HER-2 positive breast cancer and trastuzumab: lessons learnt by heart

Outhoff K, MBChB, MFPM
Department of Pharmacology, University of Pretoria, Pretoria, South Africa
Correspondence to: Dr Kim Outhoff, e-mail: kim.outhoff@up.ac.za
Keywords: HER-2 positive breast cancer; trastuzumab; cardiotoxicity

ABSTRACT
Women treated with trastuzumab have an increased risk for developing cardiac problems, particularly if they receive prior or concurrent anthracyclines. Left ventricular dysfunction associated with trastuzumab treatment may progress to severe New York Heart Association (NYHA) class III/IV heart failure which carries its own chronic disability and mortality. Whilst it would appear that the cardiac dysfunction is partially reversible and responds to standard medication, its natural course is currently unknown and longer term data are required. Preclinical studies have attempted to elucidate trastuzumab's mechanism of cardiotoxity and this is an area of innovative research. Myocardial HER-2 receptors are crucial for embryonic cardiac development and for maintaining adult ventricular structure and function. It is thought that sequential stress mechanisms may contribute to the pathogenesis of cardiac dysfunction. The challenge remains to identify the risks and to tailor trastuzumab treatment for each patient, to conscientiously monitor cardiac function and to institute appropriate measures if necessary, in order to ensure that HER-2 positive breast cancer patients receive the best possible care.

℗ Peer reviewed (Submitted: 2009-07-31, Accepted: 2009-10-23) **Southern Afr J Gynae Oncol 2009;1(2):52-27**

Introduction

Every once in a while an innovative drug is pushed to market because it has enormous potential to revolutionise the treatment of a life-threatening disease. This has certainly been true of the monoclonal antibody, trastuzumab, which has lived up to its promise of excellent efficacy – with far superior acute tolerability compared to standard chemotherapy – in the treatment of HER-2 positive breast cancer. Over the past ten years, it has captured the imagination of patients, and the medical barriers to its use have tumbled.

An unanticipated problem started to emerge in the early metastatic breast cancer registration trials, however, which somewhat tempered the initial euphoria: trastuzumab showed the potential to cause serious cardiotoxicity.[1] The extent of the problem could only be fully appreciated once further prospective trials in the adjuvant and neoadjuvant settings as well as wider clinical usage provided more evidence.

Cardiac dysfunction has continued to blemish trastuzumab's reputation, being its single most significant limiting factor and precluding its use in approximately 10% of HER-2 positive breast cancer patients.[2]

Although cardiac toxicity associated with trastuzumab may manifest as hypertension, arrhythmias or valve abnormalities, it is most commonly associated with declines in left ventricular function, both asymptomatic and symptomatic, which may ultimately progress to New York Heart Association (NYHA) class III/IV heart failure or even death.[2]

Left ventricular (LV) myocardial dysfunction begins when the myocardium is injured or stressed and it is generally progressive, even in the absence of further insults to the heart. Over time, with cardiac remodelling, the chamber becomes less ovoid and more spherical; compensatory measures include dilatation and hypertrophy. These changes eventually increase diastolic stiffness and wall tension while haemodynamic stresses on the walls of the heart increase and mechanical performance decreases. A decrease in left ventricular ejection fraction (LVEF) occurs when the tremendous compensatory ability of the myocardium has already been impaired; therefore, a decline in LVEF is actually a marker of advanced damage.[3]

Heart failure may be the result of many cardiac disorders, but most patients experience symptoms because of an impairment of LV myocardial function. The abnormal heart function results in the clinical symptoms and signs of low cardiac output including dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea, fatigue, weakness, exercise intolerance, dependent oedema, cough, weight gain, abdominal distension, nocturia and cool extremities.

The NYHA functional classification is simple and describes four grades of heart failure[4] (Table I).

Table I: The New York Heart Association functional classification of heart failure

I no symptoms
II symptoms with ordinary activity
III symptoms with less than ordinary activity
IV symptoms at rest or with minimal activity

Long-term survival of women with heart failure (6 years, 33%) approximates that of women with breast cancer with distant metastases (5 years, 22%), yet it is far worse than that of women with breast cancer and regional metastases (5 years, 97%). Furthermore, 33% of women with heart failure die within two years of the initial diagnosis.[5] Thus, the risk-benefit ratio for every patient and at every stage of the disease requires conscientious consideration both prior to initiating, and during trastuzumab treatment.

Given the enormous therapeutic benefit of trastuzumab, issues to be addressed include the following:

- Is pre-existing cardiac dysfunction, especially if it is asymptomatic, sufficient reason to withhold the drug?
- Are the classic risk factors for cardiac disease, such as hypertension, diabetes and family history important predictors for cardiac toxicity and are there ways to avoid or minimise trastuzumab-related cardiac dysfunction?
- How should patients be monitored for cardiac effects?
- What is the natural history of trastuzumab-associated cardiac dysfunction?
- Is it possible that the dysfunction will normalise in the absence of medication and if not, what are the treatments for asymptomatic and symptomatic left ventricular dysfunction and heart failure?
- Is it safe to re-institute trastuzumab if a patient has developed cardiac dysfunction whilst receiving it previously?
- What is the mechanism of trastuzumab's toxicity?
- Finally, will the incidence of heart failure increase with longer follow up?

Meticulous tracking of the potential long-term cardiotoxicity of trastuzumab is necessary if we are to ensure that patients, particularly younger survivors of breast cancer, receive appropriate and optimal treatment.

Incidence of trastuzumab-associated cardiotoxicity

Because clinical trials in cancer are usually powered to assess endpoints such as disease-free and overall survival, rather than the toxicities of the intervention, trial data are only approximations of risk and may thus underestimate the true likelihood of an adverse effect.[6]

Metastatic breast cancer

According to the prescribing information, there is a 4–6 fold increase in the incidence of symptomatic myocardial dysfunction amongst patients receiving trastuzumab as a single agent or in combination therapy compared to those not receiving trastuzumab at all. The risk of cardiac dysfunction with trastuzumab alone ranges from 2–7%.

The reported rate for trastuzumab-associated cardiotoxicity in the absence of anthracyclines is 3% (2% NYHA class III/IV). This particular rate increases to 5% (4% NYHA class III/IV) when an anthracycline is given prior to trastuzumab, and is highest at 27% (16% NYHA class III/IV) when trastuzumab is given concurrently with an anthracycline compared to 8% when anthracyclines are administered alone.[7]

When given concomitantly with paclitaxel after anthracycline exposure, 13% of trastuzumab patients develop cardiac dysfunction (2% NYHA class III/IV) versus 1% on paclitaxel alone.[1] When co-administered with the alternative taxane, docetaxel, with or without capecitabine, 18% (1% NYHA class III/IV) develop some form of cardiotoxicity (usually asymptomatic decline in LVEF) compared with 8% on docetaxel monotherapy.[8]

Studies using the combination of vinorelbine and trastuzumab have reported asymptomatic declines in LVEF of 8% (0% NYHA class III/IV).[9]

Both trastuzumab-gemcitabine[10] and trastuzumab-capecitabine[11] therapy following anthracycline-taxane regimens report no increased risk for heart failure.

Other novel approaches such as cyclophoshamide, epirubicin and trastuzumab suggest an asymptomatic decline in LVEF in 6% of patients (0% NYHA class III/IV).[12] Similarly, the combination of liposomal doxorubicin-paclitaxel-trastruzumab does not appear to be associated with undue cardiotoxicity.[13]

Early breast cancer – adjuvant therapy

The synergistic cardiotoxicity of concurrent treatment with anthracyclines and trastuzumab led to their sequential use in the adjuvant early breast cancer setting and patients were prospectively monitored for cardiac effects. Lower rates for NYHA class III or IV heart failure were thus reported, ranging from 0.5–4% in the four largest trials (NSABP B-31, NCCTG 9831, HERA, BCIRG 006) where trastuzumab was used in combination with a variety of drugs and usually after anthracycline-based therapy[14–17] (Table II).

Based on the data from the NSABP B-31 and N9831 adjuvant trials, for every 30 women treated with trastuzumab, one will develop a cardiac event defined as cardiac death or severe NYHA class III/IV heart failure at three years. In addition, one in five women treated with trastuzumab will have some form of cardiac dysfunction requiring discontinuation of treatment – approximately 15% of patients were unable to complete the planned one year duration of trastuzumab because of asymptomatic declines in LVEF. On a more optimistic note, the nine week FinHER study in which patients received either vinorelbine or docetaxel with trastuzumab prior to epirubicin-based chemotherapy showed no cardiotoxicity whatsoever.[18]

Similarly, in the neoadjuvant setting, the incidence of asymptomatic decreases in left ventricular function approximated 1% when trastuzumab was administered with docetaxel and carboplatin, prior to surgery or standard chemotherapy.[19]

The latest figures reveal a decline in severe cardiotoxicity to 1%, possibly due to more stringent cardiac exclusion criteria, sequential dosing after anthracyclines rather than concurrently, increased vigilance including monitoring of patients for a reduced LVEF, strict study-stopping rules and a broader familiarity with the early signs of heart failure.

Furthermore, the reported rate of partial improvement of LV function on cessation of drug and with standard medical therapy is 79% (median time of one and a half months to improvement), leading some to infer that the cardiotoxicity is reversible. It is also possible that cardiac dysfunction may improve spontaneously during active treatment with trastuzumab.[20]

The long-term data extends to four years only. It is impossible to project the cumulative 10-year risk of a cardiac event for patients treated with adjuvant tastuzumab.

Mechanism of cardiotoxicity

Chemotherapy-related cardiac dysfunction (CRCD Type I) has been a concern since the early 1970s, when anthracyclines were first shown to be associated with cumulative, exponential, dose-related, free radical-induced oxidative stress (peroxidation) to myocyte membranes with subsequent influx of intracellular calcium, cell death and irreversible damage. Whilst it is believed that cardiac damage takes place from the earliest administration of the drug, heart failure may take months or years to develop. The pre-exposed myocardium remains more susceptible to subsequent cardiovascular stressors, including hypertension and the effects of trastuzumab-related cardiotoxicity.

Trastuzumab-related cardiotoxicity (Type II CRCD) does not fit this model: the mechanisms and clinical effects are distinctly different. It is expressed in a broad range of severity when it does occur, is not dose related and is not associated with identifiable ultra structural abnormalities. It appears to be somewhat reversible, especially if anthracyclines are excluded entirely from the treatment regimen.[7]

The cellular and biochemical mechanisms of trastuzumab-associated cardiotoxicity are unclear and relatively few molecular modifiers of human heart failure have been identified.

Preclinical studies of genetically manipulated mice and of cells isolated from hearts have shown that HER-2 receptors are present in the myocytes of ventricular trabeculae (in a pattern suggesting their presence throughout the sarcolemmal membrane, extending to the T-tubule system) and that the physiological effects of the signalling pathways involving HER-2

Table II: Estimated cardiotoxicity associated with trastuzumab in the adjuvant early breast cancer trials

Trial and duration	Regimen	Asymptomatic declines in LVEF	Severe NYHA III/IV	Discontinuation due to trastuzumab card iotoxicity
NSABP B-31[14] 1 year	AC > T* AC > T**H**	0.8% 14%	0.8% **4.1%**	18%
NCCTG 9831[15] 1 year	AC > T* AC > T**H** AC > T> **H**	17% 34% 14.2%	0.3% **3.5%** **2.5%**	19%
HERA[16] 1 year	Any chemo Any chemo> **H**	0.5% 3%	0% **0.6%**	4.3%
BCIRG 006[17] 1 year	AC > T** AC > T**H** TC**H**	10% 18% 8.6%	0.3% **1.6%** **0.4%**	Not reported
FinHER[18] 9 weeks	**T or V > FEC T or V + **H** > FEC	0.3% 0%	0.3% **0%**	0%
A = anthracycline C = cyclophosphamide H = trastuzumab T = taxane: *paclitaxel **docetaxel	TCH= taxane, carboplatin-trastuzumab	V= vinorelbine		

(erbB2) and its other family members (erbB1, erbB3 and erbB4) and their ligands (particularly the myocardial protective growth factor, Nrg-1) are critical for both embryonic cardiac development[21] and for the postnatal heart to maintain its ventricular structure and function.[22]

HER-2 signalling pathways appear to regulate a number of processes including cell growth, survival and protection from apoptosis, sarcomere synthesis, organisation and stability, myocyte-matrix coupling, cellular adaptations to oxidative or metabolic stress in the myocardium, angiogenesis and the counteraction of undue sympathetic tone.[23]

In embryonic mice, disruption of HER-2 pathways causes death due to lack of ventricular trabeculation.[21] In adult mice deficient in HER-2 protein, the induction of cardiac stress pathways by haemodynamic overload promotes the onset of left ventricular dysfunction and a dilated cardiomyopathy. Moreover, in these mice, isolated myocytes show increased susceptibility to doxorubicin-induced cell death, suggesting a critical role of HER-2 for cardioprotection exemplified by the ability of myocytes to withstand stress conditions.[24]

It has thus been postulated that HER-2 receptors and their downstream signalling pathways ordinarily blunt the effects of cardiac stress signals, which are activated by anthracyclines and other cardiotoxic agents, ischaemia and increased cardiac load. Thus, disruption of HER-2 mediated pathways by trastuzsumab leads to a loss in survival cues which can subsequently lead to an irreversible loss of cardiac myocytes. In other words, trastuzumab's mechanism of cardiac toxicity is thought to be secondary to sequential stress mechanisms because the cardioprotective properties of the HER-2 pathway are diminished.[25] Removal of the antibody may allow the signalling pathway to recover.

Moreover, HER-2 signalling appears to be coupled to muscarinic cholinergic receptor activation, which balances sympathetic tone. If reduced HER-2 expression leads to reciprocal increases in sympathetic tone in the failing heart, this may promote progressive myocardial dysfunction.
The transition from compensated cardiac hypertrophy to heart failure is associated with a decrease in the expression of HER-2 and HER-4, raising the question of whether altered HER-signalling plays a role in the progression of heart failure.[23]

Unsuspected modifiers of cardiovascular disease will undoubtedly be uncovered, spurring a new round of basic research to identify the downstream targets that mediate trastuzumab's adverse effects on the heart.

Risk factors and preventive strategies

Cardiotoxicity of a drug depends on many different factors related to the drug itself (e.g. the dose administered during each session, the cumulative dose, the schedule of delivery, the route of administration, the combination of drugs given, the sequence of administration of these drugs, the duration and the interval between administration) and to the individual patient (e.g. age, previous cardiovascular disease, metabolic abnormalities, hypersensitivity to drugs given, previous radiation).[26]

The highest risk for trastuzumab cardiotoxicity is associated with anthracyclines, whether given sequentially (5%) or concurrently (27%), and furthermore, it would appear that the effects of trastuzumab and anthracyclines are synergistic i.e. super additive. Therefore, when anthracyclines are used with trastuzumab, sequential therapy is preferred. The risk of trastuzumab-associated contractile dysfunction appears to be lower in anthracycline-naïve patients.

Doxorubicin toxicity alone is exponentially dose-dependent and increases dramatically when cumulative doses exceed 400–450 mg/m^2. After a cumulative doxorubicin dose of 240 mg/m^2, asymptomatic

declines in LVEF are detected by prospective monitoring. After a cumulative dose of 400 mg/m^2, heart failure was estimated at 2% initially, but more recently at 5.1%.[27]

Strategies to prevent anthracycline-induced cardiomyopathy include limiting the total accumulative dose, infusional regimens rather than bolus administration, novel delivery systems such as (pegylated or non-pegylated) liposomal-encapsulated or nanoparticle-bound doxorubicin and use of doxorubicin analogues such as epirubicin (which at equimolar doses is less toxic because lower levels of secondary alcohol metabolites are produced).[27] In fact, omitting anthracyclines altogether may sometimes be appropriate. Increased survival in response to anthracyclines is seen among HER-2 positive patients that also coamplify topoisomerase II, but not in the patients with tumours that only express HER-2.[17] Molecular diagnostics holds promise in identifying patients who do not require anthracycline therapy. This remains to be proved prospectively.

The antioxidant, dexrazoxane, has not been clearly established as protective, although it does reduce troponin I release in children on anthracyclines. This drug is however, associated with myelosuppression and possibly leukaemia.

Although the cardiac drugs, carvedilol, enalapril and valsartan have shown cardioprotective effects with anthracyclines, it is unclear whether prophylactic use of these agents confers benefit in the trastuzumab setting.[27]

The FinHer study showed that minimising the duration of adjuvant trastuzumab to a short nine week course averts cardiac side-effects. In this trial, trastuzumab was given prior to epirubicin.[18]

Regarding the taxanes, it appears that a docetaxel-trastuzumab combination is less cardiotoxic than a paclitaxel-trastuzumab combination.[15,17]

The best known patient-related, independent predictors of trastuzumab-induced heart failure development include advanced age and an abnormal LVEF. Hypertension is classified as a near-significant predictor.[14] Other accepted risk factors are prior coronary artery disease and valvular dysfunction.[28]

By limiting enrolment to women with post chemotherapy LVEF of 55% or more, by employing strict exclusion criteria for cardiovascular disease and by giving trastuzumab after completion of chemotherapy, the HERA trial produced a very low heart failure rate of 0.5%.[16]

Monitoring

Prior to initiating trastuzumab therapy, all patients should undergo a thorough cardiac assessment which includes identification of risk factors, a thorough physical examination and a baseline measurement of LVEF, either by multigated acquisition/multigated radionucleotide angiography (MUGA) or echocardiography, in order to establish their baseline cardiac, and specifically, their left ventricular function.[2] Use of (biplane) Simpson's Rule method or 3-dimensional echocardiography, with contrast available for LV opacification, by an appropriately skilled echocardiographer is recommended as it can accurately measure diastolic function, haemodynamics, pericardial disease as well as valve function.[29]

Patients should be excluded from trastuzumab therapy if the cardiac risks such as a LVEF < 50%, outweigh the treatment benefits[28] (Table III).

Left ventricular function should be measured at three monthly intervals during treatment using the same measuring device, and the risk-benefit ratio should be re-evaluated. If new symptoms occur or if the ejection fraction declines by more than 10%, cessation of treatment may be required. The recently updated prescribing information advises the discontinuation of treatment in patients receiving adjuvant therapy and strong consideration of discontinuing trastuzumab in patients with metastatic breast cancer for clinically significant decreases in left ventricular function[2] (Table IV).

Trastuzumab dosing should be temporarily withheld for a minimum of four weeks if there is either a greater than 15% decrease in LVEF from baseline values or there is a greater than 9% decrease in LVEF compared to baseline levels and these levels are below the institutional limits of normal.

In this scenario, LVEF should be monitored at 4 weekly intervals. Trastuzumab may be reintroduced within four to eight weeks if LVEF returns to normal limits and the absolute decrease from baseline is < 16%.[2]

Although the long-term safety of continuation of or resumption of trastuzumab in the presence of overt trastuzumab-induced cardiac dysfunction has not been studied, experience from the Anderson Centre suggests that trastuzumab may be re-instituted in previously symptomatic patients whose cardiac function has sufficiently recovered in response to standard medical treatment. On rechallenge, 12% of these particular patients had a recurrence of LV dysfunction, whereas 88% did not.[20]

Trastuzumab should be permanently discontinued if there are persistent (more than eight weeks) declines in LVEF or if trastuzumab

Table III: Risk factors for trastuzumab-associated cardiotoxicity[28]

Risk factors that exclude patients from treatment	• Existing heart failure • LVEF < 50% (unless the risk of disease recurrence is very high)
Risk factors requiring special considerations	• Ischaemic heart disease (IHD) or significant valvulopathy • Baseline LVEF of 50–55% • Decrease in LVEF of more than 15%
Risk factors identified in metastatic breast cancer trials	• Anthracyclines: concurrent or prior
Risk factors identified by NSABP B-31	• Age • Use of hypertensive medication • Baseline LVEF of 50–54% • Post anthracycline LVEF values of 50–54%
Effects of various regimens on cardiotoxicity	• Sequential anthracycline-taxane-trastuzumab regimens may possibly be less cardiotoxic than concurrent regimens

Table IV: Summary of strategies to limit trastuzumab cardiotoxicity

Considerations	Strategies
Patient screening	Baseline cardiac assessment and LVEF Weigh benefits vs risks
Anthracyclines	Limit total accumulative dose Infusional regimens Novel delivery systems Doxorubicin analogues Dose sequentially Possible omission
Taxanes	Docetaxel-trastuzumab combination less cardiotoxic than paclitaxel-trastuzumab
Trastuzumab	Shorter duration possibly less cardiotoxic
Monitoring	Three monthly for duration of treatment Six monthly for two years following treatment
• > 10–15% decline in LVEF	• Withhold trastuzumab for 4–8 weeks • Consider medical therapy • Monitor four weekly • Re-institute trastuzumab if LVEF recovers to acceptable values • Permanent cessation of trastuzumab: Recovery not seen within eight weeks; Trastuzumab suspended more than three times for cardiotoxicity

dosing has been suspended on more than three occasions for cardiotoxicity reasons.[2]

It is possible that the incidence and severity of cardiac dysfunction will increase with longer term follow up. Therefore, LVEF measurements should be continued six monthly for at least two years following completion of trastuzumab as a component of adjuvant therapy.[2]

In the future, newer biochemical markers like troponins and natriuretic peptides may have a larger role to play: in a recent study, pre-treatment plasma prohormone brain-type natriuretic peptide (pro-BNP) levels were almost five times higher in patients who developed heart failure during trastuzumab therapy compared with those who did not experience symptomatic LV dysfunction. Equally, more sophisticated echocardiographic modalities like tissue Doppler imaging, regional strain, and strain rate might provide improved sensitivity in detecting sub-clinical dysfunction. Exciting potential monitoring tools comprise radio-labelled antimyosin antibodies (myosin is exposed when cardiac myocytes are damaged), cardiac MRI, proteomics and endomyocardial ventricular biopsy with electron microscope examination.[29]

Treatment of left ventricular dysfunction and heart failure

It should be highlighted that although symptomatic heart failure may respond to heart failure medications, the drop in LVEF in trastuzumab-treated patients does not necessarily fully recover to baseline.[30]

Two classes of agents have become the cornerstone of therapy to delay or halt progression of cardiac dysfunction and to improve survival rates: ACE-I (angiotensin converting enzyme inhibitors) and beta blockers. Although it is uncertain whether asymptomatic patients derive benefit from medical treatment, there is compelling evidence that ACE-inhibitors should be used to inhibit the renin-angiotensin-aldosterone system (RAAS) in *all* heart failure patients with left ventricular dysfunction, whether they are symptomatic or not. Typically they are instituted when left ventricular function is below 40% and considered when LVEF is between 40–50%. Beta blockers such as carvedilol, bisoprolol and metoprolol are now also firmly established as routine therapy in LV dysfunction and are usually given to all patients with a LVEF of less than 40%.

These cardiac drugs may hasten recovery after withdrawal of trastuzumab and possibly allow some patients to be re-challenged with the drug. Accelerated regimens are recommended because the normal titration schedules can take several months to reach the optimal therapeutic dosage.[31]

The duration of treatment needs to be individualised depending on the degree of left ventricular dysfunction, the symptoms, patient preference and the magnitude of functional recovery. Cardiologists lean towards continued use of therapy, whilst oncologists may be reluctant to put relatively young women on lifelong therapy. More long-term data are required to clarify the optimal approach.

Recommendations and conclusions

Women treated with trastuzumab have an increased risk for developing left ventricular dysfunction which may progress to severe NYHA class III /IV heart failure which carries its own morbidity, chronic disability and mortality. Oncologists should therefore refrain from prescribing trastuzumab until cardiac function has been thoroughly assessed, baseline LVEF (post-anthracycline if necessary) is obtained, the risks have been carefully weighed against the benefits of treatment and preventive strategies have been considered. Patients need to be aware that the survival benefit of a few percentage points may be offset by acute, chronic and late-onset toxicities.[32] This is particularly relevant for young patients with early breast cancer. Recent data suggest that women with early breast cancer are more likely to die of heart disease than recurrent cancer.

Continued cardiac monitoring is an essential component of trastuzumab treatment and should not be neglected. In the event of significant declines in left ventricular function, appropriate steps, such as cessation of treatment, should be taken. Women treated with trastuzumab who develop

heart failure, appear to derive symptomatic relief with appropriate therapy. However, heart failure, like many cancers, is a progressive disease and mortality remains high despite improvements in symptoms. There is currently no information on the potential for late cardiac dysfunction or whether short-term improvements in clinical heart failure or left ventricular dysfunction with medical treatment are permanent or will increase the risks of late cardiac dysfunction.

Trastuzumab-associated heart failure has been instrumental in spurring innovative and cutting-edge preclinical and clinical research in both oncology and cardiology. Although the precise mechanism of trastuzumab's cardiotoxicity has not yet been elucidated, the field has advanced significantly. The lessons learnt should help patients receive state of the art treatment whilst ensuring that they do not trade one potentially lethal disease for another.

Conflict of interests: None

Acknowledgement: Professor OBW Greeff for proof reading manuscript

References

1. Seidman A, Hudis C, Pierri MK, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. J Clin Oncol 2002;20(5):1215–21.
2. Herceptin (trastuzumab) Full Prescribing Information. Genentech Inc 2009; Available from: http://www.herceptin.com. (Accessed 03/06/09)
3. Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology / American Heart Association Task Force on Practice Guidelines. Circulation 2005;112:e154–235.
4. The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and blood vessels. Boston: Little Brown, 1964.
5. Feldman AM, Lorell BH and Reis SE. Trastuzumab in the treatment of metastatic breast cancer: Anticancer therapy versus cardiotoxicity. Circulation 2000; 102:272–4.
6. Erban JK and Lau J. On the toxicity of chemotherapy for breast cancer – the need for vigilance. Journal of the National Cancer Institute 2006;98(16):1096–7.
7. Ewer MS, Lippman SM. Type II Chemo-therapy-related cardiac dysfunction: time to recognize a new entity. J Clin Oncol 2005;23(13):2900–2
8. Marty M, Cognetti F, Maraninchi D, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor-2 positive, metastatic breast cancer administered as first line treatment: The M77001 study group. J Clin Oncol 2005;23:4265–74.
9. De Maio E, Pacilio C, Gravina A, et al. Vinorelbine plus 3-weekly trastuzumab in metastatic breast cancer; A single centre phase 2 trial. BMC Cancer 2007;7:50.
10. O'Shaughnessy JA, Vukelja S, Marsland T, et al. Phase II study of trastuzumab plus gemcitabine in chemotherapy pretreated patients with metastatic breast cancer. Clin Breast Cancer 2004;5:142–147.
11. Schaller G, Fuchs I, Gonsch T, et al. Phase II study of capecitabine plus trastuzumab in human epidermal growth factor receptor 2 overexpressing metastatic breast cancer pretreated with anthracyclines or taxanes. J Clin Oncol 2007;25:3246–50.
12. Untch M, Eidtmann H, du Bois A, et al. Cardiac safety of trastuzumab in combination with epirubicin and cyclophosphamide in women with metastatic breast cancer: Results of a phase I trial. Eur J Cancer 2004; 40:988–97.
13. Baselga J, Climent MA, Llluch A, et al. Results of a phase II study of liposomal doxorubicin in combination with weekly paclitaxel and trastuzumab in patients with HER-2 positive locally advanced or metastatic breast cancer. Eur J Cancer Suppl 2004;2:132.
14. Tan-Chiu E, Yothers G, Romond E, et al. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab, as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. J Clin Oncol 2005;23:7811–19.
15. Perez EA, Suman VJ, Davidson NE, et al. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. J Clin Oncol 2008;26:1231–8.
16. Suter TM, Procter M, van Veldhuisen DJ, et al. Trastuzumab-associated cardiac adverse effects in the Herceptin Adjuvant (HERA) Trial. J Clin Oncol 2007;25(25):3859–65.
17. Slamon D, Eiermann W, Robert N, et al. Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab with docetaxel, carboplatin and trastuzumab in HER 2 positive early breast cancer patients: BCIRG 006 study. Breast Cancer Res Treat 2005;94(suppl 1):S5.
18. Joensuu H, Kellokumpu-Lehtinen P-L, Bono P. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med. 2006;354:809–20.
19. Coudert BP, Largillier R, Arnould L, et al. Multicentre phase II trial of neoadjuvant therapy with trastuzumab, docetaxel and carboplatin for human epidermal growth factor-2 overexpressing stage II or III breast cancer. Results of the GETN(A)-1 trial. J Clin Oncol 2007;25:2678–84.
20. Ewer MS, Vooletich MT, Durand JB, et al. Reversibility of trastuzumab-related cardiotoxicity: New insights based on clinical course and response to medical treatment. J Clin Oncol 2005;23:7820–6.
21. Chan R, Hardy WR, Laing SE, et al. The catalytic activity of the erbB2 receptor tyrosine kinase is essential for embryonic development. Mol Cell. Biol 2002;22:1073–8.
22. Crone SA, Zhao YY, Fan L, et al. erbB2 is essential in the prevention of dilated cardiomyopathy. Nat Med 2002;(8):459–65.
23. Pentassuglia L and Sawyer DB. The role of Neuregulin-1_/ErbB signaling in the heart. Experimental Cell Research 2009;315:627–37.
24. Ozcelik C, Erdmann B, Pilz B, et al. Conditional mutation of the erbB(HER-2) receptor in cardiomyocytes leads to dilated cardiomyopathy. Proc Natl Sci USA 2002;99(13):8880–5.
25. Chien KR. Herceptin and the heart – a molecular modifier of cardiac failure. NEJM 2006;354(8):789–90.
26. Yeh ETH, Tong AT, Lenihan DJ, et al. Cardiovascular complications of cancer therapy: diagnosis, pathogenesis and management. Circulation2004;109:3122–31.
27. Healey BRJ and Swain SM. Cardiac toxicity in breast cancer survivors: review for potential cardiac problems. Clin Cancer Res 2008;14(1):14–24.
28. Mackey JR, Clemons M, Delgado D, et al. Cardiac management during adjuvant trastuzumab therapy: recommendations of the Canadian Trastuzumab Working Group. Current Oncology 2008;15:24–35.
29. Lenihan DJ and Esteva FJ. Multidisciplinary strategy for managing cardiovascular risks when treating patients with early breast cancer. The Oncologist 2008;13:1224–34.
30. Martin M, Esteva FJ, Alba E, et al. Minimizing cardiotoxicity while optimising treatment efficacy with trastuzumab: Review and expert recommendations. The Oncologist 2009;14:1–11.
31. Sengupta PP, Northfelt DW, Gentile F. Trastuzumab-induced cardiotoxicity: heart failure at the crossroads. Mayo Clin Proc 2008;83(2):197–203.
32. Hayes DF. Heart of Darkness: The downside of trastuzumab. J. Clin. Oncology 2006; (24):4056–8.