Cardiotoxicity of trastuzumab and other HER2-targeted agents

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INTRODUCTION

Trastuzumab is a monoclonal antibody that targets the human epidermal growth factor receptor 2 (HER2, also called ErbB2). For the 15 to 20 percent of patients with breast cancer whose tumors overexpress HER2, trastuzumab therapy is important in the treatment of both early and advanced disease. Its use, however, results in a small to modest risk for cardiotoxicity, which is typically manifested by an asymptomatic decrease in left ventricular ejection fraction and less often by clinical heart failure. (See "Systemic treatment for HER2-positive metastatic breast cancer" and "Adjuvant systemic therapy for HER2-positive breast cancer", section on 'Trastuzumab-based treatment'.)

In addition to trastuzumab, other HER2-targeted agents have been developed for treatment of HER2-overexpressing breast cancer including ado-trastuzumab emtansine (T-DM1), fam-trastuzumab deruxtecan, pertuzumab, and others. Although data are limited regarding cardiotoxicity in some of these newer agents, the available data support the view that these agents may be less cardiotoxic than trastuzumab. (See "Systemic treatment for HER2-positive metastatic breast cancer".)

Cardiotoxicity related to trastuzumab and related HER2-targeted agents will be presented here. The cardiotoxicity of other antineoplastic drugs, including anthracyclines and taxanes, management of heart failure, and clinical use of trastuzumab and other HER2-targeted therapies are discussed separately.

- (See "Clinical manifestations, diagnosis, and treatment of anthracycline-induced cardiotoxicity".)
- (See "Risk and prevention of anthracycline cardiotoxicity".)
- (See "Cardiotoxicity of cancer chemotherapy agents other than anthracyclines, HER2-targeted agents, and fluoropyrimidines".)
- (See "Management and prognosis of asymptomatic left ventricular systolic dysfunction".)
- (See "Overview of the management of heart failure with reduced ejection fraction in adults".)
- (See "Adjuvant systemic therapy for HER2-positive breast cancer".)
- (See "Overview of the approach to metastatic breast cancer".)
- (See "Overview of the treatment of newly diagnosed, invasive, non-metastatic breast cancer".)
- (See "Cancer survivorship: Cardiovascular and respiratory issues".)

PATHOPHYSIOLOGY OF CARDIOTOXICITY

The pathophysiology underlying cardiac dysfunction in patients treated with agents targeting human epidermal growth factor receptor 2 (HER2) is not fully understood [1,2]. Because many patients who receive trastuzumab have previously received anthracyclines, it had been initially postulated that modification or exacerbation of anthracycline-related damage was responsible. However, endomyocardial biopsies from patients with trastuzumab-related cardiac dysfunction do not show typical anthracycline-related ultrastructural changes [3]. In addition, trastuzumab-related cardiotoxicity may occur even in patients not exposed to anthracyclines [4]. Further confounding the picture is that trastuzumab-related cardiotoxicity is not dependent on cumulative dose and may be largely reversible, and rechallenge with trastuzumab may be well tolerated.

Evidence from both in vivo and in vitro studies indicate the importance of the epidermal growth factor (EGF) signaling system in the normal heart and suggest that cardiotoxicity associated with trastuzumab is directly related to HER2 blockade [5]:

- In animal models, HER2 signaling is important for embryonic cardiac development and myocyte survival as well as protection from potential cardiotoxins [6-9].
- Mice with ventricular-restricted knockout of the HER2 gene spontaneously develop signs of a dilated cardiomyopathy, and their cardiomyocytes show enhanced susceptibility to anthracycline-induced cell death [9-12].
- Although the role of HER2 in the pathophysiology of heart failure is not well understood, serum HER2 levels are increased in patients with chronic heart failure, and

levels correlate inversely with left ventricular function [13,14].

The mechanism underlying the synergistic cardiotoxicity seen with anthracyclines and trastuzumab is unclear, but upregulation of HER2 expression by anthracyclines may contribute [15].

Other mechanisms for cardiotoxicity in patients treated with HER2-targeting agents may be operative since levels of HER2 in the adult heart are much lower than those found in breast cancer cells, the intended target of the anti-HER2-directed therapy. Furthermore, lapatinib, a dual kinase inhibitor of HER2 and epidermal growth factor receptor (EGFR), and pertuzumab, a newer anti-HER2 monoclonal antibody that recognizes an epitope distant from that of trastuzumab, appear to be only rarely associated with clinically-relevant cardiotoxicity. (See 'Lapatinib' below and 'Pertuzumab' below.)

Newer data raise the possibility that trastuzumab, lapatinib, and pertuzumab also interfere with the ligand-binding-induced cardioprotective pathways that are indispensable to recover from cardiac injury pathways and that differences in cardiotoxicity may reflect the different epitopes of HER2 that are recognized by individual antibodies [16-19]. As an example, in one in vitro study, trastuzumab and pertuzumab (but not Erb-hcAb, a novel human antibody that recognizes a distinct epitope of HER2) inhibited assembly of the neuregulin 1/ErbB2/ErbB4 complex, which is required for cardiomyocyte survival [16].

TRASTUZUMAB

Clinical presentation — Trastuzumab-related cardiotoxicity is most often manifested by an asymptomatic decrease in left ventricular ejection fraction (LVEF) and less often by clinical heart failure [20-22]. In contrast to cardiotoxicity from anthracyclines, trastuzumab-related cardiotoxicity does not appear to be related to cumulative dose. It is often reversible with treatment discontinuation, and rechallenge is often tolerated after recovery. In addition, cardiac biopsy specimens after trastuzumab exposure do not show significant myocyte destruction characteristic of anthracycline-induced dysfunction.

These differences have led to the terms "Type I" and "Type II" chemotherapy-related cardiac dysfunction [23]. Type I, associated with the anthracyclines, results, at least to some degree, in myocyte destruction and clinical heart failure. Type II, a phenomenon that is not unique to trastuzumab, is more often associated with a loss of contractility (presumably a form of stunning or hibernation) that is less likely to be associated with myocyte death or clinical heart failure and is more likely to be reversible.

Incidence — The incidence of trastuzumab-related cardiotoxicity varies according to patient-related factors, such as previous chemotherapy, pre-existing heart disease, and age [24].

Data suggest that the risk for heart failure/cardiomyopathy among patients treated with trastuzumab exists but is low and may be limited by avoidance of cumulative doses of anthracycline exceeding 300 mg/m^2. Despite this low risk, close cardiac monitoring is indicated. Further details are discussed below. (See 'Cardiac monitoring' below and 'Acceptable concurrent treatment' below.)

The following data are available:

- A modest incidence of trastuzumab-associated cardiotoxicity has been observed in large randomized trials of adjuvant trastuzumab for human epidermal growth factor receptor 2 (HER2)-positive breast cancer. These trials required stringent and consistent cardiac monitoring, limited cumulative anthracycline dose to 300 mg/m^2, and excluded patients with abnormal cardiac function (table 1 and table 2) [25-37].

  A 2012 meta-analysis of randomized trials, altogether enrolling 11,991 women with HER2-positive early breast cancer, demonstrated that patients treated with trastuzumab, relative to those who did not receive trastuzumab, experienced [38]:

  - An increased risk for severe heart failure (2.5 versus 0.4 percent; relative risk [RR] 5.11, 90% CI 3.00-8.72)
  - A reduction in LVEF (RR 1.83, 90% CI 1.36-2.47)
  - There was no difference in the cardiotoxicity profile in trials with concurrent as compared to sequential administration of chemotherapy and trastuzumab. A shorter treatment period (six months or less) did not appear to be associated with an increase in the risk of heart failure (RR 0.5, 95% CI 0.07-3.74), although the analysis was based on only one trial (FinHER).

- A subsequent study including approximately 400 patients treated with paclitaxel and trastuzumab for node-negative disease demonstrated even lower rates of cardiotoxicity associated with trastuzumab relative to previous trials, with only 0.5 percent of patients developing grade 3 left ventricular systolic dysfunction and 3 percent of patients with asymptomatic LVEF decline [39]. These modest increases in cardiotoxicity compare favorably with older trials, which evaluated trastuzumab in the setting of concurrent doxorubicin exceeding 300 mg/m^2 [40,41].

Importantly, none of these trials reported a difference in the number of cardiac deaths between those who did versus did not receive an anthracycline. (See 'Risk factors' below and 'Acceptable concurrent treatment' below.)

Risk factors — Risk factors associated with a higher likelihood of developing trastuzumab-related cardiotoxicity include age greater than 50 years and previous or concurrent

anthracycline use, particularly among obese or overweight patients [27,40,42-46]. By contrast, concurrent treatment with trastuzumab and adjuvant radiation therapy does not increase the risk [47].

Other risk factors identified by multivariate analysis are pre-existing cardiac dysfunction (ie, decreased LVEF), older age, high body mass index (BMI), and antihypertensive therapy, while diabetes, valvular heart disease, and coronary artery disease did not significantly increase risk [29,42,48]. On the other hand, at least a very small dataset suggests that diabetes is a risk factor for cardiotoxicity among older adult women receiving trastuzumab. In a study of 45 older adult women receiving trastuzumab either in the adjuvant setting or for metastatic disease, the risk of cardiotoxicity was 33 versus 6 percent for patients with and without diabetes, respectively [49]. (See "Overview of the approach to early breast cancer in older women" and "Treatment of metastatic breast cancer in older women", section on 'HER2-positive disease'.)

The risk of trastuzumab-related cardiac dysfunction is highest in those patients who receive concurrent anthracyclines (especially if the cumulative doxorubicin dose is >300 mg/m^2); cardiac toxicity is modestly elevated for trastuzumab given after anthracycline. By contrast, a lesser elevation has been observed to occur with trastuzumab given after a taxane [1,26-31,40,41,50,51].

Among patients receiving either anthracyclines or sequential treatment with anthracyclines and trastuzumab for breast cancer, being obese or overweight increases the risk of developing cardiac dysfunction (either symptomatic or asymptomatic, with a decline in ejection fraction). In a meta-analysis of 15 studies including approximately 8700 breast cancer patients treated with either anthracyclines or sequential anthracyclines and trastuzumab, the odds ratio (OR) for overweight patients (those with BMI >25) for cardiac dysfunction was 1.38 (95% CI 1.06-1.80) relative to those with BMI <25 [46]. A higher magnitude of risk was observed among those who were obese (BMI ≥30; OR 1.47, 95% CI 0.95-2.28). Although this difference was not significant, this analysis consisted of far fewer patients compared with the one that included overweight patients.

A cardiac risk score that includes age and baseline LVEF has been developed by investigators from the National Surgical Adjuvant Breast and Bowel Project (NSABP), based upon data from the NSABP B-31 trial, to predict the absolute risk of heart failure in individual patients [48]. Others, using data from the linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database, have developed a seven-factor risk score to predict three-year risk of heart failure or cardiomyopathy after trastuzumab in Medicare populations [52]. However, independent validation is needed before any of these tools can be considered for general use. (See 'Reversibility and rechallenge' below.)

Reversibility and rechallenge — Trastuzumab-related cardiotoxicity is largely reversible in the majority of cases, and treatment continuation and/or resumption of trastuzumab after resolution of cardiac abnormalities may be safe in some women [3,21,40,43,53,54].

- In a phase III trial of chemotherapy with or without trastuzumab conducted in women with metastatic breast cancer, 33 patients continued trastuzumab for a median of 26 weeks despite developing a cardiac event (most often an asymptomatic decline in LVEF) [40,55]. The cardiac status of 28 patients (85 percent) improved or remained the same. Symptoms were reversible for 75 percent of those who received standard heart failure therapy.

- In a retrospective review of 49 patients who developed trastuzumab-related cardiotoxicity, 79 percent of those who stopped trastuzumab after developing symptomatic heart failure recovered with appropriate therapy [53]. However, three patients did not recover, and one died of progressive heart failure. Treatment was reinitiated in 26 patients who interrupted trastuzumab for either an asymptomatic or symptomatic cardiac event, 16 (62 percent) of whom remained without evidence of subsequent cardiac toxicity. In patients with an asymptomatic reduction in LVEF, of whom 41 percent discontinued trastuzumab, LVEF recovered completely in 89 percent, with or without heart failure therapy. Even among the 10 patients who developed recurrent cardiac dysfunction after reintroduction, five were able to continue trastuzumab while maintaining a slightly reduced LVEF as the only sign of cardiotoxicity.

- Reversibility was addressed in a seven-year follow-up analysis of the NSABP B-31 adjuvant trastuzumab trial, in which patients with node-positive, HER2-positive breast cancer were randomly assigned to doxorubicin plus cyclophosphamide, followed by paclitaxel with or without concurrent trastuzumab [48]. The cumulative risk of a cardiac event (defined as definite or probable cardiac death or heart failure manifested by dyspnea with normal activity or at rest and associated with a decline in LVEF of >10 percentage points from baseline to a value <55 percent, or a decrease of >5 percent to a value below the lower limit of normal) to seven years was 4.0 percent in the trastuzumab arm versus 1.3 percent in the non-trastuzumab arm.

  Among the 37 evaluable patients who received trastuzumab and met criteria for a cardiac event, one died because of heart failure. Of the remaining 36 patients, 33 were without symptoms of cardiac disease when assessed ≥6 months after their diagnosis of heart failure, although 21 continued to receive cardiac medications. LVEF measurements recovered to at least 50 percent in 21 patients.

  Of the 50 patients who were symptomatic but did not meet criteria for a cardiac event, 49 were observed for six months after onset of symptoms, and none reported symptoms of cardiac disease on last follow-up, although 12 continued to receive cardiac

medication. Of the 114 evaluable patients with asymptomatic decline in LVEF during therapy who discontinued trastuzumab, 27 subsequently reported symptoms of possible cardiac disease. Of the remaining 87, LVEF was reported in 69 patients at least six months after discontinuation of trastuzumab, and only 15 still had an LVEF <50 percent.

The study authors developed a cardiac risk score including age and baseline LVEF to predict the absolute risk of heart failure in individual patients. When cardiac risk scores were plotted against a modeled heart failure risk curve, it was estimated that a 45-year-old woman with a baseline LVEF of 65 percent would have a 2.3 percent predicted risk of a cardiac event, whereas a 65-year-old woman with a baseline LVEF of 55 percent would have a 13 percent predicted risk [56]. However, validation of this risk prediction tool is needed before it can be considered for use in general practice.

Clinical guidelines — When trastuzumab therapy is planned for patients in the adjuvant or metastatic setting, the patient's risk for trastuzumab-related cardiotoxicity should be carefully assessed and weighed against the benefits of trastuzumab treatment. In the adjuvant setting, trastuzumab therapy is likely to be held or discontinued for asymptomatic cardiac dysfunction, and thus baseline and serial screening of LVEF is appropriate. In the metastatic setting, the decision is more complex, given the clinical benefit provided by trastuzumab.

Increased vigilance for signs and symptoms of cardiotoxicity is appropriate for higher-risk patients. Without clinical trials specifically evaluating cardiac monitoring and trastuzumab dosing with cardiotoxicity, we generally follow the protocols used in the cooperative group clinical trials of trastuzumab.

Baseline evaluation and prevention — Cardiac function should be assessed prior to the initiation of trastuzumab therapy in both the adjuvant and metastatic settings [20,57]. When treatment with trastuzumab follows use of an anthracycline, an assessment of LVEF should be done after completion of the anthracycline and prior to initiation of trastuzumab. Further details on the approach to patients also receiving anthracyclines are discussed elsewhere. (See "Risk and prevention of anthracycline cardiotoxicity".)

Patients with a normal baseline LVEF and no signs or symptoms of heart failure on physical examination may proceed with trastuzumab therapy. For such patients, unless there are other cardiac risk factors, we do not administer beta-blockers or angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers, given toxicities and unknown effect on clinically significant heart failure or survival. In a phase III trial of 468 women with HER2-positive breast cancer treated with trastuzumab for 12 months, cardiotoxicity was comparable among those assigned to placebo, carvedilol, or lisinopril (although there were fewer interruptions among those assigned to either treatment relative to placebo) [58].

Patients with a modestly increased risk for cardiotoxicity include those with borderline LVEF (usually 40 to 50 percent), age >50 years, and hypertension; they may proceed with trastuzumab after weighing the risks and benefits of trastuzumab therapy, but we and others recommend increased vigilance [42,55] and management of comorbid conditions. Trastuzumab therapy is generally safe in patients with coronary artery disease and valvular disease but warrants careful monitoring.

Noninvasive methods for LVEF estimation are discussed separately. Whichever method is selected for a baseline assessment should be continued for serial screening. (See "Tests to evaluate left ventricular systolic function".)

Cardiac monitoring — The optimal surveillance for trastuzumab-related cardiotoxicity is not defined [20]. In the adjuvant setting, we perform a baseline evaluation for cardiac function with a repeat at 3, 6, 9, and 12 months. Typically, in patients treated for metastatic disease, LVEF is monitored at baseline and then only in the presence of symptoms. In both the adjuvant and metastatic settings, clinical signs and symptoms, including increased heart rate or weight (≥2 kg in one week), edema, third heart sound (S3) gallop, or new dyspnea on exertion, should prompt further evaluation [20,22,42].

A retrospective study of over 19,000 women suggested that adjuvant trastuzumab was associated with increased risk of heart failure during the period of adjuvant treatment but not thereafter, suggesting that routine intensive monitoring after treatment completion may not be necessary [59].

While some evidence suggests troponin levels may have utility as a diagnostic and prognostic marker in trastuzumab-related cardiotoxicity [60-62], data are still too limited to recommend their routine use.

Dose adjustments for cardiotoxicity — We follow the dosing guidelines for trastuzumab as outlined in the clinical trials of adjuvant trastuzumab (NSABP B-31 trial and the NCCTG N9831 trial) [28]. As discussed above, LVEF is infrequently monitored in the metastatic setting and instead is reserved for patients with suspicious symptoms or physical findings.

- If the LVEF declines 16 or more percentage points from baseline or 10 to 15 percentage points from baseline to below the lower limit of normal, trastuzumab is withheld for four weeks, at which time the LVEF is reassessed.
- If the LVEF remains below these levels, trastuzumab should be discontinued.
- If the patient has symptomatic heart failure while receiving trastuzumab, trastuzumab should be discontinued. Symptomatic (clinical) heart failure is defined by the presence of:

- Symptoms (dyspnea, orthopnea, pedal edema)
- Objective findings (elevated jugular venous pressure, sinus tachycardia, tachypnea, S3 gallop, crackles)
- LVEF decline or chest radiograph findings of pulmonary edema or increased vascular markings

Heart failure treatment — Trastuzumab-related cardiotoxicity usually responds to standard medical treatment for heart failure and discontinuation of trastuzumab in most, although not all, patients [20,27,41,53]. Although treatment of trastuzumab-related cardiotoxicity has not been formally studied in clinical trials, standard medical therapy for heart failure, including beta blockers and angiotensin-converting enzyme inhibitors, should be initiated. (See "Overview of the management of heart failure with reduced ejection fraction in adults", section on 'Pharmacologic therapy'.)

Acceptable concurrent treatment — As described above, the risk of trastuzumab-related cardiac dysfunction was significant when trastuzumab was administered concurrently with anthracyclines [41]. However, on further analysis, the risk began to increase when the cumulative doxorubicin dose exceeded 300 mg/m^2 and was quite low at cumulative doses below 300 mg/m^2.

There is accumulating evidence that concurrent administration of trastuzumab and doxorubicin may be safe when the cumulative doxorubicin dose is limited to 180 mg/m^2 [35,63-65]:

- In the FinHER trial, little cardiac toxicity (<1 percent with symptomatic heart failure) was detected in those patients treated with adjuvant trastuzumab administered prior to an anthracycline (trastuzumab for nine weeks with three cycles of adjuvant docetaxel or vinorelbine followed by additional adjuvant chemotherapy with three cycles of fluorouracil, epirubicin, and cyclophosphamide [FEC]) [65].
- In the NOAH trial, patients treated with trastuzumab (for a total duration of one year) concurrent with three cycles of doxorubicin (60 mg/m^2) and paclitaxel (followed by additional neoadjuvant chemotherapy) had an incidence of symptomatic heart failure of less than 2 percent and any LVEF decrease of less than 3 percent [35]. This was less than the incidence of trastuzumab-related cardiotoxicity in the adjuvant trials where trastuzumab was given concurrently with paclitaxel after completion of doxorubicin, which may have been due to the lower cumulative dose of doxorubicin in the NOAH trial. (See 'Incidence' above.)

We avoid concurrent extended administration of anthracyclines and trastuzumab due to an increased risk of cardiotoxicity. Based upon data described above, trastuzumab concurrent

with limited anthracyclines (≤3 cycles or ≤180 mg/m^2 of doxorubicin) is a potentially safe option. However, there are no data that suggest improved efficacy if trastuzumab is given concurrent with anthracyclines rather than in sequence.

Trastuzumab in combination with a taxane, even after an anthracycline, shows low rates of symptomatic or severe cardiotoxicity [26,41]. Likewise, trastuzumab is frequently administered concurrent with endocrine therapy and/or radiation therapy without significant cardiac toxicity [47].

LAPATINIB

Lapatinib is an orally active tyrosine kinase inhibitor that affects both human epidermal growth factor receptor 2 (HER2) and the epidermal growth factor receptor (EGFR, also called ErbB1). Early clinical studies suggest activity for lapatinib in women with advanced breast cancer, and there is some evidence that this drug, unlike trastuzumab, may penetrate the central nervous system and be effective against brain metastases. (See "Brain metastases in breast cancer", section on 'HER2-positive disease' and "Systemic treatment for HER2-positive metastatic breast cancer", section on 'Other tyrosine kinase inhibitor combinations'.)

Incidence and clinical course — Emerging data suggest that lapatinib may have a more favorable cardiac safety profile than trastuzumab, even among patients who have previously received anthracyclines, taxanes, and trastuzumab:

- In a phase III trial, in which lapatinib plus capecitabine was compared with capecitabine alone in women with advanced breast cancer who had progressed after treatment with regimens that included an anthracycline, a taxane, and trastuzumab, treatment-related cardiac events were infrequent (4 of 155 receiving combined therapy compared with 1 of 145 patients treated with capecitabine alone) [66]. Furthermore, three of the four were asymptomatic and not associated with a drop in left ventricular ejection fraction (LVEF). The fourth developed Prinzmetal angina, which resolved on discontinuation of lapatinib, but there was an unexplained subsequent drop in LVEF. There were no differences in the mean LVEF between treatment groups at the scheduled assessments.

- Global experience with lapatinib-related cardiotoxicity was reviewed in a pooled analysis of 3689 patients enrolled in clinical trials [67]. Only 60 (1.6 percent) patients exposed to lapatinib had a cardiac event; 53 were asymptomatic declines in LVEF, and only 7 (0.2 percent) had symptoms of a decline in cardiac function. Furthermore, of the 552 patients previously treated with anthracyclines, only 12 (2.2 percent) had a decreased LVEF while on lapatinib, as did 14 (1.7 percent) of the 826 patients previously exposed to trastuzumab. The decrease in LVEF was rarely severe; the mean nadir was

43 percent. Of the 40 patients whose outcome was determined, 35 (88 percent) had partial or full recovery regardless of whether or not lapatinib was continued.

Although these preliminary results compare favorably with historical experience of trastuzumab-related cardiotoxicity, the patients enrolled in these trials were highly selected. Additional clinical data and longer follow-up will be required to fully assess whether lapatinib has a more favorable cardiotoxicity profile than trastuzumab.

Combined lapatinib plus trastuzumab — Given their different mechanisms of action, investigators are beginning to combine lapatinib with trastuzumab in an attempt to improve antitumor efficacy in HER2-overexpressing advanced breast cancer. (See "Systemic treatment for HER2-positive metastatic breast cancer", section on 'Lapatinib plus trastuzumab'.)

Despite initial concerns about the possibility of additive cardiotoxicity, the available evidence suggests that concurrent use of lapatinib with trastuzumab is not incrementally more cardiotoxic than either drug alone [68,69]. In the only randomized trial of lapatinib alone versus trastuzumab plus lapatinib in 296 patients with trastuzumab-refractory advanced breast cancer, the incidence of asymptomatic and symptomatic cardiac events was low with combination therapy (2 and 3.4 percent, respectively, compared with 0.7 and 1.4 percent, respectively, for lapatinib alone) [68]. Importantly, all of the patients on this trial had received trastuzumab for a prolonged period, and those who developed heart failure during trastuzumab therapy were excluded. The rate of cardiotoxicity with the combination treatment in patients not previously exposed to trastuzumab is not yet known, but information should be available from the ALTTO trial. Nevertheless, clinical experience and follow-up duration are both limited.

Guidelines for management — The US Food and Drug Administration-approved manufacturer's package insert recommends that a normal LVEF be confirmed prior to starting treatment with lapatinib and periodically during treatment. They advise discontinuation of lapatinib for a drop in the LVEF to <50 percent, for those whose LVEF drops below the institution's lower limit of normal, and for any patients who develop clinical heart failure during therapy [70]. Dose reduction is recommended if the LVEF recovers to normal after a minimum of two weeks and the patient is asymptomatic.

ADO-TRASTUZUMAB EMTANSINE

Ado-trastuzumab emtansine (T-DM1) is an antibody-drug conjugate composed of trastuzumab, a thioether linker, and a derivative of the antimitotic agent, maytansine. T-DM1 is used in metastatic human epidermal growth factor receptor 2 (HER2)-positive disease, as well as for the adjuvant treatment of patients with HER2-positive disease who did not achieve a complete pathologic response to neoadjuvant therapy. The following information

represents available data regarding cardiotoxicity with T-DM1 in advanced HER2-positive disease:

- In a pooled analysis of 1961 patients exposed to T-DM1, the total cardiac event rate (including any-grade congestive heart failure, left ventricular ejection fraction [LVEF] drops, acute cardiac ischemia, or cardiac arrhythmia) was 3.4 percent, mostly involving asymptomatic LVEF drops [71].

- A phase III study compared T-DM1 versus capecitabine plus lapatinib in 991 patients with advanced HER2-overexpressing breast cancer that had previously been treated with trastuzumab and a taxane [72]. LVEF was assessed at baseline, weeks 6 and 12, and every 12 weeks thereafter. At a median 13-month follow-up, 8 of 481 patients in the T-DM1 group (1.7 percent) had an LVEF that was <50 percent and at least 15 percentage points below baseline (versus 7 of 445 in the lapatinib/capecitabine group [1.6 percent]). Only three patients in each group had a decrease from baseline to <40 percent, and only one patient receiving T-DM1 developed grade 3 left ventricular systolic dysfunction (symptomatic, responsive to intervention).

- In a phase II randomized trial of first-line T-DM1 versus trastuzumab plus docetaxel in 137 patients with HER2-positive metastatic or locally advanced breast cancer, there were no reports of symptomatic heart failure [73]. At a median follow-up of 23 months, three patients in each group had an asymptomatic decline in LVEF. There were three patients with a decline in LVEF ≤40 percent, two in the trastuzumab/docetaxel group (both of whom had received prior adjuvant anthracycline-based chemotherapy), and one who received T-DM1 (who had not received prior anthracycline and had no prior cardiac history).

Given the favorable safety profile in advanced disease, the use of T-DM1 is of interest in early-stage disease, in which T-DM1 could potentially replace trastuzumab plus a taxane. The tolerability of one year of T-DM1 after anthracycline-based chemotherapy was suggested in a trial in which 153 patients with HER2-positive early breast cancer and a prechemotherapy LVEF ≥55 percent received neoadjuvant doxorubicin plus cyclophosphamide or epirubicin plus fluorouracil and cyclophosphamide (FEC) followed by T-DM1 for four cycles; patients could then receive three or four cycles of optional docetaxel with or without trastuzumab [74]. T-DM1 was then resumed with optional radiotherapy for a total of one year of HER2-directed therapy. At a median follow-up of 25 months, four patients had asymptomatic LVEF declines (≥10 percentage points from baseline to <50 percent), which led to discontinuation of T-DM1 in only one patient. There were no other prespecified cardiac events or episodes of symptomatic heart failure. This study was performed as a pilot to precede testing of T-DM1 in a more formal, future adjuvant trial. T-DM1 should not be used in the adjuvant setting unless large randomized trial results are available showing benefit in this setting.

Importantly, all of these trials have a limited follow-up duration.

Guidelines for management — The US Food and Drug Administration-approved prescribing information recommends that all patients treated with T-DM1 have LVEF assessed at treatment initiation and at regular intervals (eg, every three months) during treatment [75]. At least temporary discontinuation of therapy is recommended if the LVEF falls to <40 percent or is 40 to 45 percent with a ≥10 percent absolute decrease below the pretreatment value.

PERTUZUMAB

Pertuzumab is a monoclonal antibody that binds to a different epitope of the human epidermal growth factor receptor 2 (HER2) extracellular domain than does trastuzumab, and it prevents HER2 homo- and heterodimerization with other HER-family receptors. While initial studies showed limited activity for women with HER2-negative metastatic breast cancer, subsequent data demonstrate benefit when it is combined with trastuzumab for women with HER2-positive disease who had progressed on prior trastuzumab treatment, and in the first-line setting, in combination with trastuzumab and docetaxel. (See "Systemic treatment for HER2-positive metastatic breast cancer", section on 'Trastuzumab plus pertuzumab plus a taxane'.)

Cardiotoxicity of combined therapy has been addressed in the following studies:

- In a phase II trial of pertuzumab plus trastuzumab in 66 patients with HER2-overexpressing breast cancer that progressed during prior trastuzumab therapy, only three patients had a decrease in left ventricular ejection fraction (LVEF) of ≥10 percentage points and less than a 50 percent value, and no patient experienced symptomatic cardiac toxicity [76]. Two patients, one with an LVEF drop of 25 percentage points and the other by 13 percentage points, both recovered without treatment interruption, and both continued to receive pertuzumab and trastuzumab. The third patient with a decline of 14 percentage points in LVEF remained asymptomatic but withdrew from the study.

- The phase III CLEOPATRA trial randomly assigned 808 patients with HER2-positive breast cancer to first-line treatment with trastuzumab and docetaxel plus either pertuzumab or placebo [77]. Combined therapy with pertuzumab and trastuzumab was not associated with significantly worse cardiotoxicity. Among patients in whom LVEF was assessed after the baseline assessment, a decline of ≥10 percentage points that resulted in an LVEF of <50 percent occurred in 3.8 percent of the pertuzumab group versus 6.6 percent of the control group. Notably, 72 percent of patients on the placebo

arm and 87 percent of those on the pertuzumab arm recovered to a value of ≥50 percent.

Guidelines for management — The US Food and Drug Administration-approved prescribing information recommends that all patients treated with pertuzumab have LVEF assessed at treatment initiation and at regular intervals (eg, every three months in the metastatic setting and every six weeks in the neoadjuvant setting) during treatment. If LVEF is <45 percent, or is 45 to 49 percent with a ≥10 percent absolute decrease below the pretreatment value, withhold both pertuzumab and trastuzumab and repeat LVEF assessment within approximately three weeks. Discontinue pertuzumab and trastuzumab if the LVEF has not improved or has declined further, unless the benefits for the individual patient outweigh the risks.

FAM-TRASTUZUMAB DERUXTECAN

Fam-trastuzumab deruxtecan is an antibody-drug conjugate composed of an anti-HER2 antibody, a cleavable tetrapeptide-based linker, and a cytotoxic topoisomerase I inhibitor [78]. It is appropriate for adult patients with unresectable or metastatic HER2-positive breast cancer who have received multiple anti-HER2-based regimens in the metastatic setting. (See "Systemic treatment for HER2-positive metastatic breast cancer", section on 'Fam-trastuzumab deruxtecan'.)

In the 234 patients with unresectable or metastatic HER2-positive breast cancer who received fam-trastuzumab deruxtecan, two cases (0.9 percent) of asymptomatic left ventricular ejection fraction (LVEF) decrease were reported [79].

Guidelines for management — According to the US Food and Drug Administration-approved prescribing information, clinicians should assess LVEF prior to initiation of fam-trastuzumab deruxtecan, and at regular intervals during treatment, as clinically indicated. Our approach is to assess at baseline and for symptoms concerning for heart failure.

Clinicals should permanently discontinue fam-trastuzumab deruxtecan if LVEF drops to less than 40 percent, or decreases from baseline of more than 20 percent; or if patients experience symptomatic congestive heart failure [79].

Treatment with fam-trastuzumab deruxtecan has not been studied in patients with a history of clinically significant cardiac disease or LVEF <50 percent prior to initiation of treatment.

MARGETUXIMAB

Margetuximab is an Fc-engineered anti-HER2-receptor monoclonal antibody that is US Food and Drug Administration approved, in combination with chemotherapy, for treatment of metastatic HER2-positive breast cancer in patients who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease [80]. In SOPHIA, left ventricular dysfunction occurred in 1.9 percent of patients treated with margetuximab [81]. This agent has not been evaluated in patients with a pretreatment left ventricular ejection fraction (LVEF) value of <50 percent, a prior history of myocardial infarction or unstable angina within six months, or congestive heart failure New York Heart Association class II to IV.

As for other agents used in metastatic disease, our approach is to assess at baseline and subsequently only for symptoms concerning for heart failure. However, according to the United States Prescribing Information, baseline LVEF measurement should occur within four weeks prior to initiation of treatment, and every three months during and upon completion of treatment [80]. It advises to withhold the agent for ≥16 percent absolute decrease in LVEF from pretreatment values, or LVEF value below institutional limits of normal (or 50 percent, if no limits are available) and ≥10 percent absolute decrease in LVEF from pretreatment values. The reason for our difference in monitoring relative to the prescribing information is reluctance to withhold treatment that is effectively controlling a patient's cancer in the absence of symptoms of heart failure.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Breast cancer".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or email these topics to your patients. You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Beyond the Basics topics (see "Patient education: Treatment of early HER2-positive breast cancer (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Trastuzumab**
  - Treatment with trastuzumab is associated with a risk of cardiac toxicity that is mechanistically distinct from that caused by anthracyclines. Trastuzumab-related cardiotoxicity is typically manifested by an asymptomatic decrease in the left ventricular ejection fraction (LVEF) and less commonly by clinical heart failure.
  - Previous or concurrent anthracycline use and age greater than 50 years are the strongest risk factors for development of trastuzumab-related cardiotoxicity. (See 'Risk factors' above.)
  - In the adjuvant setting, a baseline assessment prior to starting trastuzumab and serial LVEF monitoring (at 3, 6, and 12 months after initiating trastuzumab and 18 months after initiating an anthracycline or other chemotherapy) are appropriate to screen for cardiac dysfunction. (See 'Baseline evaluation and prevention' above and 'Cardiac monitoring' above.)
  - In the metastatic setting, after a baseline assessment, LVEF is infrequently monitored in the absence of symptoms. (See 'Baseline evaluation and prevention' above and 'Cardiac monitoring' above.)
  - Guidelines for trastuzumab dosing for patients who develop trastuzumab-related cardiotoxicity are based upon the reduction in LVEF and patient symptoms. (See 'Dose adjustments for cardiotoxicity' above.)
  - Trastuzumab-related cardiotoxicity is reversible in many patients and responds to standard treatment for heart failure. Many patients tolerate continued treatment or rechallenge with trastuzumab. (See 'Reversibility and rechallenge' above and 'Heart failure treatment' above.)
  - Trastuzumab can be safely administered with taxanes, radiation therapy, and endocrine therapy. (See 'Acceptable concurrent treatment' above.)
- **Other HER2-targeted agents**
  - In contrast to trastuzumab, the risk of cardiotoxicity seems to be less with other human epidermal growth factor receptor 2 (HER2)-targeted agents, such as lapatinib, ado-trastuzumab emtansine (T-DM1), and pertuzumab. Nonetheless,

experience with all three of these agents is limited, and there is a potential risk of cardiotoxicity with all agents. (See 'Lapatinib' above and 'Ado-trastuzumab emtansine' above and 'Pertuzumab' above.)

- A baseline assessment of LVEF is appropriate. As with trastuzumab, in the metastatic setting, LVEF is infrequently monitored during therapy in the absence of symptoms.
- Guidelines are available regarding dose adjustment in patients who develop cardiotoxicity during therapy with these agents. (See 'Guidelines for management' above.)

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Topic 774 Version 44.0

GRAPHICS

Design of adjuvant trials using trastuzumab

Trial (number of patients)	Treatment arms	Definition of severe cardiotoxicity	Monitoring frequency
NSABP B-31[1] (n = 2030)	AC for four cycles, paclitaxel for four cycles, then observation AC for four cycles, followed by paclitaxel for four cycles, with concurrent trastuzumab, continued for one year	Grade III/IV HF or cardiac death; or LVEF decrease >15 percentage points*	MUGA three weeks, six months, and nine months after end of initial AC, and three months after last trastuzumab dose
HERA[2] (n = 5090)	Any chemotherapy regimen, then observation Any chemotherapy regimen, then trastuzumab for one year Any chemotherapy regimen, then trastuzumab for two years	Severe HF; symptomatic HF; or LVEF decrease >10 percentage points*	LVEF (echo or MUGA) at baseline, 3, 6, 12, 18, 24, 30, 36, and 60 months
BCIRG-006[3] (n = 3222)	AC for four cycles, docetaxel for four cycles, then observation AC for four cycles, followed by docetaxel for four cycles, with concurrent trastuzumab, continued for one year Docetaxel and carboplatin for six cycles, with concurrent	Grade III/IV HF; cardiac death; grade 3 to 4 arrhythmias; grade 3 to 4 ischemia/infarction; or LVEF decrease >10 percentage points*	After AC, after second dose of docetaxel, at end of chemotherapy, and 3, 12, and 36 months after randomization

	trastuzumab, continued for one year		
FinHer[4] (n = 232)¶	Docetaxel (every three weeks) and vinorelbine (weekly) for three cycles, then CEF for three cycles Docetaxel (every three weeks) and vinorelbine (weekly) for three cycles, plus trastuzumab for nine weeks, then CEF for three cycles	Myocardial infarction; HF; or LVEF decrease >15 percentage points	Echo or MUGA before chemotherapy, after CEF, and 12 and 36 months after chemotherapy
NCCTG N9831[5] (n = 3505)	AC for four cycles, weekly paclitaxel for 12 weeks, then observation AC for four cycles, weekly paclitaxel for 12 weeks, with concurrent trastuzumab, continued for one year AC for four cycles, weekly placlitaxel for 12 weeks, followed by trastuzumab for one year	Grade III/IV HF or cardiac death; or LVEF decrease >15 percentage points*	MUGA or echo at entry, after AC, and 6, 9, 18, and 21 months after entry

AC: doxorubicin and cyclophosphamide; HF: heart failure; LVEF: left ventricular heart failure; MUGA: multi-gated acquisition scan; CEF: cyclophosphamide, epirubicin, and fluorouracil.

* Measured from baseline.

¶ Only patients with HER2-positive disease.

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Graphic 70022 Version 9.0

NYHA and other classifications of cardiovascular disability

Class	NYHA functional classification[1]	Canadian Cardiovascular Society functional classification[2]	Specific activity scale[3]
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	Ordinary physical activity, such as walking and climbing stairs, does not cause angina. Angina with strenuous or rapid prolonged exertion at work or recreation.	Patients can perform to completion any activity requiring ≥7 metabolic equivalents (ie, can carry 24 lb up 8 steps; do outdoor work [shovel snow, spade soil]; do recreational activities [skiing, basketball, squash, handball, jog/walk 5 mph]).
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair-climbing after meals, in cold, in wind, or when under emotional stress, or only during the few hours after awakening. Walking more than 2 blocks on the level and climbing more than 1 flight of ordinary stairs at a normal pace and in normal conditions.	Patients can perform to completion any activity requiring ≥5 metabolic equivalents (eg, have sexual intercourse without stopping, garden, rake, weed, roller skate, dance foxtrot, walk at 4 mph on level ground) but cannot and do not perform to completion activities requiring ≥7 metabolic equivalents.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less-than-ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.	Marked limitation of ordinary physical activity. Walking 1 to 2 blocks on the level and climbing 1 flight in normal conditions.	Patients can perform to completion any activity requiring ≥2 metabolic equivalents (eg, shower without stopping, strip and make bed, clean windows, walk 2.5 mph, bowl, play golf, dress without

			stopping) but cannot and do not perform to completion any activities requiring >5 metabolic equivalents.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Inability to carry on any physical activity without discomfort. Anginal syndrome may be present at rest.	Patients cannot or do not perform to completion activities requiring >2 metabolic equivalents. Cannot carry out activities listed above (specific activity scale III).

NYHA: New York Heart Association.

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Graphic 52683 Version 19.0

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