Trastuzumab, a drug targeting human epidermal growth factor receptor 2, improves survival rate in women with metastatic breast cancer. Symptomatic heart failure, a serious adverse effect of trastuzumab, occurs in 1% to 4% of patients treated with the antibody, whereas left ventricular ejection fraction declines substantially in 10% of patients. The prevalence of cardiotoxic effects of trastuzumab appears to increase with exposure to anthracyclines. Serial assessment of left ventricular function with 2-dimensional echocardiography or radionuclide ventriculography is the most practical means of monitoring cardiotoxicity. Patients who develop cardiotoxicity while receiving trastuzumab therapy generally improve once use of the agent is discontinued.


CHF = congestive heart failure; CREC = Cardiac Review and Evaluation Committee; EF = ejection fraction; EGFR = epidermal growth factor receptor; ERBB2 = human epidermal growth factor receptor 2; HERA = Herceptin Adjuvant trial; LV = left ventricular; NSABP = National Surgical Adjuvant Breast and Bowel Project; NYHA = New York Heart Association

Cardiac cells do not divide after birth, but they often become “innocent bystander” targets of anticancer drugs designed to interfere with cell signaling pathways.1,2 Trastuzumab (Herceptin, Genentech Inc, South San Francisco, CA), a humanized monoclonal antibody directed against the extracellular domain of human epidermal growth factor receptor 2 (ERBB2, formerly HER2 or HER2/ neu), is a recent addition to the anticancer armamentarium that improves survival rate in women with metastatic breast cancer; however, it causes heart failure, particularly when used in combination with anthracyclines.2,3 Using PubMed, we searched the literature in September 2007 using the query “("trastuzumab"[Substance Name] OR trastuzumab[Text Word]) AND (("heart"[TIAB] NOT Medline[SB]) OR "heart"[MeSH Terms] OR cardiac[Text Word]) AND ("toxicity"[Subheading] OR toxicity[Text Word]) AND English[lang]” and identified 82 published articles. In limiting the number of articles evaluated, preference was given to larger cohort studies, randomized controlled trials, comprehensive reviews, meta-analyses, quality of peer-reviewed publications, and published guidelines.

CLINICAL BENEFITS OF TRASTUZUMAB

Breast cancer is the second most common form of cancer in women and the leading cause of death caused by malignancy. The ERBB2 gene is amplified in approximately 25% of breast cancers, and ERBB2 protein overexpression is associated with poorly differentiated, high-grade tumors; high rates of cell proliferation; lymph node involvement; and resistance to chemotherapy agents.4,5

Trastuzumab was approved by the US Food and Drug Administration in September 1998 for the treatment of metastatic breast cancer. The first phase 2 trial of trastuzumab involved 46 women with metastatic breast cancer.6 Clinical benefit of trastuzumab was seen in 12% of patients6 and was further confirmed in a larger, multicenter, phase 2 trial.7 In the pivotal phase 3 trial, addition of trastuzumab to doxorubicin and cyclophosphamide or to paclitaxel chemotherapy resulted in a 20% reduction in the risk of death among patients with metastatic disease.8 A later randomized trial of docetaxel alone or with trastuzumab showed similar results.9

Use of trastuzumab has been extended to treat ERBB2-positive early breast cancer.10 Among 4 major adjuvant trials (Herceptin Adjuvant trial [HERA], National Surgical Adjuvant Breast and Bowel Project [NSABP] B-31, North Central Cancer Treatment Group [NCTCG] N9831, and Breast Cancer International Research Group [BCIRG] 006), more than 13,000 women with ERBB2-positive early breast cancer were enrolled.10-11 A cumulative analysis of these trials showed that trastuzumab reduced the 3-year risk of recurrence of breast cancer by about one-half.10 Therefore, trastuzumab therapy given in combination with one of several chemotherapy regimens is currently considered the standard of care for the treatment of early-stage, ERBB2-positive breast cancer.14

PREVALENCE OF TRASTUZUMAB-INDUCED CARDIOTOXICITY

Cardiotoxicity was not reported in the preclinical and early clinical trials of trastuzumab and therefore was an unantici-
TRASTUZUMAB-INDUCED CARDIOTOXICITY

Pate finding in the phase 3 clinical trials.\textsuperscript{13} Although heart failure was seen in some patients participating in phase 2 trials, the rate of occurrence was sufficiently low, and patients were at increased risk because of anthracycline preexposure. Moreover, the phase 2 program focused on single-agent therapy and the interaction of trastuzumab with cisplatin, and data regarding the combined use of anthracyclines and trastuzumab were not initially available.\textsuperscript{15}

Subsequent reports of trastuzumab-related cardiotoxicity in the phase 3 combination chemotherapy trials resulted in establishment of an independent Cardiac Review and Evaluation Committee (CREC) to assess the adverse cardiac effects of trastuzumab therapy.\textsuperscript{16} Data from 1219 patients enrolled in 7 trials were retrospectively analyzed. A comprehensive assessment of cardiotoxicity in these trials was difficult because the trials varied in design with respect to the number of patients, definition of cardiotoxicity, analysis of end points, and duration of follow-up. CREC used a new set of criteria to identify or revise a preliminary diagnosis of cardiotoxicity: (1) cardiomyopathy characterized by a decrease in left ventricular (LV) ejection fraction (EF) that was either global or more severe in the septum; (2) symptoms of congestive heart failure (CHF); (3) associated signs of CHF, including but not limited to S3 gallop, tachycardia, or both; and (4) decline in LVEF of at least 5% to less than 55% without accompanying signs or symptoms of CHF or decline in LVEF of at least 10% to below 55% without accompanying signs or symptoms. Any 1 of the 4 criteria was sufficient to confirm a diagnosis of cardiotoxicity. Events were also categorized by the New York Heart Association (NYHA) functional classification system. Using these criteria, cardiotoxicity was identified in 112 patients (9.2%). The rate of cardiac dysfunction with use of trastuzumab varied from 1% to 27% in different arms of these trials and was higher when trastuzumab was used concurrently with anthracyclines.\textsuperscript{16}

Despite the findings of CREC, the profound improvement in outcomes in women with metastatic breast cancer led investigators to incorporate trastuzumab in later trials with appropriate cardiac monitoring (Table). The study design in these trials mandated baseline measurement of LVEF using radionuclide scans or echocardiograms and excluded patients with abnormal cardiac function, high doses of cumulative anthracycline exposure, and/or preexisting heart disease. A pooled analysis from the randomized controlled trials and case control studies suggested that the prevalence of cardiotoxicity was 10% (95% confidence interval, 0.07-0.15).\textsuperscript{17} In contrast, the pooled prevalence of cardiotoxicity in studies using the non-trastuzumab comparator arm was 2% (95% confidence interval, 0.01-0.04).\textsuperscript{17} In a separate meta-analysis of 5 randomized controlled trials, a significant increased risk in severe CHF was found in the treatment arm in which trastuzumab was administered for 1 year, with an absolute difference of 1.61% (P<.0001), meaning that if 62 patients are treated, I will have an adverse effect.\textsuperscript{18}

**CLINICAL COURSE OF TRASTUZUMAB-INDUCED CARDIOTOXICITY**

In the CREC review, NYHA class III/IV symptoms were more common among patients in the anthracycline plus trastuzumab arm than in those in the paclitaxel plus trastuzumab arm.\textsuperscript{16} Approximately 75% of the patients with cardiac dysfunction presented with symptoms. Most of these patients were treated with diuretics (78%), angiotension-converting enzyme inhibitors (58%), cardiac glycosides (58%), or other inotropes, and 79% responded to these therapies. Cardiac deaths were rare and were reported in 9 patients from the 7 trials reviewed by CREC.\textsuperscript{16} The prevalence and progression of cardiotoxicity in patients receiving trastuzumab in the neoadjuvant trials are summarized in the Table.

Patients who develop cardiotoxicity while receiving trastuzumab therapy generally improve once use of the agent is discontinued. However, current information is limited regarding the potential long-term effects of trastuzumab on cardiac function. In a study performed at the M.D. Anderson Cancer Center, University of Texas, 38 patients with trastuzumab-induced toxicity were identified during a period of 4 years.\textsuperscript{19} The mean time to recovery of LVEF was 1.5 months after discontinuation of trastuzumab. Twenty-five of these patients were re-treated with trastuzumab while continuing their therapeutic regimen for heart failure. Three had recurrence of LV dysfunction, whereas 22 (88%) did not.\textsuperscript{19}

**RISK FACTORS**

Old age and concurrent or prior exposure to anthracycline are the best known independent risk factors for trastuzumab-induced cardiotoxicity.\textsuperscript{20,21} Other suspected risk factors, similar to those for anthracycline-induced cardiotoxicity, are previous cardiac disease and NYHA class II symptoms. Preexisting hypertension and prior radiation to the left side of the chest have not been identified as risk factors for cardiac dysfunction. In patients receiving concurrent anthracyclines and trastuzumab, the risk of cardiac dysfunction increases after a cumulative dose of doxorubicin exceeds 300 mg/m\textsuperscript{2}.\textsuperscript{20} The sequence in which chemotherapy agents are administered could also affect development of cardiotoxicity. In a recent study, trastuzumab was administered alone as the first agent and was not given concomitantly with or after agents known to be cardiotoxic.
**TRASTUZUMAB-INDUCED CARDIOTOXICITY**

<table>
<thead>
<tr>
<th>Study variable</th>
<th>NSABP B-31</th>
<th>NCCTG N9831</th>
<th>HERA</th>
<th>BCIRG 006</th>
<th>FinHer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy regimen</td>
<td>AC followed by Pac; same regimen + Trast</td>
<td>AC followed by Pac; same regimen + Trast; same regimen + Trast with Pac</td>
<td>4 chemotherapy cycles; same regimen + 1 y of Trast; same regimen + 2 y of Trast</td>
<td>AC followed by Doc; same regimen + 1 y of Trast, Doc + Cp and 1 y of Trast</td>
<td>Doc + Trast followed by FEC; Doc followed by FEC; Vin + Trast followed by FEC; Vin followed by FEC</td>
</tr>
<tr>
<td>Technique of LV function assessment</td>
<td>MUGA or Echo</td>
<td>MUGA or Echo</td>
<td>Not reported</td>
<td>Not reported</td>
<td>MUGA or Echo</td>
</tr>
<tr>
<td>Timing of assessment</td>
<td>Baseline; after AC; and 6, 9, 18 mo after randomization</td>
<td>Baseline; after AC; and 6, 9, 18 mo after randomization</td>
<td>Baseline; and 3, 6, 12, 18, 24, 30, 36, 60 mo after randomization</td>
<td>Not reported</td>
<td>Baseline; after FEC; and 12, 36 mo after chemotherapy</td>
</tr>
<tr>
<td>Criteria for discontinuation of Trast</td>
<td>Symptomatic cardiac dysfunction</td>
<td>Symptomatic cardiac dysfunction</td>
<td>Symptomatic and LVEF &lt;45% or LVEF &lt;50% with an absolute decrease of 10% from baseline</td>
<td>Not reported</td>
<td>None</td>
</tr>
<tr>
<td>Criteria for withholding Trast</td>
<td>Asymptomatic and LVEF decline 16% from baseline or LVEF decline 10%-15% from baseline to below LLN</td>
<td>Asymptomatic and LVEF decline 16% from baseline or LVEF decline 10%-15% from baseline to below LLN</td>
<td>Asymptomatic and LVEF &lt;50% with an absolute decrease of 10% from baseline</td>
<td>Not reported</td>
<td>None</td>
</tr>
<tr>
<td>Decrease in LVEF requiring discontinuation of Trast in 14% of patients</td>
<td>Asymptomatic decrease in LVEF requiring discontinuation of Trast in 10.8% of patients</td>
<td>Asymptomatic decrease in LVEF requiring discontinuation of Trast in 10.8% of patients</td>
<td>Decrease in LVEF (LVEF &lt;50% with absolute decrease of 10% from baseline at any time) in 2.3% of controls and in 7.4% of Trast-treated patients</td>
<td>&gt;10% relative LVEF decline from baseline occurred in 9% of patients treated with AC + Trast; in 17.3% treated with AC + Trast + Doc; in 8% treated with Doc + Cp + Trast</td>
<td>1 measurement of LVEF &gt;15% below baseline was noted in 6% of controls and in 3.5% of Trast-treated patients; decline in LVEF &gt;10% resulting in LVEF &lt;50% occurred in 2.6% of controls and in no Trast-treated patients</td>
</tr>
<tr>
<td>Symptomatic CHF</td>
<td>Symptoms of cardiac dysfunction not meeting criteria for a cardiac event at 3 y occurred in 1% of controls and in 5% of Trast-treated patients</td>
<td>Not reported</td>
<td>Symptomatic CHF, including severe CHF (any degree of symptoms and LVEF &lt;50% with decrease of 10% from baseline at any time) occurred in 0.2% of controls and in 2.1% of Trast-treated patients</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Cardiac events</td>
<td>NYHA III/IV CHF or death from cardiac causes at 3 y occurred in 0.8% of controls and in 4.1% of Trast-treated patients</td>
<td>NYHA III/IV CHF or death from cardiac causes at 3 y occurred in 0.8% of controls and in 3.5% of Trast-treated patients</td>
<td>Cardiac death occurred in 0.06% of controls and in 0% of Trast-treated patients; severe CHF (NYHA III/IV symptoms and LVEF &lt;50% with a decrease of 10% from baseline at any time) occurred in 0% of controls and in 0.6% of Trast-treated patients</td>
<td>No cardiac deaths occurred; grade 3/4 CHF occurred in 0.3% of patients treated with AC + Trast; in 1.6% treated with AC + Trast + Doc; and in 0.4% treated with Doc + Cp + Trast</td>
<td>No cardiac deaths occurred; CHF/MI occurred in 3.4% of controls and in 0% of Trast-treated patients</td>
</tr>
</tbody>
</table>

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**Note:**

- AC = doxorubicin (Adriamycin) and cyclophosphamide; BCIRG = Breast Cancer International Research Group; CHF = congestive heart failure; Cp = carboplatin; Doc = docetaxel (Taxotere); Echo = echocardiogram; EF = ejection fraction; FEC = fluorouracil, epirubicin, cyclophosphamide; FinHer = Finland Herceptin trial; HERA = Herceptin Adjuvant trial; LLN = lower limit of normal; LV = left ventricular; MI = myocardial infarction; MUGA = multiple gated acquisition scan; NCCTG = North Central Cancer Treatment Group; NSABP = National Surgical Adjuvant Breast and Bowel Project; NYHA = New York Heart Association; Pac = paclitaxel; Vin = vinorelbine.

*Adapted from J Clin Oncol.2*

**MECHANISM**

The **ERBB2** gene belongs to a family of epidermal growth factor receptors (EGFRs) (EGFR, HER2, HER3, and...
TRASTUZUMAB-INDUCED CARDIOTOXICITY

HER4) that regulate many essential cell type–specific functions, particularly cell growth, proliferation, and survival.\textsuperscript{22,23} Mutant mouse models have documented a key role of the ERBB2 gene in postnatal cardiomyocyte function and development.\textsuperscript{24,25} A knockout mice model for a ventricle with restricted ERBB2 expression developed dilated cardiomyopathy and poor contractility, had impaired ability to withstand stress, and showed enhanced susceptibility to anthracycline-induced cardiotoxicity.\textsuperscript{25} Reduction of ERBB2 signaling induces cardiomyocyte apoptosis.\textsuperscript{26} Conversely, augmentation of ERBB2 signaling in cardiomyocytes confers protection and improves myocardial function.\textsuperscript{26,27} Trastuzumab blocks the extracellular domain of ERBB2, thereby reducing the myocardial homeostasis and exposing the myocardium to unopposed damaging effects of stress-signaling pathways. Prior treatment with anthracyclines increases cell surface receptors that are subsequently blocked by trastuzumab.\textsuperscript{28} However, toxic effects of trastuzumab, unlike those of anthracyclines, are not cumulative or dose related.

Although inhibition of ERBB2 signaling is implicated as a central mechanism of trastuzumab-related cardiotoxicity, the pathophysiologic mechanism is likely more complex. Early clinical results with lapatinib (GW572016), a quinazoline compound that is an orally available dual kinase inhibitor of EGFR and ERBB2, show minimal cardiotoxicity.\textsuperscript{29,30} The underlying mechanism for this paradox is not sufficiently clear at this time and remains an area of intense investigation.

Trastuzumab-mediated inhibition might specifically alter mitochondrial integrity, leading to adenosine triphosphate depletion and contractile dysfunction without profound changes in cardiomyocyte ultrastructure.\textsuperscript{30} For example, endomyocardial biopsy specimens from a series of patients with trastuzumab-related toxicity showed no apparent light microscopic or electron microscopic evidence of injury.\textsuperscript{31} However, a recent investigation from the M.D. Anderson Cancer Center documented evidence of focal vacuolar changes, pleomorphic mitochondria, myocardial cell hypertrophy, and mild interstitial fibrosis on electron microscopy of the endomyocardial biopsy specimens with no light microscopic abnormalities, a finding consistent with a reversible pattern of cardiac injury.\textsuperscript{31}

Monitoring

The American Heart Association/American College of Cardiology heart failure staging scheme recognizes a need to detect cardiac dysfunction at its earliest, minimally symptomatic stage (stages A and B).\textsuperscript{32} Recent adjuvant studies have suggested that the most frequent manifestation of trastuzumab-induced cardiotoxicity is an asymptomatic decline in LVEF.\textsuperscript{33} In HERA, asymptomatic decline in LVEF occurred in 7.1% of trastuzumab-treated patients, whereas symptomatic heart failure was seen in 1.7% of patients.\textsuperscript{14} Similarly, data from the analysis of NSABP B-31 and North Central Cancer Treatment Group N9831 trials revealed that 14.2% of patients treated with trastuzumab discontinued therapy because of asymptomatic decline in LVEF, whereas only 4.7% of the patients discontinued therapy because of clinical heart failure or other adverse effects.\textsuperscript{34}

When adjuvant trastuzumab is administered outside of a clinical trial, the optimal cardiac monitoring strategy remains uncertain. Although the Heart Failure Society of America guidelines do not recommend routine reevaluation of cardiac function by noninvasive or invasive methods, the reversibility of trastuzumab-induced cardiotoxicity mandates reevaluation of LV function at regular intervals. The British Society of Echocardiography recently issued a statement regarding the evaluation of LV function for patients being considered for or receiving trastuzumab therapy.\textsuperscript{35} The statement specifies that LV function must be measured before treatment is started and at 3-month intervals during treatment. A similar algorithm that could be used for monitoring cardiac function during trastuzumab therapy is shown in the Figure. Risk and benefits of using trastuzumab need to be carefully assessed in the presence of diastolic or systolic dysfunction (baseline EF, ≤50%). If new symptoms occur or if EF declines by more than 10%, cessation of treatment might be required. Current information regarding the long-term safety of trastuzumab therapy in the presence of overt cardiac dysfunction is insufficient. Experience at the M.D. Anderson Cancer Center has provided some reassuring preliminary information about symptomatic control of heart failure in most patients and consideration for reinstitution of trastuzumab therapy in those with recovery of cardiac function.\textsuperscript{31}

Echocardiography is ideal for evaluating LV function. Utmost care is essential for reducing intraobserver and interobserver variability during serial measurements of LVEF.\textsuperscript{35} Use of (biplane) Simpson’s Rule method or 3-dimensional echocardiography, with contrast available for LV opacification, by an appropriately skilled echocardiographer is recommended. Echocardiography laboratories performing such studies should have evidence (eg, through audit or other quality control processes), not more than 12 months old, that they can reproducibly measure EF to the requirements of the guidelines. This would ensure that the laboratory can identify a threshold difference (10% change) in EF as a true change. For a small number of patients, transthoracic windows might yield unacceptable cardiac images because of local surgery or radiation-re-
TRASTUZUMAB-INDUCED CARDIOTOXICITY

**FIGURE.** Proposed algorithm for monitoring trastuzumab-induced cardiotoxicity. Serial transthoracic echocardiography (ECG) is the preferred technique for assessment of ejection fraction (EF) and diastolic function. Radionuclide ventriculography can be used for determining EF if transthoracic echocardiograms are suboptimal. LV = left ventricular.

Review baseline physical examination findings, ECG, EF, diastolic function

- EF >50%
  - Start chemotherapy
  - Review EF, diastolic function once every 12 wk

- EF ≤50%, diastolic dysfunction, risk factors
  - Risk-benefit assessment
  - Start chemotherapy
  - Review EF, diastolic function once every 12 wk

- Asymptomatic, stable EF, stable diastolic function
  - Review EF, diastolic function every 12 wk

- Asymptomatic, stable EF, new diastolic dysfunction
  - Risk-benefit assessment, start heart failure therapy
  - Review EF, diastolic function every 1 wk

- Asymptomatic, EF decline by 10%, stable or worsening diastolic function
  - Risk-benefit assessment, consider discontinuing chemotherapy due to worsening heart failure
  - Reinstitute chemotherapy while continuing heart failure therapy (preferably if symptoms reverse and LV function stabilizes)
  - Review baseline physical examination findings, ECG, EF, diastolic function once every 8 wk

- Symptomatic with or without EF decline
  - Risk-benefit assessment, start heart failure therapy
  - Review EF, diastolic function every 1 wk

- Reinstitute chemotherapy while continuing heart failure therapy (preferably if symptoms reverse and LV function stabilizes)
  - Review baseline physical examination findings, ECG, EF, diastolic function once every 12 wk

lated changes. An alternative imaging modality like radionuclide scanning should be considered for such patients.

**TREATMENT**

Treatment of trastuzumab-induced cardiotoxicity does not differ from the general treatment approach to patients with heart failure, as outlined in the Heart Failure Society of America guidelines. Polypharmacy is required for optimal management to slow progression and improve outcome in patients with LV systolic dysfunction. Therapy with diuretics should be started to restore and maintain normal volume status in patients with clinical evidence of fluid overload. If echocardiography or 2-dimensional echocardiography reveals evidence of impaired LV contraction but the patient is not hypotensive, addition of an angiotensin-converting enzyme inhibitor and β-adrenergic blockade should be considered. The addition of angiotensin receptor blockade to angiotensin-converting enzyme inhibitors in patients who develop features of chronic heart failure has been suggested to provide additional blockade of the renin-angiotensin-aldosterone system. Sustained or recurrent cardiac arrhythmias should be treated with appropriate antiarrhythmic agents and correction of possible precipitating factors, including sepsis and electrolyte disturbances. In patients with pericardial effusions, therapeutic aspiration is indicated if cardiac tamponade is evident.

**UNANSWERED QUESTIONS AND FUTURE DIRECTIONS**

Although trastuzumab therapy for patients with ERBB2-positive metastatic breast cancer is now well established, several questions remain unanswered, including patient selection for anti-ERBB2 treatment of metastatic disease based on ERBB2 testing, dose scheduling of trastuzumab, duration and tolerability of therapy, role of alternative
agents like lapatinib, and clinical importance of trastuzumab resistance and efficacy. A limitation of the existing data is that the median follow-up in the trastuzumab adjuvant trials is between 2 and 3 years. Therefore, there is no information on the potential for late cardiac dysfunction or whether short-term improvements in clinical heart failure or LVEF with medical treatment are permanent or will increase the risks of late cardiac dysfunction. Future trials with longer follow-up are necessary for addressing these remaining issues.

Cardiac monitoring in clinical trials has been based on sequential assessments of LVEF. However, LVEF has important limitations in quantifying CHF. Left ventricular EF in patients with CHF presents as one continuous unimodal measure of global LV function. Therefore, the EF cutoff values commonly used for defining presence or absence of cardiac muscle dysfunction are arbitrary and introduce selection bias. Moreover, measurements of regional cardiac muscle performance in patients with preserved EF reveal presence of markedly depressed systolic function despite a normal EF. Thus, the exact prevalence of cardiotoxicity in trastuzumab trials could have been appreciably underestimated. Newer echocardiographic modalities like tissue Doppler imaging, regional strain, and strain rate might provide improved sensitivity in detecting subclinical LV dysfunction.

Newer biochemical markers like troponins and natriuretic peptides could have potential roles in early detection and follow-up; however, their role has not been systematically investigated. In a recent study, pretreatment plasma prohormone brain-type natriuretic peptide levels were almost 5-fold higher in patients who developed heart failure during trastuzumab treatment compared with those who did not experience symptomatic LV dysfunction. Plasma prohormone brain-type natriuretic peptide might have utility in early-risk stratification of patients who are more likely to develop cardiotoxicity.

Regarding the effects of cardiovascular risk factor modification on cancer outcomes, information is limited. A substantial proportion of patients with early breast cancer present with preexisting or heightened cardiovascular disease risk factors that increase the risk of adjuvant therapy–associated cardiovascular injury. Trials are needed to specifically focus on preventive and/or treatment strategies to define the short- and long-term clinical consequences of the multiple risk factors that can work in concert to cause cardiovascular injury (multiple-hit hypothesis).

CONCLUSION

Trastuzumab-induced cardiotoxicity is not dose related, does not appear to occur in all patients, is expressed in a broad spectrum of severity, and appears to be reversible once use of the agent is discontinued. Future clinical trials need to carefully focus on redefining the range of subclinical LV dysfunction associated with use of trastuzumab. Markers that can serve as surrogates for impending cardiac events such as tissue Doppler imaging, troponin, and natriuretic peptides and their exact prognostic importance need to be defined in longer follow-up studies. Meanwhile, given the substantial benefits in breast cancer outcome, clinicians must continue to evaluate the risks and benefits of trastuzumab therapy in their clinical practice on an individual patient basis.

REFERENCES

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