Minimizing Cardiotoxicity While Optimizing Treatment Efficacy with Trastuzumab: Review and Expert Recommendations

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Key Words. Breast cancer • Cardiotoxicity • Heart failure • Left ventricular ejection fraction • Trastuzumab

Disclosures
Miguel Martín: Honoraria: Roche; Francisco J. Esteva: Honoraria: Roche; Emilio Alba: Honoraria: Roche; Bijoy Khandheria: Honoraria: Roche; Leopoldo Pérez-Isla: Honoraria: Roche; José Ángel García-Sáenz: Honoraria: Roche; Antonia Márquez: Honoraria: Roche; Partho Sengupta: None; José Zamorano: Honoraria: Roche

Section editors Gabriel N. Hortobágyi and Kathleen I. Pritchard have disclosed no financial relationships relevant to the content of this article.

The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias.

Target audience: Physicians who wish to advance their current knowledge of clinical cancer medicine in breast cancer.

ABSTRACT
Numerous clinical studies have demonstrated the therapeutic benefit of trastuzumab in women with breast cancer. However, a small but not insignificant proportion of patients have experienced trastuzumab-associated cardiotoxicity during these trials. This phenomenon is generally characterized by an asymptomatic reduction in left ventricular ejection fraction (LVEF) or, less often, congestive heart failure (CHF). Concomitant anthracycline therapy significantly increases the risk for cardiotoxicity during trastuzumab therapy. CME credit is available with this article. The Oncologist, 2009;14:1–11 www.TheOncologist.com

The Oncologist 2009;14:1–11 www.TheOncologist.com
treatment, and such regimens are therefore not recommended. The cardiac dysfunction associated with trastuzumab is most often reversible upon discontinuation of treatment and initiation of standard medical therapy for CHF.

Prior to treatment initiation, a risk–benefit analysis should be performed for each individual patient, including a thorough assessment of potential risk factors and cardiac function. Cardiac monitoring should be continued throughout trastuzumab therapy and the follow-up period, because early recognition of trastuzumab-associated cardiac dysfunction can allow effective medical intervention. Following the occurrence of asymptomatic LVEF reduction or CHF and appropriate medical intervention, reintroduction of trastuzumab may be considered in patients following resolution of normal cardiac function, or in those for whom the benefit of antitumor therapy outweighs the risk for CHF. The Oncologist 2009;14:1–11

INTRODUCTION
Trastuzumab (Herceptin®; F. Hoffmann-La Roche, Basel, Switzerland) is a humanized monoclonal antibody that selectively inhibits the growth and proliferation of breast cancer cells overexpressing the type-1 tyrosine kinase membrane receptor human epidermal growth factor receptor (HER)-2/neu [1–6]. Evidence for the efficacy of trastuzumab was initially provided in phase II clinical trials involving patients with breast cancer overexpressing HER-2/neu who were refractory to chemotherapy [7–9] and a pivotal study involving 479 women with metastatic breast cancer (MBC) overexpressing HER-2/neu [10]. Chemotherapy plus first-line trastuzumab resulted in a significantly higher response rate than with chemotherapy alone, as well as longer durations of response and survival.

This demonstration of trastuzumab efficacy in treating MBC led to the initiation of four international clinical studies in the postsurgery adjuvant setting, involving a total of nearly 12,000 women with HER-2/neu overexpression. In those trials, the experimental arm included trastuzumab concomitantly administered with chemotherapy or sequentially upon chemotherapy completion. Results indicated substantially better recurrence rates, disease-free survival times, and overall survival times with trastuzumab treatment [11–15]. Different chemotherapeutic regimens plus trastuzumab have also been evaluated in women with HER-2-overexpressing breast cancer in the neoadjuvant setting, with significantly greater pathological complete response rates observed [16–19].

Trastuzumab is generally well tolerated. However, in a number of these clinical studies, cardiac dysfunction was observed, secondary to trastuzumab therapy. This paper aims to identify the incidence of this phenomenon, together with potential risk factors and strategies for minimizing its occurrence in clinical practice. Management of trastuzumab-associated cardiotoxicity is also discussed.

INCIDENCE AND CHARACTERISTICS OF CARDIOTOXICITY IN PATIENTS RECEIVING TRASTUZUMAB
A summary of the incidence of cardiotoxicity and the definitions used in the key clinical trials evaluating trastuzumab is presented in Table 1.

MBC
Trastuzumab-associated cardiotoxicity was first described in a small number of patients with MBC who participated in two phase II studies. The reported incidence of cardiac dysfunction was 2% of patients receiving trastuzumab alone and 31% of patients treated with paclitaxel plus trastuzumab [9, 20]. In the pivotal phase III trials, trastuzumab-associated cardiotoxicity was an unexpected finding; prospective cardiac monitoring was therefore not conducted at that time. Cardiotoxicity occurred more frequently in patients who received combined chemotherapy and trastuzumab treatment, particularly in those patients treated with anthracyclines (27%, versus 13% in patients treated with paclitaxel plus trastuzumab) [10]. In the chemotherapy arms, the incidence of cardiotoxicity was 8% in patients receiving anthracyclines, and it was 1% in those treated with paclitaxel.

Subsequently, these pivotal phase II and III studies were reviewed by a cardiac review and evaluation committee (CREC) [21]. The CREC defined trastuzumab-associated cardiotoxicity as a complication consisting of either asymptomatic decreased left ventricular ejection fraction (LVEF) or the presence of symptoms consistent with grade III or IV congestive heart failure (CHF) (Table 2). Using the New York Heart Association (NYHA) criteria [22], toxicity was identified in nearly 9% of patients, and, although it was observed that trastuzumab by itself was able to induce cardiac dysfunction (2%), the incidence of this complication was substantially greater when trastuzumab was administered concomitantly with anthracyclines (16%). Most of the patients suffering from trastuzumab-induced cardiotoxicity were asymptomatic, and 79% responded to medical treat-
Table 1. Summary of cardiotoxicity incidence in clinical studies evaluating trastuzumab in breast cancer

<table>
<thead>
<tr>
<th>Study design</th>
<th>Treatment regimens</th>
<th>Definition(s) of cardiac dysfunction</th>
<th>Incidence of cardiotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic breast cancer</td>
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<tr>
<td>Open-label phase I study (n = 74) [31]</td>
<td>E, 60 mg/m², + C, 600 mg/m², every 3 weeks for six cycles + T, 4 mg/kg LD, then 2 mg/kg weekly until disease progression; or E, 90 mg/m², + C, 600 mg/m², every 3 weeks for six cycles + T, 4 mg/kg LD, then 2 mg/kg weekly until disease progression; or EC90 &gt;10% reduction from baseline in LVEF; LVEF &lt;50%; NYHA cardiac dysfunction class I-IV; severe arrhythmia; acute coronary syndrome/acute myocardial infarction; requirement for cardiodysrhythmia resuscitation</td>
<td>EC90 + T: &gt;10% reduction from baseline in LVEF; 48% &gt;10% reduction from baseline in LVEF and LVEF &lt;50%; 4%; arrhythmia, 8%; atrioventricular block, 4%; supraventricular tachycardia, 4%; EC90 + T: &gt;10% reduction from baseline in LVEF, 50%; &gt;10% reduction from baseline in LVEF and LVEF &lt;50%; 8%; transient arrhythmia, 4%; EC90: &gt;10% reduction from baseline in LVEF, 24%. Patients continuing on trastuzumab monotherapy: LVEF &lt;50%, n = 3</td>
<td></td>
</tr>
<tr>
<td>Randomized, single-blind phase II study (n = 114) [9]</td>
<td>T, 4 mg/kg LD then 2 mg/kg weekly or 8 mg/kg LD then 4 mg/kg weekly until disease progression</td>
<td>CHF, cardiomyopathy, or &gt;10% reduction from baseline in LVEF</td>
<td>&gt;10% reduction from baseline in LVEF, 2%; strial and ventricular enlargement with tricuspid regurgitation, 1%</td>
</tr>
<tr>
<td>Open-label phase II study (n = 32) [20]</td>
<td>T, 8 mg/kg LD, + P, 175 mg/m², then T, 6 mg/kg, + P, 175 mg/m², every 3 weeks for seven cycles</td>
<td>≥15% reduction from baseline in LVEF; LVEF &lt;40% NYHA class III or IV cardiac dysfunction</td>
<td>Decrease in LVEF to &lt;40%, 6%; ≥15% reduction from baseline in LVEF, 28%</td>
</tr>
<tr>
<td>Open-label phase II study (n = 95) [23]</td>
<td>T, 4 mg/kg LD, + P, 90 mg/m², then T, 2 mg/kg, + P, 90 mg/m², every 7 days until disease progression</td>
<td>None</td>
<td>Asymptomatic &gt;20% decrease from baseline in LVEF, 7%; LVEF &lt;10%; 1%; acute myocardial infarction, severe left ventricular dysfunction, and LVEF &lt;40%, 1%; myocardial infarction, 1%</td>
</tr>
<tr>
<td>Open-label phase II study (n = 54) [25]</td>
<td>T, 4 mg/kg LD, then 2 mg/kg weekly, + V, 25 mg/m² weekly, until disease progression, or docetaxel 100 mg/m² every 3 weeks</td>
<td>Grade 3 cardiac toxicity (symptomatic CHF); LVEF &lt;40%</td>
<td>Symptomatic CHF, 2%; LVEF &lt;40%, 2%</td>
</tr>
<tr>
<td>Open-label phase II study (n = 50) [26]</td>
<td>T, 8 mg/kg LD, then 6 mg/kg on day 1 + V, 30 mg/m², on days 2 and 8 of 3-week cycles until disease progression</td>
<td>LVEF ≤44%; LVEF &lt;50% with a ≥10% reduction from baseline</td>
<td>Grade 1 asymptomatic decline from baseline in LVEF, 4%; grade 2 asymptomatic decline from baseline in LVEF, 4%</td>
</tr>
<tr>
<td>Open-label phase II study (n = 27) [28]</td>
<td>T, 4 mg/kg LD then 2 mg/kg weekly, + capecitabine, 2,500 mg/m² per day over 14 days, for 3-week cycles until disease progression</td>
<td>None</td>
<td>Heart failure, 4%</td>
</tr>
<tr>
<td>Randomized, open-label phase II study (n = 188) [24]</td>
<td>Docetaxel 100 mg/m² every 3 weeks for 6 cycles + T 4 mg/kg LD then 2 mg/kg every 7 days until disease progression, or docetaxel 100 mg/m² every 3 weeks</td>
<td>None</td>
<td>Docetaxel + trastuzumab: Symptomatic CHF (2%); Asymptomatic ≥15% decrease from baseline in LVEF (17%); LVEF &lt;40% (1%); Docetaxel monotherapy: Asymptomatic ≥15% decrease from baseline in LVEF (8%)</td>
</tr>
<tr>
<td>Randomized, phase III study (n = 469) [10]</td>
<td>A 60 mg/m² or E 75 mg/m² + C 600 mg/m² or P 175 mg/m² (once every 3 weeks for 6 cycles) + T LD 4 mg/kg then 2 mg/kg until disease progression</td>
<td>NYHA class III or IV cardiac dysfunction</td>
<td>A/C + C + trastuzumab (27%); A/C + C (8%); P + trastuzumab (13%); P monotherapy (1%)</td>
</tr>
<tr>
<td>Early breast cancer: adjuvant therapy</td>
<td></td>
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<tr>
<td>Randomized, open-label phase III study (n = 1,010) [15]</td>
<td>Docetaxel 100 mg/m² on day 1, or V, 25 mg/m² on days 1, 8, and 15, of 21-day cycles for three cycles with or without T, 4 mg/kg LD then 2 mg/kg weekly for 9 wks then F, 600 mg/m², + E, 60 mg/m², + C, 600 mg/m², on day 1 of 21-day cycles for three cycles</td>
<td>None</td>
<td>Trastuzumab: &gt;15% reduction from baseline in LVEF, 4%. Control: &gt;15% reduction from baseline in LVEF, 6%; &gt;10% reduction from baseline in LVEF and LVEF &lt;50%, 3%; heart failure, 3%; myocardial infarction, 1%</td>
</tr>
<tr>
<td>Randomized, open-label phase III study (n = 3,387) [12]</td>
<td>T, 8 mg/kg LD then 6 mg/kg every 3 weeks (after chemotherapy) for 1 year versus observation only</td>
<td>Severe CHF (NYHA class III or IV cardiac dysfunction) and &gt;10% reduction from baseline in LVEF to &lt;50%; symptomatic CHF; asymptomatic &gt;10% reduction from baseline in LVEF to &lt;50%; cardiac death</td>
<td>T: severe CHF, 0.5%; symptomatic CHF, 2%; asymptomatic &gt;10% reduction from baseline in LVEF to &lt;50%, 7%. Observation: symptomatic CHF, &lt;0.1%; asymptomatic &gt;10% reduction from baseline in LVEF to &lt;50%, 2%; cardiac death, &lt;0.1%</td>
</tr>
<tr>
<td>Randomized, phase III study (n = 2,043) [33]</td>
<td>A, 60 mg/m², + C, 600 mg/m², every 21 days for four cycles then P, 175 mg/m², every 3 weeks for four cycles with or without T, 4 mg/kg LD then 2 mg/kg for 51 weeks</td>
<td>Symptomatic CHF: NYHA class III or IV cardiac dysfunction with &gt;10% reduction from baseline in LVEF to &lt;55%, or &gt;5% reduction from baseline in LVEF to less than the upper limit of normal</td>
<td>AC→P + T: symptomatic CHF, 4%; asymptomatic &gt;10% reduction from baseline in LVEF to &lt;55%, 34%; AC→P, symptomatic CHF, 0.5%; asymptomatic &gt;10% reduction from baseline in LVEF to &lt;55%, 1%; probable cardiac death, 0.1%</td>
</tr>
</tbody>
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(continued)
ment. This finding led to a general consensus that the concomitant use of trastuzumab and anthracyclines should be avoided and that cardiac monitoring should be included in all subsequent clinical trials involving trastuzumab.

In a study including cardiac monitoring that assessed weekly paclitaxel plus trastuzumab, 7% of patients developed asymptomatic decreased LVEF, but only 3% presented with symptoms suggestive of CHF [23]. The M77001 trial assessed the combination of trastuzumab and docetaxel weekly or every 3 weeks and included monitoring of LVEF every three treatment cycles. Only 1% of the patients receiving combination therapy developed CHF symptoms, whereas 17% experienced asymptomatic reductions in LVEF ≥15%, compared with 8% of patients receiving docetaxel monotherapy [24].

In a single-center study including cardiac monitoring, the combination of vinorelbine and trastuzumab was associated with asymptomatic decreased LVEF in three of 40 patients, with none developing CHF [25]. A separate phase II trial evaluating combination therapy with trastuzumab and vinorelbine reported that two patients (4%) experienced a >20% reduction from baseline in LVEF and two (4%) experienced a >10% reduction from baseline in LVEF [26].

The results from clinical trials evaluating the combination of trastuzumab and gemcitabine or capecitabine in patients who had previously received anthracyclines and taxanes indicate no increased risk for CHF with these regimens [27–29]. The results from an interim safety analysis of preliminary data from an ongoing randomized study of docetaxel plus trastuzumab with or without capecitabine in patients with locally advanced breast cancer or MBC reported a CHF incidence of 2% [30].

Combinations of trastuzumab with other anthracyclines less cardiotoxic than doxorubicin, such as epirubicin or liposomal doxorubicin, have also been investigated. Preliminary analyses during stage I of the Herceptin®, Cyclophosphamide, and Epirubicin study showed that there was no dose-limiting toxicity. Of the 50 patients assigned to trastuzumab, only three experienced asymptomatic decreased LVEF, and one had an episode of uncomplicated tachyarrhythmia [31]. The combination of liposomal doxorubicin with paclitaxel and trastuzumab exhibits potent antitumor activity with no cases of cardiotoxicity observed [32].

### Early Breast Cancer: Adjuvant Therapy

In the National Surgical Adjuvant Breast and Bowel Project B31 study of adjuvant doxorubicin followed by paclitaxel with or without trastuzumab, regular LVEF monitoring was


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**Table 1.** (Continued)

<table>
<thead>
<tr>
<th>Study design</th>
<th>Treatment regimens</th>
<th>Definition(s) of cardiac dysfunction</th>
<th>Incidence of cardiotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early breast cancer: neoadjuvant therapy</td>
<td>T, 4 mg/kg LD then 2 mg/kg for a total of 17 injections, + docetaxel, 75 mg/m², + carboplatin, AUC 6, every 3 weeks for six cycles</td>
<td>&gt;20% reduction from baseline in LVEF; LVEF &lt;50%</td>
<td>LVEF &lt;50%, 3%; &gt;10% reduction from baseline in LVEF, 29%; &gt;20% reduction from baseline in LVEF, 12%</td>
</tr>
<tr>
<td>Randomized phase II study (n = 42) [19]</td>
<td>P, 225 mg/m², every 3 weeks for four cycles with or without T, 4 mg/kg LD, then 2 mg/kg weekly for 24 weeks followed by F, 500 mg/m², on days 1 and 4 + E, 75 mg/m², + C, 500 mg/m², on day 1 of 21-day cycles for four cycles</td>
<td>None</td>
<td>T: &gt;10% reduction from baseline in LVEF, 30%; control: &gt;10% reduction from baseline in LVEF, 26%</td>
</tr>
<tr>
<td>Retrospective analysis of a randomized phase III trial (n = 40) [39]</td>
<td>P, 80 mg/m², weekly for 12 weeks + T, 4 mg/kg LD, then 2 mg/kg weekly for 24 weeks followed by F, 500 mg/m², + E, 75 mg/m², + C, 500 mg/m², every 3 weeks for four cycles</td>
<td>Symptomatic decrease in LVEF of any percentage; CHF</td>
<td>Asymptomatic &gt;10% reduction from baseline in LVEF, 13%</td>
</tr>
</tbody>
</table>

Abbreviations: A, doxorubicin; AUC, area under the concentration–time curve; C, cyclophosphamide; CHF, congestive heart failure; E, epirubicin; F, fluorouracil; LD, loading dose; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; P, paclitaxel; T, trastuzumab; V, vinorelbine.

**Table 2.** Cardiac review and evaluation committee definition of trastuzumab-associated cardiotoxicity [21]

<table>
<thead>
<tr>
<th>Symptom(s) associated with HF</th>
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<tbody>
<tr>
<td>Cardiomyopathy defined as a reduction in LVEF, either global or more severe in the septum</td>
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<td></td>
</tr>
<tr>
<td>Signs associated with HF, e.g., S3 gallop, tachycardia, or both</td>
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</tr>
<tr>
<td>Reduction in LVEF from baseline of ≥5% to &lt;55% with accompanying signs or symptoms of HF, or a reduction in LVEF of ≥10% to &lt;55%, without accompanying signs or symptoms</td>
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</tr>
</tbody>
</table>

Abbreviations: HF, heart failure; LVEF, left ventricular ejection fraction.
performed [33]. When LVEF decreased by >15% below the baseline value, it remained below the normal value, or there were symptoms of CHF, treatment was discontinued. Despite this strict continuous monitoring, NYHA class III or IV CHF was observed in 4.1% of the patients who had received trastuzumab, relative to 0.8% of patients receiving chemotherapy alone. There were no cases of cardiac death. In 18% of the patients, trastuzumab treatment had to be discontinued (in 4% because of symptomatic cardiotoxicity and in the remaining cases as a result of asymptomatic decreased LVEF). When trastuzumab was assessed in the N9831 trial as an adjuvant therapy without concomitant anthracyclines and careful baseline and continued heart monitoring was implemented, systolic dysfunction was seen in approximately 5% of patients, and of these, 1% developed CHF [34].

In the Herceptin® Adjuvant trial, patients were randomly assigned to receive adjuvant trastuzumab for 1 year, adjuvant trastuzumab for 2 years, or observation, upon chemotherapy completion [12]. Patients who had received a cumulative doxorubicin dose >360 mg/m² or a cumulative epirubicin dose >720 mg/m² or who exhibited marginal decreased LVEF were excluded. LVEF was assessed at baseline and then regularly until 60 months after randomization. Decreased LVEF was seen in 7.1% of patients treated with trastuzumab, compared with 2.2% of patients in the control arm. Only 1.7% of patients experienced symptomatic CHF. After 2 years of follow-up, 0.6% of patients in the trastuzumab group had developed severe CHF (versus 0% in the control group; p < .0001). In addition, symptomatic CHF was experienced by 2% of patients receiving trastuzumab, compared with 0.1% of control patients (p < .0001). Significant reductions in LVEF were observed in 3% and 0.5% of patients receiving trastuzumab and no treatment, respectively (p < .0001) [13].

In the Breast Cancer International Research Group 006 study, three adjuvant treatment arms were compared: (a) doxorubicin plus cyclophosphamide followed by docetaxel (AC→T), (b) AC followed by docetaxel with trastuzumab for 1 year, and (c) docetaxel plus carboplatin and concomitant trastuzumab for 1 year (TCH) [35]. Severe cardiotoxicity was seen in 1% of patients assigned to the AC→T arm, in 2.3% of patients in AC followed by docetaxel and trastuzumab arm, and in 1.3% of patients in the TCH arm. Significant LVEF diminution was higher in the AC followed by docetaxel and trastuzumab arm (17%, versus 9% in the AC→T arm and 8% in the TCH arm). Severe CHF was observed in 0.3%, 1.6%, and 0.4%, of patients, respectively.

Two different approaches have been used with the aim of diminishing, without reducing efficacy, the incidence of cardiotoxicity from adjuvant treatments including trastuzumab: (a) using adjuvant chemotherapy regimens without anthracyclines and (b) reducing the duration of trastuzumab administration. In a small randomized Finnish study, a regimen of adjuvant trastuzumab lasting only 9 weeks combined with chemotherapy (vinorelbine or docetaxel followed by 5-fluourouracil, epirubicin, and cyclophosphamide) was compared with chemotherapy alone [15]. After a median follow-up of 3 years, there were no reports of either severe CHF or asymptomatic decreased LVEF. However, this superior cardiac safety may not be attributable uniquely to the reduced duration of trastuzumab administration, because patients participating in the study received epirubicin instead of doxorubicin, and the cumulative dose (180 mg/m²) was lower than in other clinical trials in the adjuvant setting.

Data from four large, international trastuzumab adjuvant therapy clinical trials have been pooled and analyzed. Grade III or IV cardiac toxicity was reported for 4.5% of the patients receiving trastuzumab-containing regimens, versus 1.8% of the patients who did not receive trastuzumab [36]. A separate meta-analysis including a total of 11,187 patients revealed that the relative risk for cardiotoxicity with adjuvant trastuzumab versus no trastuzumab was 5.59 (95% confidence interval [CI], 1.99–15.7; p = .011), with an absolute difference of 1.49%. Additionally, a relative risk for a reduction of ≥10% from baseline in LVEF of 2.12 was calculated (95% CI, 1.52–2.97; p < .0001) [37]. However, it should be borne in mind that data regarding trastuzumab-induced cardiotoxicity are not comparable across the clinical trials in the adjuvant setting because some studies used stricter inclusion criteria with regard to cardiac safety. In addition, chemotherapy plus trastuzumab was given concomitantly in some trials but sequentially in others, and the way cardiac monitoring was conducted varied from one trial to the next.

Early Breast Cancer: Neoadjuvant Therapy
A phase II clinical study involving 70 patients with stage II or III breast cancer evaluated the combination of trastuzumab, docetaxel, and carboplatin. Two patients discontinued treatment as a result of a transient, asymptomatic decrease in LVEF, but no cases of symptomatic cardiac dysfunction were reported [38]. A separate analysis of pooled data evaluating trastuzumab in combination with paclitaxel and epirubicin reported no severe adverse cardiac events [39]. When comparing neoadjuvant trastuzumab, paclitaxel, and epirubicin with paclitaxel and epirubicin alone, the incidence of a ≥10% decrease from baseline in LVEF was reported for five and seven patients, respectively [19].
MANAGING AND MINIMIZING TRASTUZUMAB-RELATED CARDIOTOXICITY

Multidisciplinary Care Approach: Cardiology–Oncology

The selection of breast cancer patients who are potential candidates to receive trastuzumab should be performed by a multidisciplinary team (MDT) comprised of cardiologists and oncologists. At the initial evaluation, a risk–benefit assessment regarding the decision to add trastuzumab to chemotherapy should be performed. First, clinical evaluation is needed, in addition to cardiac imaging, in order to identify additional potential risk factors for cardiotoxicity. Later, both clinical follow-up and cardiac monitoring on a regular basis are required.

It is necessary for MDT staff to be familiar with trastuzumab-related cardiotoxicity, because this differs from that induced by chemotherapeutic drugs [40]. Chemotherapy-related cardiac dysfunction (CRCD) directly affects the myocardium and manifests as decreased LVEF, which may progress rapidly to CHF. Type I CRCD is defined as cardiac toxicity caused by anthracyclines and has been widely studied. Trastuzumab-related cardiac toxicity is referred to as type II CRCD. Its mechanism(s) has not yet been completely elucidated. Moreover, the strategy for diagnosis, follow-up, monitoring, treatment, and prevention remains to be established. The most important differences between type I and type II CRCD are that the latter is not dose-dependent, its clinical manifestations vary between patients, it may be reversible, and it apparently does not cause ultrastructural alterations within the myocardium [21, 41–43].

It is crucial to identify those patients for whom trastuzumab treatment should be resumed following initial discontinuation and intervention for decreased LVEF or CHF, because the long-term survival of breast cancer patients with left ventricular dysfunction (LVD) may be worse than that seen in the least advanced stages of the cancer. Thus, the MDT should know and compare the different prognoses of CHF and breast cancer. While the 6-year survival rate is 33% for women with CHF, the 5-year survival rate is 97% for women with very early breast cancer, 77% in the case of breast cancer with locoregional metastases, and just 22% for women with distant metastases [44].

Definitions and Classification of Cardiac Dysfunction

Stages of cardiac dysfunction have been defined in a number of national and international management guidelines. The American College of Cardiology/American Heart Association and the Heart Failure Society of America (HFSAA) describe heart failure (HF) as a functional cardiac disorder in which the ability of the ventricle to fill with or eject blood is impaired [45, 46]. It may be differentiated from LVD, which can often be an underlying cause of HF. Most HF is associated with left ventricular systolic dysfunction, although diastolic impairment at rest is also common [47]. Stages A and B are asymptomatic decreases in LVEF, whereas stage C is considered as symptomatic HF and stage D is classified as refractory HF. Classical symptoms of HF include shortness of breath, fatigue, fluid retention, and reduced exercise tolerance. The NYHA categorizes HF according to the degree of effort required to elicit symptoms, from I (no limitation upon normal physical exertion) to IV (at rest) [22].

Evaluation of Potential Risk Factors

Prior to the initiation of trastuzumab treatment, every patient should undergo a complete medical history and thorough physical examination in order to detect those conditions that may increase the risk for cardiac dysfunction during treatment (Table 3), and in some cases they may also reveal symptoms and/or signs of pre-existing cardiac dysfunction.

Currently, it is unclear whether or not classical cardiac risk factors, for example, hypertension and diabetes, are predisposing factors for trastuzumab-related cardiotoxicity. In the review conducted by Seidman et al. [21], a multivariate analysis for potential risk factors (i.e., age, hypertension, previous radiation therapy to the chest wall, cumulative anthracycline dose, baseline LVEF) was performed. Of these, only age (when trastuzumab was administered concomitantly with doxorubicin) was significantly positively associated with the risk of developing trastuzumab-related cardiotoxicity (risk ratio, 1.56 per 10-year increase in age).

All trials with trastuzumab have excluded those patients with pre-existing CHF, and therefore the presence of LVD or CHF symptoms should exclude the use of trastuzumab even in those patients with borderline postchemotherapy

<table>
<thead>
<tr>
<th>Cardiovascular factors</th>
<th>Noncardiovascular factors</th>
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</thead>
<tbody>
<tr>
<td>Left ventricular dysfunction</td>
<td>Doxorubicin exposure</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>Older age</td>
</tr>
<tr>
<td>Uncontrolled hypertension</td>
<td>Chest wall irradiation</td>
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<tr>
<td>(especially to the left side)</td>
<td></td>
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<tr>
<td>Valvular heart disease</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
<td>Obesity</td>
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</table>
LVEF <50%. In a retrospective clinical experience study, the authors attempted to identify those pre-existing factors that may be used as predictors for the development of trastuzumab-related cardiotoxicity [48]. Results suggested that advanced age, hypertension, radiation therapy to the left chest wall, or previous exposure to anthracyclines did not result in a higher risk for cardiotoxicity, but a clear correlation between baseline LVEF and the risk for cardiac events was established. However, the number of cardiac events was too small, which notably diminished the statistical power of the study. Diabetes, history of coronary artery disease, and valvular disease were all factors clearly associated with a higher incidence of cardiac events, though these associations did not reach statistical significance, probably as a result of this lack of sufficient statistical power. These data must be considered with caution, and not as definitive results, because in another study smoking, family history, taking lipid-lowering or hypoglycemic medications, and radiation to the left side of the chest were not identified as risk factors [49]. Other conditions usually considered to exclude patients from enrollment in large trials of trastuzumab are a history of myocardial infarction or angina, uncontrolled hypertension, valvular disease, or arrhythmia, so limited data must be considered with caution, and not as definitive results, because in another study smoking, family history, taking lipid-lowering or hypoglycemic medications, and radiation to the left side of the chest were not identified as risk factors [49]. Other conditions usually considered to exclude patients from enrollment in large trials of trastuzumab are a history of myocardial infarction or angina, uncontrolled hypertension, valvular disease, or arrhythmia, so limited knowledge exists regarding the effects of trastuzumab in patients from enrollment in large trials of trastuzumab are a history of myocardial infarction or angina, uncontrolled hypertension, valvular disease, or arrhythmia, so limited knowledge exists regarding the effects of trastuzumab in patients with these conditions. Every patient should be interrogated regarding these problems and, if any are present, treatment with trastuzumab should be reconsidered and a risk–benefit assessment should be carefully performed.

Evaluation of Cardiac Function Before and During Trastuzumab Therapy

While a detailed clinical record is the most useful tool for the identification of potential cardiac dysfunction in a breast cancer patient receiving trastuzumab, it should be borne in mind that, in many cases, initially, cardiac damage is asymptomatic. Therefore, it is advisable to perform cardiac monitoring on a regular basis, even in the case of women who do not present with cardiac signs. However, in clinical practice there are not yet any universally accepted guidelines for cardiac monitoring of breast cancer patients receiving trastuzumab [50].

Electrocardiography (ECG) should be routinely used in every patient prior to trastuzumab therapy, although rhythm disturbances or intraventricular conduction abnormalities usually appear only in advanced stages of cardiac disease. Currently, a diagnosis of CHF relies on clinical evaluation based on history, physical examination, and complementary tests [47]. The main components are the presence of symptoms (fatigue, breathlessness, ankle swelling) and objective evidence of cardiac dysfunction at rest. But such symptoms are often nonspecific and may mimic those of pulmonary disease. Furthermore, although a large proportion of patients with cardiac dysfunction induced by trastuzumab present with clinical impairment (64%) [21], a considerable number of them remain asymptomatic. The use of adequate imaging methods to monitor cardiac function during treatment is therefore of critical importance in these patients.

Alongside ECG, measuring plasma concentrations of natriuretic peptides can be helpful in ruling out significant cardiac disease, whereas elevated concentrations may indicate the presence of diastolic dysfunction [47]. However, the HFSA recommends using this test only in patients presenting with symptoms of suspected HF [46].

Echocardiography is the most widely used imaging method for the evaluation of left ventricular function. It is also valuable for the detection of pulmonary hypertension, myocardial damage, valvular disease, and hemodynamic abnormalities [45]. However, measurement is somewhat dependent upon the individual who performs the procedure and on the acoustic window of the patient, which is one of the main determinants of image quality. The rates of inter- and intraobserver variability are relatively high, and variations in LVEF >10% are often found in the absence of any true modification [12]. Three-dimensional (3D) echocardiography and cardiac magnetic resonance imaging (MRI) have greater reproducibility in evaluating LVEF [51–53]. This technique provides morphological, functional, perfusion, and viability information in one assessment. It is expensive and time-consuming but is the diagnostic method of choice for patients with technically limited images from ECG and in patients with discordant information that is clinically significant from prior tests [54].

The British Society for Echocardiography has published recommendations for LVEF monitoring in breast cancer patients receiving trastuzumab [55]. These state that an accurate value for LVEF can be determined by 3D echocardiography, provided that the technique is performed by an experienced technician. The technique should be reliable enough to identify 10% changes from baseline in LVEF. In a small percentage of patients, notably in those undergoing surgery or local radiation therapy, the echocardiographic image quality is not good enough; therefore, these patients require alternative imaging techniques. The guidelines suggest LVEF determination prior to trastuzumab treatment initiation and every 3 months thereafter. It is not recommended to start trastuzumab therapy if the LVEF is <55%. If the LVEF drops to <10% at any point or remains <50%, trastuzumab therapy should be stopped.

Management of Trastuzumab-Associated Cardiotoxicity

The vast majority of patients developing trastuzumab-induced cardiac dysfunction present solely with an asymp-
tomatic reduction in LVEF that can be reversed with trastuzumab discontinuation and conventional medical treatment [8]; only a small percentage of patients experience a progression to HF. Indeed, in some clinical studies reporting reduced LVEF of <40% following trastuzumab therapy, discontinuation of trastuzumab (without additional intervention) was sufficient to prevent cardiac events [9]. In other studies, patients experiencing a >20% reduction from baseline in LVEF or LVD received angiotensin-converting enzyme inhibitors (ACEIs), diuretics, or beta-blockers, which subsequently increased the LVEF [23, 31, 48].

Following such treatment, repeat echocardiographic evaluations should be performed until symptom and sign stabilization and recovery of ventricular function. In many cases, following such an approach, trastuzumab therapy can be resumed following recovery of LVEF, without the development of further LVEF impairment [28, 38, 43]. However, one in five patients does not regain normal cardiac function following appropriate cardiac therapy [21]. If an individual patient experiences new episodes of HF upon trastuzumab resumption, treatment should be definitively discontinued. As stated previously, it is necessary to perform a risk–benefit analysis on an individual basis when making a decision to continue with trastuzumab in patients presenting either with risk factors or with systolic/diastolic dysfunction. In a percentage of patients who experience cardiac damage, trastuzumab resumption should be considered because of the advanced stage of their cancer, that is, patients with MBC [56], because the risk for cardiac dysfunction is offset by the benefit of antitumor therapy.

Although management guidelines published by international cardiology societies have not, as yet, described specific medical therapy for the treatment of trastuzumab-related cardiotoxicity, there is a wealth of evidence to support the use of certain drug classes in any patients with asymptomatic decreased LVEF, whereas these drugs plus diuretics for the specific treatment of fluid retention are recommended in patients with symptomatic HF [45]. The European Society of Cardiology (ESC) and the HFSA recommend ACEIs as first-line therapy in patients with LVEF <40%, with or without symptoms, administered at doses demonstrated to be effective in large, controlled trials [46, 47]. In patients intolerant to ACEIs, ARBs may be substituted. Diuretics are administered for the symptomatic treatment of fluid retention. According to the ESC guidelines, beta-blockers are added to initial therapy for all patients with NYHA class II–IV HF, starting with a low dose and titrating upward to those demonstrated to be effective in clinical studies of HF [47]. Cardiac glycosides such as digoxin may be beneficial in combination with a beta-blocker in patients with...
symptomatic HF. The HFSA also recommends beta-blocker therapy for asymptomatic decreased LVEF [46].

A proposed algorithm for the management of patients receiving trastuzumab is presented in Figure 1.

Patient Education
In clinical practice, the decision-making process is usually shared between the physician and the patient. Patients make their decisions based not only on the information and guidance provided by the physician, but also on their preferences, moral values, and personal life goals. From an ethical and legal point of view, the adult competent patient has the right to accept or reject treatments proposed by his/her physician.

In the case of breast cancer treatment, the physician should first clearly explain the different therapeutic options that are available in the individual case, including expected efficacy and adverse effects, especially irreversible toxic effects. Secondly, the physician must obtain the patient’s informed consent, but only when they are certain that the patient has understood the risks, advantages, and disadvantages of the proposed treatment, as well as alternatives. In oncology, the risk–benefit analysis is a routine procedure, based on two major ethical principles: to do what is considered the best for the patient and to not cause him/her excessive damage. In addition, there is another principle that tips the balance: to preserve life, even at the expense of its quality. For the information and education of patients with breast cancer who are candidates for trastuzumab therapy, the following recommendations may be useful:

1. Patients should be informed about the expected efficacy and potential risks of trastuzumab therapy. It is important that the patient understands that breast tumors overexpressing HER-2/neu are more aggressive, but that there is a specific therapy for these tumor types. Results from controlled clinical studies provide information regarding trastuzumab efficacy and toxicity. The patient should be warned that trastuzumab may cause cardiotoxicity, and that such cardiotoxicity, in turn, may result in CHF.

2. In conducting a detailed history and physical examination, special attention should be paid to potential risk factors (cardiac and noncardiac) and this presents an optimal time to perform a risk–benefit analysis for the particular patient.

3. Patients should be informed about the results from the cardiac evaluation performed prior to the initiation of trastuzumab and about the results from monitoring of left ventricular function carried out on a regular basis after trastuzumab treatment initiation. The patient should be informed that the initial evaluation will enable the physician to know whether she possesses factors associated with an increased risk for cardiotoxicity. Also, the patient should know that cardiac monitoring on a regular basis is the best method to detect any potential cardiac damage early.

4. Patients should be encouraged to adopt a healthy lifestyle in order to protect the myocardium, including a balanced diet, moderate exercise, and smoking cessation.

5. Clinical signs and symptoms caused by trastuzumab-induced cardiotoxicity are not specific, and can be seen in other diseases or conditions, such as pulmonary derangements or the breast cancer itself. The patient should be informed that in the event of lower limb edema, palpitations, dyspnea, or jugular ingurgitation she must report to the treating physician as soon as possible.

CONCLUSIONS
Trastuzumab may be associated with cardiac dysfunction (mostly an asymptomatic decline in LVEF or overt HF) in a small but significant proportion of patients. Prior to initiating treatment with trastuzumab, a risk–benefit analysis for individual patients must be performed, taking into account their prognosis, pre-existing risk factors, and personal preference. Monitoring of cardiac function must be performed throughout the treatment period and also during follow-up. In many cases, early recognition of trastuzumab-associated cardiac dysfunction can allow effective medical intervention, symptom resolution, and continuation with trastuzumab therapy.

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