ORIGINAL ARTICLE

Cardiotoxicity associated with trastuzumab (Herceptin) therapy in the treatment of metastatic breast cancer

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Summary Trastuzumab (Herceptin) is a humanised monoclonal antibody that specifically targets HER2-positive breast cancer cells. Safety data collected from pivotal trials with trastuzumab indicate that this therapy is generally well tolerated. However, trials of the combination of trastuzumab plus chemotherapy, and in particular chemotherapy with anthracyclines, have revealed an elevated incidence of cardiotoxicity in some patients, which was not apparent in preclinical or early clinical studies. Analyses of the available data suggest that in most cases the cardiotoxicity observed may reflect an exacerbation of anthracycline-induced cardiotoxicity. The biological mechanism of the cardiotoxicity has been investigated in several studies, and current data indicate that the heregulin/HER2-signalling pathway may have an important role. It is of note that the cardiotoxicity is generally reversible and can usually be managed with standard medical treatment. Improvement in cardiac function is seen both in patients who continue trastuzumab and in those in whom further therapy is withdrawn, indicating that with careful management anticancer therapy can be continued.

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\textbf{KEYWORDS}
HER2; Trastuzumab; Cardiotoxicity; Metastatic breast cancer

Introduction

Human epidermal growth factor receptor-2 (HER2; also known as \textit{neu}, \textit{c-erbB-2}, or \textit{erbB2}) is a member of the transmembrane tyrosine kinase growth factor receptor family which is made up of four homologous receptors. In normal cells, the HER receptors are involved in the regulation of cell differentiation, growth, and survival\textsuperscript{1-3} This is achieved through the binding of a ligand to HER homo- or heterodimers, which results in activation of intrinsic tyrosine-kinase activity. This leads to tyrosine kinase autophosphorylation and is followed by a cascade of events that ultimately
result in the transmission of signals across the cell membrane into the nucleus, where gene activation occurs, leading to mitogenic stimulation and cell division.\textsuperscript{4,5} Although a ligand has not been identified for HER2,\textsuperscript{6} heterodimerisation between HER2 and other members of the HER family allows HER2 to participate in signal transduction.

The HER2 gene is amplified or the receptor strongly overexpressed in approximately 15–25\% of breast cancers (HER2-positive tumours).\textsuperscript{7–10} HER2 amplification/overexpression is associated with a poor prognosis, involving lower rates of relapse-free and overall survival,\textsuperscript{11} and may also be predictive of the response to hormonal therapy\textsuperscript{12–16} and chemotherapy.\textsuperscript{17–20} Trastuzumab is a humanised monoclonal antibody (MAb) that specifically targets HER2-positive breast cancer cells.\textsuperscript{21} Treatment with trastuzumab results in impressive clinical benefits, whether given as a single agent\textsuperscript{22,23} or in combination with chemotherapy: these include significantly better survival than with chemotherapy alone.\textsuperscript{14} Overall, safety data collected from pivotal trials of trastuzumab indicate that this therapy is generally well tolerated and is not associated with chemotherapy-related adverse events, such as alopecia, myelosuppression and severe nausea or vomiting.\textsuperscript{22,24,25}

Trastuzumab is currently approved for the treatment of HER2-positive metastatic breast cancer in women, both as first-line therapy in combination with paclitaxel and as a single agent in women who have received prior therapy with anthracyclines and taxanes and those who are unsuitable for treatment with these agents. Anthracyclines, such as doxorubicin and epirubicin, are a mainstay of treatment for breast cancer and would most probably be used in combination with trastuzumab were it not for the fear of cardiac complications;\textsuperscript{26} the use of anthracyclines is limited by the cardiotoxicity known to be associated with this class of chemotherapeutic agent.\textsuperscript{27} Trials involving the combination of anthracyclines, or other agents, with trastuzumab\textsuperscript{24} have revealed an elevated incidence of cardiotoxicity in some patients, which was not apparent in preclinical or in phase I and II clinical studies.\textsuperscript{21,27–30} This article therefore describes a retrospective analysis of data derived from pivotal trials of trastuzumab and outlines prospective data focusing on cardiotoxicity. In addition, it provides a review of the possible mechanisms of trastuzumab-associated cardiotoxicity and indicates how the risk of cardiotoxicity impacts on patient management.

Clinical trials with trastuzumab

Trastuzumab monotherapy in HER2-positive metastatic breast cancer

A total of 222 patients with HER2-positive metastatic breast cancer were investigated in a pivotal phase II open-label, single-arm trial of trastuzumab (4 mg/kg loading dose followed by 2 mg/kg weekly thereafter) given as second- or third-line monotherapy (H0649g).\textsuperscript{22} Analysis of patient characteristics indicates that subjects in the study had a poor prognosis by virtue of treatment failure (32\% had received one, and 68\% had received two prior chemotherapy regimens, and 94\% of these had previously received anthracyclines) and also in relation to other factors.\textsuperscript{22}

The objective tumour response, the primary endpoint of the study, was 15\% (8 complete and 26 partial responses) in the intent-to-treat population. It is of note that response rates were higher (18\%) in patients whose tumours were characterised by high HER2 overexpression (3 plus as determined by immunohistochemistry [IHC]). The median duration of response was 9.1 months, which compares favourably with the 5.2-month duration associated with previous chemotherapy in responders.\textsuperscript{22}

In this trial, trastuzumab was generally well tolerated, with a low incidence of the adverse events commonly seen with traditional cytotoxic agents. The most common adverse events were mild to moderate infusion-related symptoms consisting in fever and chills, which occurred in approximately 40\% of patients.\textsuperscript{22} The clinically most significant adverse event was cardiac dysfunction, which is discussed in detail below.

A study assessing the efficacy of trastuzumab as first-line monotherapy (H0650g) in women with HER2-positive metastatic breast cancer has also been conducted.\textsuperscript{23} In this study, 114 women with metastatic breast cancer were randomised to receive either standard low-dose or higher dose trastuzumab. Fifty-one per cent of patients had previously received adjuvant anthracyclines. The overall response rate was 26\% in the overall patient population and 35\% in the subgroup of patients with IHC 3 plus disease.

Combination therapy with trastuzumab and anthracyclines in HER2-positive metastatic breast cancer

The efficacy and safety of trastuzumab were also assessed in a randomised, multicentre phase III trial.
alone (trastuzumab plus paclitaxel (anthracyclines, were randomised to receive either trastuzumab plus anthracyclines (N = 143; doxorubicin N = 123; epirubicin N = 20) or anthracyclines alone (N = 138: doxorubicin N = 119; epirubicin N = 16). The remaining 188 patients, who had received prior anthracyclines, were randomised to receive either trastuzumab plus paclitaxel (N = 92) or paclitaxel alone (N = 96). Of the 469 patients recruited to the trial, 281 had not received prior anthracyclines and were randomised to receive either trastuzumab plus anthracyclines (N = 143: doxorubicin N = 123; epirubicin N = 20) or anthracyclines alone (N = 138: doxorubicin N = 119; epirubicin N = 16). The remaining 188 patients, who had received prior anthracyclines, were randomised to receive either trastuzumab plus paclitaxel (N = 92) or paclitaxel alone (N = 96).24

The addition of trastuzumab to chemotherapy was associated with greater clinical benefits than chemotherapy alone,24 including a 25% increase in median survival (25.3 vs. 20.1 months, respectively). In patients whose tumours overexpressed HER2 at the IHC 3+ level, the addition of trastuzumab to chemotherapy increased median survival by an impressive 45% (29 vs. 20 months, respectively).31

As in the pivotal phase II monotherapy trial, the most common adverse events observed with combination therapy were typically mild to moderate infusion-related symptoms. The most clinically significant serious adverse events were rare severe infusion-related reactions and an increased risk of cardiac dysfunction, especially in patients receiving trastuzumab plus anthracyclines.24,25 Nevertheless, it is of note that a retrospective analysis of the pivotal trastuzumab combination trial indicated that the addition of trastuzumab to chemotherapy improved treatment outcomes even when development of cardiotoxicity was taken into account.32

The CREC’s retrospective analysis of cardiac dysfunction in clinical trials up to December 1997 was included in the United States (US) and European Union (EU) regulatory submissions. However, as part of the European marketing submission the European Committee for Proprietary Medicinal Products (CPMP) requested a repeat analysis of the incidence of cardiac dysfunction associated with trastuzumab therapy. A Cardiac Task Force, comprised of F. Hoffmann-La Roche physicians and an external cardiac advisory board, performed this. The repeat analysis included follow-up trial safety data up to March 1999 that had not been included in the original CREC report and was based purely on clinical data reported on Case Report Forms. Retrospective analysis of each adverse event report was carried out using the available data, and the most likely aetiology of each was attributed by consensus among the Cardiac Task Force. For the purposes of this retrospective analysis, and because baseline left ventricular ejection fraction (LVEF) was not routinely measured prior to trial entry, a distinction was made between cases of symptomatic heart failure and an asymptomatic decrease in LVEF (defined as LVEF <60%). The incidence of symptomatic heart failure is summarised in Table 1.

In the pivotal phase II trial of trastuzumab as second- or third-line monotherapy,22 6.0% of patients (N = 213) were identified as having symptomatic heart failure. When follow-up data were included this rate rose to 8.5%. Interestingly, all but 1 of these patients had received prior anthracyclines. In the pivotal phase III combination trial,24 cardiac events occurred after the six cycles of chemotherapy were complete. The incidence of cardiac dysfunction in the trastuzumab plus paclitaxel subgroup was 13% (N = 12). Four of these patients had a small asymptomatic drop in LVEF. On re-analysis of symptomatic heart failure alone, the rate was 8.8% (N = 8). For the paclitaxel group alone, later analysis showed that 4.2% (N = 4) of patients who had received treatment for symptomatic heart failure events, as against 1% (N = 1) in the earlier analysis. Again, all patients in the paclitaxel arm had received prior anthracyclines for metastatic breast cancer before entry into the combination trial.

The incidence of symptomatic cardiac dysfunction was significantly higher in patients receiving trastuzumab in combination with anthracyclines (28.0%; N = 40) than in those receiving anthracyclines alone (9.6%; N = 13). For patients receiving anthracyclines, the median cumulative doses of doxorubicin were 349 and 352 mg/m² when given in combination with trastuzumab and alone, respectively, and those for epirubicin were 446 and

Retrospective analysis of the incidence of trastuzumab-associated cardiotoxicity

On the basis of preclinical data and early clinical trials, treatment with trastuzumab was not expected to be associated with cardiotoxicity. Consequently, formal cardiac monitoring was not included in the trastuzumab pivotal trial protocols. However, emerging safety data from the pivotal phase III combination trial (H0648g), revealing that the incidence of symptoms consistent with cardiac dysfunction was relatively high for the study as a whole, prompted retrospective analyses of trastuzumab-associated cardiac dysfunction. An independent Cardiac Review Evaluation Committee (CREC) was established to monitor cardiac events in clinical trials of trastuzumab.33
447 mg/m² when given with trastuzumab and alone, respectively. It is noteworthy that in the trastuzumab plus anthracycline subgroup the clinical profile of the symptomatic cardiotoxicity was typical of that associated with anthracycline therapy, being characterised by dyspnoea, pulmonary oedema, peripheral oedema and cardiomegaly.

Further stratification of patients recruited to the pivotal phase II trial of trastuzumab as second- or third-line monotherapy (N = 213) and to the first-line monotherapy trial (N = 114) revealed that 84 of these patients had not received prior anthracycline therapy. Retrospective analysis of data from these anthracycline-naive patients indicated that the rate of trastuzumab-induced heart failure in this subgroup was 3.6%, with symptomatic cardiac dysfunction occurring in 3 patients: 2 patients had documented coronary artery disease, and 1 patient was being treated for angina pectoris. All 3 of these patients were elderly (71, 76 and 79 years). Importantly, all of these patients improved with standard treatment for heart failure.

### Outcome of cardiotoxicity

A subanalysis of the data was also conducted, to assess the outcome and reversibility of cardiotoxicity observed with trastuzumab therapy. Of the patients in pivotal trials with trastuzumab as either second- or third-line monotherapy or in combination therapy (N = 677), 41 had symptomatic cardiac dysfunction (6%). When treated for heart failure (with angiotensin-converting enzyme [ACE] inhibitors, diuretics and cardiac glycosides) the majority of the patients (78%; 32/41) experienced a demonstrable improvement, as assessed by the investigator, while in 12% (5/41) the heart failure worsened. The outcome was unknown for 4 patients.

Furthermore, cardiac function improved whether trastuzumab was continued or withdrawn (Fig. 1). Trastuzumab was continued in 28 of the 41 patients affected and withdrawn in 13. Of the 28 who continued to receive treatment, 21 (75%) improved and 4 (14%) worsened. The outcome was unknown for the remaining 3 patients. Of the 13 who had no

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*Preferred terms: congestive heart failure, cardiomyopathy, heart failure, left ventricular failure, lung oedema and CRF information indicating cardiac failure (e.g. a combination of shortness of breath, dyspnoea, increased coughing, pulmonary congestion on X-ray, echo or MUGA scan).
further treatment with trastuzumab for their metastatic breast cancer, 11 (84.6%) improved and 1 worsened. The outcome for 1 patient was unknown.

Risk factors for cardiotoxicity

In view of the results of preclinical studies and early clinical trials, an increased incidence of cardiotoxicity associated with trastuzumab therapy in the pivotal trials was unexpected. However, on multivariate analysis, the independent risk factors for development of cardiac failure included concomitant use of anthracyclines, prior anthracycline exposure, age >50 years, and New York Heart Association (NYHA) dyspnoea class >II before enrolment in the trial (Table 2). Traditional cardiac risk factors, such as hyperlipidaemia, were risk factors for the patients in the paclitaxel subgroup ($P = 0.01$), although patient numbers were low in this subgroup ($N = 12$). Many of these risk factors are similar to the risk factors for doxorubicin-induced cardiac dysfunction.

Anthracyclines are the best known of the chemotherapeutic agents that cause cardiotoxicity, and cardiotoxicity may occur in a dose-dependent manner in 4% to >20% of patients treated with doxorubicin. In the pivotal trial of trastuzumab as second- or third-line monotherapy, 6.0–8.5% of patients ($N = 19$) experienced some degree of cardiac dysfunction, while in the first-line monotherapy trial, 2.6% of patients ($N = 3$) experienced cardiac dysfunction. Thus, cardiotoxicity is relatively rare with trastuzumab monotherapy. The rather low incidence of cardiotoxicity observed in patients receiving trastuzumab plus paclitaxel (8.8–11.0%) is also worthy of note. Although this figure is higher than that for patients receiving paclitaxel alone (1.0–4.2%), almost all these patients had received prior anthracyclines. Interestingly, the incidence of cardiac dysfunction in anthracycline-naive patients (3.6%) was not dissimilar to that in patients receiving trastuzumab as first-line monotherapy (2.6%).

Comment

The data reported above indicate that the cardiotoxicity seen with trastuzumab therapy is mainly, but not solely, associated with concomitant anthracyclines. However, the analysis is limited inasmuch as the data are based on a retrospective analysis of cardiac adverse events reported from the pivotal trials. It is possible that some case reports that appeared to demonstrate heart failure events were misclassified: for example, symptoms such as progressive dyspnoea are also consistent with respiratory tract disease. Another feature of this analysis is that baseline cardiac function was not routinely assessed in these patients. Furthermore, to avoid the possibility of missing cardiac events, an ejection fraction of 60% was used as a cut-off for ventricular dysfunction during the retrospective review. It is possible, therefore, that the incidence of cardiac dysfunction was over-reported in this analysis. However, it is important to note that the trastuzumab-associated cardiac dysfunction in these trials was generally manageable and reversible and did not always preclude continued trastuzumab therapy.

Prospective analysis of the incidence of trastuzumab-associated cardiotoxicity

Because of the retrospective nature of the analysis of cardiotoxicity in the pivotal trials, the quality of the cardiac data is unknown. Consequently, subsequent trials have included careful cardiac monitoring in order to elucidate the real extent of trastuzumab-associated cardiotoxicity and determine the risk factors for this event. Since the completion of the pivotal trastuzumab trials, only moderately sized trials of up to about 100 patients have been completed. So far, the incidence of symptomatic heart failure with trastuzumab in these and ongoing studies appears to be lower than that estimated from premarketing data (up to 4% across different studies and regimens; Roche data on file). In a preliminary analysis of pooled LVEF data from six trials involving 403 patients receiving trastuzumab and 200 control patients not receiving trastuzumab, 20 patients (4.7%) experienced a fall in LVEF by at least 15 percentage points to less than 50%, on at least one occasion (19 of the 294 trastuzumab-treated patients had received prior anthracyclines).
patients and 1 of the 135 control patients), although only 5 cases of symptomatic cardiac failure were reported.

As expected, previous anthracyclines appeared to be the main risk factor for this fall in LVEF: trastuzumab-treated patients who had received prior anthracyclines were 6 times as likely as anthracycline-naive patients to experience a fall in LVEF (11.6% vs. 1.9%, respectively). When the data were reanalysed using a more inclusive cut-off of a fall in LVEF by at least 10 percentage points to less than 50%, prior anthracyclines still appeared to be the most significant risk factor, although the effect was less striking (likelihood 2.5 times) that without anthracyclines.

Several studies are currently investigating trastuzumab in combination with less cardiotoxic anthracyclines. These trials include prospective cardiac monitoring and to date have shown acceptable levels of cardiac toxicity. Although asymptomatic falls of >10% in LVEF were relatively common when trastuzumab was combined with epirubicin/cyclophosphamide (occurring in 26 of 51 patients), only 3 patients experienced cardiac toxicity as defined in the protocol. Studies of trastuzumab plus liposomal doxorubicin are also promising, with no observation of symptomatic cardiac events observed in one study ($N = 28$) and 2 cases of reversible cardiotoxicity among 39 patients in a further study (each of these 2 patients had previously received doxorubicin 240 mg/m$^2$). Trastuzumab has also been investigated concurrently with doxorubicin and paclitaxel (AT) followed by paclitaxel (T), with trastuzumab administered with AT (cohort 1) or T (cohort 2). A reversible decrease in cardiac function was more common when trastuzumab was started with AT than when it was started with T; 9 of the 16 evaluable patients in cohort 1 experienced CTC grade 1/2, and 2 of 16 patients in cohort 2 experienced CTC grade 1 decreases in cardiac function. Clinical cardiac toxicity was not observed.

Comment

When monitored prospectively, the incidence of trastuzumab-associated cardiotoxicity appears to be lower than that estimated retrospectively from premarketing data. This may be due partly to over-reporting of cardiotoxicity in the pivotal clinical trials in the retrospective review, and also partly because of vigilant baseline cardiac monitoring of patients prior to the initiation of trastuzumab therapy in more recent clinical trials, which has allowed patients at risk of developing cardiac events to be identified and excluded. Although LVEF monitoring is now routine in patients treated with trastuzumab, the significance of LVEF changes within an individual patient is not always clear. Minor asymptomatic declines are commonly seen, and their significance is uncertain, and yet congestive heart failure may also occur without any preceding decline in LVEF. Further analyses of prospectively gathered LVEF data are awaited.

Possible mechanisms of trastuzumab-induced cardiac toxicity

So far, the mechanism of trastuzumab-induced cardiac toxicity is unknown. HER2 (also called erbB2) can heterodimerise with erbB3 and erbB4 and form a receptor for neuregulins, including heregulins. Neuregulins have distinct effects, such as growth, differentiation and activation of survival pathways in epithelial cells, neurons and muscle cells. Neuregulin signalling is essential in the developing heart. Mice that are deficient in neuregulin, erbB2 receptors or erbB4 receptors die in mid-gestation as a result of impaired ventricular trabeculation, and postnatal cardiac myocytes express erbB2 and erbB4, but not erbB3. Furthermore, neuregulin splice variants are expressed in the adult heart by microvascular endothelial cells, but not by cardiac myocytes.

Neuregulin signalling in the heart leads to protein synthesis, stabilisation of contractile proteins, induction of a foetal gene programme and attenuation of apoptosis. It also induces protein synthesis by activating the p42/p44 mitogen-activated protein kinase (MAPK) and promotes cell survival by inhibiting apoptosis via activation of 1-phosphatidylinositol 3-kinase and AKT kinase. The biological effects of the neuregulin/erbB system in the heart appear to be very similar to that of glycoprotein 130, another recently well-characterised cardiomyocyte survival pathway.

The physiological role of neuregulin in the postnatal myocardium has recently been investigated in a cardiac-restricted genetically modified mouse model. ErbB2-deficient conditional knockout mice were viable and initially demonstrated no overt phenotype. However, over time these animals developed features of a dilated cardiomyopathy with left ventricular dilatation, left ventricular hypertrophy and systolic dysfunction. Furthermore, when these animals were subjected to increased cardiac stress, such as
Cardiotoxicity associated with trastuzumab in MBC

aortic banding, mortality was significantly higher in erbB2-deficient mice than in control mice. Ventricular cardiomyocytes from erbB2-deficient mice were also more sensitive to anthracycline toxicity than were control cells. These data indicate that erbB2 signalling is important for the maintenance of cardiac contractile function and structure, and that erbB2 might be a protective factor in the stressed heart.

The subcellular mechanisms responsible for trastuzumab-associated cardiotoxicity remain poorly understood. It is of interest that the majority of patients with trastuzumab-associated cardiac dysfunction improve within weeks to months when the heart failure is treated. This indicates that the cardiotoxicity associated with trastuzumab use, at least in the short term, is partially reversible and is unlikely to be due to independent major structural damage caused by trastuzumab. Sawyer et al. recently described an increased susceptibility of myofilaments to anthracycline in the presence of an antibody to the erbB2 receptor. Conversely, the investigators showed that neuregulin could attenuate anthracycline-induced structural damage to cardiac myocytes. However, other mechanisms of trastuzumab-associated cardiotoxicity must also be considered, including changes in excitation contraction coupling and oxidative stress. Interestingly, Özcelik et al. have recently found that erbB2 and erbB4 receptors are located predominantly in the transverse tubuli of cardiac myocytes. They are therefore in close proximity to the calcium-handling proteins, such as sarcolemmal calcium channels and sarcoplasmatic reticulum calcium release channels, and might directly influence calcium homeostasis in cardiac myocytes. Changes in intracellular calcium concentration can have multiple effects. Notably, these changes can activate cytosolic proteinases, alter myocardial contractility and induce myocyte death.

Finally, the erbB-2 receptor seems to be differentially regulated in normal, hypertrophied and failing myocardium. In an in vivo rat model with aortic stenosis, mRNA message and protein levels for the erbB-2 receptor were unchanged in hypertrophied myocardium, but down-regulated in failing myocardium. Conversely, Uray et al. have recently shown that in patients with end-stage heart failure treatment with a left ventricular assist device leads to up-regulation of erbB2 and erbB4 mRNA expression.

The preclinical data reviewed suggest that the erbB/neuregulin system, in a similar way to the glycoprotein 130 system, is pivotal for the survival of myocytes, particularly in the stressed heart. If true, this would also explain the relatively low toxicity of trastuzumab when it is used in anthracycline-naive patients.

Cardiac safety: impact on patient management

Prior to trastuzumab therapy

Prior to the commencement of trastuzumab therapy, we recommend that all patients should be evaluated for risk factors for cardiac disease. This evaluation should include a careful history taking and a physical examination (Table 3). Furthermore, although certain patient groups may be at greater risk of trastuzumab-associated cardiotoxicity (notably patients with a history of prior anthracycline exposure or a history of heart failure, but probably also patients with symptoms or signs of prior myocardial infarction or uncontrolled hypertension), left ventricular function should be evaluated prior to the initiation of trastuzumab therapy in all patients, either by nuclear imaging or by echocardiogram (ECG). An LVEF of 50–60% indicates mild cardiac dysfunction, and these patients should not be excluded from trastuzumab therapy, because the overall benefit outweighs the risk, at least for patients with advanced/metastatic disease; in the pivotal trials there was an overall survival benefit for patients receiving trastuzumab, despite the occurrence of cardiac dysfunction. Therefore, if LVEF is more than 50% trastuzumab treatment can be started. However, if LVEF is lower than 50% the risk/benefit ratio of treatment with trastuzumab should be carefully evaluated.

During trastuzumab therapy

Throughout the treatment period, every symptomatic patient should be screened at least on every hospital visit for symptoms and signs of heart failure. Typical symptoms of new-onset heart failure are dyspnoea on exertion, orthopnoea, paroxysmal nocturnal dyspnoea and fatigue. A physical examination can be helpful in differentiating dyspnoea of cardiac origin from dyspnoea of non-cardiac aetiology. Weight gain over a few days, jugular vein distension and a third heart sound make cardiac dysfunction a likely diagnosis, and in those circumstances further diagnostic tests should be performed. Regular non-invasive monitoring of LVEF may detect evidence of early asymptomatic cardiac dysfunction.
Management of cardiac dysfunction when associated with use of trastuzumab

Every patient with cardiac dysfunction should be referred to a cardiologist. Pharmacological treatment should be similar to that in patients with systolic dysfunction of any other aetiology. Data on anthracycline-induced cardiotoxicity indicate that every patient with LVEF of less than 40% should be treated with ACE inhibitors.51

In view of the favourable results obtained with beta blockers in anthracycline-induced cardiotoxicity, these drugs should also be considered in systolic dysfunction associated with trastuzumab.52 In patients with symptomatic heart failure, diuretics and possibly digoxin should be added to ACE inhibitors and beta blockers.

Should trastuzumab treatment be continued?

Any risk-benefit analysis for continued trastuzumab treatment in patients with cardiac dysfunction should consider the prognosis for each patient on an individual basis and balance potential cardiotoxicity against clinical benefit. However, since cardiac failure may be progressive and fatal, patients who do continue trastuzumab must be closely monitored for any evidence of deterioration. This evaluation should include a careful history and a physical examination. It is noteworthy that the patients in the trastuzumab pivotal trials comprised a group with a particularly poor prognosis in terms of prior treatment failure, advanced disease and HER2 positivity.22,24 The median survival time has traditionally been shorter for patients with visceral disease (6–13 months) than for those with bone-only disease (18–30 months).53 Furthermore, the 1-year mortality of patients with severe heart failure54,55 (NYHA class III and IV) is better than that for breast cancer patients with distant metastases (approximately 9.0–12.0% vs. 16.0%).56

Conclusions and future perspectives

In summary, the clinical safety database of trastuzumab indicates that this anti-HER2 MAb has a favourable safety profile that lacks the typical adverse events generally associated with cytotoxic chemotherapy. The most common side effects seen with trastuzumab are mild to moderate fevers and chills. Severe infusion-related reactions and cardiotoxicity have emerged as the two most serious adverse events.

Retrospective analyses of the pivotal phase II and III trial data and prospective analysis of data from six clinical trials have indicated that in MBC

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trastuzumab-associated cardiotoxicity is higher with concomitant anthracyclines: the median cumulative doses of doxorubicin and epirubicin in combination with trastuzumab in the pivotal phase III trial were 349 and 446 mg/m², respectively. The mechanism underlying the exacerbation of anthracycline-induced cardiotoxicity by trastuzumab is not yet understood and is under investigation. However, it is important to note that the acute cardiac dysfunction is largely reversible with standard medical heart treatment. Thorough patient assessment prior to therapy and cardiac monitoring during therapy are recommended.

This and other issues are being addressed in ongoing trials with trastuzumab in MBC and will continue to be investigated in future studies. Owing to the unexpected cardiotoxicity observed with the combination of trastuzumab plus anthracyclines (mainly doxorubicin), new studies are ongoing to assess cardiac function prospectively and incorporate anthracyclines associated with lower cardiotoxicity, such as epirubicin and liposomal doxorubicin, into chemotherapy regimens. It is possible that the advent and potential routine use of such cardioprotective drugs as dexrazoxane will also influence the future of trastuzumab therapy. As combination studies are not limited to cytotoxic agents, combinations with other therapies, such as hormonal treatment, are also being studied. Finally, the integration of trastuzumab into adjuvant and neoadjuvant treatments is also being assessed. Further studies should serve to elucidate the nature and mechanisms of the cardiotoxicity observed with trastuzumab therapy and may lead to treatment modalities that combine efficacy with improved cardiac safety.

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