Research Review
SPEAKER SERIES

Chemotherapy-related cardiac safety - June 2011

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Michael Ewer is Professor of Medicine at The University of Texas MD Anderson Cancer Center where he has been active in the field of cardiotoxicity of anti-cancer treatment for more than three decades. Dr Ewer is a graduate of the University of Basel Medical Faculty in Switzerland and undertook his post-doctoral work in the United States.

Dr Ewer has established the concept that some forms of cardiotoxicity start with the first cardiotoxic exposure, and subsequent treatments constitute additive or sequential stresses. He was the first to recognise the distinction between Type I and Type II cancer treatment-related cardiotoxicity. Dr Ewer has over two hundred publications, including the book *Cancer and the Heart*. He has lectured frequently throughout the United States, Europe, and Asia.

Additionally, Dr Ewer is an attorney with an advanced (Master's or LLM) degree in health law; he is an Adjunct Professor of Law at the University of Houston Law Center.

Dr Ewer has a special interest in cardiotoxicity of anti-cancer treatments, medical ethics and patients' rights, all areas where he is recognised as an international authority.

This publication is a summary of a presentation by Dr Michael S Ewer, Professor of Medicine at The University of Texas MD Anderson Cancer Center, US. He spoke throughout New Zealand in June 2011 about chemotherapy-related cardiac safety.

Cardiovascular toxicity due to chemotherapy may not only result in a loss of contractility of the heart, but may result in ischaemia, arrhythmia, dyslipidaemia, hypertension, hypotension with or without vascular collapse and cardiomyopathy. Of particular interest to Dr Ewer and colleagues is heart failure associated with the use of chemotherapeutic agents. Heart failure, a haemodynamic disorder caused by an impaired muscular pump, can be categorised into mild or severe, and may be potentially of future importance, symptomatic or life threatening. Heart failure may be considered in terms of systolic dysfunction, where the myocardium is unable to contract effectively, and diastolic dysfunction, in which the heart is unable to relax satisfactorily. Systolic dysfunction is the focus of this presentation.

Clinical symptoms of heart failure include breathlessness, fatigue, weight gain, an increased cardiac silhouette, paroxysmal nocturnal dyspnoea and engorged veins.

New and old cancer drugs – not just the same old cardiotoxicity!

It is now known that there are two main types of heart failure associated with the use of chemotherapeutic agents, Type I which is irreversible and Type II which is reversible; in some settings, a continuum exists between these two types. In Type II heart failure, temporary dysfunction may result from myocyte stunning, whereas in Type I heart failure cell death results in permanent damage. The clinical presentation of Type I and II cardiotoxicity is identical and only time hints at the contributions of the type of injury in any given case.

Type I heart failure – mostly an anthracycline phenomenon

Type I heart failure is mostly an anthracycline phenomenon. While anthracyclines such as doxorubicin continue to play a prominent role in the treatment of breast cancer, lymphoma and leukaemia, cardiotoxicity associated with these agents can be a devastating and sometimes fatal event. There is a definite need to maintain the therapeutic benefits of these agents while minimising cardiotoxic risk. Unfortunately, the potential cardiac sequel of these agents is usually delayed and may be discovered decades after chemotherapy.

In Type 1 cardiotoxicity, cellular death occurs from the first administration of the chemotherapeutic agent and this insult continues with each dose. Therefore, a cumulative dose-related response is seen. Biopsy changes are typical of anthracyclines and this damage is permanent as cardiac myocytes generally do not replace themselves. Furthermore, newer agents have complicated the picture, but an understanding of their cardiotoxicity is now becoming clear.

Drugs associated with impaired muscle function

The agents listed below are the drugs responsible for Type I damage (left) and Type II damage (right).

Anthracyclines

- doxorubicin
- idarubicin
- epirubicin
- daunorubicin

Anthraquinones

- mitoxantrone

Toxicity Intensifiers

- cyclophosphamide
- mitomycin-C
- etoposide
- vincristine
- bleomycin
- ifosfamide

Other

- trastuzumab
- lapatinib
- sunitinib

Acute and chronic cardiotoxicity of anthracyclines

The cardiotoxicity associated with the use of anthracyclines appears to have two phases, acute and chronic. Acute cardiotoxicity associated with anthracyclines occurs days to weeks after therapy. Patients experiencing such an event may present with small ECG changes, vague chest pain assumed to be myopericarditis, and/or low-grade fever. Such patients tend to improve and their ejection fractions are usually normal.

Previously, acute toxicity was not considered to be of major clinical importance. However, investigations by Cardinale and colleagues revealed that troponin I, a marker of cell death, is released at the time of exposure to high-dose chemotherapy.[1] In fact, they discovered that the troponin I release pattern after high-dose chemotherapy identifies patients who are at different levels of risk for cardiac events in the 3 years following exposure. It is clear that early toxicity may reflect damage seen months or years later.

Chronic anthracycline-induced cardiotoxicity may result in heart failure and this may have a sub-acute onset, often occurring months after treatment. However, this can occur as early as weeks after treatment in severe forms and it is more likely to occur early when cardiac protection has not been utilised. Late-onset cardiotoxicity may take years to occur and is more frequently reported in children. It reflects the end stage of the damage that occurs at the time of exposure and this may be related to sequential stresses.

Why the heart?

The heart has a relative lack of biochemical reserves to handle free radical burden; the myocardium lacks catalase and glutathione peroxidase is quickly depleted by doxorubicin. Furthermore, the myocardium has a low capacity for cell renewal, with possibly only a low percentage of cells renewed each year.

Clinical presentation and risk factors for cardiac damage

The clinical presentation of cardiac damage typically consists of congestive heart failure (CHF), shortness of breath, a reduction of functional capacity, resting tachycardia and a symptom commonly missed by oncologists, persistent exercise-induced tachycardia. Exercise-induced persistent tachycardia is, in fact, the earliest sign of cardiac damage. It is important that clinicians make the diagnosis of chemotherapy-induced cardiotoxicity as early as possible in order to intervene before significant irreversible damage occurs.

It became evident fairly shortly after the introduction of anthracyclines that not all patients develop cardiotoxicity at the same time, with some developing heart failure sooner after the initiation of therapy than others. Several risk factors for cardiotoxicity include cumulative drug dose, combination chemotherapy, prior or concomitant mediastinal radiotherapy, age (paediatric and elderly), and previous cardiac disease including hypertension and valvular disease.

Prevention/reduction of anthracycline cardiotoxicity

The initial goal in therapy was to mitigate the toxicity associated with anthracyclines. An obvious way was to reduce the total (cumulative) dose to ≤400 mg/m^2, but a more effective approach was to use a continuous infusion of the agent over 48-96 hours, thus reducing the peak plasma concentration of the drug compared with that achieved with a more rapid infusion. Another effective approach was the liposomal formulation of the agent. As too were cardiac protectors such as dexrazoxane and the use of less toxic anthracyclines such as epirubicin.

The mechanism of anthracycline-induced cardiotoxicity

Immediate and irreversible cardiac damage occurs acutely, with increased troponin T and structural abnormalities evident on cardiac biopsy. This immediate injury is followed by a period of compensation where hypertrophy, increased heart rate, slight heart enlargement and changes in the Starling curve result in maintenance of a grossly normal ejection fraction. However, these patients are still vulnerable, and in about 5% of patients who receive the highest dosages (>400 mg/m^2) a failure to compensate adequately results in an abnormal resting ejection fraction. Such patients are extremely vulnerable to sequential stress, often suffering end-stage heart failure. Mann in the late 90s devised a general conceptual framework for explaining the pathogenesis of heart failure (see **Figure 1**).[2] In their model showing a single myocyte, damage is seen to occur after an index event, such as the use of anthracyclines and this produces an initial decline in the pumping capacity of the heart. In response to this, a number of compensatory mechanisms are activated in the short-term. These responses are able to restore cardiovascular function to a point where the patient appears asymptomatic. However, with time, the sustained activation of these mechanisms leads to cardiac decompensation.

Dr Ewer emphasises that it is thought that such injury occurs in all patients receiving the maximum tolerated dosages of anthracyclines and that compensatory changes are attempted in all of those patients, but that 5% of patients fail to compensate. He also says that if we monitor and treat such patients in a manner to reduce sequential stress, the mechanism leading to heart failure will move ahead more slowly. Furthermore, patients may remain stable for long periods despite considerable cardiac damage.

How do we look for subclinical damage?

Left ventricular ejection fraction (LVEF) is an imperfect marker of cardiotoxicity because any decrease in LVEF is assumed to be due to chemotherapy, but may in fact relate to other concomitant medications. In contrast, an unchanged LVEF is often equated to a lack of cardiotoxicity, but this may instead reflect adequate capacity for cardiac compensation. A decreased LVEF in association with other cardiac biomarkers may provide more convincing evidence of early damage. When a decreased LVEF is truly related to the drug, it indicates that a patient is no longer able to compensate and is a marker for advanced myocyte damage.

What is the evidence for early damage?

The relationship between the percentage of congestive heart failure (CHF) and cumulative doxorubicin dose first published by Von Hoff in the 1970s indicates a flat curve at cumulative doses up to 400 mg/m^2, but an acceleration in loss of function above this dosage.[3] However, while compensation maintains LVEF at lower anthracycline doses, cardiac biopsy data from patients who had received doxorubicin revealed significant cellular damage at doses between 200 and 400 mg/m^2.[4] Furthermore, the study showed exceptional cellular damage at doses of 400-500 mg/m^2, but a normal LVEF in 95-98% of those patients.

An example of the type of myocyte damage that may be seen in patients receiving even low-doses of anthracyclines is shown in **Figure 2**. Patients such as this one can have a normal LVEF, but cells damaged to this extent are destined not to survive.

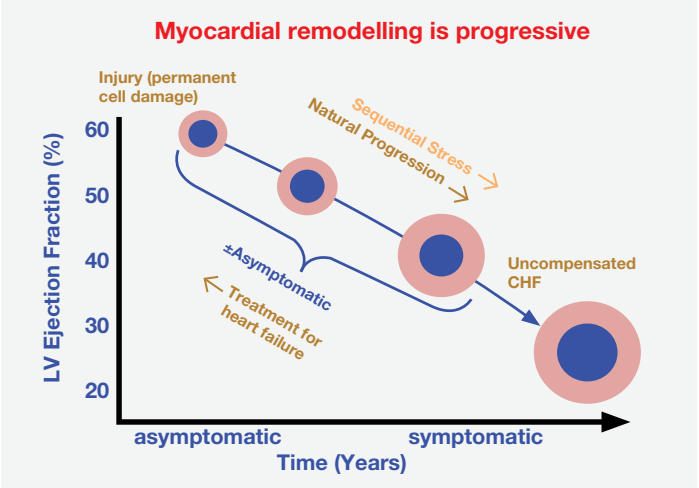


Figure 1: Diagram showing that myocardial remodelling is progressive and that changes such as hypertrophy occur initially in response to an initial insult such as exposure to anthracyclines, but that with further sequential stress the patient is unable to compensate and becomes symptomatic. (Adapted from Mann 1999[2])

CHF = congestive heart failure; LV = left ventricular

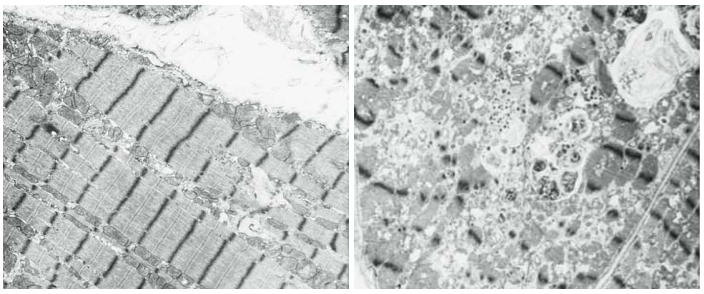


Figure 2: Normal heart cell (left) and heart cell in a patient receiving 200 mg/m^2 doxorubicin (right). The extent of cellular damage is such that this cell would be destined not to survive.

A mathematical prediction indicating that the likelihood of developing CHF is a function of the number of cycles of chemotherapy squared, divided by a correction factor of 16 for a dosage of 50 mg/m^2 per cycle, allowed the correct prediction of the incidence of cardiotoxicity in ongoing adjuvant trials to be ~1% (see **Figure 3**).

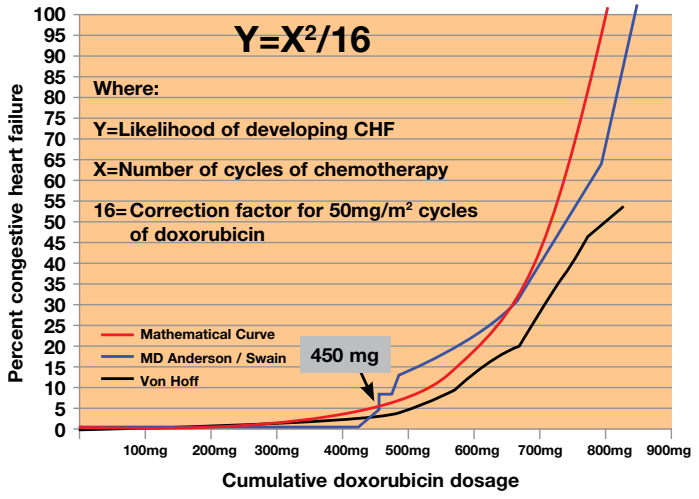


Figure 3: Mathematical model for the prediction of the likelihood of doxorubicin-induced congestive heart failure according to cumulative dose.

Early prevention of damage is paramount

The earlier anthracycline damage is prevented, the more successful that prevention will be, and the greater the possibilities for future therapies. Protection should be initiated prior to evidence of CHF; however, early interruption of treatment also risks treatment failure, so a balance is required. In other words, too sensitive detection of heart damage may impact oncological survival and cardiologists and oncologists need to keep this in mind.

Type II treatment-related cardiac dysfunction

While cardiac dysfunction associated with newer agents was initially thought to be similar to that of the anthracyclines, several aspects did not fit with that model, and a variant form of cardiac dysfunction was ultimately defined.

Trastuzumab

The cardiac effects seen with trastuzumab were clearly not the same as those observed with anthracyclines. Trastuzumab seems to cause cellular dysfunction, but does not cause typical anthracycline-like biopsy changes, is not cumulative and the injury is predominantly reversible. Dr Ewer first identified this phenomenon in treating a patient with metastatic breast cancer who had developed a LVEF in the 30s while on trastuzumab, and in whom the agent had been discontinued. She subsequently requested re-initiation of the agent and was granted this on compassionate grounds. Reinstigation of the agent did not cause CHF, her LVEF remained within the normal range, and she died approximately 18 months later as a result of her cancer. Subsequent investigations of 30 similar patients revealed the same findings, with such patients continuing on trastuzumab for years without cardiac sequelae.

Risk factors for this new type of toxicity include prior or concomitant anthracyclines or paclitaxel, age, previous cardiac disease or hypertension and a BMI >25 kg/m^2. Thus, while toxicities seemed different to those seen with Type I agents, the risk factors were similar.

Is the timing of trastuzumab important?

Examination of the data from several trials suggested that concomitant use of anthracyclines and trastuzumab produced much more severe effects than when the application of trastuzumab was delayed by approximately 30 (incidence of CHF 1.9-3.8%) or 90 days (0.6%) (see **Figure 4**).[5] In the Finland Herceptin (FinHer) Study, trastuzumab preceded the anthracycline and no CHF was reported.[6]

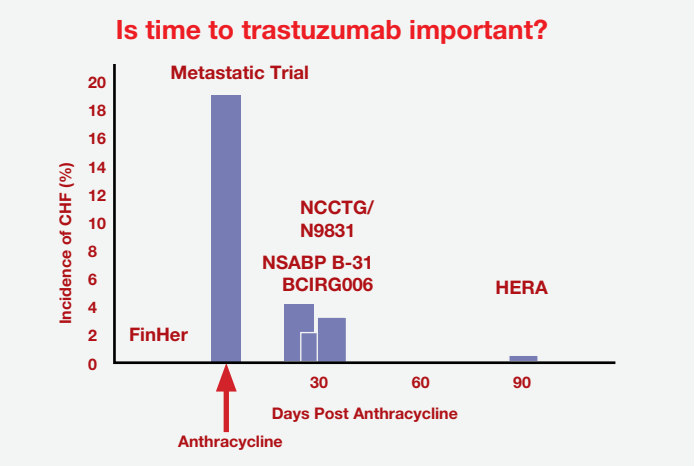


Figure 4: The relationship between the observed incidence of congestive heart failure (CHF) and the time between the administration of doxorubicin and trastuzumab. Data from the pivotal and adjuvant trastuzumab trials. The worst cardiotoxicity was seen in the metastatic trial where trastuzumab and the anthracycline were given concomitantly. (Adapted from Ewer et al[5])

BCIRG006 = Breast Cancer International Research Group 006[7]; FinHer = Finland Herceptin Study[6]; HERA = Herceptin Adjuvant Trial[8]; Metastatic Trial = a Single Agent in First-Line Treatment of HER2-Overexpressing Metastatic Breast Cancer[9]; NCCTG/N9831 = North Central Cancer Treatment Group N9831 adjuvant breast cancer trial[10]; NSABP B-31 = National Surgical Adjuvant Breast and Bowel Project B-31[11]

It appears that any cell that is damaged by anthracycline treatment is then susceptible to trastuzumab interfering with cellular repair and is more likely to die, thus trastuzumab enhances anthracycline induced damage. In fact, de Korte and colleagues have demonstrated that myocardial HER2 may be transiently upregulated by a compensatory mechanism following cardiac stress in humans shortly after anthracycline administration.[12]

Therefore, the timing of trastuzumab use is critically important and the risk factor profile of trastuzumab may be reduced by considering whether anything has already damaged the heart and if there is anything that makes the heart more susceptible to ongoing stresses. Clearly, waiting for a period of time for cellular recovery post-anthracycline to occur before treating with trastuzumab, results in less damage.

In the BCIRG006 trial, in the absence of anthracycline use (within the docetaxel + carboplatin + trastuzumab arm) the incidence of grade 3 or 4 CHF was 0.4%, with a decreased ejection fraction of >10% in 8.6% of patients.[7] If trastuzumab is used sequentially more than 90 days after use of anthracycline the incidence of CHF is also very low (0.6% HERA). This provides evidence that if one waits long enough after anthracycline therapy, trastuzumab does not cause any significant additional damage.[8]

Why, if Type II cardiac damage is reversible, do some patients not recover?

It appears that the Type II agent interferes with cellular repair of vulnerable cells that might have otherwise recovered and results in a greater overall injury (see **Figure 5**). The greater the underlying injury, the more vulnerable the heart, the smaller the cardiac reserves, and the more likely it is that the Type II agent will augment the Type I injury. Taken in isolation, the Type II agent causes reversible injury, but when additional myocardial stresses are imposed, additional cellular death may occur. Despite this finding, the low level of risk is reflected through the paucity of deaths seen in the trastuzumab adjuvant trials. In the 10 000 women who have received trastuzumab in such trials, only one death appears to have occurred.

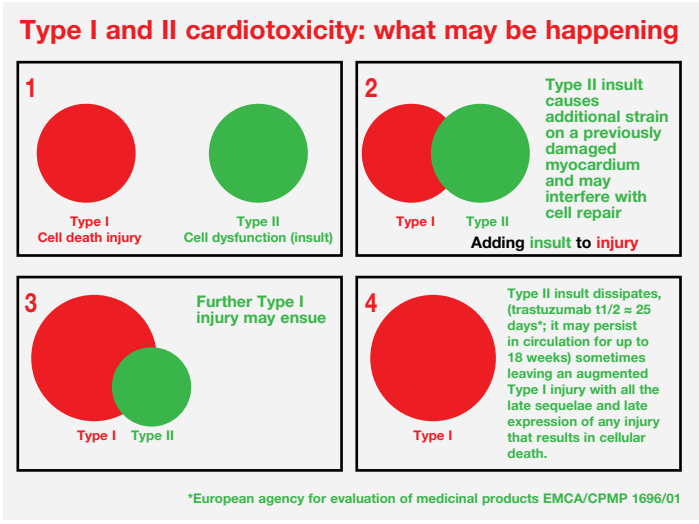
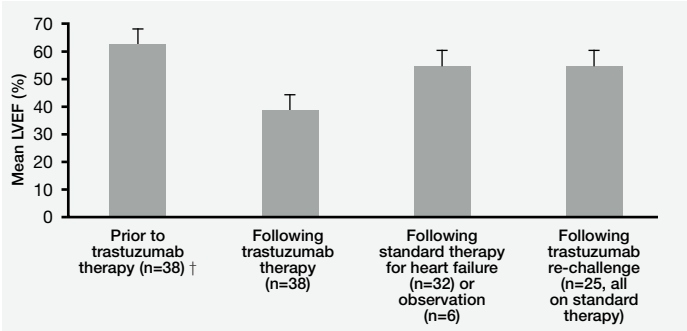


Figure 5: A schematic explanation for the mechanisms involved in Type 1 and II chemotherapy-induced cardiotoxicity.

In most patients, the effects of trastuzumab are highly reversible and rechallenge does not appear to induce further damage (see **Figure 6**).



† = prior anthracyclines in 37 of 38 patients

Figure 6: Changes in left ventricular ejection fraction (LVEF) from baseline to re-treatment with trastuzumab in a selected population (38 cardiac events suspected to be due to trastuzumab therapy were identified from 1000 patients previously treated with anthracyclines). Standard therapy for heart failure included an angiotensin-converting enzyme inhibitor and beta-blocker therapy.[13]

It may therefore be concluded that cardiac damage induced by anthracycline is often sub-clinical and difficult to measure because the heart compensates for minor damage and the tools to measure the damage are suboptimal. Subsequent insult with trastuzumab which might normally be reversible may then cause the sub-clinical dysfunction to reach a threshold where it progresses to full-blown CHF.

Long-term effects

It is unclear at this point what the long-term implications for Type II decreases in ejection fraction are. The effects are probably different from those of Type I, but as yet patients have

not been followed for long enough to know what will happen over decades. Will cardiac treatment have the same impact as it does in Type I toxicity and, if it is beneficial, how long should treatment be continued?

Guidelines for use of trastuzumab

Clinical guidelines developed by an international group of cardiologists and oncologists for initiating adjuvant trastuzumab, divided patients into three groups: those with an LVEF ≥50% in which there are no restrictions on chemotherapy from a cardiac safety perspective (although trastuzumab should not be given concurrently with anthracyclines), those with an LVEF of 40-50% in whom trastuzumab monotherapy following all chemotherapy or with non-anthracycline-containing chemotherapy should be considered, and patients with an LVEF <40% in which treatment options should be at the discretion of the clinician balancing the risk of cardiac toxicity versus the risk of under-treatment of the tumour. All patients should be regularly monitored after completion of treatment.

Patients with an asymptomatic decline in LVEF (≥15% or ≥10% and below the lower limit of normal [50%]) during adjuvant trastuzumab are considered in two groups. Those in whom the LVEF is 40-50% should continue on trastuzumab with monthly LVEF monitoring, whereas those with an LVEF ≤40% should be removed from trastuzumab treatment and a cardiologist consulted. If LVEF recovers to ≥40% treatment may be reinitiated with cardiac support at the discretion of the cardiologist. If LVEF falls below 40%, and remains there, trastuzumab should be reconsidered only if compelling reasons require it and with cardiac support at the discretion of the cardiologist (see **Figure 7**).

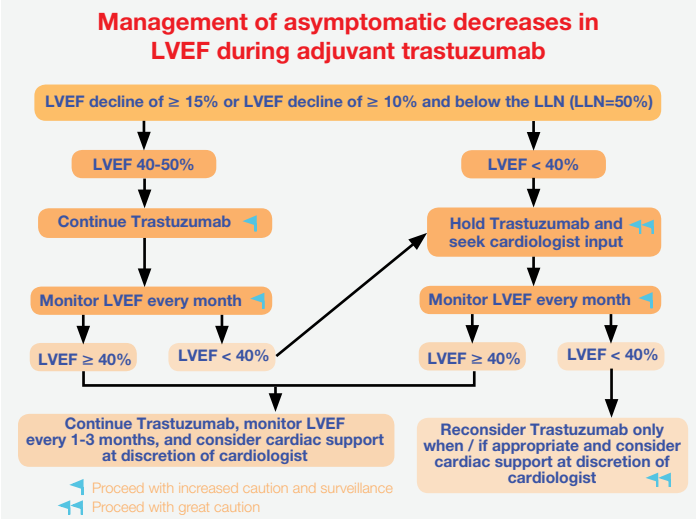


Figure 7: Algorithm for the management of asymptomatic decreases in left ventricular ejection fraction (LVEF) during treatment with adjuvant trastuzumab.
LLN = Lower Limit of Normal

In patients with symptomatic cardiac events, treatment for patients with New York Heart Association (NYHA) functional class II mild symptomatic disease should follow the asymptomatic algorithm (see **Figure 7**). In patients with NYHA class III/IV severe symptomatic disease not due to other causes, trastuzumab should be halted and the patient monitored in consultation with a cardiologist. (see **Figure 8**).

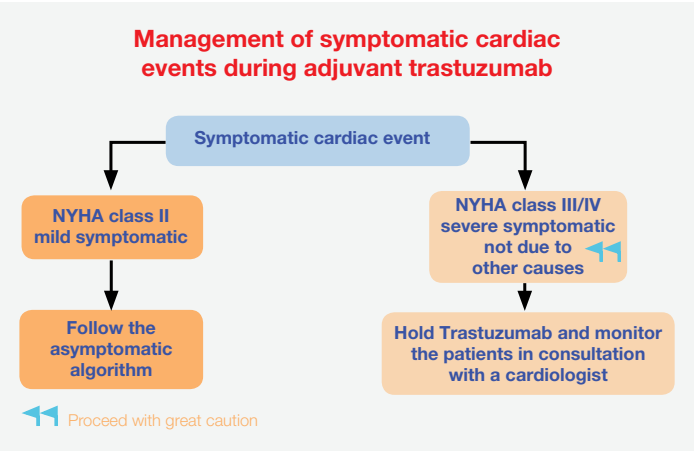


Figure 8: Algorithm for the management of symptomatic cardiac events during treatment with adjuvant trastuzumab.

Treatment for patients with symptomatic CHF include ACE inhibitors and beta blockers. For these patients, further treatment with anthracyclines is contraindicated.

In conclusion

There are two types of chemotherapy-related cardiac dysfunction. Anthracycline-associated cardiotoxicity and trastuzumab-associated cardiac dysfunction are qualitatively different. Anthracyclines are associated with acute and chronic events with early destruction of cardiac myocytes and compensation followed by decompensation in a small number of patients. Better tools are needed for early detection of cardiac toxicity and improving cardiac outcomes. Clearer indications are required for the use of anthracycline and non-anthracycline regimens. Also needed are better imaging modalities and biologic markers for early recognition of dysfunction, and clear guidelines on starting, holding, stopping and post-treatment surveillance.

Take home messages

Anthracycline toxicity;

- Is cumulative dose related
- Can be mitigated
- Probably starts at first administration
- Causes characteristic biopsy changes
- Results in cell death
- Can lead to fatal cardiac damage
- Can cause reversible early damage

Type II cardiotoxicity is different from Type I in that;

- It is reversible
- Typical anthracycline biopsy findings are absent
- There is no cumulative dosage phenomenon
- There is a paucity of cardiac deaths in adjuvant trials

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