth review on anti-HER2 therapy-related cardiotoxicity, including data on both trastuzumab and the recently developed anti-HER2 targeted agents.

INTRODUCTION

Breast cancer is the most common type of cancer among women as well as the first cause of cancer-specific mortality for women worldwide.[1] It is, however, not a single disease but rather several distinct diseases that arise from the same organ.[2] Among the currently identified subtypes, HER2-positive (HER2+) disease has been the focus of particularly intense and productive research in the past 20 years. Representing up to 20% of the total cases, HER2+ disease was traditionally considered a subtype with poor prognosis, a situation that has changed by the development of anti-HER2 targeted therapies (table 1).[3 4]

HER2 is part of the ErbB family of transmembrane growth factor receptor tyrosine kinases (that also includes HER3 and epidermal growth factor receptor (EGFR) among others). These proteins can be activated independently from ligands via homodimerisation or heterodimerisation (with HER3) or through neuregulin-1 (NRG-1), a panHER ligand that plays a significant role in multiple physiological and pathological processes.[5] HER2+ tumour cells possess a highly proliferative phenotype, with increased capacity to invade, disseminate and stimulate angiogenesis.[6] The success of trastuzumab in countering this aggressive behaviour has been, however, not total, with some patients either recurring after adjuvant trastuzumab in the early setting, or proving primary or secondary resistant to trastuzumab in the metastatic setting. This resistance can originate from multiple causes, such as alterations to the conformation of the extracellular domain, or autoactivation of intracellular downstream signalling pathways.[7 8] To circumvent this, a new generation of anti-HER2 agents has been developed, each with unique mechanisms of action. Among these compounds several are already in clinical use or in phase 3 studies, while other agents still in earlier stages of development.[9]

Besides its usefulness during the process of neoplastic progression, just as any of the receptors and pathways that tumour cells exploit, HER2 plays physiological roles that are reflected in the toxicity profile of anti-HER2 agents. In mutated mice without HER2 expression, no embryos reached full development and all had cardiac malformations (such as lack of trabeculae in the myocardium) among other important lethal organic dysfunctions.[10] In another murine model, genetically engineered mice lacking HER2 expression exclusively in the heart developed features of dilated cardiomyopathy, with left ventricular chamber dilation, wall thinning and reduced contractility.[11] Additionally, these mice were more susceptible to anthracycline cardiotoxicity. In a similar study, mice had increased apoptosis of ventricular cells, and cardiac dysfunction was reversed through suppression of apoptosis.[12] In models of cardiac lesions (ischaemia, viral and dilated cardiomyopathies),

cardiac performance was improved and survival extended by the infusion of recombinant NRG-1 receptor-active peptide (rhNRG-1).[13] Taken together, these data point towards a fundamental role for HER2 signalling in heart development during embryogenesis and in cardiomyocyte survival especially in situations of stress, through the promotion of survival pathways that inhibit apoptosis and maintain cardiac function. Thus, cardiotoxicity is the main concern during anti-HER2 therapy, as clinical trials with trastuzumab have pointed out.[4]

In this review, we will explore the state-of-the-art on anti-HER2 therapy-related cardiotoxicity, starting with trastuzumab and exploring the recently developed anti-HER2 targeted agents.

MONOCLONAL ANTIBODIES

Trastuzumab

Trastuzumab is a monoclonal antibody that binds to the extracellular domain of HER2. Its mechanisms of action include activation of antibody-dependent cytotoxicity, inhibition of signal transduction, inhibition of neoangiogenesis and inhibition of repair of DNA damage caused by the treatment.[14] Trastuzumab is approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for HER2+ patients with breast cancer in the adjuvant, neoadjuvant and metastatic settings (table 1).

Cardiotoxicity is the only significant toxicity that trastuzumab treatment entails. From a clinical stand point, it manifests most often as an asymptomatic drop in left ventricular ejection fraction (LVEF) or, infrequently, as congestive heart failure (CHF).[15] Remarkably, although a plethora of studies have revealed much about its clinical course, risk factors and incidence in different settings, much remains unknown regarding its pathophysiology.[16] Available research suggests that trastuzumab affects the heart in multiple ways:

A. Blocking NRG-1-mediated activation of HER2 reduces fundamental intracellular mechanisms that allow cardiomyocytes to adequately carry out their highly specialised function (repetitive contraction). Affected mechanisms include the ability to maintain the structure and function of sarcomeres and scavenging of proapoptotic oxidative subproducts of ATP production in a cell that has high and constant ATP demands;[17 18]
B. Trastuzumab binding leads to the downregulation of the antiapoptotic protein BCL-XL and to the upregulation of the proapoptotic protein BCL-XS.[19] The ratio between antiapoptotic and proapoptotic stimuli is also a key regulator of mitochondrial function;
C. Oxidative stress leads to the upregulation of angiotensin II. Angiotensin II is an inhibitor of NRG-1 that prevents its binding to other ErbB family receptors to compensate for HER2 blockade, leading to even more inhibition of the pathway, and thus to more oxidative stress forming a cytotoxic vicious cycle. It also activates NADPH oxidase leading to mitochondrial dysfunction and cell death. Furthermore, angiotensin II also induces apoptosis through the AT1 receptor.[20 21]

Twenty years of clinical experience, based on a set of pivotal phase 2 and 3 trials with trastuzumab have allowed the construction of a picture of the different aspects of trastuzumab-related cardiotoxicity. Table 2 summarises the incidence of trastuzumab-associated cardiotoxicity from the most relevant trials in the metastatic, neoadjuvant and adjuvant settings.[4 22–37]

Metastatic setting

In the phase 3 trial that led to the approval of trastuzumab in the metastatic setting, patients with metastatic breast cancer received either a combination of doxorubicin and cyclophosphamide (AC) or paclitaxel monotherapy both with or without trastuzumab.[4] Thirty-nine (27.2%) of 143 patients in the AC plus trastuzumab arm versus 11 (8.1%) of 135 in the AC alone arm and 12 (13.2%) of 91 in the paclitaxel plus trastuzumab arm versus 1 (1.1%) of 95 in the paclitaxel alone arm experienced CHF. Moreover, a proportionally higher number of patients who received concomitant anthracycline and trastuzumab had New York Heart Association (NYHA) class III and IV CHF when compared with paclitaxel and trastuzumab (16% vs 2%, respectively). These findings confirmed what has already been shown in smaller phase 1 and 2 trials that trastuzumab causes asymptomatic drops in LVEF or symptomatic and potentially deadly (one patient died) CHF.[15] The large disparity between chemotherapy regimens suggests that the concomitant association of anthracycline and trastuzumab is potentially cardiotoxic. From a physiological point of view, their mechanisms of cardiotoxicity, though different, overlap significantly in the formation over oxidative

Table 1 Agents and approval status

Agent	Class	Status of approval
Trastuzumab	Monoclonal antibody	Early and advanced disease
Pertuzumab	Monoclonal antibody	Early (neoadjuvant) and advanced disease
Trastuzumab-emtansine (T-DM1)	Drug–antibody conjugate	Advanced disease
Lapatinib	Tyrosine kinase inhibitor	Advanced disease
Afatinib	Tyrosine kinase inhibitor	Not approved
Neratinib	Tyrosine kinase inhibitor	Not approved

Table 2 Trastuzumab-associated cardiotoxicity in clinical trials

Author (year)	Setting	Study design	Treatment arms	Number of patients	Any LVEF drop Number (%)	Any CHF Number (%)
Slamon *et al* (2001)[4]	MBC first line	Phase 3	AC+trastuzumab	143	Not reported	39 (27.2)
			AC	135		11 (8.1)
			Paclitaxel+trastuzumab	91		12 (13.2)
			Paclitaxel	95		1 (1.1)
Marty *et al* (2005)[22]	MBC first line	Phase 2	Docetaxel+trastuzumab	86	16 (18)	2
			Docetaxel	76	7 (8)	0
Gasparini *et al* (2007)[23]	MBC first line	Phase 2	Paclitaxel+trastuzumab	28	Not reported	0
			Paclitaxel	40	Not reported	0
Von Minckwitz *et al* (2011, 2009)[24 38]	MBC beyond first line	Phase 3	Capecitabine	78	0	0
			Capecitabine+trastuzumab	78	1 (1.28)	1 (1.28)
Kaufman *et al* (2009)[25] (Tandem)	MBC first line	Phase 3	Anastrozole+trastuzumab	103	1 (0.97)	1 (0.97)
			Anastrozole	104	0	0
Buzdar *et al* (2007)[26]	Neoadjuvant	Phase 2	FEC+paclitaxel+trastuzumab (concomitant)	45	Not reported	1
			FEC+paclitaxel	19	1	0
Gianni *et al* (2010)[27]	Neoadjuvant	Phase 3	A+paclitaxel+CMF+trastuzumab	117	30 (27)	2 (1.7)
			A+paclitaxel+CMF	217	33 (15)	0
Untch *et al* (2010)[28] (Gepar quattro)	Neoadjuvant	Phase 3	Chemotherapy+trastuzumab	445	4 (0.89)	1 (0.22)
			Chemotherapy	1050	0	2 (0.19)
Buzdar *et al* (2013)[29]	Neoadjuvant	Phase 3	FEC+paclitaxel+trastuzumab (concomitant)	142	35 (24.6)	1 (0.7)
			FEC+paclitaxel+trastuzumab (sequential)	138	21 (15.2)	0
de Azambuja *et al* (2014)[30] (HERA)	Adjuvant	Phase 3	Chemotherapy+trastuzumab 1 year	1682	120 (7.2)	19 (0.8)
			Chemotherapy+trastuzumab 2 years	1673	69 (4.1)	14 (0.8)
			Chemotherapy	1744	15 (0.9)	0
Romond *et al* (2012)[31] (NSABP-B31)	Adjuvant	Phase 3	AC+paclitaxel	743	Not reported	9 (1.2)
			AC+paclitaxel+trastuzumab	947	114 (12)	36 (3.8)
Advani *et al* (2016)[32] (N9831)	Adjuvant	Phase 3	AC+paclitaxel	664	64 (9.6)	6 (0.9)
			AC+paclitaxel+trastuzumab	710	119 (16.7)	19 (2.6)
			AC+paclitaxel/trastuzumab	570	136 (23.8)	20 (3.5)
Slamon *et al* (2011, 2015)[33 39]	Adjuvant	Phase 3	AC+docetaxel	1073	114 (11.2)	8 (0.8)
			AC+docetaxel+trastuzumab	1074	206 (19.1)	21 (2.0)
			Docetaxel+carboplatin+trastuzumab	1075	97 (9.4)	4 (0.4)
Spielman *et al* (2009)[34]	Adjuvant	Phase 3	FEC/ED	268	7 (2.6)	1 (0.37)
			EC/ED+trastuzumab	260	29 (11.1)	4 (1.5)
Joensu *et al* (2006)[35]	Adjuvant	Phase 3	Docetaxel/vinorelbine+FEC	116	0	2 (1.72)
			Docetaxel/vinorelbine+trastuzumab+FEC	115	0	1 (0.86)
Pivot *et al* (2015)[36]	Adjuvant	Phase 3	Chemotherapy+trastuzumab 6 months	1690	45 (2.7)	9 (0.53)
			Chemotherapy+trastuzumab 1 year	1690	70 (4.1)	11 (0.65)
Tolaney *et al* (2015)[37]	Adjuvant	Phase 2	Paclitaxel+trastuzumab	406	13 (3.2)	2 (0.5)

A, doxorubicin; AC, doxorubicin, cyclophosphamide; CHF, cardiac heart failure; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; EC, epirubicin, cyclophosphamide; ED, epirubicin, docetaxel; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; HERA, herceptin adjuvant; LVEF, left ventricular ejection fraction; MBC, metastatic breast cancer.

stress, making increased risk a reasonable hypothesis.[40] Recent models of anthracycline toxicity also suggest that HER2 signalling is essential to protect cardiomyocytes from it.[41]

In the pivotal trial, patients who suffered from cardiac dysfunction mostly were treated with standard cardiac agents used for CHF, with 75% of patients experiencing cardiac recovery.[4] In this study, older age was the only significant risk factor associated with cardiotoxicity.[4] Other smaller trials also suggested that previous cardiovascular disease and hyperlipidaemia are risk factors for the development of cardiotoxicity.[42]

Subsequent trials in the metastatic setting, with either chemotherapy or hormonotherapy showed significantly less cardiac events as shown in table 2.[22–25] This reduction is explained by a different design of the trials and eligible population: trastuzumab was not given concomitantly with anthracyclines (though patients could in all cases have received previous adjuvant anthracyclines during adjuvant treatment), patients with an LVEF of <50% were excluded, and cardiovascular follow-up during study treatment included clinical examinations and serial cardiac assessment, mostly echocardiography. It is important to note that the initial results of trastuzumab impacted on the development of all anti-HER2 agents, the selected population in clinical trials does not always represent patients with HER2+ metastatic breast cancer treated in daily clinical practice. As shown in large cohort studies conducted in an unselected population, the risk of cardiotoxicity with the use of trastuzumab seems to be higher. Thus, it is likely that in daily clinical practice, the reported cardiotoxicity is higher than in trials as reported in some cohorts of patients.[43 44] In the meta-analysis of randomised trials versus cohort studies conducted by Mantarro *et al*,[43] cohort studies consistently reported higher cardiotoxicity rates than randomised trials in the metastatic setting: 4.4% vs 2.8%, respectively.

Neoadjuvant setting

The neoadjuvant strategy has been explored extensively in HER2+ disease.[45] The academic debate has been centred from an early point on the issue of associating anthracyclines and trastuzumab concomitantly versus sequentially and the need to balance potential benefits (ie, higher pathological complete response rate) with potential risks (ie, higher cardiotoxicity).[46] In the seminal trial by Buzdar and colleagues, 45 women received fluorouracil, epirubicin, cyclophosphamide (FEC) and trastuzumab followed by paclitaxel and trastuzumab. A total of 19 women in the control group received only FEC followed by paclitaxel. The results of the trial suggested for the first time that concurrent administration of anthracycline and trastuzumab was safe (only one patient developed CHF) and yielded increased benefits (response rates were also significantly higher in the combination arm), putting into question the conclusions taken from the initial experience with metastatic disease.[26]

Subsequently, the larger NeOAdjuvant Herceptin (NOAH) trial further investigated the safety of combining anthracyclines with trastuzumab concomitantly. Of the 117 patients who received combined therapy, 27% suffered LVEF drops (grades 2–3) and 1.7% had symptomatic CHF versus 15% and 0%, respectively, in the non-trastuzumab group (215 patients).[27] Similarly, in the geparQUATTRO trial with 1495 patients, only 4 had LVEF drops and 2 CHF in the three groups that received combined therapy.[28] Although a combined analysis of these three neoadjuvant trials showed that the trastuzumab regimens where more cardiotoxic than the non-trastuzumab (significant increase in the rate of cardiotoxicity (OR 1.95, 95% CI 1.16 to 3.29, p=0.36)),[47] none of these trials had a design capable of resolving the critical question of the cardiac safety of concurrent treatment with anthracycline and trastuzumab.

The ACOSOG Z1401 was designed to answer this question with a total of 280 patients randomised between two trastuzumab containing regimens, one with concomitant anthracycline and one with trastuzumab after anthracycline. The dose of epirubicin in the FEC regimen was 75 mg/m^2. The combination arm had a non-significantly higher number of LVEF drops and CHF (24.6% and 0.7%, respectively) as compared with the sequential group (15.2% and 0%, respectively). The response rate was the same in the two treatment arms.[29] Therefore, given the data presented above, it is generally recommended not to combine trastuzumab with anthracyclines in the curative setting, as well as in the metastatic setting, due to increased risk of cardiac events.

Adjuvant setting

The large adjuvant randomised phase 3 trials, with higher number of patients and predefined close cardiac follow-up, provided the most detailed and extensive information on trastuzumab-related cardiotoxicity (table 2). Specific cardiotoxicity analyses with long-term follow-up have been published for most of these trials.[30–32]

In the herceptin adjuvant (HERA) trial, 5102 patients were randomised to observation or trastuzumab for 1 or 2 years.[48] Cardiac assessment included LVEF assessment by either echocardiogram or multiple gated acquisition scintigraphy (MUGA) in predefined time points. After a median follow-up of 8 years, the study confirmed that the incidence of trastuzumab-associated toxicity remained low, that most cases of cardiac events occurred during trastuzumab use and that the majority were reversible after the interruption of trastuzumab.[30] The incidence of LVEF decline was 0.9%, 4.1% and 7.2% in the observation, 1-year and 2-year trastuzumab arms, respectively. The observed incidence of CHF remained very low (0% in the observation arm and 0.8% in the 1-year and 2-year trastuzumab arms). It is important to note that the very low risk of cardiotoxicity is likely connected to patient selection and study design. The 2-year arm suffered more LVEF drops than the 1-year arm, suggesting that time of exposure plays a role in the risk of

developing this side effect. Since there was no added clinical benefit for the 2-year arm, 1 year of trastuzumab remains the standard of care in the adjuvant setting. In the metastatic setting, however, considering the longer exposure times that are likely to issue from recently introduced regimens exposure times to trastuzumab may go beyond 2 years.[49–51] Registries are currently in progress to better elucidate the safety of prolonged exposure to anti-HER2 targeted agents in the clinical practice setting.[52] Other adjuvant trials showed a similar low number of cardiac events (table 2); however, selection criteria, cardiac follow-up and definitions of cardiac events varied across the studies, making direct comparisons difficult. Recently published long-term follow-up data (median follow-up 9.2 years) of the B31 trial showed that only 6 (0.9%) and 19 (2.6%) patients in the control arm and experimental arm, respectively, experienced CHF. An analysis for risk factors was conducted: 60 years or older, baseline LVEF between 50% and 54.9% (a group that was excluded from HERA by design) or 55% and 64.9%, use of antihypertensive medications proved to be significantly associated with increased risk of cardiotoxicity. Interestingly, the use of radiation therapy and BMI were not associated with significant increased risk in this trial, nor in the N9831 study.[32] It is also important to note that the nature of cardiac vigilance during the study treatment varied widely between studies. For example, in the N9831 trial, LVEF assessment was maintained for 21 months at most, except in cases where there was a suspicion of cardiac toxicity, while in the HERA study cardiac assessment was mandated for 10 years.[30] LVEF drops occurred in 15.4% of patients in the control arm (AC+paclitaxel), 31.1% in the sequential (AC+paclitaxel followed by trastuzumab) arm and 27.1% in the concomitant arm (AC+paclitaxel/trastuzumab; table 2). CHF grades 2–4 were respectively 0.3%, 2.8% and 3.3%.[53] Long-term data of the same trial revealed a stably low 6-year incidence of cardiac events. In this trial, as in the HERA and B31 trials, most events happened during treatment and were reversed quickly when treatment was interrupted and cardiac intervention established.

Recently, the BCIRG 006 trial presented the 10-year results. This is the only trial testing a non-anthracycline regimen (TCH). Cardiac events were lower in the TCH arm compared with AC-TH (0.4% vs 2%, respectively). A recently published meta-analysis of all the adjuvant trials, with a total of 18 111 patients concluded that adjuvant therapy with trastuzumab significantly increases the risk of grades 3 and 4 CHF (RR 3.04 (95% CI 1.12 to 7.85; p<0.00001)).[54]

Pertuzumab

Pertuzumab is a monoclonal antibody that acts by binding to domain II of HER2 receptor with consequent inhibition of HER2–HER3 heterodimerisation.[55] It has been recently approved for clinical use (table 1) in combination with trastuzumab and chemotherapy as neoadjuvant therapy and first-line therapy in patients with HER2+ metastatic breast cancer.[56]

One early phase 2 study of the combination suggested increased cardiotoxicity, leading to early interruption of pertuzumab.[57] Improved patient selection (exclusion of high-risk groups such as patient who had a history of trastuzumab-related cardiotoxicity) and cardiac assessment, led to a reduction in events during subsequent studies.[58–61] In a large pooled analysis, Lenihan and colleagues evaluated the pertuzumab cardiac safety data. Overall, out of 598 patients included in the analysis, 35 (5.9%) developed asymptomatic left ventricular systolic dysfunction (LVSD), defined as a decrease from baseline in LVEF of ≥10 points to a value of <50% at any postbaseline LVEF assessment) and 4 (0.7%) patients developed symptomatic CHF.[62]

The main evidence supporting the cardiac safety of the trastuzumab–pertuzumab combination comes from the CLEOPATRA phase 3 trial in metastatic patients (table 3). The incidence of adverse cardiac events of any grade was 16.4% in the placebo arm and 14.5% in the pertuzumab arm.[63] LVSD of any grade was the most frequently reported cardiac event (8.3% in the placebo arm vs 4.4% in the pertuzumab arm).[63] Few cases of CHF were reported, 7 (1.8%) in the placebo arm and 4 (1.0%) in the pertuzumab arm.[63] Prior exposure to anthracyclines and prior radiotherapy were identified as potentially important risk factors irrespective of treatment arm.[63] Interestingly prior exposure to trastuzumab was not significantly associated with the development of LVSD,[63] but only 10% of the study population was previously exposed in the early setting to anti-HER2 targeted therapy. Overall, the cardiotoxicity profile of the combination was favourable: adverse cardiac events were largely reversible and clinically manageable.[63] Two studies of pertuzumab-based therapy in the neoadjuvant setting (ie, NeoSphere and TRYPHAENA) showed a similar low incidence of cardiac events.[64 65] Hence, the available data coming from the neoadjuvant and metastatic settings do not suggest dual anti-HER2 blockade with trastuzumab and pertuzumab increases the incidence of cardiac events. This was also confirmed by a meta-analysis combining the cardiotoxicity data from the CLEOPATRA and NeoSphere studies: as compared with trastuzumab alone, the addition of pertuzumab was not associated with an increased risk of LVEF drops (OR 0.66, p=0.19).[66] No published data are available so far on the use of pertuzumab in the adjuvant setting; the results of the APHINITY trial (NCT01358877) will give further insight into the cardiac safety of combining two anti-HER2 monoclonal antibodies.

ANTIBODY DRUG CONJUGATE

Trastuzumab-emtansine

Trastuzumab-emtansine (T-DM1) is an antibody drug conjugate composed of a monoclonal antibody (ie, trastuzumab) connected to a potent cytotoxic antimicrotubule

Table 3 Cardiotoxicity in the main phase 3 clinical trials with the use of anti-HER2 targeted agents other than trastuzumab

Author	Setting	Treatment arms	Number of patients	LVEF drop (≥10 points and <50%) N (%)	CHF N (%)
Pertuzumab					
Swain *et al*[49]	MBC, first-line	Docetaxel+trastuzumab +placebo	396	27 (6.6)	13 (3.3)
		Docetaxel+trastuzumab +pertuzumab	408	27 (6.6)	6 (1.5)
T-DM1					
Verma *et al*[67]	MBC, first-line and beyond first-line	T-DM1	495	8 (1.7)	1 (0.2)
		Lapatinib+capecitabine	496	7 (1.6)	0 (0.0)
Krop *et al*[68]	MBC, beyond first-line	T-DM1	404	6 (1.0)	0 (0.0)
		Treatment of physician's choice	198	2 (1.0)	0 (0.0)
Lapatinib					
Geyer *et al*[69]	MBC, beyond first-line	Lapatinib+capecitabine	163	4 (2.5)	0 (0.0)
Cameron *et al*[70]		Capecitabine	161	4 (2.5)	0 (0.0)
de Azambuja *et al*[71]	Neoadjuvant setting	Lapatinib+paclitaxel	154	2 (1.3)	1 (0.6)
		Trastuzumab+paclitaxel	149	2 (1.3)	0 (0.0)
		Lapatinib+trastuzumab +paclitaxel	152	7 (4.6)	2 (1.3)
Piccart-Gebhart *et al*[72]	Adjuvant setting	CT+trastuzumab	2097	97 (4.6)	53 (2.5)
		CT+lapatinib	2100	63 (3.0)	37 (1.8)
		CT+trastuzumab → lapatinib	2091	57 (2.7)	37 (1.8)
		CT+trastuzumab +lapatinib	2093	103 (4.9)	68 (3.2)
Neratinib and afatinib					
Harbeck *et al*[73]	MBC, first-line and beyond first-line	Afatinib+vinorelbine	332	1 (0.3)	0 (0.0)
		Trastuzumab+vinorelbine	168	3 (1.8)	2 (1.2)
Awada *et al*[74]	MBC, first-line	Neratinib+paclitaxel	242	Not reported 3 (1.3%)*	Not reported
		Trastuzumab+paclitaxel	237	Not reported 7 (3.0)*	Not reported
Chan *et al*[75]	Adjuvant setting	Neratinib	1420	4 (0.3)	1 (0.1)
		Placebo	1420	2 (0.1)	0 (0.0)

*Defined as CHF, decreased LVEF, LVSD and peripheral oedema.
CHF, cardiac heart failure; CT, chemotherapy; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; MBC, metastatic breast cancer; T-DM1, trastuzumab-emtansine.

agent (ie, emtansine or DM1).[76] This formulation has been recently approved for the treatment of patients with HER2+ metastatic breast cancer previously exposed to taxane and trastuzumab (table 1).

All the published phase 2 studies available showed a favourable cardiotoxicity profile with the use of T-DM1.[77–81] Most of these studies were conducted in patients with metastatic breast cancer beyond first-line therapy: hence, the majority of them had prior exposure to trastuzumab. Nevertheless, the risk of developing a cardiac event with the use of this compound is low, as also confirmed by the available phase 3 studies[67 82] (table 3).

In the EMILIA trial,[67] T-DM1 was compared with lapatinib plus capecitabine in 991 patients with HER2+ metastatic breast cancer. Only three patients in each arm had a decrease in LVEF from baseline to <40%.[67] A total of eight patients (1.7%) in the T-DM1 arm and 7 (1.6%) in the lapatinib plus capecitabine arm had a LVEF reduction ≥15 points below the baseline value and to <50%.[67] Only one patient in the T-DM1 arm developed grade 3 LVSD.[67] The TH3RESA trial in a heavily pretreated population showed similar results.[82]

In the early setting, two studies with the use of neoadjuvant T-DM1-based therapy have reported results, but no cardiotoxicity data were reported.[83 84] In the adjuvant setting, the single-arm phase 2 TDM4874g (BO22857) trial investigated the cardiac safety and overall feasibility of T-DM1 for ~1 year after prior exposure to anthracycline-based chemotherapy in the (neo) adjuvant setting.[68] Patients received 4 cycles of (neo) adjuvant AC or 3–4 cycles of FEC followed by 4 cycles of T-DM1; then, patients could have received an optional 3–4 cycles of docetaxel with or without trastuzumab, and finally all patients continued T-DM1 for a planned 17

cycles of HER2-directed therapy.[68] A total of 153 patients were randomised: no symptomatic CHF were reported and mean LVEF was stable throughout T-DM1 treatment.[68] A total of four patients (2.6%) experienced a LVEF decline ≥10 points below the baseline value and to <50%, and one of these women discontinued T-DM1 with an LVEF of 45%.[68] Two of four LVEF declines occurred during treatment with optional docetaxel plus trastuzumab.[68] Ongoing studies in this setting (eg, the KATHERINE (NCT01772472), the KAITLIN (NCT01966471) and the ATEMPT (NCT01853748) trials) are awaited to better define the safety profile of long-term exposure to T-DM1.

TIROSINE KINASE INHIBITORS

Lapatinib

Lapatinib is a FDA and EMA approved dual tyrosine kinase inhibitor (TKI) of EGFR and HER2 available for patients with advanced disease (table 1).[85] Lapatinib activates the AMP-kinase pathway which increases ATP reserves and induces a metabolic stress response in human cardiomyocytes that may protect against TNF-α-induced cell death.[86] Hence, preclinical evidence suggested that lapatinib may ultimately protect the heart against the cardiotoxicity induced by anti-HER2 targeted agents.[86] Table 3 show the most relevant phase 3 studies for lapatinib.

In the registration phase 3 study, 324 patients with HER2+ metastatic breast cancer progressing after anthracycline, taxane and trastuzumab were randomly allocated to receive lapatinib combined with capecitabine or capecitabine alone.[87] In the study, lapatinib showed a favourable cardiotoxicity profile. Overall, 11 patients developed 12 events.[70] A total of 11 patients experienced 12 events of LVEF drop; 4 patients in each arm, developed grade ≥3 LVSD or ≥20 points absolute decrease in LVEF from the baseline value, but all these episodes were reported as asymptomatic.[70] The patients with LVEF drop were previously exposed to cardiotoxic agents (anthracyclines and trastuzumab) and/or had other cardiac risk factors (ie, hypertension, left chest radiation and cardiopulmonary diseases).[70]

Following the results of this study, several other phase 3 randomised trials evaluated the efficacy and safety of lapatinib as single-agent or combined with chemotherapy, endocrine therapy or trastuzumab in the treatment of patients with HER2+ metastatic breast cancer.[87–92] Overall, these studies confirmed the low risk of cardiotoxicity with lapatinib; however, the definition of cardiac events used in these studies was not homogeneous and thus a clear comparison with other results becomes more difficult.

A large combined analysis conducted by Perez *et al*[93] investigated the cardiotoxicity profile of lapatinib in 3689 patients treated with the TKI as monotherapy (54%) or in combination (41% with chemotherapy or endocrine therapy, and 5% with trastuzumab). This large analysis confirmed the low incidence of cardiac events (1.6%) with a high rate of demonstrated reversibility of LVEF (88%) with the use of lapatinib. It is, however, important to note that only a small part of the patient population (14.9%) had previously received anthracyclines.[93]

In the neoadjuvant and adjuvant settings, all phase 3 trials confirmed the safety of the combined treatment of lapatinib–trastuzumab and of lapatinib alone.[71 72 94–96] In the NeoALTTO study there were three arms: trastuzumab alone, lapatinib alone and the combination of trastuzumab and lapatinib were compared in the neoadjuvant setting; a low incidence of primary cardiac events was observed in all treatment arms (<1%) although there were more primary and secondary cardiac events in the combined arm (7, 5%) than in either the lapatinib arm (2, 1%) or the trastuzumab arm (2, 1%). No significant difference for primary or secondary cardiac events was observed between the three treatment arms.[71 96] In the ALTTO trial, 8381 patients with centrally confirmed HER2+ early-stage breast cancer were randomly assigned to 1 year of adjuvant anti-HER2 targeted therapy with trastuzumab, lapatinib, their sequence (trastuzumab followed by lapatinib) or their combination (trastuzumab plus lapatinib). Cardiac events were defined in the protocol as in the NeoALTTO study.[71] The incidence of primary and secondary cardiac events was low in all the treatment arms. Between 0.25% and 0.97% of patients developed primary cardiac end points with three fatal cardiac events in the sequential arm and one in each of the other treatment arms.[72] These studies support the cardiac safety of lapatinib both as single anti-HER2 agent and as dual anti-HER2 blockade in combination with trastuzumab. As shown in the meta-analysis by Valachis *et al*,[66] the combination of lapatinib and trastuzumab seems not to be associated with an increased risk of developing CHF nor LVEF drops (CHF OR 0.64; p=0.42 and LVEF OR 0.53; p=0.54).

Afatinib and neratinib

Neratinib and afatinib are novel next-generation TKIs targeting EGFR, HER2 and HER4.[85] They are not yet approved for use in breast cancer (table 1). In the metastatic setting, several phase 2 trials evaluated the activity of neratinib and afatinib either as monotherapy or in combination with chemotherapy (neratinib in combination with paclitaxel or capecitabine, afatinib in combination with vinorelbine) or endocrine therapy (afatinib in combination with letrozole). Overall, the cardiotoxicity profile of these compounds showed to be favourable as demonstrated in the phase 3 studies (NEfERT-T and LUX-Breast 1) in the metastatic and early (ExteNET) settings[73 74] (table 3). The only phase 3 trial exploring the use of neratinib in the adjuvant setting reported a low rate of cardiac events (table 3).

ELDERLY POPULATIONS

Elderly patients (more than 70 years old) benefit from adjuvant treatment, although to a lesser extent than

younger patients due to issues of comorbidity, functionality and life expectancy.[97] However, it is clear that well-selected patients can safely receive and benefit from adjuvant therapy.[98 99] Data for use of trastuzumab in the elderly populations are limited, since most studies placed age limitations for inclusion.[100] The available data from phase 3 trials suggested higher risk of cardiotoxicity (both in B31 and N9831) in patients above 60 years of age.[31 32 101] Although there are few trials specifically studying the use of trastuzumab in the elderly populations, observational studies suggest high treatment completion rates.[102 103] In the APT phase 2 study of weekly paclitaxel and trastuzumab, 10.1% of patients were older than 70. The study showed no significant increase in cardiac toxicity.[37] A cohort study in the elderly population (median age 71 years) focused specifically on cardiotoxicity: a total of 9535 patients were included and 2203 (23.1%) received trastuzumab. The CHF rate was 29.4% and 18.9% among patients who received trastuzumab and those that did not, respectively.[104]

Pertuzumab studies, designed in recent times, are more likely to have larger elderly populations. In the landmark CLEOPATRA trial, 127 out of 808 patients (15.7%) were above 65 years old. The risk of developing cardiac events did not seem to be significantly higher (≥65 vs <65 years, HR=1.25; 95% CI 0.61 to 2.56, p=0.5502) in the elderly population, although the low number of events limits the reliability of this finding.[105]

From the cardiotoxicity point of view, the limited available data support the use of anti-HER2 agents in the elderly population.

BIOMARKERS

The search and clinical testing of biomarkers for cardiotoxicity has been a central area for research in cardio-oncology. An ideal biomarker could help stratify patients between different risks, thus allowing for more personalised follow-up regimens during treatment, as well as early interruption before functional alteration LVEF is established.[106] Several different potential biomarkers have been studied, including troponins I and T (TnI and TnT, both markers of myocardial injury), B-natriuretic peptide (BNP a marker of wall stress), and C reactive protein (CRP; a marker of inflammation).

Multiple studies dealt with the role of TnI in predicting trastuzumab cardiotoxicity, with discordant results. The largest study conducted so far investigated the role of TnI in 251 women receiving trastuzumab therapy. TnI levels were measured before and after each dose of trastuzumab.[107] A total of 42 (17%) patients suffered cardiac toxicity (LVEF drop or CHF) and the cardiac events were positively correlated to TnI elevation. Approximately 60% of these patients recovered, but a significantly lower number of those who were TnI-positive recovered as compared with women who were TnI-negative (35% vs100%, HR 2.88, 95% CI 1.78 to 4.65; p<0.001). Thus, the results of this study suggest that TnI predicts which patients will not recover. It is, however, significant to note that 7 of the 36 patients with elevated TnI had elevated level already at baseline, suggesting that possibly they already had otherwise undetectable cardiac injuries (from anthracyclines or other causes). Furthermore, these results are not corroborated by other smaller studies (77). A recently published study where 214 women were receiving adjuvant EC followed by docetaxel with or without trastuzumab (depending on HER2 status) showed no correlation between trastuzumab and elevated TnI levels (4.2% in trastuzumab group and 3% in trastuzumab-free group).[108]

TnT, CRP and BNP have less evidence in favour of their usefulness as biomarkers. In one study, 54 women with early-stage HER2+ breast cancer, elevated CRP predicted decreased LVEF, but no association was found between LVEF and BNP or TnI.[109] Another study testing eight biomarkers in 78 patients receiving adjuvant trastuzumab, found no positive correlation between CRP and BNP and the risk of cardiotoxicity.[110] An exploratory cardiac substudy within the phase 2 study of first-line weekly paclitaxel in combination with trastuzumab and pertuzumab,[61] investigated cardiac biomarkers (TnI and BNP) and speckle-tracking echocardiography (to measure global longitudinal strain) as adjuncts to LVEF monitoring for the early detection of treatment-related cardiotoxicity.[111] No changes in global longitudinal strain were observed during the study. TnI was detectable in 3 (4.3%) patients and BNP in 2 (3.0%) but they were not associated with LVEF decline.[111] Looking specifically at TnT, a small study with only 19 patients suggests that TnT increase predicts LVEF decrease at 15 months.[112] Another, larger study (42 patients), however, found no correlation.[113]

Another possible strategy in risk stratification is the use of variations in single nucleotide polymorphisms (SNPs). Evidence has associated SNPs with enhanced toxicity or efficacy in cancer treatments. Small studies suggest that SNPs in the HER2 gene, namely Pro1170Ala and Ile655Val, can predict the occurrence of trastuzumab-associated cardiotoxicity.[114 115] However, this deserves further confirmation before being used in clinical practice.

Currently, there is not enough evidence to recommend routine use of any biomarker, including TnI in daily practice.[116]

FUNCTIONAL IMAGING

Functional imaging has a crucial role in identifying patients at risk of developing adverse cardiac events when treated with anti-HER2 agents and those experiencing cardiac vents while on treatment. The serial measurement of LVEF is the mainstay of cardiac surveillance in patients under treatment with anti-HER2 agents.

Echocardiography is the most well-established and widely used technique in the monitoring of cardiac patients during treatment. Major advantages of this technique include widely availability, no use of radiation, no

side effects and the relative low cost.[117] Echocardiography allows volumetric measures, ejection fraction evaluation and assessment of diastolic heart function. Recent data suggest that newer echocardiography-derived measures of myocardial mechanics (ie, strain indices and ventricular–arterial coupling) can provide additional insights into cardiac function during cancer treatments and may serve as a sensitive marker of early myocardial dysfunction.[118]

MUGA is more accurate than echocardiography in determining ejection fraction and has an important role in the surveillance of cardiotoxicity associated with cancer treatments.[119] Nevertheless, MUGA requires the injection of a radiotracer, which is very expensive and is not available in all cancer centers.[117]

Cardiac MR (CMR) is an extremely accurate technique in determining cardiac volumes and ejection fraction with a potential role in identifying small regions of scarring and inflammation.[117] Recently, CMRI with myocardial strain showed to be a potential useful mean of detecting trastuzumab-related cardiotoxicity.[120] However, the high cost and lack of availability are likely to limit the clinical use of this technique.[119]

CARDIOPROTECTIVE STRATEGIES

A number of pharmacological agents are currently in use to treat CHF with high-quality evidence of improvements in outcomes (including β-blockers and ACE inhibitors).[121 122] As we have seen these standard CHF treatment agents have been used in patients experiencing cardiac events due to trastuzumab-associated cardiotoxicity, and most patients experience cardiac recovery with these treatments. This has led to interest in investigating such agents as cardioprotective strategies during anthracycline and/or trastuzumab treatments. In the case of anthracycline-associated cardiotoxicity, few small studies suggest that this strategy may be useful.[123 124] This has led to the design of randomised trials exploring this pharmacological strategy, including two recently reported trials—MANTICORE and PRADA.

MANTICORE is a randomised trial of perindopril (ACE inhibitor) in comparison to bisoprolol (β-blocker) and placebo in patients who are to start adjuvant trastuzumab. The planning accrual was 153 patients, but this trial was interrupted early (99 patients) due to the evident superiority of one of the strategies. In this trial, bisoprolol significantly prevented reduction in LVEF and trastuzumab treatment interruptions when compared with perindopril or placebo (p value of <0.001). No significant change was detected in left ventricular remodelling (a possible early marker of trastuzumab cardiotoxicity).[125]

In the PRADA study candesartan (an angiotensin receptor blocker) and metoprolol were compared in combination or alone against placebo in 130 early breast cancer treated patients with adjuvant anthracyclines and trastuzumab. Study treatment was started before chemotherapy with FEC and only 22.2% of patients received trastuzumab. The overall decline of LVEF in the placebo group was 2.6% (95% CI 1.5% to 3.8%) and 0.8% (95% CI 20.4% to 1.9%) in the candesartan group (p=0.026). Combination or metoprolol alone did not show significant benefit. This result suggests that candesartan may reduce the incidence of LVEF drops.[126]

Though the results of MANTICORE and PRADA are interesting, it is very important to bear in mind that both studies are small in size and exclude patients with cardiac comorbidities, and therefore their results are not at the moment a solid basis for clinical decision-making and should be further explored in larger studies.

CONCLUSIONS

Cardiotoxicity remains a clinically significant toxicity of anti-HER2 therapies. Novel agents seem to have a reduced potential for cardiotoxicity. However, the findings from clinical trials should be considered in the context of the patient selection criteria: the eligible population in these studies (ie, younger age, higher LVEF at baseline and less cardiovascular comorbidities) do not always fit with average patients in clinical practice. Further analysis of data is also made more difficult by the myriad of different criteria used to define cardiac events in each study, as well as the different follow-up plans during and after study treatments. Therefore, a common definition on cardiac events should be applied in future clinical trials.

In practice, longer periods of combined treatment, more lines of therapies and longer survival is likely to increase the relevance of cardiotoxicity in the context of metastatic disease. The data available to be applied in clinical practice are almost exclusively derived from trastuzumab trials, and can provide some guidance on some risk factors that can help in deciding the chemotherapy choice and cardiac assessment during treatment. Importantly, at the first suspicion of cardiac toxicity, patients should have a cardiac assessment because of its high proportion of reversibility with anti-HER2 interruption and proper cardiac intervention. Unfortunately, at this moment, there is no validated biomarker or any other means of selecting patients who need less exhaustive cardiac follow-up or less cardiotoxic chemotherapy regimens, with the exception of clinical cardiac risks (eg, hypertension, obesity, etc).

Guidelines and position papers by the European Society for Medical Oncology (ESMO), the European Society of Cardiology (ESC) and the American Society of Clinical Oncology (ASCO) address the issue of trastuzumab-associated cardiotoxicity.[127–129] These guidelines highlight the importance of patient selection, treatment of potential risk factors for increased cardiotoxicity and of adequate cardiac assessment during treatment. It is important to note, however, that no studies showed that such methods may change cardiac outcomes.[130] The recently published ASCO guidelines on treatment of HER2+ early disease suggests the use of trastuzumab, carboplatin and docetaxel in patients considered to be at

high risk for cardiotoxicity as a reasonable approach.[129] As more data from new studies with pertuzumab and T-DM1 become available, further insights into this phenomenon will probably be available.

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