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Detection, monitoring, and management of trastuzumab-induced left ventricular dysfunction: an actual challenge

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The antibody trastuzumab, targeted to inhibit the signalling of ErbB2, a tyrosine kinase receptor overexpressed in 20–30% of breast cancers, improves the prognosis in women affected by this tumour, but produces cardiotoxicity, since ErbB2 is also involved in myocardial homeostasis. In this review, we discuss the pathophysiology of trastuzumab cardiomyopathy and the complex interplay between ErbB2 inhibition and anthracyclines, and we focus on the actual challenges of detecting, monitoring, and managing trastuzumab cardiotoxicity: the research of new, sensitive markers of early trastuzumab toxicity, before the ejection fraction is reduced, is an active field of research.

Keywords Trastuzumab cardiomyopathy • ErbB2 • Anthracyclines • Ejection fraction • Biomarkers • New echocardiographic techniques

Introduction

Cardiovascular side effects of anticancer treatments are a relevant problem, which have emerged with the improvement in cancer survival, especially in the last decade. In the USA, the 5-year relative survival rate of patients diagnosed with cancer between 1975 and 1977 compared with those diagnosed between 1999 and 2005 improved significantly from 50% to 68%.[1] It is a testament to this success that delayed cardiotoxicity has emerged as an appreciable problem, with some estimates suggesting that 2 000 000 people in the USA alone may be at risk of delayed anthracycline toxicity.[2]

Potential cardiovascular toxicities linked to anticancer agents include QT prolongation and arrhythmias, myocardial ischaemia and infarction (e.g. with antimetabolites), hypertension or thrombo-embolism (e.g. with the antiangiogenic agents bevacizumab, sorafenib, sunitinib, and pazopanib), cardiac dysfunction, or heart failure (HF). The latter is variable in severity, may be reversible or irreversible, and can occur immediately or as a delayed consequence of treatment.[3] The induction of late-onset HF after anthracyclines has historically been the most relevant problem. However, also newer agents, 'targeted' to affect specific growth signalling pathways, are not specific to cancer cells. This is especially true for the heart, particularly when it is under stress.

Since 1998, trastuzumab, the monoclonal antibody against the human epidermal growth factor receptor-2 (EGFR2, or ErbB2), overexpressed in 20–25% of breast cancers, has been used to treat > 450 000 women with breast cancer worldwide. In 2005, adjuvant studies demonstrated that trastuzumab either following or in combination with chemotherapy reduced the risk of relapse by ~ 50% and the risk of death by 33% in these patients.[4] Unfortunately, cardiotoxicity was recognized as an important side effect. Manifested as symptomatic HF or asymptomatic left ventricular (LV) ejection fraction (EF) decline, trastuzumab cardiotoxicity has been attributed to ErbB2 blockade in cardiomyocytes. The cardiac safety of anti-ErbB2 therapy might be agent specific, as the early clinical experience with lapatinib, a dual tyrosine kinase inhibitor of the EGFR and ErbB2 receptors, suggests that it may produce less cardiotoxicity compared with trastuzumab; however, of note, only a few trials with lapatinib exist. Interestingly, the newer antibody pertuzumab also has very recently been reported to decrease EF,[5] in line with our recent studies on mice.[6]

Here we analyse clinical and pathophysiological aspects of trastuzumab cardiotoxicity, and review and discuss recent findings on

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the role of early, sensitive markers of cardiac dysfunction, to predict trastuzumab cardiomyopathy before EF is reduced. Also, we propose recommended monitoring algorithms for management of patients with such cardiomyopathy.

ErbB2 and the myocardium

The mechanisms of trastuzumab cardiotoxicity are not clear yet, but differ from those of anthracyclines: in particular, trastuzumab does not seem to cause myocyte loss. In patients with trastuzumab cardiac dysfunction, myocytes appear histologically normal; changes may be seen only by using electron microscopy, in keeping with a reversible cardiomyopathy.[7] This has led to the classification of type II cardiotoxicity,[8] as opposed to the irreversible changes associated with anthracyclines (type I). Unlike anthracycline toxicity, it has been shown that trastuzumab cardiotoxicity is not dose dependent, is reversible upon therapy withdrawal, and the drug can be safely re-administered after recovery of EF. In type I cardiotoxicity, the earliest damage is myofibrillar disorganization, likely to progress into myocyte apoptosis and necrosis. When HF occurs, the clinical picture may stabilize, but the damage appears to be permanent and irreversible. Disease relapse after months or years can be correlated to sequential cardiac stress.[9] In contrast, in type II cardiotoxicity, EF is likely to recovery and there is evidence of relatively safe re-administration at treatment resumption after discontinuation. Unlike anthracyclines, there is a low likelihood of HF induced by sequential stress.[8]

The pathophysiological mechanisms underlying trastuzumab cardiotoxicity are not completely clear.[10] Neuregulin-1, a member of the EGF-like growth factors family, binds to ErbB3 and ErbB4, leading to heterodimerization and transphosphorylation of ErbB2, and activation of cardioprotection through ERK1/2 and PI3K/AKT signalling in animals and humans.[1] In animal models it has been observed that the ErbB2 signal is important for embryonic heart development and for protection from cardiotoxins.[11] Mice with cardiac ErbB2 gene deletion developed signs of dilated cardiomyopathy, and their cardiomyocytes showed increased susceptibility to cell death induced by anthracyclines.[12] Also, ErbB2 serum levels are increased in patients with chronic HF not correlated to anthracycline toxicity;[13] these levels correlate inversely with LV function, but ErbB2's role in cardiac pathophysiology is not well clarified.

There is evidence that trastuzumab cardiotoxicity is mediated through the binding of trastuzumab to the extracellular domain of ErbB2 on cardiomyocytes, blocking ErbB2–ErbB4 signalling, thus disabling the myocardial cell-protective, growth-promoting pathway.[14] The ErbB2 pathway is required for cell survival and continuing function, and seems to be stimulated when the myocardium faces adverse haemodynamics or other stress, such as anthracycline therapies.[15] Withdrawal of trastuzumab allows return of function of the pathway and reversal of EF decline, in contrast to the permanent myocyte dysfunction induced by anthracyclines. This proposed mechanism is consistent with the increase in cardiac effects when trastuzumab is used in association with anthracyclines: the damage caused by anthracyclines is increased or uncovered by trastuzumab. Once the repair mechanisms for ErbB2 are blocked, the oxidative damage induced by anthracyclines is free to progress.[16] Indeed, experimental studies have shown that neuregulin-1 modulates doxorubicin damage in rat cardiomyocytes.[17,18] (*Figure 1*)

Breast cancer treatment with anthracyclines and trastuzumab: findings from clinical trials

A type II drug (trastuzumab) may exacerbate the damage caused by a type I agent (doxorubicin) by interfering with homeostatic mechanisms and survival pathways that mediate myocyte recovery[16] (*Figure 2*). De Korte *et al.*[19] showed that indium-111-labelled trastuzumab scintigraphy identified ErbB2 overexpression in 50% of patients immediately after treatment with anthracyclines. They concluded that indium-111-labelled trastuzumab scintigraphy, performed immediately after anthracyclines and before adjuvant trastuzumab, allowed the identification of patients susceptible to trastuzumab toxicity and could be useful in deciding to postpone the initiation of trastuzumab until normalization of ErbB2 expression.

An extensive review[20] on six phase III studies, involving 1219 women with metastatic breast cancer, highlighted that in patients treated with trastuzumab alone the incidence of systolic dysfunction occurred in 3–7% of cases; such a percentage was significantly higher when trastuzumab was associated with anthracyclines and cyclophosphamide (27%) or with paclitaxel (13%). The incidence of severe HF [New York Heart Association (NYHA) grades III–IV] in the association of trastuzumab with anthracyclines was markedly higher (16%) than in the association with other chemotherapeutic drugs. A total of 83 patients experienced symptomatic HF; 79% of them, treated with pharmacological therapy for HF, showed EF recovery and improvement of clinical symptoms.

These data led to the recommendation of avoiding concomitant employment of anthracyclines and trastuzumab. A lower exposure of the myocardium to anthracyclines can be accomplished by decreasing their total administered dose or by adopting liposomal anthracyclines: since lipid particles contain the chemotherapeutic agents, they allow a greater spread in the tumour, through the fenestrated structure of capillary endothelium in pathological tissues, and a less extensive spread in myocardium. Therapeutic association regimens of trastuzumab with liposomal anthracyclines did not have a significant increase in cardiotoxicity in comparison with trastuzumab alone.[21,22]

On the basis of metastatic disease, where an increase in cardiac toxicity has been ascribed to the concomitant association of anthracyclines and trastuzumab, adjuvant trials provide treatment schedules with sequential use of anthracyclines and trastuzumab, thereby avoiding concomitant treatment. In particular, trastuzumab cardiotoxicity is reduced if its use following anthracycline is delayed[23] (*Figure 3*). In the HERA trial, in which 90 days elapsed between the end of chemotherapy and the start of trastuzumab, the rate of HF was 0.6% and that of systolic dysfunction 3%,[24] lower than in the other trials in which trastuzumab was administered with or shortly after anthracyclines. For instance, HF rates reached 3.6% in the NSABP B-31 trial,[25] while the incidence of systolic dysfunction reached 16%. Obvious differences exist in

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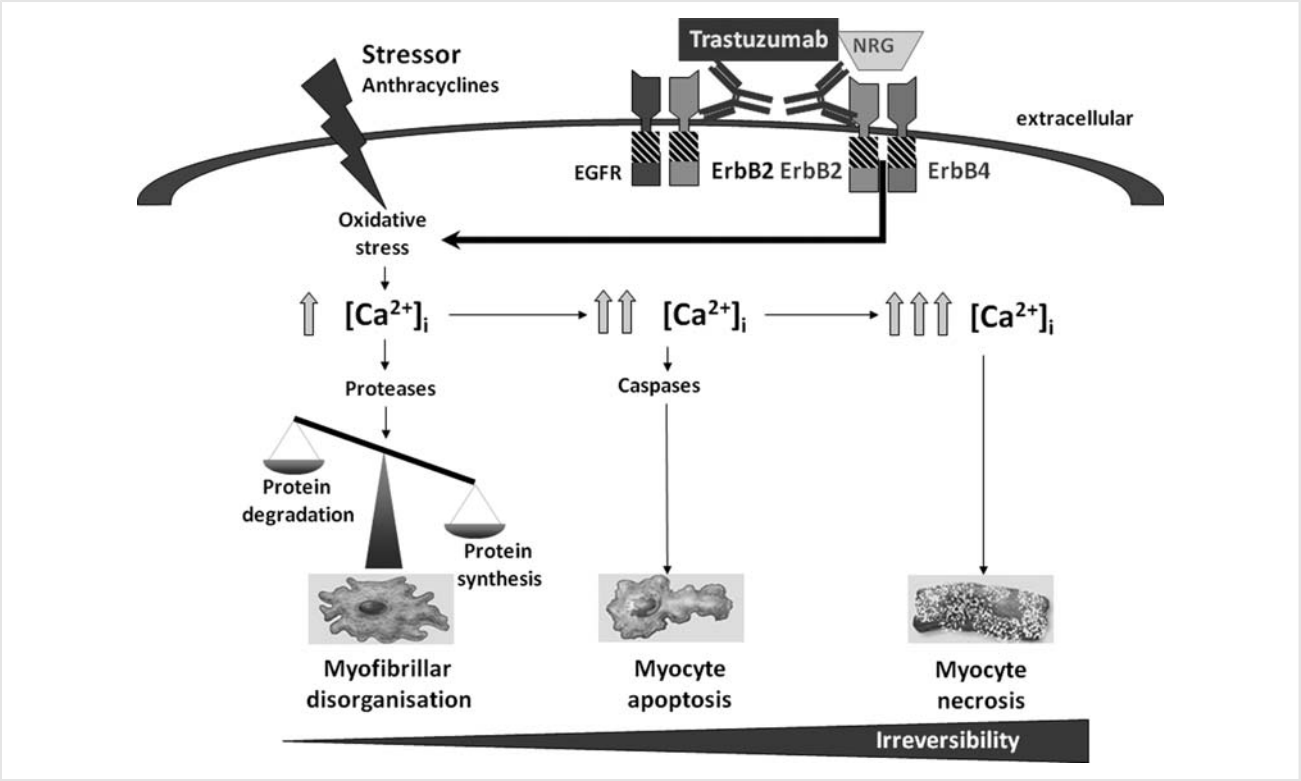

Figure 1 Intracellular interplay between anthracyclines and trastuzumab in cardiac damage.[17,18] NRG, neuregulin.

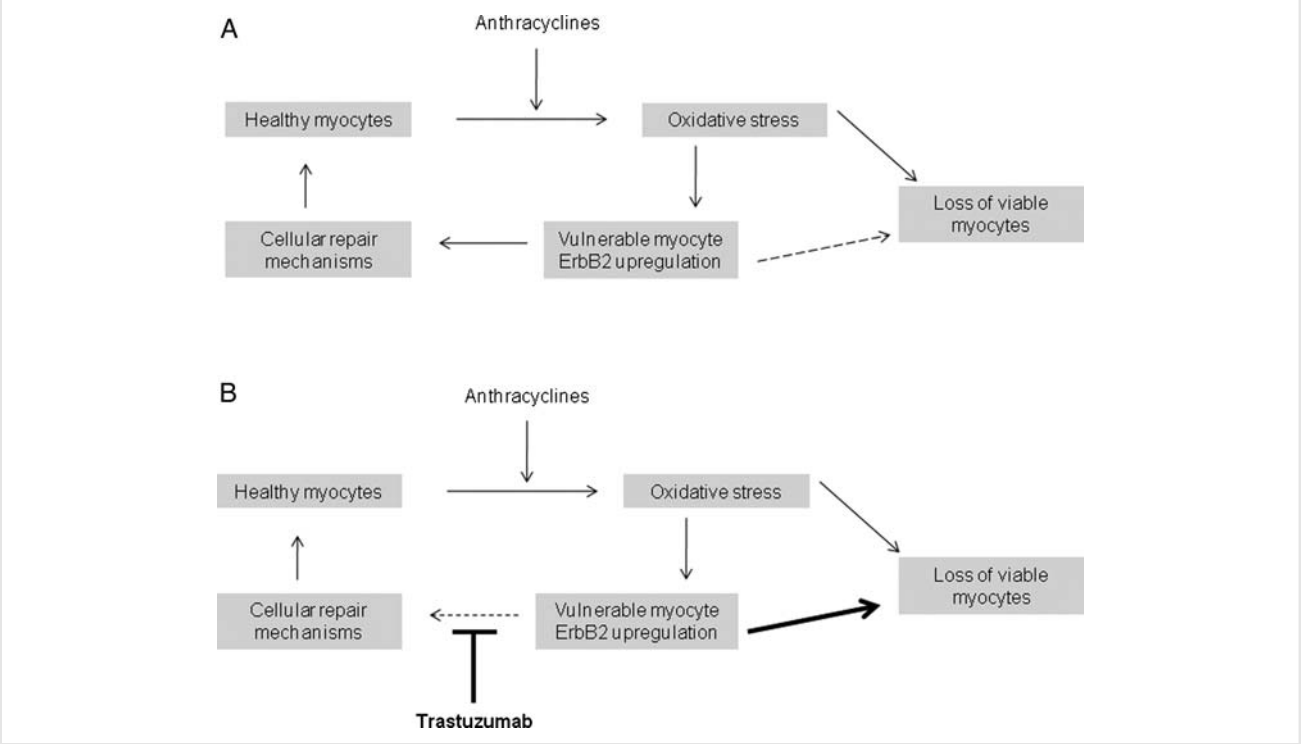

Figure 2 Myocyte injury after anthracycline administration. Cell death is preceded by a period of vulnerability during which cell repair may occur. The addition of trastuzumab (bold) inhibits cell repair, leading to loss of cardiomyocytes (modified from Ewer and Ewer[16]).

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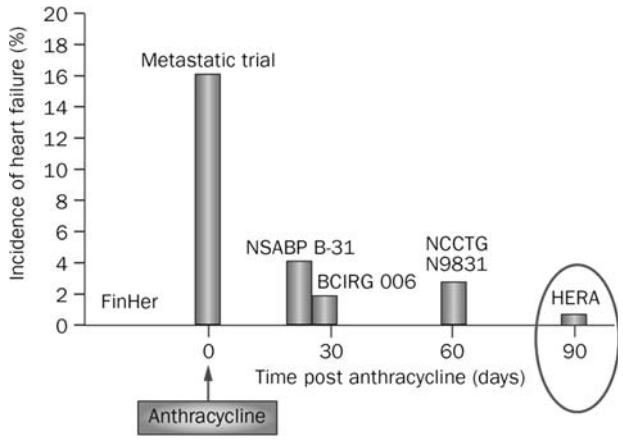

Figure 3 Incidence of heart failure following therapy with doxorubicin and trastuzumab. Incidence of New York Heart Association III or IV heart failure on the basis of the interval of time between the completion of doxorubicin and trastuzumab administration, as reported in the major adjuvant trials. In a pivotal metastatic trial, the drugs were given concomitantly, and, in the FinHer trial, trastuzumab administration preceded anthracycline. The HERA trial (circle) had a lower incidence of heart failure: trastuzumab was administered later than in the other trials (modified from Ewer and Ewer[23]).

the inclusion criteria and protocols across such adjuvant trials (see Supplementary material online, *Table S1*); nevertheless the trend supports the hypothesis that timing might be important in the apparent synergy of anthracyclines and trastuzumab as a cause of HF.[23] Notably, patients in the HERA and B31 trials were relatively young, with a median age of 49 and 51 years, respectively, so the 'real world' problem might be even larger.[1] In fact, established risk factors for trastuzumab-related cardiotoxicity include: age >50 years, exposure to anthracyclines (worse with higher cumulative doses) and taxanes, antihypertensive medications, borderline EF, and increased body mass index.[26]

Assessing and monitoring cardiac risk

On the basis of these risk factors, a detailed clinical assessment is essential in identifying individuals at risk for cardiovascular side effects. A careful assessment of current functional capacity, volume status, and blood pressure is required. Cardiac evaluation in patients at particular risk of cardiotoxicity should be carried out in conjunction with the oncologist, so that the choice of therapy may be optimized. Besides the above-described risk factors, other factors that could contribute to cardiac stress should not be ignored. Risk factors should be modified or reduced by treating hypertension, normalizing lipids, and encouraging weight reduction and smoking cessation. Early identification of patients at risk for cardiotoxic effects is a primary goal for both cardiologists and oncologists. It could allow a more personalized evaluation of the anticancer treatments and/or the use of cardioprotective agents, and a closer monitoring of cardiac function and an early introduction of cardiac therapy.

Plasma markers such as brain natriuretic peptide (BNP; an index of elevated filling pressures) and troponin I (TnI; an index of cardiomyocyte damage) may be used to identify the risk of developing cardiac dysfunction during treatment. The clinical utility of measuring troponin and BNP to detect cardiotoxicity has already been demonstrated in patients receiving high-dose chemotherapy.[27] The NCCTG N9831 adjuvant trastuzumab trial included the measurement of eight cardiac biomarkers, including Tn and BNP, and an assessment of their relationship with EF.[28] The investigators concluded that the baseline measurements of BNP and Tn levels, and serial measurements of BNP, have potential for use in both predicting and detecting cardiac dysfunction in this setting. Ongoing clinical trials have been designed to identify any sensitive/specific markers that could be used to aid the prevention or treatment of cardiac dysfunction at the earliest possible time (NCT00968682 and NCT01022086, clinicaltrials.gov).

A recent study by Cardinale *et al.*[29] identified a subgroup of patients treated with trastuzumab who exhibit elevations in serum TnI who were more likely to develop trastuzumab cardiotoxicity and less likely to recover, even when treated for cardiac dysfunction. Indeed, prior anthracyclines was a significant risk factor, and the cumulative anthracycline dose was significantly higher in that subgroup. Also, elevation of TnI was observed exclusively in patients with prior anthracyclines, and was also found in seven patients prior to trastuzumab, despite normal EF, suggesting ongoing anthracycline-mediated myocyte damage that would have otherwise gone unrecognized.[16] All in all, it appeared that TnI leak was not a 'pure' marker of trastuzumab cardiotoxicity. Rather, trastuzumab exerted a modulating effect on the vunerable myocyte, previously damaged by anthracyclines (a cause of TnI leak).

To date, the optimal method, duration, and frequency of cardiac monitoring for patients receiving trastuzumab have not yet been established. Baseline EF measured by echocardiography or multiple gated acquisition (MUGA) scanning should be determined immediately before initiation of trastuzumab. Since these techniques are not exactly comparable and there is some

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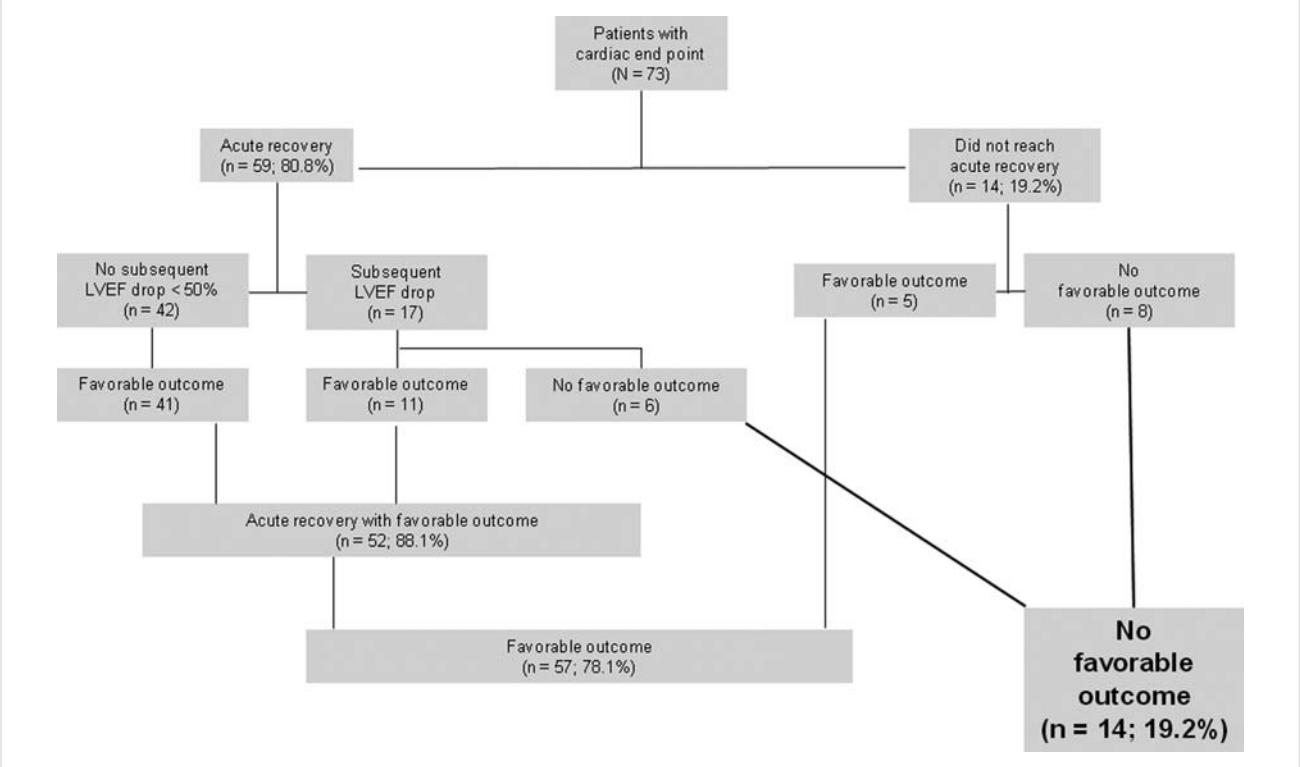

Figure 4 Longer term assessment for patients with any type of cardiac endpoint in the trastuzumab group in the HERA trial: there are still 19.2% of patients (bold) who do not have a favourable outcome (modified from Procter *et al.*[32]). LVEF, left ventricular ejection fraction.

interinstitutional variation, serial studies should be performed with the same modality, in the same facility. Echocardiography can provide additional information (tissue Doppler, diastolic function) and may be more sensitive in detecting early or asymptomatic cardiac dysfunction. Recommendations for echo monitoring were published in 2006:[30] during trastuzumab treatment, EF should be measured at baseline, every 3 months, and upon completion of treatment. Although the prescribing information states that EF should be monitored every 6 months for 2 years post-completion of adjuvant treatment, there is no published evidence that EF deteriorates after treatment completion in patients who had no reduction during therapy. Updated UK national Cancer Research Institute recommendations were published in 2009,[31] based on the protocol for the HERA trial in the online appendix of Suter *et al.*[24]

One of the problems that were evident from the HERA trial is that 19% of patients did not recover after trastuzumab and did not have a favourable outcome[32] (*Figure 4*). Early identification (before changes in EF occur) of those patients in order to optimize monitoring and management is a very actual challenge. The normal heart has tremendous recruitable contractile ability, and for the LV to exhibit a decrease in EF the myocardium must have undergone sufficient damage to exceed its ability to compensate.[33] Thus, decreased EF after treatment is a marker for advanced myocyte damage; it is an imperfect marker influenced by many cardiac stressors and volume status on one hand, and significant interpretative variation on the other.

New echocardiographic indexes

Traditional echocardiographic indexes of cardiac function (fractional shortening, EF) may underestimate subtle changes that occur with trastuzumab. In the last years, new echocardiographic studies have been published, in an attempt to evaluate whether alternative indices of systolic function would be useful to predict trastuzumab cardiotoxicity.

A 2010 study[34] demonstrated that for serial monitoring of EF in patients with breast cancer receiving adjuvant trastuzumab after treatment with anthracyclines, real-time three-dimensional transthoracic echocardiography yields measurements comparable with those of conventional MUGA, using cardiac magnetic resonance as the gold standard. The same group had demonstrated that tissue velocity imaging (TVI) results were abnormal in mice receiving either doxorubicin or trastuzumab + doxorubicin as early as 24 h after treatment, and were predictive of ensuing LV systolic dysfunction and increased mortality.[35] Very recently they[36] confirmed partial data from two earlier small clinical studies that evaluated the utility of myocardial deformation in the pre-clinical detection of trastuzumab cardiotoxicity.[37,38] In this 2011 study,[36] TVI and strain allowed for early detection of subclinical cardiac dysfunction before conventional echocardiography, in patients receiving adjuvant trastuzumab. Of note, there was no change in plasma biomarkers (TnT, C-reactive protein, and BNP). In their analysis, the authors did not include TnI levels (we have already discussed the utility of TnI in a previous section), which Sawaya *et al.*[39]

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showed to predict the development of cardiotoxicity in patients treated with anthracyclines and trastuzumab, along with longitudinal strain.

Interestingly, the study of Fallah-Rad[36] seems to re-evaluate another important aspect of trastuzumab cardiotoxicity. In line with our data on speckle tracking detection of early LV dysfunction in mice treated with anti-ErbB2 agents, with increased cardiac fibrosis at histology,[6] they show that in trastuzumab cardiomyopathy there is evidence of subepicardial linear delayed enhancement in the LV lateral wall, with progressive decline in EF, despite discontinuation of trastuzumab and initiation of HF therapy. These data suggest that the paradigm of reversibility of trastuzumab cardiomyopathy needs to be re-evaluated.

Management

Use of the Suter algorithm[24] for monitoring cardiac function in trastuzumab-treated patients has resulted in a low incidence of clinical HF. Still, such an algorithm has limitations that need to be integrated, since it requires the determination of EF with a precision and reproducibility that cannot often be achieved in routine clinical practice; does not consider the normal ranges for EF of different imaging modalities, in different institutions; requires high frequency of monitoring, compared with the risk of HF; does not specify a pre-chemotherapy EF assessment as a baseline for evaluation of cytotoxic drug-related cardiac damage and dysfunction; does not provide guidance for cardiac health optimization before trastuzumab initiation; and does not make recommendations on the treatment of patients with systolic dysfunction other than trastuzumab interruption: therefore, it does not facilitate successful rechallenge with trastuzumab.[31]

Instead, assessment of baseline EF before chemotherapy in all patients informs the choice of cytotoxic regimen: patients with low or borderline EF may benefit from a non-anthracycline-containing regimen.[31] Before starting trastuzumab, careful evaluation of medical history and baseline EF, and correction of risk factors [hypertension treatment with angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, or angiotensin receptor blockers (ARBs)] are needed. Patients who are not eligible to commence trastuzumab should be started on an ACE inhibitors and referred to a cardiologist[27] (*Table 1*). Repeat assessment of cardiac function should occur after 3 months. Of notice, studies are ongoing that investigate the role of prevention of the development of declines in EF during treatment with trastuzumab, such as the ongoing study with candesartan (NCT00459771, clinicaltrials.gov).

Upon intiation of trastuzumab, if a patient's EF declines according to Suter's limits (EF $\leq$ 44, or EF 45–49 and $\geq$ 10 from baseline[24]), trastuzumab should be held for 4 weeks. Trastuzumab cardiotoxicity treatment does not differ from the treatment of HF patients, as shown in guidelines.[40] The target dose of HF drugs should be achieved by: increasing the dose every 1–2 weeks; monitoring renal function and electrolytes every week or two; and maintaining a constant blood pressure; and trying to reach the target dose within 4 weeks. In contrast to the traditional approach of guidelines to HF patients, the therapeutic target should be achieved faster in order to re-administer trastuzumab.[41] Therapy with diuretics should be started only when normal

Table 1 Prevention, monitoring, and management of cardiac events in patients undergoing cytotoxic chemotherapy

Treatment phase	Patient profile	Management strategy
Before trastuzumab-based therapy	**A. No cardiac history or risk factors with normal EF**	**Treat and monitor EF every 3 months**
	B. Cardiac history and/or risk factors with normal EF	**Treat. Ask of symptoms and perform PE before each cycle. Measure Tn level after therapy and BNP level before next cycle**
	C. Decreased EF	**Treat low EF (ACE-I or ARB, BB) and remeasure. Individual decisions about initiating trastuzumab**
During trastuzumab-based therapy	First decrease in EF	Trastuzumab holiday for 1 month A. Treat HF and remeasure 1. Return to baseline. Restart trastuzumab 2. If EF remains low: intensify HF treatment and remeasure. 3. If EF remains low: individual decisions A. Stop trastuzumab B. If trastuzumab only option: 'Holiday' and maximize HF therapy
	Second decrease in EF	
Completion of trastuzumab-based therapy	No change in EF and no symptoms during treatment	No monitoring post-treatment completion
	EF decreased or symptoms	Continue HF treatment. Monitor according to clinical practice for HF

In bold is management of cardiac dysfunction before trastuzumab, a major integration to Suter's algorithm (modified from Carver [27]).
ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; BNP, brain natriuretic peptide; EF, ejection fraction; HF, heart failure; PE, physical examination; Tn, troponin.
The ejection fraction is considered to be reduced when it declines according to Suter's limits (EF $\leq$ 44, or EF 45–49 and $\geq$ 10 from baseline[24]).

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volume status has to be restored, i.e. in patients with clinical evidence of salt and water retention. Sustained or recurrent cardiac arrhythmia should be treated with adequate antiarrhythmic therapy and correction of possible precipitating factors including sepsis and electrolyte imbalance.

After dose titration, EF should be remeasured and, if it returns to baseline, HF medication should be continued, and trastuzumab can be restarted. Most patients have a return of EF to baseline within 1–2 months. In the case of persistent low EF or in symptomatic patients, aldosterone inhibitors, an ARB, and digoxin should be administered. If EF returns to normal, trastuzumab may be restarted. If EF stays low, individual decisions are made, based on patients' clinical conditions and prognosis.

If the patient is receiving trastuzumab and the EF declines a second time while receiving a stable HF treatment, it is recommended to discontinue trastuzumab permanently.

In metastatic breast cancer, trastuzumab treatment has imminent life-extending potential; therefore, the benefits of treatment may outweigh the risks of cardiac dysfunction, and every attempt to allow the use of trastuzumab should be made, with the conjunct work of oncologists and cardiologists. According to Carver,[27] patients with asymptomatic HF may continue to receive trastuzumab unless their EF has decreased $>$ 20 percentage points to $<$ 40%, or their EF is $<$30%. In these cases, trastuzumab is held for at least one cycle, titrating to the maximal tolerated doses of HF medical therapy, and EF is remeasured. If it improves to $>$44%, trastuzumab may be restarted. In patients with symptomatic HF, or if EF is $<$ 30%, trastuzumab should be discontinued permanently.

Concluding remarks

The percentage of clinically overt trastuzumab HF is low; nevertheless, the incidence of asymptomatic LV dysfunction is higher. HF due to trastuzumab is precocious ($<$ 6–12 months), not dose dependent, and seems to be reversible in most cases. Once trastuzumab is discontinued, standard HF therapy is efficacious. ACE inhibitors, ARBs, and beta-blockers can be used in patients with early signs of cardiotoxicity. The balance between optimal antitumour efficacy and prevention/reduction of the development of cancer treatment complications is very difficult, and the risk of prevention of complications should be viewed in the light of a possible less optimal anticancer treatment. This has to be kept in mind when designing a cardioprotective approach, without dampening anticancer drug efficacy. Experimental animal models with breast cancer xenografts are particularly useful in this setting, as we are presently examining in our laboratory.

The prognostic meaning of TVI and speckle tracking echocardiography, Tn dosage, and BNP is an active and promising research area, as is the development of less cardiotoxic ErbB2 inhibitors.[6,42,43]

It has to be considered that follow-up trials with trastuzumab are relatively short, while HF is a progressive syndrome: less stringent selection, management, and follow-up may be possible outside trials.

Meanwhile, we recommend continuing to assess risks and benefits on an individual basis. We believe that the optimal treatment of patients with ErbB2 + breast cancer and trastuzumab cardiomyopathy is achieved through close cooperation between oncologists and cardiologists. We agree with Jones[31] that before starting trastuzumab, cardiologists should evaluate oncology patients for EF and general assessment of cardiovascular conditions and risks factors, and report any abnormality to oncologists: the final decision should be made by the cardio-oncological team on the basis of cardiological and oncological assessments. A close cardiological monitoring and early cardiovascular treatment will be helpful to prevent patients who really need trastuzumb for survival from discontinuing this drug, since we have and are developing tools to detect early cardiac effects concomitant with the infusion of the drug. Nevertheless, since ErbB2 blockade is a relatively 'young' therapeutic approach, we do not have very long follow-ups, and we should always consider the possibility of late cardiotoxicity due to previous anthracyclines.

Supplementary material

Supplementary material is available at *European Journal of Heart Failure* online.

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