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Clinical Pharmacology: Concise Drug Reviews

Trastuzumab

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ABSTRACT

Trastuzumab is standard of care in the treatment of human epidermal growth factor receptor (HER)-2$^+$ early and advanced breast cancer. Recently, it has been approved for the treatment of HER-2$^+$ advanced gastric cancer. Trastuzumab is an IgG1 humanized monoclonal antibody administered by intravenous infusion on a weekly or three weekly schedule. In all registered indications, trastuzumab is almost always given in combination with chemotherapy. In hormonal receptor-positive breast cancer in postmenopausal women, trastuzumab can be combined with an aromatase inhibitor. Main toxicity is reduction in the left ventricular ejection fraction, which in a minority of patients can become symptomatic, but in many patients is at least partly reversible. Long-term safety needs to be further determined. ***The Oncologist*** 2011;16:800–810

INTRODUCTION

Trastuzumab (Herceptin®; F. Hoffmann-La Roche, Basel, Switzerland) is registered for the treatment of human epidermal growth factor receptor (HER)-2$^+$ metastatic breast cancer, for adjuvant treatment of localized HER-2$^+$ breast cancer, and for HER-2$^+$ metastatic adenocarcinoma of the stomach or gastroesophageal junction. In the U.S. and European Union (EU), trastuzumab is indicated for breast cancer patients with a proven amplification of the *HER-2* oncogene or overexpression of the HER-2 protein in the tumor. Overexpression of HER-2 or amplification of *HER-2* is associated with adverse disease prognosis and shorter overall and disease-free survival times [1, 2]. Trastuzumab is indicated in metastatic HER-2$^+$ breast cancer patients: (a) as monotherapy after at least one or more chemotherapy regimens, (b) in combination with paclitaxel (U.S., EU), (c) in combination with docetaxel, and (d) in combination with an aromatase inhibitor in postmenopausal women with endocrine-responsive breast cancer not previously treated with trastuzumab (EU). Patients with endocrine-responsive breast cancer must have failed hormonal therapy before trastuzumab is indicated (EU) [3–6]. Trastuzumab is indicated in HER-2$^+$ early breast cancer: (a) as adjuvant treatment (U.S., EU) and (b) as neoadjuvant treatment (EU). Trastuzumab is also indicated in HER-2$^+$ metastatic adeno-

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Table 1. Trastuzumab treatment in metastatic breast cancer (phase III studies)

Line of treatment	Treatment plan	*n* of patients	Primary endpoint	Median OS	Incidence of CHF
First [2]	Anthracycline-based chemotherapy (A-E) + C (600 mg/m^2) or P (175 mg/m^2) (every 3 wks) versus A-E + C followed by T or P followed by T	469	Median TTP, Chemotherapy, 4.6 mos; chemotherapy + T: 7.4 mos ($p < .001$)	Chemotherapy, 20.3 mos; chemotherapy + T, 25.1 mos ($p < .046$)	Class III or IV CHF: A-E + C, 8%; A-E + C +T, 27%; P, 1%; P + T, 13%
Previous chemotherapy or endocrine therapy was permitted [51]	Anastrozole monotherapy versus anastrozole plus T (TAnDEM study) in postmenopausal women with ER$^+$/HER$^+$ breast cancer	207	PFS: HR, 0.63 ($p = .0016$); anastrozole, 2.4 mos; anastrozole + T, 4.8 mos	Anastrozole, 23.9 mos; anastrozole + T, 28.5 mos ($p = .325$)	Class II CHF: anastrozole + T, 1%
First [52]	P (175 mg/m^2) + T or P (175 mg/m^2) + carboplatin (AUC, 6) + T	196	ORR: P + T, 36%; P + carboplatin + T, 52% ($p = .04$)	P + T, 32.2 mos; P + carboplatin + T, 35.7 mos ($p = .76$)	P + T, 2%; P + carboplatin + T, 0%

Abbreviations: A-E, anthracycline derivate: doxorubicin (60 mg/m^2) or epirubicin (75 mg/m^2); AI, aromatase inhibitor; AUC, area under the concentration–time curve; C, cyclophosphamide; CHF, congestive heart failure; D, docetaxel; DFS, disease-free survival; E, epirubicin; ER, estrogen receptor; FEC, fluorouracil, epirubicin, and cyclophosphamide; HER, human epidermal growth factor receptor; HR, hazard ratio; ORR, objective response rate; OS, overall survival; P, paclitaxel; PFS, progression-free survival; T, trastuzumab; TAnDEM, Trastuzumab and Anastrozole Directed Against ER-Positive HER-2–Positive Mammary Carcinoma; TTP, time to progression.

carcinoma of the stomach or gastroesophageal junction: (a) in combination with capecitabine or 5-fluorouracil and cisplatin in patients who have not received prior anticancer therapy for their metastatic disease (U.S., EU).

Side effects of trastuzumab treatment are often mild and mostly manageable. The major side effect of trastuzumab treatment is a reduction in left ventricular ejection fraction (LVEF), in a small proportion of patients even leading to advanced congestive heart failure (CHF), which appears to be at least partly reversible [7].

Clinical Benefit of Trastuzumab Treatment

Trastuzumab has been shown to benefit patients with HER-2$^+$ metastatic breast cancer when applied as monotherapy or used in combination with chemotherapy. In phase II studies, trastuzumab treatment was effective and well tolerated. An overview of the phase II studies in which trastuzumab was tested in advanced breast cancer was presented in a recent review [8]. In phase III studies, the addition of trastuzumab to standard chemotherapy was associated with a longer time to disease progression (7.4 months versus 4.6 months), longer duration of response (9.1 months versus 6.1 months), and longer overall survival time (25.1 month versus 20.3 months) (Table 1).

The addition of trastuzumab in the (neo)adjuvant setting resulted in an lower risk for recurrence or death. Three large, randomized trials evaluating the use of trastuzumab after adjuvant standard chemotherapy showed beneficial effects of the addition of trastuzumab to standard adjuvant treatment. A combined analysis of the North Central Cancer Treatment Group (NCCTG) N9831 trial and the National Surgical Adjuvant Breast and Bowel Project (NSABP)-B31 trial ($n = 3,351$) showed beneficial effects in terms of the disease-free survival rate (87% versus 75%) and overall survival rate (94% versus 92%) after a median follow-up of 3 years [9] . A large European study, Herceptin® Adjuvant (HERA), showed that patients treated with trastuzumab had an absolute disease-free survival benefit of 6.3% (80.6% versus 74.3%) at 3 years [10]. A fourth adjuvant trastuzumab trial, the Breast Cancer International Research Group 006 study, also showed a disease-free survival benefit for patients treated with trastuzumab when combined with standard chemotherapy. Table 2 presents an overview of the published adjuvant trastuzumab trials.

Recently, clinical benefit was demonstrated in other malignancies with HER-2 overexpression, in particular, gastric cancer. The international phase III Trastuzumab for Gastric Cancer trial showed an overall survival duration of 13.5 months in the treatment group, compared with 11 months in the control group (hazard ratio, 0.74; 95% confidence interval, 0.60–091; $p = .0048$) [11]. This clinical improvement was considered convincing enough to halt the

Table 2. Trastuzumab treatment in primary breast cancer, the adjuvant setting

Study	Treatment plan	*n* of patients	Median follow-up time in mos	DFS and OS endpoint	Asymptomatic cardiotoxicity in trastuzumab-treated patients	Incidence of class III or IV CHF in the trastuzumab group
NSABP-B31 and NCCTG N9831 [9, 23]	A (60 mg/m^2) + C (600 mg/m^2), 4× every 3 wks, followed by P (175 mg/m^2), 4× every 3 wks, or P (80 mg/m^2), 12× weekly versus AC followed by P plus T for 1 yr	3,351	36	DFS: HR, 0.48 ($p < .0001$); absolute difference in DFS, 12%; OS: HR, 0.67 ($p = .015$)	NSABP-B31, 34%; NCCTG N9831, 1.9%	NSABP-B31, 4.1%; NCCTG N9831, 1.9%
	Long-term follow-up of cardiac events	173	24	Not reported	Not reported	2%
BCIRG 006	A (60 mg/m^2) + C (600 mg/m^2), 4× every 3 wks, followed by D (100 mg/m^2), 4× every 3 wks versus AC followed by D, 4× every 3 wks, + T for 1 yr versus D + carboplatin, 6× every 3 wks + T for 1 yr	32,222	36	DFS: HR, 0.61 ($p < .0003$); OS: HR, 0.59 ($p = .004$)	AC-D group, 0.6%; AC-DH group, 2.4%; DCH, 0.4%	AC-D group, 1.2% versus AC-DH group, 2.3%; AC-D group versus DCH group, 1.2%
FinHer [25]	D (100 mg/m^2) followed by FEC (E, 60 mg/m^2) or V (25 mg/m^2) (weekly) followed by FEC (E, 60 mg/m^2) versus D followed by FEC + T or V followed by FEC + T for 9 wks	232	36	DFS: HR, 0.42 ($p = .01$); OS: HR, 0.41 ($p = .07$)	3.5%	3%
HERA [10, 24]	Anthracycline-based chemotherapy followed by T (every 3 wks) for 1 or 2 yrs versus observation	Observation group, $n = 1,698$; 1-yr T group, $n = 1,703$	23.5	DFS: HR, 0.64 ($p < .0001$); OS: HR, 0.66 ($p = .0115$)	7%	Severe CHF, 0.5%; symptomatic CHF, 2%
	Long-term follow-up of cardiac events	Observation group, $n = 1,698$; 1-yr T group, $n = 1,703$	42	Not reported	9.8%	Severe CHF, 0.8%; symptomatic CHF, 1.9%

Abbreviations: A, doxorubicin; C, cyclophosphamide; CHF, congestive heart failure; D, docetaxel; DFS, disease-free survival; E, epirubicin; FEC, 5-fluorouracil, epirubicin, and cyclophosphamide; HR, hazard ratio; NCCTG, North Central Cancer Treatment Group; NSABP, National Surgical Adjuvant Breast and Bowel Project; OS, overall survival; P, paclitaxel; T, trastuzumab; V, vinorelbine.

trial and to obtain U.S. Food and Drug Administration and European Medicines Agency registration for the first-line treatment of HER-2$^+$ gastric cancer.

Clinical Use

Trastuzumab is administrated by i.v. infusion and is applied in a weekly or 3-weekly schedule. The weekly schedule is initiated for monotherapy or in combination with chemotherapy. The weekly dose of trastuzumab is 2 mg/kg starting 1 week after a loading dose of trastuzumab of 4 mg/kg. The 3-weekly schedule of trastuzumab starts with a loading dose of trastuzumab of 8 mg/kg, followed by 6 mg/kg trastuzumab every 21 days. Trastuzumab in doses of 2 mg/kg can be administered as

SUMMARY TABLE

Generic name	Trastuzumab
Commercial name	Herceptin®
Synonym	Anti–HER-2
Average molecular weight	approximately 150 kDa
Mechanism of action (Fig. 1)	Trastuzumab binds to the extracellular domain of HER-2, prevents cleavage of the extracellular domain of HER-2 and thereby activation of the receptor, blocks dimerization of HER-2, mediates activation of antibody-dependent cell-mediated cytotoxicity resulting in tumor cell lysis, and promotes HER-2 internalization.
Route of administration	i.v.
Elimination	Elimination predominantly intracellularly in epithelial cells; renal elimination is very low.
Terminal half-life	28 days
Main toxicities	Infusion-related toxicities such as fever, chills, dyspnea, hypotension, bronchospasm, reduced oxygen saturation, and respiratory distress. Cardiotoxicity, such as an asymptomatic decrease in left ventricular ejection fraction or congestive heart failure.
Pharmacogenetics	No pharmacogenetic status to individualize trastuzumab treatment
Resistance	Several mechanisms are responsible for trastuzumab resistance—loss of phosphatase and tensin homologue deleted on chromosome ten, activation of the phosphoinositide 3-kinase pathway, and overexpression of other surface receptors (insulin-like growth factor) may play a role.
Unique features	Side effects are generally mild and manageable
Main drug and complementary and alternative medicine interactions	No controlled clinical data are available.
Dose adaptations	No controlled clinical data are available.

a 30-minute infusion, but higher doses, of 4 mg/kg or 6 mg/kg, require approximately 90 minutes.

MECHANISM OF ACTION

Trastuzumab is a recombinant humanized IgG_1 monoclonal antibody against the extracellular domain of the HER-2 receptor (ErbB-2). The HER-2 receptor consists of an extracellular ligand-binding domain, a transmembrane region, and an intracellular or cytoplasmic tyrosine kinase domain. Trastuzumab binds to the extracellular domain of HER-2 and prevents cleavage of the extracellular domain of HER-2 and thereby activation of the receptor; blocks the dimerization of HER-2; mediates activation of antibody-dependent cell-mediated cytotoxicity, resulting in tumor cell lysis; and promotes HER-2 internalization (Fig. 1). Trastuzumab treatment is effective only in patients with amplified *HER-2* or overexpression of HER-2 [12].

MOLECULAR PATHOLOGIC DIAGNOSIS

The accuracy of HER-2 assays is essential for testing HER-2 status in breast and gastric cancer patients; however, the outcome of assays to determine HER-2 status varies substantially among laboratories. Validated methods for HER-2 testing need to be used for resolving discrepancies in HER-2 testing. HER-2 status is mostly tested by immunohistochemistry (IHC, HercepTest™; Dako, Glostrup, Denmark), and in some cases by fluorescent in situ hybridization (FISH) or by chromogenic in situ hybridization (CISH) [12]. In current practice, the use of HercepTest™ is considered insufficient in patients with, for example, a HER-2 2+ outcome. Equivocal IHC samples (2+) must be retested for *HER-2* amplification by FISH or CISH [13]. Equivocal FISH or CISH results must be confirmed by counting additional cells or repeating the test with a different method. The pathologist scores the test as 0, 1+, 2+, or 3+, and only 3+ and/or showing *HER-2* amplification by FISH or CISH identifies patients for trastuzumab treatment. In the case of gastric cancer a 3+ IHC score combined with a positive FISH result is considered necessary for trastuzumab treatment [13].

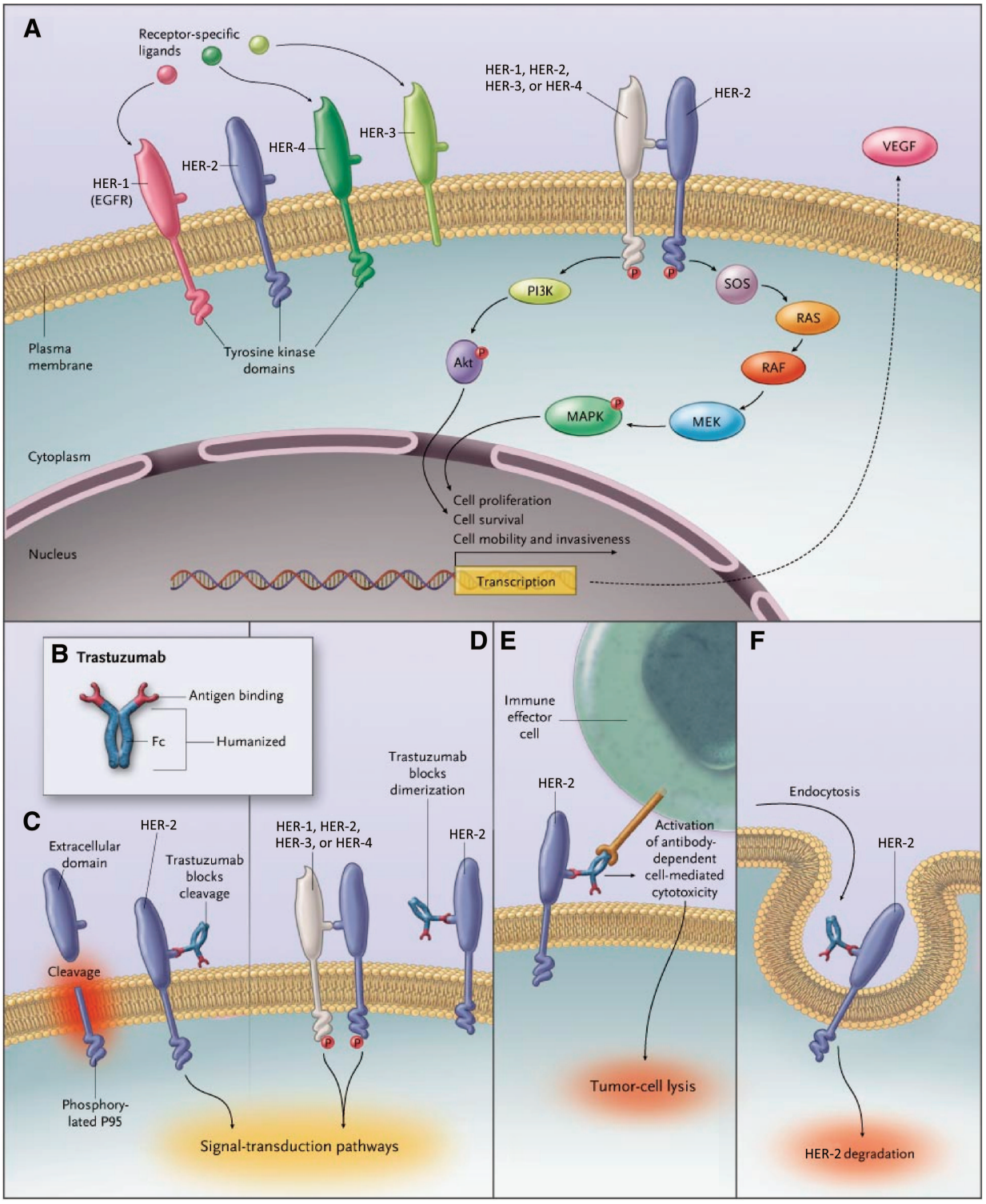

Figure 1. Signal transduction by the HER family and potential mechanisms of action of trastuzumab.

Abbreviations: EGFR, epidermal growth factor receptor; HER, human epidermal growth factor receptor; MAPK, mitogen-activated protein kinase; MEK, MAPK/extracellular signal–related kinase kinase; PI3K, phosphoinositide 3-kinase; SOS, son of sevenless; VEGF, vascular endothelial growth factor.

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Bioanalysis of Trastuzumab

Trastuzumab can be quantified in human serum by an enzyme-linked immunosorbent assay (ELISA). A precipitate-enhanced immunoassay (PEIA) has also been developed and results demonstrate good correlation between the ELISA and PEIA methods [14]. It is presently not clear whether variations in plasma concentrations are predictive of toxicity or treatment failure.

Pharmacokinetics

The relevance of trastuzumab pharmacokinetics is unclear in relation to response or toxicity.

Elimination

Trastuzumab is metabolized to peptides and amino acids. The elimination is a complex of processes in humans but is specifically mediated by epithelial cells. Trastuzumab binds to HER-2 and is metabolized intracellularly. The consequence of intracellular binding explains a dose-dependent (nonlinear) elimination. The elimination of antibodies from the plasma is complex and dependent on factors such as genetics and the clinical status of the patient. The half-life of trastuzumab is approximately 28 days. The washout period is up to 24 weeks after cessation of trastuzumab treatment. The renal excretion of trastuzumab is very low.

Contraindications for Trastuzumab Treatment

Contraindications for trastuzumab treatment include a history of hypersensitivity to trastuzumab treatment or murine proteins, severe dyspnea at rest resulting from complications of advanced malignancy, and requiring supplementary oxygen therapy.

Pregnancy and Lactation

Data on the effect of trastuzumab treatment on the development of the human fetus are limited [15]. Some cases of oligohydramnios during the second and third trimesters and reversible fatal renal failure have been reported in pregnant women receiving trastuzumab treatment [16]. Trastuzumab treatment is indicated if the potential benefit for the mother outweighs the potential risk to the fetus, but the fetus must be strictly monitored. Lactation should be avoided during trastuzumab treatment and for 6 months after the last administration of trastuzumab.

Drug Interaction and Complementary and Alternative Medicine Interaction

No controlled clinical data are available on drug interactions or complementary and alternative medicine interactions.

Alterations in Patient Characteristics

Data suggest that the disposition of trastuzumab is not influenced by age or renal function.

Pharmacogenetics

The aim of pharmacogenetics and trastuzumab treatment is to determine whether there is a correlation between genetic polymorphism, such as in *HER-2*, and response to trastuzumab treatment or the development of trastuzumab-associated toxicity, such as cardiotoxicity. Most reported polymorphisms affecting the efficacy of anticancer treatment are single nucleotide polymorphisms (SNPs) [17]. Several SNPs in the extracellular, transmembrane, and intracellular regions of HER-2 have been studied; however, their reported influence on trastuzumab efficacy remains controversial [18, 19]. Currently, there are no arguments to determine the pharmacogenetic status of *HER-2* to individualize trastuzumab treatment.

Pharmacodynamics

Recommended trastuzumab dosages are for monotherapy and for trastuzumab in combination with chemotherapy, used in the (neo-)adjuvant or metastatic setting. Higher doses and longer dosing intervals show no significant benefit over standard dose schedules. There are no algorithms for dose reductions of trastuzumab if significant toxicity develops.

Special Precautions

Caution should be exercised in patients who are experiencing dyspnea at rest as a result of complications of advanced malignancy and comorbidities; in patients with chronic heart failure, hypertension, and coronary artery disease; and in patients treated with prior anthracycline-based chemotherapy.

Cardiac Dysfunction

Short-term side effects of trastuzumab are generally mild and manageable. However, cardiac dysfunction is an important side effect of trastuzumab treatment. Cardiac dysfunction has been reported in patients who received trastuzumab as a single agent or in combination with chemotherapy for metastatic disease and in primary breast cancer [20, 21]. An indirect comparison of cardiac events among clinical studies is hampered by differences in the applied treatments, in inclusion and exclusion criteria, in the time interval between anthracycline-based chemotherapy and trastuzumab treatment, and in the definition of cardiotoxicity. A meta-analysis of randomized clinical trials in patients treated with sequential anthracycline-based chemotherapy and trastuzumab in the adjuvant setting reported significantly higher risks of 1.4% and 5.6% for grade III–IV CHF and asymptomatic cardiotoxicity, respectively [22].

However, the highest incidence of cardiac dysfunction was reported in metastatic breast cancer patients who were treated concurrently with anthracycline-based chemotherapy and trastuzumab [2]. Based on this observation, strict cardiac monitoring was incorporated into the adjuvant trastuzumab trials.

Recently, long-term cardiac safety data from three large randomized adjuvant trastuzumab trials (NCCTG N983, NSABP-B31, and HERA) were presented. Patients with CHF in the NSABP-B31 and NCCTG N9831 trials were reviewed by an independent Adjuvant Cardiac Review and Evaluation Committee (ACREC) [23]. CHF was defined as clinical symptoms, objective physical findings, and an LVEF drop of 10% or an LVEF drop to an absolute LVEF $<50\%$. Based on previously documented cardiotoxicity data, 173 patients were evaluated: 40 patients treated with chemotherapy alone and 133 trastuzumab-treated patients. The ACREC confirmed CHF in eight patients (0.45%) who received chemotherapy alone and in 36 trastuzumab-treated patients (2%) after a median follow-up of 2 years. A higher rate of CHF was associated with age >50 years and a lower LVEF at the start of trastuzumab treatment.

A long-term follow-up study of the HERA trial evaluated the incidences of asymptomatic cardiotoxicity and CHF after a median follow-up of 3.6 years [24]. A significant LVEF decrease (asymptomatic cardiotoxicity) was defined as an absolute decline of at least 10 percentage points from the baseline LVEF and to $<50\%$. Severe CHF was defined as New York Heart Association class III or class IV CHF, confirmed by a cardiologist, and a significant LVEF decrease. Symptomatic CHF was defined as symptomatic CHF confirmed by a cardiologist and a significant LVEF decrease. A total of 164 trastuzumab-treated patients (9.8%) and 49 patients (2.9%) who received chemotherapy alone experienced asymptomatic cardiotoxicity. Thirteen trastuzumab-treated patients (0.8%) developed severe CHF, versus none treated with chemotherapy alone. Thirty-two trastuzumab patients (1.9%) developed symptomatic CHF, versus two patients (0.1%) in the chemotherapy alone group.

In a subset of patients, trastuzumab treatment was discontinued because of cardiac disorders. In the NSABP-B31 and NCCTG N9831 trials, 16.4% of patients discontinued trastuzumab treatment because of a confirmed asymptomatic decline in LVEF and 4.7% of patients discontinued trastuzumab treatment because of symptoms of CHF [9]. In an analysis of the HERA study, 5.1% of patients discontinued trastuzumab treatment before completion of the treatment plan because of cardiac dysfunction. Premature discontinuation of trastuzumab treatment might limit trastuzumab-associated treatment benefit in the adjuvant setting. However, the optimal duration of adjuvant trastuzumab treatment has not yet been determined. The efficacy of 9 weeks of trastuzumab in one small adjuvant trastuzumab study (the Finland Herceptin® study) was similar to that seen in the large adjuvant trials [25]. This raises the question of whether or not discontinuation of trastuzumab treatment is associated with a worse prognosis. Currently, the standard duration of adjuvant trastuzumab treatment is 1 year. However, the optimal duration of trastuzumab treatment has yet to be determined.

Results from the NCCTG N9831 trial, NSABP-B31 trial, and HERA trial suggest that trastuzumab-associated cardiac dysfunction has a high rate of reversibility. Complete or partial recovery was observed in 86.1% of the trastuzumab-treated patients with CHF in the combined analysis of the NSABP-B31 and NCCTG N9831 trials. In the HERA trial, 81% of the patients reached acute recovery of a cardiac event. An acute recovery was defined as two or more sequential LVEF assessments $\geq 50\%$ after the date of the cardiac event.

In their editorial, Morris and Hudis criticized these reports on the point of data collection [26]. Data from the long-term follow-up studies were not selected prospectively but were based on retrospectively documented cardiotoxicity data. The retrospective design of these studies can lead to an underestimation of the incidence and reversibility of cardiotoxicity. Incomplete follow-up of the patient and underdiagnosis of other cardiac diseases can influence the accuracy of trastuzumab-associated cardiotoxicity.

All adjuvant trials had strict exclusion criteria concerning pre-existing cardiovascular morbidity. This makes the outcome of these trials difficult to translate to an unselected patient population. It is unclear whether or not classical cardiac risk factors are predisposing factors for trastuzumab-associated cardiotoxicity. The incidence of cardiotoxicity may well be higher in unselected patient populations than reported in clinical trials in selected patients. Pre-existing hypertension, a smoking history, and a family history of coronary artery disease were risk factors for developing CHF in a retrospective trial in a Canadian trastuzumab-treated patient population [27]. Another retrospective trial suggested no relationship between these factors and trastuzumab-associated cardiotoxicity, but there was a significant relationship between baseline LVEF and the risk for cardiotoxicity ($p = .001$) [28]. Therefore, more studies are needed to investigate the cardiac safety of trastuzumab treatment in a general population.

In conclusion, trastuzumab treatment is associated with cardiac dysfunction, is mostly medically manageable with CHF medication, and is in most cases reversible when tras-

tuzumab is discontinued. Trastuzumab-associated cardiotoxicity is different from anthracycline-associated cardiotoxicity, which is dose dependent, not reversible, and results in ultrastructural abnormalities, as observed in myocardial biopsies. Based on current data, HER-2^+ breast cancer patients can be safely treated with trastuzumab. However, we need longer follow-up from adjuvant studies, further research to establish the incidence of trastuzumab-induced cardiotoxicity in general patient populations, and research on screening methods and cardioprotective drugs in trastuzumab-treated patients.

It is important to decrease the morbidity and mortality of trastuzumab treatment in breast cancer patients. Currently, a prospective, randomized, double-blind, placebo-controlled trial is ongoing in The Netherlands to evaluate the efficacy of the angiotensin II receptor blocker candesartan in the prevention of trastuzumab-associated cardiotoxicity.

Mechanisms of Trastuzumab-Associated Cardiotoxicity

In embryonic wild-type mice, HER-2 is immunohistochemically present in myocardial and endocardial cells [29, 30]. Cardiomyocyte HER-2 expression is mostly restricted to the T-tubular network, indicating a nonrandom cardiac distribution pattern [31]. It is therefore likely that HER-2 regulates circumscriptive processes in cardiac physiology. Evidence of HER-2 involvement in the physiology and pathophysiology of the heart is demonstrated in conditional mutant mice with cardiac-restricted *HER-2* deletion. These mice showed no abnormalities at birth, but shortly after birth they developed dilated cardiomyopathy [29, 31–33].

HER-2 appears to play an important role in compensatory cardiac hypertrophy. Hypertrophic growth can serve as a compensatory mechanism for different mechanical, hemodynamic, hormonal, and pathologic stimuli. Aortic banding in conditionally mutated mice with cardiac-restricted HER-2 deficiency did not result in a hypertrophic growth response.

The precise role of HER-2 in human cardiac physiology and disease is still unknown. Myocardial HER-2 mRNA expression was studied in left ventricle biopsies from 36 patients with severe CHF resulting from ischemic or nonischemic cardiomyopathy undergoing left ventricular assist device implantation. HER-2 was upregulated after implantation of the device, whereas HER-2 prior to implantation was comparable with that of healthy controls [34]. Recently, in six of 60 severe CHF patients, immunohistochemical expression of HER-2 (and HER-4) was shown in myocardial biopsies [35].

Clinical Monitoring

Monitoring Cardiac Function

For identification of trastuzumab-related cardiotoxicity, all trastuzumab-treated patients should undergo a complete medical history, physical examination, electrocardiogram, and measurement of LVEF at baseline of trastuzumab treatment. Furthermore, it is recommended that cardiac function be monitored by LVEF evaluation every 3 months during trastuzumab treatment.

Preliminary data suggest that plasma N-terminal pro B-type natriuretic peptide (NT-proBNP) and troponin I may be parameters to detect or predict trastuzumab-induced cardiotoxicity. In a study by Perik et al. [36], pretreatment plasma NT-proBNP levels were higher in patients with heart failure during trastuzumab treatment ($n = 3$) than in patients without heart failure ($n = 12$). A recently published trial revealed a significant relationship between troponin I, a well-established specific and sensitive marker of myocardial injury, and trastuzumab-associated cardiotoxicity. Patients with elevated troponin I levels were at risk for trastuzumab-associated cardiotoxicity, and recovery of trastuzumab-associated cardiotoxicity was unlikely [37]. These findings suggest that NT-proBNP and troponin I may be useful parameters for identifying patients at risk for trastuzumab-induced cardiotoxicity. However, more evidence is needed before these parameters can be applied as biomarkers to identify patients at risk for the development of trastuzumab-associated cardiotoxicity during trastuzumab treatment.

Infusion-Related Reactions of Trastuzumab

Trastuzumab may cause infusion-related reactions. Most trastuzumab-related reactions occur during the first infusion or within 24 hours after infusion. These are generally mild and occur infrequently with subsequent trastuzumab infusions. The overall incidence of severe infusion-related reactions is rare and is $<1\%$. These infusion-related reactions include fever, chills, dyspnea, hypotension, bronchospasm, reduced oxygen saturation, and respiratory distress. Fatal reactions, however, have been reported. In patients with severe trastuzumab-related hypersensitivity, the safety of rechallenge is unknown. In 33 (85%) of 39 patients with a previous severe hypersensitivity reaction, rechallenge of trastuzumab treatment was safe with supportive therapy [38].

Patient Instructions and Recommendations for Supportive Care

Trastuzumab should be administrated by i.v. infusion. Patients should be observed for hypersensitivity reactions dur-

ing trastuzumab administration, especially during the first infusion. It is advised to monitor cardiac function before the start of trastuzumab treatment, every 3 months during trastuzumab treatment, and at least 6 months after discontinuation of trastuzumab treatment.

Biomarkers of Trastuzumab Resistance

Not all HER-2$^+$ breast cancer patients respond to trastuzumab treatment. Several mechanisms have been proposed that might explain intrinsic trastuzumab resistance. Deficiency of phosphatase and tensin homologue and activation of phosphoinositide 3-kinase results in greater activity of the Akt–mammalian target of rapamycin signal transduction pathway and these have been shown to be important biomarkers of trastuzumab resistance [39, 40]. Also, the overexpression of other surface receptors, such as insulin-like growth factor, provides alternative growth-factor signaling and is related to lower trastuzumab sensitivity [41]. In vitro studies have shown that greater expression of mucin 4 results in greater retention of HER-2 and HER-3 at the cell surface. As a result, growth factor receptors cannot be degraded, with greater signaling potential and lower trastuzumab sensitivity as results [42].

Trastuzumab Treatment Beyond Progression

The optimal therapeutic strategy beyond progression during trastuzumab treatment is not well known. A prospective trial (prematurely closed) described the clinical outcome of 156 patients after progressive disease during treatment with trastuzumab. Patients received capecitabine alone or in combination with trastuzumab. The addition of trastuzumab to capecitabine was associated with a longer time to disease progression (8.2 months versus 5.6 months), longer overall survival time (25.5 months versus 20.4 months), and higher overall response rate (48.1% versus 27%) [43]. Although prospective data are limited, on the basis of retrospective analysis, there is consensus that trastuzumab should be continued until tumor progression. Trastuzumab is also applied beyond progression, whereby the accompanying chemotherapy is switched. For example, trastuzumab plus paclitaxel is changed into trastuzumab plus capecitabine or trastuzumab plus vinorelbine. Phase II studies to support this strategy are lacking, as are studies to compare this strategy with replacement of trastuzumab by lapatinib. At present, we should focus on well-designed clinical trials to establish the optimal strategy in this setting for patients.

Novel Anti-ErbB-2 Therapies

Patients with HER-2$^+$ breast cancer eventually experience relapse or progression on trastuzumab treatment. Trastuzumab binds to the extracellular domain of HER-2, but inhibition of one signal transduction pathway may not be enough because it does not control all HER-2$^+$ breast cancer tumors. Therefore, there is a need for novel, effective anti-ErbB-2 therapies. Several studies in patients with HER-2$^+$ metastatic breast cancer have been initiated to develop multiple lines of anti-ErbB-2 therapy. Small molecule tyrosine kinase inhibitors (TKIs) may add therapeutic benefit to established antibody-based treatment. TKIs bind to the intracellular domain of HER-2, usually the ATP-binding domain, thereby blocking the HER-2 dimerization step by kinase inhibition and interrupting downstream pathways. Lapatinib, an orally available small molecule, is the only TKI registered for the treatment of HER-2$^+$ metastatic breast cancer (U.S., EU). The most frequently reported side effects of lapatinib therapy are diarrhea, skin rash, and asymptomatic cardiotoxicity. Lapatinib is established as effective treatment in advanced breast cancer patients, including those with cancers progressing on trastuzumab-based therapy [44]. In a phase III study, 321 HER-2$^+$ metastatic breast cancer patients (previously progressive on trastuzumab treatment) were randomized to receive lapatinib plus capecitabine or capecitabine alone. The median time to progression was 8.4 months in the combination therapy group, compared with 4.4 months in the capecitabine monotherapy group ($p < .001$) [45, 46]. Lapatinib in combination with endocrine therapy provided clinical benefit in untreated estrogen receptor–positive or HER$^+$ postmenopausal patients. Patients received lapatinib plus letrozol or letrozol plus placebo. The median progression-free survival (PFS) interval was significantly longer in the combination group of lapatinib with letrozol compared with letrozol plus placebo—8.2 months, versus 3 months. A combination of trastuzumab and lapatinib resulted in a significantly longer median PFS time—12 weeks in the lapatinib plus trastuzumab group versus 8.1 weeks in the lapatinib alone group. The overall tumor response rate was not significantly different between the two treatment arms [47].

Neratinib, a pan-ErbB receptor TKI, was shown to be clinically active and well tolerated in patients previously treated with trastuzumab [48]. Patients with advanced HER-2$^+$ breast cancer received neratinib at a dose of 240 mg once daily. Sixty-six patients had received prior trastuzumab treatment and 70 patients were trastuzumab naïve. The median PFS times were 22.3 weeks for patients with prior trastuzumab exposure and 39.6 weeks for patients with no prior trastuzumab treatment. Diarrhea was the most frequently reported side-effect [48]. Phase I and II studies of trastuzumab-DM1 (T-DM1), an antibody-drug conjugate, have shown activity and was well tolerated in patients with prior trastuzumab treatment [49].

The combination of trastuzumab and pertuzumab, a recombinant humanized monoclonal antibody preventing HER-2 dimerization with HER-1, HER-3, and HER-4, was evaluated in a phase II study. The combination of trastuzumab and pertuzumab showed activity, with a median PFS interval of 5.5 months, and was well tolerated in patients who had progressed during prior trastuzumab treatment [50]. Ongoing trials are investigating the efficacy of various new TKIs of HER-2. Moreover, other studies are aiming to define subsets of patients with specific characteristics of the *ERB* gene who will most likely benefit from these new strategies.

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