REVIEW ARTICLE

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Cardiotoxicity Profile of Trastuzumab

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Abstract

Trastuzumab is a monoclonal antibody that targets the human epidermal growth factor receptor tyrosine kinase HER2/ErbB2. This agent has shown a highly significant antitumour effect for patients with HER2-positive breast cancer, and is now considered part of the standard regimens for the treatment of this disease in both the metastatic and adjuvant setting.

Cardiotoxicity has been associated with trastuzumab, and this issue has now been studied and documented in a number of adjuvant trials for which data have now been released. Cardiotoxicity has been shown to be potentiated when the agent is used concurrently or sequentially with an anthracycline, and this has limited the use of trastuzumab in some patients. Determining the overall impact of trastuzumab is further complicated by the administration of other cardiotoxic agents such as the taxanes and cyclophosphamide as well as by pre-existing cardiac disease.

The incidence of severe congestive heart failure (New York Heart Association class III or IV) was 0–3.9% in the trastuzumab arms versus 0–1.3% in the control arms in the five major randomized adjuvant trials. Only one cardiac death was related to trastuzumab whereas two cardiac deaths occurred in the control arms. Ejection fraction decline of ≥10% or 15% was reported in 3–34% of trastuzumab recipients in these trials.

Patients affected by trastuzumab-related cardiotoxicity do not exhibit the cellular death and distinctive ultrastructural myocardial changes seen on electron microscopy with anthracycline-induced cardiotoxicity. The cardiotoxicity of trastuzumab also differs from traditional chemotherapy-induced cardiotoxicity in that it appears to be at least partially reversible, not related to the cumulative dose, and re-challenge is generally tolerated.

There remain a number of uncertainties regarding the diagnosis and management of trastuzumab-related cardiotoxicity. While no formal guidelines or consensus statements exist at present regarding cardiac monitoring during use of trastuzumab, proposed recommendations include a careful assessment of ejection fraction prior to initiating trastuzumab, avoidance of concurrent administration of trastuzumab with anthracyclines, and regular monitoring of symptoms and cardiac function during and for several years after therapy. Increased vigilance is appropriate for higher risk patients.

1. Clinical Overview

Trastuzumab is a recombinant humanized monoclonal antibody (rhumAb 4D5) directed against an extracellular region of human epidermal growth factor receptor 2 (HER2). This agent was the first HER2-targeted breast cancer therapy approved for use in the US. Trastuzumab is effective in HER2-positive tumours, a feature present in approximately 20–25% of breast malignancies.[1] The drug was initially approved for treatment of patients with metastatic HER2-positive breast cancer, and has been highly effective in that group of patients. More recently, as a consequence of the data released from the major clinical trials conducted in patients in the adjuvant setting, the drug has been approved for that indication as well.[2-5]

Trastuzumab was initially not thought to be cardiotoxic, based on early small trials; however, analysis of complications during the first large phase III trial demonstrated significant cardiac dysfunction.[6] In contrast to the adjuvant trials discussed in section 2, this trial evaluated trastuzumab in the metastatic breast cancer setting, comparing standard chemotherapy with standard chemotherapy plus trastuzumab. The incidence of heart failure was 22% in the group who received chemotherapy concurrently with trastuzumab, compared with 5% for chemotherapy without trastuzumab. Cardiotoxicity was even more apparent in the group of patients who received trastuzumab with an anthracycline and cyclophosphamide (AC), amongst whom 28% of 143 patients met the study's criteria for cardiac dysfunction and 19% were deemed to have New York Heart Association (NYHA) class III or IV congestive heart failure (CHF).[6,7] The only risk factor that independently predicted trastuzumab cardiotoxicity was advanced age.

While in retrospect these numbers seem high (perhaps in part due to the criteria used in defining heart failure in that trial), the relative incremental increase in the incidence of cardiac dysfunction by a factor of 4–5 when trastuzumab is used together with other chemotherapeutics was of great concern and led to the development of a number of large multicentre trials. These trials are discussed further in section 2. All incorporated at least one arm that included or allowed an anthracycline to be used sequentially with trastuzumab.

2. Trastuzumab Adjuvant Trials

Five major randomized trials involving trastuzumab as adjuvant therapy for HER2-positive breast cancer form the bulk of our knowledge regarding the cardiotoxicity related to this drug: the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31, the North Central Cancer Treatment Group (NCCTG) N9831, The Breast Cancer International Research Group (BCIRG) 006, the HERA (Herceptin Adjuvant) trial, and the FinHer (Finland Herceptin) trial.[2-5,8-10] These trials, which included approximately 10 000 patients randomized to receive trastuzumab, have shown a much more modest overall incidence in cardiotoxicity than was reported in the pivotal metastatic breast cancer trial,[6] but the increased relative risk of cardiac events in the trastuzumab-treated patients when compared with controls was again clearly noted. The incidence of severe CHF (NYHA class III or IV) was 0–3.9% in the trastuzumab arms versus 0–1.3% in the control arms. However, only one

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cardiac death occurred in the collective trastuzumab arms, whereas two cardiac deaths were observed in the control arms. A wide variation in incidence of lesser cardiac events (in both the trastuzumab and control arms) was reported and can be explained, at least in part, by differences in the baseline patient populations, trial designs, sequencing of the various agents, and criteria used to define specific events. Comparison across trials is thus problematic, but still useful for providing a range for the incidences of various cardiac events.

In the NSABP B-31 trial, 5-year cumulative data showed a 3.9% incidence of NYHA class III or IV heart failure in the group who received AC followed by paclitaxel and trastuzumab compared with 0.8% in the control group (AC followed by paclitaxel alone); this number did not change when compared with the initial report providing the 3-year follow-up, and suggests some degree of stabilization.[9] However, the burden of cardiotoxicity was not trivial; 31% of patients in the trastuzumab arm had the drug temporarily or permanently withheld for cardiac reasons, and 34% had a decrease in their left ventricular ejection fraction (LVEF) of >10% compared with 17% in the control arm.

In the HERA trial, cardiotoxicity was less common. Severe CHF occurred in 0.6% of patients treated with trastuzumab versus 0.0% in the observation arm, and a decrease in LVEF of >10% was seen in 7.0% of patients in the trastuzumab arm versus 2.1% in the observation arm. Only 4.3% of patients had to discontinue trastuzumab for cardiac reasons.[5] The HERA trial differed from the other large trials in at least three ways that may have affected cardiotoxicity: (i) patients both with and without prior anthracycline treatment were eligible; (ii) epirubicin, a doxorubicin isomer that may demonstrate less cardiotoxicity than does the parent compound, was used extensively in the HERA population; and (iii) the time between completion of the anthracycline treatment and the start of trastuzumab treatment was considerably longer (mean of 89 days for patients in the HERA trial compared with 21 days in the NSABP B-31 trial and the BCIRG-006 trial).

The BCIRG-006 and NCCTG N9831 trials showed an intermediate level of trastuzumab cardiotoxicity, with severe CHF reported in 1.9% and 2.9% of patients treated with trastuzumab, respectively, versus 0.4% and 0.0% in the control arms, respectively.[2,3,11] An LVEF decrease of >10% occurred in 17% of patients treated with trastuzumab versus 9% in the control arm.[3] An additional arm of the BCIRG trial also included trastuzumab given with docetaxel and carboplatin but without prior anthracycline exposure; in this arm, severe CHF events occurred in 0.4%, a level without significant difference from the control arm.

Although of relatively modest size (232 randomized patients with 116 in each arm), the FinHer trial is important given its unique trial design.[4] Trastuzumab was given prior to an anthracycline (epirubicin), and a very low incidence of cardiac events was subsequently observed. There were no severe heart failure events reported in the trastuzumab arm, and decrease in LVEF of >15% occurred more frequently in the control arm. Failure to detect significant trastuzumab-mediated cardiotoxicity in this trial has been attributed to the timing of trastuzumab relative to epirubicin as well as the lower dose of epirubicin used in this trial compared with others.

Subset analyses from these trials have identified several risk factors for the development of trastuzumab-related cardiac dysfunction. These include older age,[6,9] higher body mass index,[10] antihypertensive therapy,[9] pre-trastuzumab LVEF,[9,10] concurrent anthracycline use[6] and cumulative anthracycline dose.[10] Prior cardiac disease, traditional cardiac risk factors (e.g. diabetes mellitus), and chest irradiation did not significantly increase risk, however these negative data should not be overinterpreted as the trials were not adequately powered to identify such risk factors.

A number of intriguing findings have come from both the adjuvant trials and from analysis of the clinical course of patients who have received trastuzumab as part of their regimen for metastatic disease. Initially it was assumed that the cardiotoxicity of trastuzumab would be clinically similar to

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what had been seen with the anthracyclines, i.e. that cardiac dysfunction would be dependent on cumulative dose, that the cellular damage would result in cell death leading to permanent cardiac damage, that re-exposure to the agent in patients who had been diagnosed with drug-related cardiac damage would prove devastating, and that the ultrastructural morphology would be similar to that seen with doxorubicin.[12] However, clinical experience has not supported these assumptions.

Several unexpected aspects of trastuzumab-associated cardiac dysfunction arose: firstly that it is largely reversible and, secondly, that re-challenge with trastuzumab after an initial event was generally well tolerated. Trastuzumab-associated cardiac dysfunction was not found to be related to cumulative dose. Within a subgroup of 38 patients who experienced cardiac dysfunction attributed to trastuzumab at a major cancer centre, all recovered some or all of their cardiac function (figure 1).[13] Thirty-two of these patients received cardiac medications, but the remaining six did not. Despite the fall and recovery of the LVEF of the patients, 25 of these patients were re-challenged with trastuzumab because of progressive metastatic disease; all were receiving specific treatment for their cardiac dysfunction, and 22 of the 25 showed no recurrent decrease in LVEF (figure 1).[13]

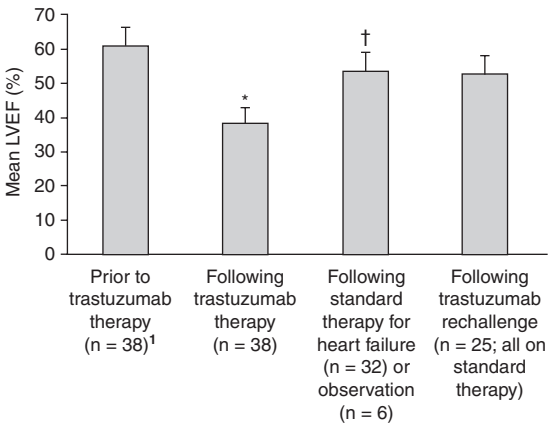

Fig. 1. Changes in left ventricular ejection fraction (LVEF) from baseline to re-challenge with trastuzumab in a selected population of patients with breast cancer. The 'T' bars represent the standard deviations. * $p < 0.05$ versus prior to trastuzumab therapy; † $p < 0.05$ versus following trastuzumab therapy. **1** 37 of 38 patients received prior anthracycline therapy (reproduced from Ewer et al.,[13] with permission from the American Society of Clinical Oncology).

Follow-up data from both the NSABP B-31 trial and the HERA trial likewise revealed evidence of substantial reversibility of trastuzumab-related cardiotoxicity. The HERA trial noted that 60% of patients treated with trastuzumab who developed a severe CHF event recovered to an LVEF ≥55%, as did 69% of patients with a confirmed initial decrease in their LVEF.[10] In the NSABP B-31 trial, 6-month follow-up data showed that 29% of patients with severe CHF demonstrated complete recovery of LVEF to pre-trastuzumab baseline, and only 25% of patients with an asymptomatic decline in LVEF after trastuzumab treatment were found to have an LVEF <50% at follow-up.[8] One risk factor for trastuzumab-related cardiotoxicity identified for the NSABP cohort was a post-anthracycline LVEF 50–54%. In the NCCTG trial, approximately 50% of patients who had trastuzumab withheld for cardiac dysfunction demonstrated recovery of LVEF and were able to restart trastuzumab.[14,15]

Strongly supporting the notion that trastuzumab cardiac dysfunction may be reversible is the finding that myocardial biopsies from patients with trastuzumab-related cardiac dysfunction do not show the typical ultrastructural changes by electron microscopy (figure 2). These observations offer substantial evidence that trastuzumab cardiac dysfunction is fundamentally different from the classic anthracycline cardiotoxicity, and this has led to the distinction of type I and type II chemotherapy-related cardiac dysfunction (table I).[16]

The concept that trastuzumab cardiotoxicity is largely reversible, however, is not uniformly accepted.[17] In a recent review, Telli et al.[17] highlight the failure of many patients to demonstrate full recovery of cardiac function after receiving trastuzumab, especially in the NSABP B-31 trial. While it is true that none of the trials demonstrated 100% recovery after a cardiac insult, the striking differences between trastuzumab- and anthracycline-mediated cardiotoxicity cannot be ignored. Furthermore, it is impossible to precisely discern the relative contribu-

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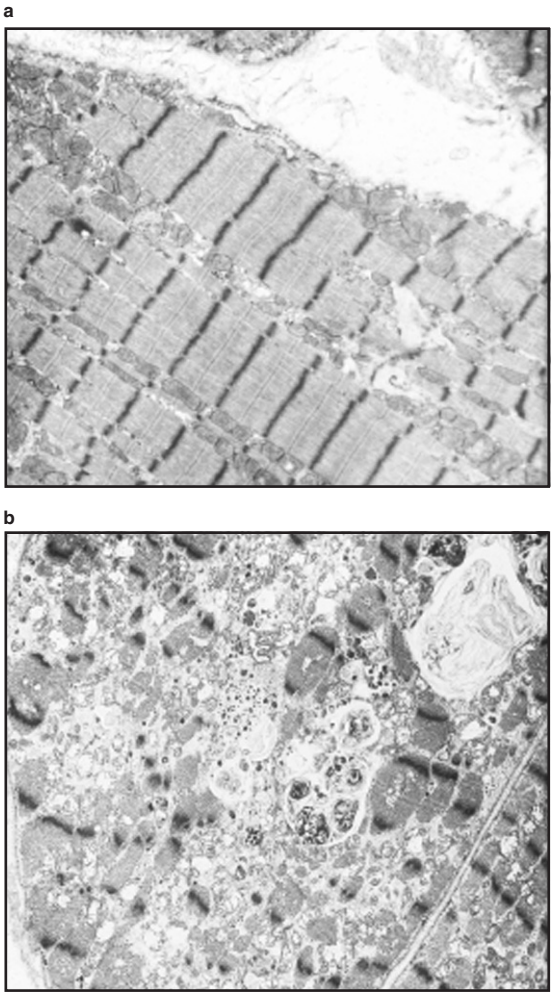

Fig. 2. (**a**) Electron micrograph of a myocardial biopsy of a patient who experienced cardiomyopathy following treatment with trastuzumab. Notably, the myocardium has a normal ultrastructural appearance. (**b**) Electron micrograph of a myocardial biopsy of a patient who experienced severe cardiotoxicity following treatment with doxorubicin. Myofibril dropout and necrosis are highly evident.

tions of anthracyclines and trastuzumab to decreases in LVEF in these groups.[18] It should also be noted that no trials have yet provided data about longer-term outcomes, and thus the possibility of late complications of trastuzumab has not yet been adequately evaluated. The authors correctly note that these follow-up data will certainly be needed to assess the impact of trastuzumab cardiotoxicity fully.

Another interesting observation is the interaction between trastuzumab and other chemotherapeutics, especially anthracyclines, with respect to cardiac dysfunction. Prior administration of the anthracycline is clearly a very important risk factor for the development of trastuzumab cardiotoxicity, as suggested by the FinHer[4] results and the non-anthracycline arm of the BCIRG 006.[3] Some trials have shown an association between cumulative anthracycline dose and future risk of trastuzumab-induced dysfunction.[10] Likewise, subtle deficits in LVEF after anthracycline therapy (reflecting subclinical myocyte damage) markedly increased risk of trastuzumab cardiotoxicity. The timing of these two drugs may also be very important. Although based primarily on data from the relatively small FinHer[4] study, it does appear that the risk of significant cardiotoxicity is quite small when trastuzumab is given prior to the anthracycline. The risk appears to be highest when the drugs are given concurrently. As more time is allowed to recover from anthracycline-mediated cardiotoxicity, a lower incidence of events is observed with trastuzumab (table II). While this observation is intriguing, it must be pointed out that strong data to support a cause-and-effect relationship between time interval of anthracycline and trastuzumab administration with the development of cardiotoxicity have not been established; clearly, additional data will be required to establish or disprove such a relationship.

3. The Mechanisms of Cardiotoxicity

The observed clinical distinctions between the cardiac effects of trastuzumab and the anthracyclines are undoubtedly explained by differences in their underlying mechanism of cardiac injury.

Table I. Clinical features distinguishing type I and type II chemotherapy-related cardiac dysfunction (CRCD)[16]

Type I CRCD (model: *doxorubicin*)	Type II CRCD (model: *trastuzumab*)
Cellular death	Cellular dysfunction
Typical anthracycline biopsy changes noted (resolve with time)	No typical anthracycline-like biopsy changes
Cumulative dose-related	Not cumulative dose-related
Permanent damage	Generally reversible

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Table II. Incidence of cardiac dysfunction correlated to timing of trastuzumab and anthracycline

Trial	FinHer[4]	Pivotal metastatic trial[6]	NSABP B-31[9]	BCIRG 006 (AC-TH)[3]	HERA[10]
Timing of trastuzumab relative to anthracycline	Pre	Concurrent	Post 21 days	Post 21 days	Post 89 days
LVEF decline ≥10% (% of pts)	3[a]	28	34	18	7
Incidence of CHF (% of pts)	0	19	4	2	0.6
Substantial reversibility reported	NA	Unconfirmed	Yes	NA	Yes

a FinHer reported incidence of LVEF decline ≥15%.

AC-TH = doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab; **CHF** = congestive heart failure; **FinHer** = Finland Herceptin; **HERA** = Herceptin Adjuvant; **LVEF** = left ventricular ejection fraction; **NA** = not available; **pts** = patients.

In the case of doxorubicin, the process is due, at least in part, to iron-based free radical-induced oxidative stress on the myocyte. Free radicals cause peroxidation of the myocyte membranes and subsequent influx of intracellular calcium.[19,20] While other mechanisms probably contribute to anthracycline cardiotoxicity as well, the collective phenotype includes myofibrillar disarray and dropout, vacuole formation and frank necrosis, leading to its irreversible nature.

The mechanism of trastuzumab cardiotoxicity is unknown, but is thought, at least in part, to be related to disruption of the epidermal growth factor signalling system that is present within the heart. Of the four ErbB receptor tyrosine kinases, ErbB2 and ErbB4 are expressed after birth.[21] Epidermal growth factor ligands such as neuregulins bind to the ErbB receptors and induce heterodimer formation and autophosphorylation, which lead to activation of G proteins and stimulation of mitogen-activated protein kinase. Among other functions, this pathway mediates the hypertrophic response of myocytes to different stimuli, and controls sarcomeric organization.[22,23] While it is known that neuregulins as well as ErbB2 and ErbB4 receptors are essential in the developing heart, it is also clear that neuregulin signalling mediates synthesis and stabilization of structural proteins and attenuates myocyte death. ErbB2-deficient adult mice develop cardiomyopathy with left ventricular dysfunction and dilation, and they are more susceptible to cardiac stress.[21] Trastuzumab likely disrupts this signalling cascade temporarily, resulting in decreased ability to mount an intact stress response.

In support of this hypothesis is the finding that myocytes from ErbB2-deficient mice are also more sensitive to anthracycline toxicity.[24] Conversely, ErbB2 receptors were found to be up-regulated in the heart within 3 weeks of anthracycline therapy, but not in controls with non-anthracycline-related heart failure.[25] These observations may in part explain the unusually high incidence of cardiotoxicity in the subgroup of patients who were treated with an anthracycline and trastuzumab concomitantly during the pivotal trials. In this setting, perhaps trastuzumab acts not only as a sequential stress upon the heart already vulnerable because of its exposure to an anthracycline – an example of an insult added to an injury[1] – but could also interfere with repair of myocyte damage related to the anthracycline injury. Thus, in the setting of recent or concurrent anthracycline-related cardiotoxicity, potentiation of cardiac dysfunction by trastuzumab could carry an irreversible contribution that would otherwise be reversible in the absence of anthracycline administration. Further studies will be required to place in perspective these alternative but coexisting mechanisms, and the extent that either plays in the clinical picture of an individual patient.

4. Clinical Considerations Regarding Cardiotoxicity

A wealth of data has been accumulated from the women treated with trastuzumab in the five large

1 This terminology was originally suggested by Dr Lynne W. Stevenson, Boston, MA, USA (personal communication).

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adjuvant clinical trials. Nevertheless, there is still confusion regarding treatment with trastuzumab, including how big a problem cardiotoxicity really is, how clinicians should manage patients likely to receive this agent, how best to monitor cardiac function of patients during their course of therapy, and how to follow-up patients adequately after exposure to trastuzumab. Some of this uncertainty stems from the fact that the trials were initiated before the concept of reversibility of cardiotoxicity was considered: the trials simply report cardiotoxicity as an event. Another problem is the difficulty in distinguishing type I and type II cardiotoxicity clinically when a patient has received multiple agents.

There are a number of additional factors that complicate recognition and monitoring of trastuzumab-related cardiac dysfunction. There is no easily performed cardiac test to assess cardiac damage. Measuring ejection fractions may not be reliable because this parameter can fluctuate with conditions unrelated to the medication under surveillance and measurement is subject to inter-observer variations. Furthermore, the heart has very significant reserves, and symptoms as well as ejection fraction decreases may only occur after the loss of significant myocardial function. Cardiac biopsy, notwithstanding its invasive nature, cost and risk, does not provide satisfactory answers with regard to trastuzumab cardiotoxicity. The available biochemical markers, although highly promising, are not yet sufficiently well developed to be used as a routine screening test. Serum biomarkers of cardiac disease such as B-type natriuretic peptide and troponin-T have been examined in the context of anthracycline therapy and show potential as sensitive indicators of chemotherapy-related cardiac dysfunction.[26,27] Although this has not been explored in any depth for trastuzumab to date, ongoing research may show utility in early detection of cardiac complications.

When all of these problems are taken into consideration, we are left with the fact that some patients have clearly decreased left ventricular function on imaging studies that may or may not be related to trastuzumab, that may or may not recover (either with or without treatment), and that if it is related to chemotherapy may result from either trastuzumab or another agent that was given prior to or concomitantly with the antibody. What will happen with these patients over years and decades is also not fully known, and remains a matter of considerable concern. It is, therefore, not surprising that algorithms to deal with these problems have been slow to evolve.

4.1 Preliminary Guidelines for Cardiac Monitoring for Trastuzumab

A number of groups are currently addressing the question of appropriate cardiac monitoring of patients treated with trastuzumab, but to date there has not been a consensus, nor have formal recommendations been published. Nevertheless, some guidance with regard to monitoring can be presented; these are based on material presented in abstract form at the St. Gallen Breast Cancer Congress of March 2007 as well as on the preferences of the authors.[28]

All patients with breast cancer are now routinely screened for HER2 positivity by either fluorescence *in situ* hybridization or immunohistochemistry. Where use of trastuzumab is appropriate, a baseline assessment of LVEF should be obtained, and if an anthracycline is to be used, consideration of some form of cardioprotection should be considered.[29] The concomitant use of an anthracycline with trastuzumab is not recommended at present. Following completion of the anthracycline-based phase of treatment, a follow-up estimation of LVEF should be undertaken; patients with normal function may proceed with trastuzumab administration. Patients with increased cardiac risks, defined as those with borderline ejection fractions (usually 40–50%), the elderly, and those with underlying heart disease, may be considered as intermediate risk in terms of trastuzumab cardiotoxicity; they may start trastuzumab, but increased surveillance is recommended, and risk-benefit relationships should be carefully considered.

Follow-up studies for patients without elevated risk may be undertaken after 6 months, at the conclusion of trastuzumab therapy, and yearly thereafter for 3 years. Those with elevated risk should

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have follow-up examinations and repeat estimation of their ejection fraction every 3 months while on therapy, and every 6 months for 5 years thereafter. If late cardiac complications attributable to trastuzumab are discovered, even longer term monitoring may be appropriate.

Any patient receiving trastuzumab who develops symptoms deemed to be cardiac in origin should be evaluated at the time of presentation, and strong consideration should be given to stopping the drug. We have generally not reintroduced trastuzumab after a patient has reached a cardiac endpoint when the drug is used in the adjuvant setting. However, for patients being treated in the metastatic setting, if trastuzumab therapy is interrupted because of changes in cardiac function, it may be appropriate to re-initiate therapy in some patients; this should only be undertaken in selected patients for whom the risks and benefits have been considered carefully.[13] Ejection fraction parameters for stopping trastuzumab (based on the parameters used in some of the clinical trials) include an absolute decrease of 15% from the pre-anthracycline baseline, or a decrease of 10% that results in a level below the lower limit of normal for the laboratory.

Although no studies have examined the role of medical therapy for trastuzumab cardiotoxicity, standard medical therapy for heart failure, including β-adrenoceptor blockers and ACE inhibitors, should be considered once cardiac dysfunction has been identified. Even considering the potentially reversible nature of the insult, trastuzumab-related cardiac dysfunction may in fact be unmasking prior anthracycline damage with associated loss of contractile reserve. The predilection for heart failure in this group of patients argues for neurohumoral blockade to prevent further remodelling.

It must be emphasized that these guidelines should be regarded as preliminary, and they may be modified as groups actively involved in this field of cardiology review additional data as it evolves; recommendations of such consensus groups should be carefully scrutinized and updated.

5. Conclusions

Trastuzumab cardiac dysfunction is inherently different from the cardiotoxicity of the anthracyclines in its mechanism, pathology and clinical features. A clear understanding of these differences is essential to enable the antineoplastic potential of this agent to be maximized while avoiding severe or protracted cardiac adverse effects. While often reversible, it is difficult at the time of presentation to separate cardiac effects of trastuzumab from those of other agents that may demonstrate similar clinical cardiac effects, but from a different mechanism and with different implications.

At present, monitoring consists of standard non-invasive assessments of cardiac systolic function; although the methods are neither sensitive nor specific for trastuzumab-related disease, these remain the most commonly used parameters for following these patients clinically. Biomarkers in the field of cardiotoxicity offer considerable hope but are not yet sufficiently well studied.

Preliminary guidelines include a careful assessment of ejection fraction prior to initiating trastuzumab, avoidance of concurrent administration of trastuzumab with anthracyclines, and regular monitoring of symptoms and cardiac function during and for some period after therapy. Increased vigilance is appropriate for higher risk patients.

While there are few hard data available, it now appears that trastuzumab-related cardiac dysfunction, especially in its mildest manifestations, may be missed frequently because it resolves in so many of the cases. Along with the possibility of under-appreciation of the incidence, there may well be an over-appreciation of the clinical significance. In all five of the adjuvant trastuzumab clinical trials there was only one death deemed related to trastuzumab cardiotoxicity. Thus, severe cardiomyopathy and cardiac deaths are rare with trastuzumab.

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