Monitoring the introduction of new drugs – Herceptin to cardiotoxicity

HC Routledge, DW Rea and RP Steeds

HC Routledge[1] MD MRCP, Specialist Registrar in Cardiology

DW Rea[2] PhD FRCP, Senior Lecturer in Medical Oncology

RP Steeds[1] MA MD MRCP, Consultant Cardiologist

[1]Department of Cardiology, University of Birmingham

[2]Institute for Cancer Studies, Queen Elizabeth Hospital, Birmingham

Clin Med 2006;6:478–81

ABSTRACT – Trastuzumab (Herceptin), currently prescribed for metastatic breast cancer, has recently been shown to be effective as adjuvant therapy in early receptor 2 (HER2)-positive breast cancer. Cardiotoxicity is a serious adverse effect. A decrease in left ventricular ejection fraction (LVEF) occurs in as many as 27% of women treated with trastuzumab when combined with standard chemotherapy. The pathophysiology of this effect, which differs from the cardiotoxicity of anthracyclines, remains poorly understood. While overt heart failure is reversed with standard therapy, the longer-term consequences of asymptomatic declines in LVEF remain unknown. Monitoring 3-monthly for 5–10% changes in LVEF, the criteria for cessation of trastuzumab therapy in the clinical trials, is not possible for the population of women who might benefit from trastuzumab for early breast cancer. Extension of this therapy to an older and less fit population than those enrolled in the trials, with less rigorous cardiac screening, may result in significantly more cardiotoxicity.

KEY WORDS: breast cancer, cardiac failure, cardiotoxicity, echocardiography, trastuzumab (Herceptin)

Key Points

- **Trastuzumab (Herceptin) may be indicated for 25% of women with breast cancer**
- **Cardiotoxicity is a serious adverse effect occurring in up to 27% of those treated**
- **Herceptin-related cardiotoxicity is different to that from other cytotoxic drugs and improves with intervention**
- **Evidence-based monitoring requires identification of changes in left ventricular ejection fraction of 5–10%**
- **Intensive cardiac monitoring for such changes is subject to significant limitations and may not be imitated in the clinical setting**

Introduction

Trastuzumab (Herceptin) was introduced in the late 1990s for use in the treatment of metastatic breast cancer and this is now standard practice in the UK. According to recent evidence, trastuzumab is now indicated as adjuvant therapy during or after chemotherapy, in women with early stage breast cancers whose tumours over express the growth factor receptor (HER-2) protein. 20–25% of breast cancers overexpress HER-2, suggesting that this therapy might be indicated in as many as 3,700 women per year in the UK. Aside from the issues related to the cost of the drug, which have recently brought Herceptin into the spotlight, an important but less publicised aspect concerns its cardiotoxicity. Trastuzumab-associated cardiac dysfunction has been reported with an incidence of between 3% and 27% in phase II/III trials and close monitoring is recommended. This article reviews the evidence regarding the cardiotoxicity of trastuzumab and raises questions concerning cardiac monitoring.

The role of trastuzumab in breast cancer therapy

HER-2 is a proto-oncogene that codes for the transmembrane receptor tyrosine kinase protein p185HER2. The HER-2 gene is amplified and protein overexpressed in 20–25% of breast cancers. HER-2 mediated signalling has a direct role in the pathogenesis of these cancers, the HER-2 positive phenotype being associated with increased proliferation, angiogenesis and resistance to apoptosis.[1] In patients with tumours demonstrating this alteration prognosis is poor compared to HER-2 negative disease.[2]

Trastuzumab is a recombinant humanised monoclonal antibody that selectively binds to the extracellular domain of the HER-2 protein. It shows single agent activity in metastatic disease with response rates of up to 35% depending on the context in which it is used.[3,4] Trastuzumab when added to chemotherapy is superior to chemotherapy alone, improving response rate and extending survival by up to eight months.[5,6]

Recently, in women with operable HER-2 positive

breast cancer, the addition of trastuzumab to adjuvant chemotherapy (paclitaxel) after standard doxorubicin and cyclophosphamide improved disease-free survival at two years (hazard-ratio 0.48).[7] At four years, event-free survival was 85% in the trastuzumab groups compared with 67% in those managed with standard therapies alone and mortality was reduced by one third.[7] Simultaneously, the one-year results of the HERA trial, in which trastuzumab monotherapy was commenced after completion of standard surgery and chemotherapy regimes, demonstrated a reduction in the rate of recurrence of early stage breast cancer of 50%.[8] This was described as 'the largest to be reported since the introduction of tamoxifen', considerably exciting public opinion and leading to in excess of 2,000 UK press articles devoted to this 'life-saving new therapy'. The National Institute for Health and Clinical Excellence had recommended the use of trastuzumab for metastatic breast cancer in specified situations only, with an estimated cost of £17 million:

- in combination with paclitaxel for women whose HER-2 protein is measured as 3+, who have not had chemotherapy and for whom anthracycline treatment is not appropriate.
- or on its own for women with breast cancer and HER-2 levels of 3+ who have had at least two chemotherapy treatments for metastatic breast cancer. Previous chemotherapy must have included at least an anthracycline drug and a Taxane drug where these treatments are appropriate. It should also have included hormonal therapy in patients sensitive to oestrogen.[9]

A review of these guidelines which recommends Trastuzumab therapy for all women with early-stage HER2-positive breast cancer following surgery, chemotherapy and (if applicable) radiotherapy has been published in draft form. Final guidance is expected in October 2006 pending the results of an appeal.

Incidence of trastuzumab-associated cardiotoxicity

Although trastuzumab is not associated with the typical adverse effects of cytotoxic chemotherapy, cardiotoxicity poses a significant risk. Despite being well documented in the medical papers, this risk has largely escaped the attention of the media and patient action groups. In the initial clinical trials, cardiac dysfunction was seen in 27% of the group given trastuzumab in conjunction with doxorubicin compared to 8% of the group given an anthracycline and cyclophosphamide alone.[5] This unpredicted adverse event prompted a retrospective analysis of seven phase II and III trials in 2002, conducted by an independent cardiac review committee. Cardiac dysfunction was defined as a decrease in LVEF of at least 10% to less than 55%, or by a decrease of 5% in left ventricular ejection fraction (LVEF) in the presence of symptoms and signs.[10] By these definitions, cardiac dysfunction had occurred in 7% of patients receiving trastuzumab alone, in 13% of those receiving trastuzumab and paclitaxel, and in up to 27% of those receiving trastuzumab and doxorubicin. The majority (64%) of those with cardiac dysfunction presented with significant functional impairment (New York Heart Association (NYHA) III or IV). The factors predisposing to cardiotoxicity are listed in Table 1. The increased risk when trastuzumab is combined with an anthracycline has led to the alteration of subsequent trial protocols. These have incorporated much more stringent cardiac monitoring and excluded patients with pre-existing heart disease or impaired function after anthracycline chemotherapy. This is likely to have contributed to the lower rates of cardiac dysfunction reported in the most recent trials (Table 2).

Pathophysiology of trastuzumab-associated cardiotoxicity

The pathophysiology of trastuzumab-associated cardiotoxicity remains incompletely understood but is clearly different from that observed with anthracyclines. The risk of cardiotoxicity is greater when used in conjunction with doxorubicin but cardiac biopsy specimens show no evidence of typical anthracycline-related or other identifiable ultra-structural abnormality.[11] Instead, trastuzumab cardiotoxicity is assumed to be HER-2 mediated. HER-2 knockout mice develop features of cardiomyopathy and HER-2 signaling is likely to be crucial to maintenance of cardiac structure and contractility.[12] Cardiotoxicity following trastuzumab may present with a variable degree of clinical severity and is not dose-related.[11] The most important clinical difference from that observed with anthracyclines, is that the cardiac dysfunction caused by trastuzumab appears to be reversible.[11]

Prognosis and treatment of trastuzumab-related cardiac dysfunction

So far, the majority of patients with cardiac dysfunction attributable to trastuzumab and anthracycline regimens appear to respond to standard heart failure therapy, but this is not always the case. In the review of the early trials, 79% patients were said to have improved (by NYHA class) on treatments including diuretics, angiotensin-converting enzyme (ACE)-inhibitors, and beta-blockers.[10] In an observational study of 38 patients with trastuzumab-related cardiotoxicity, mean LVEF had decreased from 61% to 43% over a median of 4.5 months treatment. All patients improved after withdrawal of trastuzumab with an increase in LVEF to 55% and a mean time to recovery of six weeks.[11] In six patients, this recovery occurred without any

Table 1. Factors pre-disposing to trastuzumab-associated cardiotoxicity.

Age
Concomitant use of an anthracycline
Previous anthracycline exposure (temporal proximity to, rather than dose received)
Prior chest wall irradiation
Pre-existing cardiac dysfunction

specific treatment but the remaining 84% received heart failure therapy. Twenty-five patients were re-challenged with trastuzumab after a period of stability. Congestive heart failure (CHF) recurred in just three, whilst in 88% LVEF remained unchanged during a second course of therapy.

Risk assessment and the limitations of cardiac monitoring

Cardiac monitoring in the ongoing HERA-trial includes assessment of LVEF (by echocardiography or multigated blood pool imaging (MUGA)) at baseline and after 3, 6, 12, 18, 24, 30, 36 and 60 months.[8] Inclusion required an LVEF >55% following adjuvant chemotherapy. Exclusion criteria included a history of CHF, myocardial infarction (MI) or angina, uncontrolled hypertension, valve disease or arrhythmia. A >10% decrease from baseline or an LVEF <45% led to cessation of trastuzumab therapy. With this regime, there was no additional death rate in the trastuzumab arm but there remained a higher incidence of both symptomatic CHF and asymptomatic decrease in LVEF. Current product characteristics recommend that 'all candidates for treatment undergo careful cardiac monitoring and risk-benefit assessment'. However, a number of important issues remain.

Firstly, the likelihood of 'cardiac dysfunction' as defined in the trials can be estimated providing the same doses and combinations of chemotherapy are being used. The significance that should be attached to asymptomatic changes in LVEF caused by trastuzumab is unclear. Data are lacking regarding the long-term implications and in whom and for how long heart failure therapy should be prescribed. How frequently patients should be re-assessed following transient dysfunction and which patients are most at risk of adverse long-term outcomes remain unknown.

Secondly, the optimum mode for cardiac monitoring is unclear. Serial MUGA offers high reproducibility[11] but at the cost of radiation exposure to a potentially young population. Based on the exposure in our institution (average dose 7.4 mSieverts), the lifetime risk of a fatal cancer is one per 2,700 MUGA scans, translating to a risk for nine scans (as in HERA) of 0.33% per patient. 2D-echocardiography has largely replaced MUGA in the clinical setting due to widespread availability. Monitoring in the HERA-trial was based on recognition of a 10% fall in LVEF, a measurement which, when assessed echocardiographically, is subject to a number of limitations. Quantifying LVEF by echo is dependent on operator and acoustic window. Even in a multicentre study, which required good-quality echocardiograms as an entry criterion, the core laboratory could not analyse LVEF in 31%.[14] In addition, there is considerable inter-study and inter-operator variability in the 2D-echo assessment of LVEF. This variability is such that when scanned on two occasions a week apart, a >10% change in LVEF (as used in the HERA study) is found in up to 25% of studies in the absence of any true clinical change.[15] Furthermore, the variability of 2D-echo assessment becomes larger when faced with remodelled hearts due to the reliance on standard geometric models of left ventricular shape. This aspect has not been considered in trastuzumab-associated cardiotoxicity, where it is unknown whether remodelling is uniform or eccentric. Both 3D-echocardiography and cardiovascular magnetic resonance (CMR) have greater reproducibility but at present neither is widely available. Of note, it is not possible to switch between imaging modalities because LVEF measurements by MUGA, 2D-echo and CMR are not interchangeable.[14]

The costs of implementing the 2002 NICE guidelines (in which trastuzumab was added to taxane chemotherapy for those with metastatic disease only) included an estimate of the cost of monitoring LVEF before, during and after treatment. For four

Table 2. Incidence of trastuzumab-related cardiac dysfunction on those trials incorporating prospective cardiac monitoring.

	Number treated with trastuzumab	Therapy	Definition	Cardiotoxicity (*v* control)
Esteva SJ *et al*[15]	30	Weekly trastuzumab + dosetaxel (average 24 weeks)	Symptomatic CHF ↓ LVEF >20%	3.3% 16%
Seidman *et al*[16]	95	Weekly trastuzumab + paclitaxel (average 25 weeks)	Cardiac Events ↓ LVEF >20%	3.1% 7.4%
Burnstein HJ *et al*[17]	40	Trastuzumab + vinorelbine (average 27 weeks)	Symptomatic CHF ↓ LVEF >20%	0 7.5%
Burris H *et al*[18]	62	16 weeks trastuzumab then 6 weeks trastuzumab + paclitaxel + carboplatin	Symptomatic CHF ↓ LVEF >20%	1.5% 6.6%
NCCTG trial N9831[7]	690	Doxorubicin + cyclophosphamide then paclitaxel ± trastuzumab	Class III/IV CHF/ death	2.9% (*v* 0%)*!
NSABP trial B-31[7]	850	Doxorubicin + cyclophosphamide then paclitaxel ± trastuzumab	Class III/IV CHF/ death Asymptomatic ↓ LVEF	4.1% (*v* 0.8%)*! 14.2%
HERA trial[8]	3,388	1 or 2 years trastuzumab following adjuvant chemotherapy	Symptomatic CHF ↓ in LVEF	1.7% (*v* 0.1%)* 7.1% (*v* 2.2%)*

* = statistically significant; ! = led to posting of an FDA alert; CHF = congestive heart failure; FDA = Food and Drug Administration; LVEF = left ventricular ejection fraction; NCCTG = North Central Cancer Treatment Group; NSABP = National Surgical Adjuvant Breat and Bowel Project.

cardiac tests per patient, a cost of £580 was added. No additional price was attached for those requiring further cardiac assessment, medication and follow-up. Using a similar calculation, the additional cost of cardiac monitoring (aside from the cost of testing for HER-2 status and that of the drug itself) for women requiring treatment for operable, locally invasive breast cancer in the UK would total £2.1 million per year.

Cost aside, the availability of cardiac monitoring of up to 3,700 extra women per year must be considered. Although echo is more widely available than MUGA or CMR, a recent internal survey by the British Society of Echocardiography has identified a four-fold shortfall of trained sonographers in the UK. This figure does not account for a conservative four scans per trastuzumab patient which alone translates into an additional need for 14,800 scans per year. In addition, between 100 and 1,000 women with cardiac dysfunction will require the input of a cardiologist. The demand for cardiac services will depend ultimately upon the appropriate duration of trastuzumab therapy, which remains undetermined pending the two-year results of the HERA-trial.

Conclusion

Trastuzumab has proven beneficial in metastatic as well as early invasive breast cancer in patients whose tumours overexpress the HER-2 protein. In addition to the cost of the drug there are important concerns regarding adequate provision of cardiac safety to a new population of breast cancer patients. Currently, monitoring to the standard achieved in the HERA-trial would not be reproducible in the UK. These concerns form the basis of an appeal delaying issue of new NICE guidance. Extension of this therapy to a generally older and less fit population than those enrolled in HERA with less rigorous cardiac screening, may result in significantly more cardiotoxicity than reported in the trial context. The consequences of an asymptomatic decline in LVEF following trastuzumab are poorly understood. Determination of the optimum method, frequency and duration of cardiac monitoring is essential to rationalisation of service provision allowing the safe administration of this agent to all those women who are likely to benefit.

References

1 Pietras RJ, Arboleda J, Reese DM *et al.* HER-2 tyrosine kinase pathway targets estrogen receptor and promotes hormone-independent growth in human breast cancer cells. *Oncogene* 1995;10:2435–46.

2 Slamon DJ, Clark GM, Wong SG *et al.* Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 1987;235:177–82.

3 Cobleigh MA, Vogel CL, Tripathy D *et al.* Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. *J Clin Oncol* 1999;17:2639–48.

4 Vogel CL, Cobleigh MA, Tripathy D *et al.* Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. *J Clin Oncol* 2002;20:719–26.

5 Slamon DJ, Leyland-Jones B, Shak S *et al.* Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001;344:783–92.

6 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.

7 Romond EH, Perez EA, Bryant J *et al.* Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 2005;353:1673–84.

8 Piccart-Gebhart MJ, Procter M, Leyland-Jones B *et al.* Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005;353:1659–72.

9 National Institute for Clinical Excellence. *Guidance on the use of trastuzumab for the treatment of advanced breast cancer*. London: NICE, 2002. www.nice.org.uk/page.aspx?0=TA034

10 Seidman A, Hudis C, Pierri MK *et al.* Cardiac dysfunction in the trastuzumab clinical trials experience. *J Clin Oncol* 2002;20:1215–21.

11 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.

12 Crone SA, Zhao YY, Fan L *et al.* ErbB2 is essential in the prevention of dilated cardiomyopathy. *Nat Med* 2002;8:459–65.

13 Wackers FJ, Berger HJ, Johnstone DE *et al.* Multiple gated cardiac blood pool imaging for left ventricular ejection fraction: validation of the technique and assessment of variability. *Am J Cardiol* 1979;43:1159–66.

14 Bellenger NG, Burgess MI, Ray SG *et al.* Comparison of left ventricular ejection fraction and volumes in heart failure by echocardiography, radionuclide ventriculography and cardiovascular magnetic resonance; are they interchangeable? *Eur Heart J* 2000;21:1387–96.

15 van Royen N, Jaffe CC, Krumholz HM *et al.* Comparison and reproducibility of visual echocardiographic and quantitative radionuclide left ventricular ejection fractions. *Am J Cardiol* 1996;77:843–50.

16 Esteva FJ, Valero V, Booser D *et al.* Phase II study of weekly docetaxel and trastuzumab for patients with HER-2-overexpressing metastatic breast cancer. *J Clin Oncol* 2002;20:1800–8.

17 Seidman AD, Fornier MN, Esteva FJ *et al.* Weekly trastuzumab and paclitaxel therapy for metastatic breast cancer with analysis of efficacy by HER2 immunophenotype and gene amplification. *J Clin Oncol* 2001;19:2587–95.

18 Burstein HJ, Kuter I, Campos SM *et al.* Clinical activity of trastuzumab and vinorelbine in women with HER2-overexpressing metastatic breast cancer. *J Clin Oncol* 2001;19:2722–30.

19 Burris H 3rd, Yardley D, Jones S *et al.* Phase II trial of trastuzumab followed by weekly paclitaxel/carboplatin as first-line treatment for patients with metastatic breast cancer. *J Clin Oncol* 2004;22:1621–9.