REVIEW ARTICLE

DRUG THERAPY

Trastuzumab — Mechanism of Action and Use in Clinical Practice

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Overexpression of human epidermal growth factor receptor type 2 (HER2, also referred to as HER2/neu or ErbB-2), a 185-kD receptor first described more than two decades ago,[1] occurs in 20 to 30% of invasive breast carcinomas. In general, patients with breast-cancer cells that overexpress this receptor or that have a high copy number of its gene have decreased overall survival and may have differential responses to a variety of chemotherapeutic and hormonal agents.[2-6] Thus, strategies to target HER2 appear to be important in treating breast cancer. One such medication is trastuzumab (Herceptin, Genentech), a humanized monoclonal antibody. Trastuzumab binds to the extracellular juxtamembrane domain of HER2 and inhibits the proliferation and survival of HER2-dependent tumors. It is approved by the Food and Drug Administration (FDA) for patients with invasive breast cancers that overexpress HER2. This review considers trastuzumab's mechanism of action and its clinical value.

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N Engl J Med 2007;357:39-51.

BACKGROUND

HUMAN EPIDERMAL GROWTH FACTOR RECEPTORS AND THEIR FUNCTIONS

HER1, HER2, HER3, and HER4 (also called epidermal growth factor receptors ErbB-1, ErbB-2, ErB-3, and ErB-4, respectively) are transmembrane tyrosine kinase receptors with partial homology that normally regulate cell growth and survival, as well as adhesion, migration, differentiation, and other cellular responses.[7] Each of these receptors consists of an extracellular binding domain, a transmembrane lipophilic segment, and (except for HER3) a functional intracellular tyrosine kinase domain. The tyrosine kinase domains are activated by both homodimerization and heterodimerization, generally induced by ligand binding. In contrast to the extracellular domains of the three other HER receptors, the extracellular domain of HER2 can adopt a fixed conformation resembling a ligand-activated state, permitting it to dimerize in the absence of a ligand.[8] Receptor overexpression or mutation can also induce dimerization.[9] Once activated, the signal-transduction cascades of these receptors promote cellular proliferation and survival.[10] In addition, cleavage of the extracellular domain of HER2 leaves a signaling remnant (p95) at the cell membrane (Fig. 1).[11]

HER2 SIGNALING AND OVEREXPRESSION

HER2 signaling promotes cell proliferation through the RAS–MAPK pathway and inhibits cell death through the phosphatidylinositol 3′-kinase–AKT–mammalian target of rapamycin (mTOR) pathway.[10] AKT includes three distinct enzymes, each of which is a member of the protein kinase family that is specific for serine–threonine and that inhibits apoptosis (programmed cell death); mTOR regulates the cellular functions that integrate upstream signaling inputs. HER2-dependent cell proliferation was first reported in a rat model of chemically induced rat neuroblastoma.[12] Although HER2

Glossary

BCIRG: Breast Cancer International Research Group

EGFR: epidermal growth factor receptor

HER2/neu, HER2, p185HER2, c-ErbB-2, or c-ErbB-2/neu: human epidermal growth factor receptor type 2

HER3: human epidermal growth factor receptor type 3

HER4: human epidermal growth factor receptor type 4

HERA: Herceptin Adjuvant Trial

NCCTG: North Central Cancer Treatment Group

NSABP: National Surgical Adjuvant Breast and Bowel Project

RAS/MAPK: RAS is a regulatory G protein that cycles between activated and inactivated forms. Mitogen-activated protein kinases (MAPKs) are serine- and threonine-specific kinases that regulate cellular activities in response to mitogens.

VEGF: vascular endothelial growth factor

17-AAG: 17-allylamino-17-demethoxygeldanamycin

overexpression has since been described in a variety of human malignant conditions, gene amplification is rare except in breast cancer; anti-HER2 therapy is currently indicated only in this disease.[13-20]

HER2 overexpression is observed in 20 to 30% of invasive breast carcinomas. Amplification of the gene for HER2, detected by fluorescence in situ hybridization (FISH), occurs in approximately the same proportion.[21] Serum assays detect overexpression of HER2, which is associated with an increase in circulating shed fragments of its extracellular domain.[22] The correlations among the various clinical methods of detecting HER2 are imperfect with regard to both prognostication and the prediction of a response to trastuzumab.[23,24]

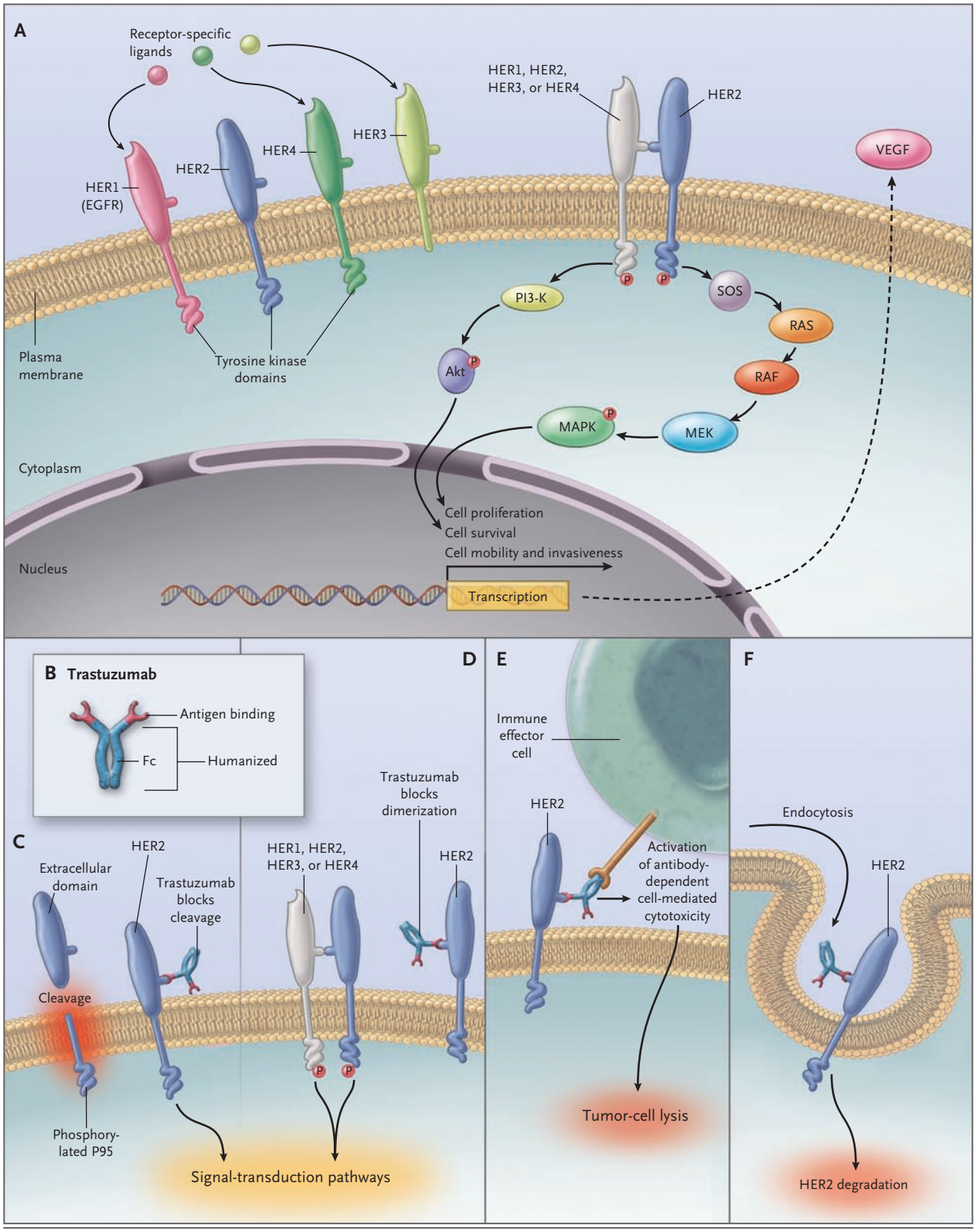
MECHANISM OF ACTION OF TRASTUZUMAB

Trastuzumab consists of two antigen-specific sites that bind to the juxtamembrane portion of the extracellular domain of the HER2 receptor and that prevent the activation of its intracellular tyrosine kinase.[2] The remainder of the antibody is human IgG with a conserved Fc portion. Several possible mechanisms by which trastuzumab might decrease signaling include prevention of HER2-receptor dimerization, increased endocytotic destruction of the receptor, inhibition of shedding of the extracellular domain, and immune activation[25] (Fig. 1B). Pertuzumab (a newer antibody that binds farther from the cell membrane) appears to be more efficient because of increased inhibition of heterodimerization, but this is not the only mechanism of action of trastuzumab.[26,27]

Preclinical models suggested that trastuzumab recruits immune effector cells that are responsible for antibody-dependent cytotoxicity.[28] The finding that animals deficient in immune-cell–activating Fc receptors (on effector cells) do not have a response to trastuzumab provides support for this hypothesis.[29] Preoperative administration of trastuzumab has been reported to increase tumor infiltration by lymphoid cells and modulation of in vitro antibody-dependent cytotoxicity.[30] Ongoing

Figure 1 (facing page). Signal Transduction by the HER Family and Potential Mechanisms of Action of Trastuzumab.

As shown in Panel A, the four members of the HER family are HER1, HER2, HER3, and HER4. There are receptor-specific ligands for HER1, HER3, and HER4. An intracellular tyrosine kinase domain exists for HER1, HER2, and HER4. Phosphorylation of the tyrosine kinase domain by means of homodimerization or heterodimerization induces both cell proliferation and survival signaling. HER2 is the preferred dimerization partner for the other HER family members. The phosphorylated (activated) tyrosine residues on the intracellular domain of HER2 activate the lipid kinase phosphoinositide 3-kinase (PI3-K), which phosphorylates a phosphatidylinositol that in turn binds and phosphorylates the enzyme Ak transforming factor (Akt), driving cell survival. In parallel, a guanine nucleotide exchange factor, the mammalian homologue of the son of sevenless (SOS), activates the rat sarcoma (RAS) enzyme that, in turn, activates receptor activation factor (RAF) and then the mitogen-activated protein kinase (MAPK) and mitogen extracellular signal kinase (MEK). MEK phosphorylates, among others, the MAPK, driving cellular proliferation. One of many other downstream effects is the production of vascular endothelial growth factor (VEGF) supporting angiogenesis. The most well-documented potential mechanisms of action are shown in Panels B through F. Cleavage of the extracellular domain of HER2 leaves a membrane-bound phosphorylated p95, which can activate signal-transduction pathways (Panel B). Binding of trastuzumab to a juxtamembrane domain of HER2 reduces shedding of the extracellular domain, thereby reducing p95 (Panel C). Trastuzumab may reduce HER2 signaling by physically inhibiting either homodimerization, as shown, or heterodimerization (Panel D). Trastuzumab may recruit Fc-competent immune effector cells and the other components of antibody-dependent cell-mediated cytotoxicity, leading to tumor-cell death (Panel E). Additional mechanisms such as receptor down-regulation through endocytosis have been postulated (Panel F).



studies are examining the effect of combining trastuzumab with HER2-targeted vaccines and activated CD8+ lymphocytes to make use of the immunomodulatory facets of trastuzumab.[31] Antibodies to the HER2 receptor might serve as targeted delivery mechanisms for conjugated toxins or radioisotopes.[32]

Studies in an animal model of breast cancer in which HER2 is overexpressed indicate that angiogenesis may be inhibited by trastuzumab, which induces normalization and regression of the vasculature by modulating proangiogenic and antiangiogenic factors.[33,34] Heregulin (a ligand of HER3 and HER4) regulates the production of vascular endothelial growth factor (VEGF), and HER-family receptor blockade leads to reductions in VEGF.[35] A preliminary clinical trial designed to increase this effect by combining trastuzumab with bevacizumab, which inhibits VEGF, showed promising activity against HER2-positive breast cancer.[36,37]

RESULTS OF CLINICAL TRIALS

The earliest preclinical studies tested a panel of mouse anti-HER2 antibodies, including 4D5, which was selected for humanization because it had the most favorable binding affinity.[38,39] Humanization, which is required because a human antimouse antibody response limits clinical use, was achieved by insertion of the complementarity-determining regions of the mouse monoclonal antibody into the framework of a consensus human IgG-1, thereby maintaining target specificity but limiting immunogenicity (Fig. 1B).[40]

The first phase 2 trial of trastuzumab, which involved 46 women, used a loading dose of 250 mg followed by 100 mg every week for 10 weeks to maintain a serum trough antibody concentration of more than 10 μg per milliliter.[41] All patients in the initial phase 2 study had previously treated metastatic breast cancer and tumors that overexpressed HER2 at the 2+ or 3+ level, as determined by an immunohistochemical scoring system (range, 0 to 3+). These patients received treatment until toxic effects or disease progression occurred. Responses were observed in 12% of patients, providing proof-of-principle that the agent might be effective in some patients. A larger, multicenter, phase 2 trial had similar results (Table 1).[42] Several factors may explain the modest response rates in these early trials, including extensive previous therapy and, as subsequently clarified, the inclusion of patients with tumors that had only 2+ immunostaining for HER2.

The current dose and schedule of trastuzumab were subsequently established by prospective, randomized studies. Dose escalation did not increase the response rate in one trial in which 114 patients with metastatic breast cancer received either a loading dose of 4 mg of trastuzumab per kilogram of body weight followed by 2 mg per kilogram each week or precisely twice the dose at the same frequency.[43] The response rate (35%) in this study of patients who had not received chemotherapy was greater than the rates among patients who had received trastuzumab in earlier trials, despite the fact that some of these patients had received previous antiestrogen therapy for metastatic disease.[43] These results suggest that trastuzumab might be appropriate for use as a single agent before the initiation of conventional chemotherapy in patients with metastatic disease. However, a randomized study of trastuzumab in patients who receive or do not receive concurrent chemotherapy has not been reported.

Trastuzumab has a long serum half-life, permitting infrequent dosing.[44] Phase 2 trials testing a loading dose of 8 mg per kilogram followed by 6 mg per kilogram given intravenously over a 90-minute period every third week showed serum levels that were no lower than those in earlier trials of weekly dosing.[45] Although no data are available from phase 3 trials comparing administration once a week to every third week are available, both intervals have been used in phase 2 and 3 trials and in actual practice.

The pivotal randomized clinical trial that showed the activity of trastuzumab in combination with chemotherapy enrolled 469 patients with previously untreated, HER2-positive, metastatic breast cancer.[46] Patients received first-line chemotherapy either alone or in combination with the antibody. A central laboratory reviewed the tumor specimens to quantify the degree of baseline HER2 overexpression on the basis of immunohistochemical staining, scored semiquantitatively as 2+ for weak-to-moderate staining of the entire tumor-cell membrane or 3+ for more than moderate immunostaining. Patients who had not previously received an adjuvant anthracycline received chemotherapy consisting of doxorubicin or epirubicin combined with cyclophosphamide; paclitaxel was

Table 1. Results of Studies of Trastuzumab as Monotherapy for Metastatic Breast Cancer.

Study	No. of Patients	Immunohistochemical Staining Grade (Assay)	Dose		No. of Previous Chemotherapy Regimens	Overall Response Rate	Median Treatment Duration (range)
			Loading	Maintenance			
						%	*wk*
Baselga et al.[41]	46	2–3+ (4D5)	250 mg	100 mg weekly	0 to 5	11	20 (4–240)
Cobleigh et al.[42]	222	2–3+ (4D5 or CB11)	4 mg/kg	2 mg/kg weekly	1 or 2	15	12 (0–118)
Vogel et al.[43]	114	2–3+ (4D5 or CB11)	4 mg/kg or 8 mg/kg	2 mg/kg weekly or 4 mg/kg weekly	0	26	15 (13–21)

administered in those who had received an anthracycline previously. At the time of disease progression, patients receiving chemotherapy alone were permitted to cross over to receive trastuzumab, and those already receiving trastuzumab could continue to receive it at the discretion of their physicians. Thus, all patients had the opportunity to receive trastuzumab.

The primary end point of this study[46] was time to disease progression, which increased from 4.6 months among patients who received chemotherapy alone to 7.4 months among those who received trastuzumab in addition to chemotherapy (P<0.001) (Table 2). Trastuzumab was also associated with an increase in the objective response rate (50% vs. 32%, P<0.001) and a longer duration of response (median, 9.1 vs. 6.1 months; P<0.001). Despite the availability of trastuzumab as a "salvage" therapy after progression for patients who received chemotherapy alone, patients receiving trastuzumab with first-line chemotherapy for metastatic disease had a lower death rate at 1 year (22% vs. 33%, P=0.008), a longer median survival (25.1 vs. 20.3 months, P=0.046), and a 20% reduction in the risk of death. Hence, not only did this study show a significant increase in the median time to progression of disease, but it also showed improved overall survival, even though the experimental intervention ultimately was available to all the patients.[46] A subsequent randomized trial of docetaxel alone or with trastuzumab had similar results.[47]

Various nonrandomized trials have shown the efficacy and relative safety of trastuzumab in combination with most other chemotherapeutic agents used in the treatment of breast cancer (Table 3). It is not clear that any specific chemotherapeutic agent or class is more or less clinically effective with trastuzumab.[3,47-60]

TOXICITY

When trastuzumab is used alone, myelosuppression, nausea, and emesis are rare and alopecia has not been reported. An acute, hypersensitivity-like reaction is seen in less than 10% of patients and is preventable when antihistamines, antiinflammatory drugs, and corticosteroids are used.[61]

Sporadic cases of congestive heart failure were reported in the early trials of trastuzumab, but an association between impairment of the left ventricular ejection fraction (LVEF) and trastuzumab became evident during the randomized study described above.[46] A total of 27% of patients treated concurrently with trastuzumab and anthracyclines, 13% with trastuzumab and paclitaxel, and 5% with trastuzumab alone had cardiotoxic effects. A retrospective chart review of seven phase 2 and 3 studies of trastuzumab, performed by an independent cardiac review and evaluation committee, showed a small number of cases of cardiac dysfunction in all previous studies, but the risk was greatest among patients who received concurrent anthracyclines.[62]

The absence of a relevant animal model and the paucity of cardiac-biopsy specimens from affected patients has limited our understanding of the cardiotoxicity of trastuzumab.[63-65] Some studies suggest a role of HER2 in embryogenesis and in the prevention of dilated cardiomyopathy.[66,67] Hence, HER2 signaling may be required for repair of anthracycline-induced cardiac myocyte damage.[68,69] Although the cardiac dysfunction seen with trastuzumab initially appeared to be similar to anthracycline cardiotoxicity, it appears to be less severe and more readily reversible, as suggested by the very few trastuzumab-related deaths attributed to cardiac failure and the retrospective observation that

Table 2. Randomized Trials Comparing Chemotherapy Alone with Chemotherapy plus Trastuzumab for Metastatic Disease.

Trial and End Result	Chemotherapy	Chemotherapy plus Trastuzumab	P Value
Slamon et al.[46]			
No. of patients	234 (doxorubicin and cyclophosphamide or paclitaxel)	235 (doxorubicin and cyclophosphamide or paclitaxel)	
Time to disease progression (mo)	4.6	7.4	<0.001
Response rate (%)	32	50	<0.001
Median overall survival (mo)	20	25	0.046
Marty et al.[47]			
No. of patients	94 (docetaxel)	92 (docetaxel)	
Time to disease progression (mo)	6.1	10.7	0.001
Response rate (%)	34	61	0.001
Median overall survival (mo)	23	31	0.032

some patients with apparent toxic cardiac effects who continued to receive trastuzumab treatment did not have additional cardiac damage.[62,70]

Data from prospective studies are lacking, but it may be reasonable to consider continuing trastuzumab in patients with metastatic disease who appear to be benefiting from the agent but in whom asymptomatic cardiomyopathy develops. Although a clinically meaningful continued response to trastuzumab is not guaranteed, cardiomyopathy can be monitored and possibly treated, whereas metastatic disease that progresses as a consequence of discontinuing the antibody may not respond to subsequent interventions.[71] The long half-life of trastuzumab may delay the clinical improvement of cardiac symptoms after discontinuation of the antibody. After undergoing cardiac evaluation, patients with symptomatic congestive heart failure are typically treated with afterload reduction, a cardiac glycoside, and diuretics. Given the minimal data, physicians must exercise discretion and caution in deciding to continue treatment with trastuzumab.

There are no validated screening and treatment algorithms for trastuzumab-induced cardiomyopathy; thus, individualized surveillance and care are needed. Although no single approach to monitoring for heart failure has been standardized, most clinical trials involving patients with metastatic disease include a screening study to document the baseline LVEF, followed by serial monitoring at 8-to-16-week intervals initially. Longer intervals for LVEF surveillance may be considered on the basis of symptoms; absolute LVEF and relative LVEF decrease during therapy.[49] The recently reported trials of adjuvant trastuzumab incorporated ongoing cardiac screening to determine the risk and effect of heart failure on patients who, when treated, were likely to be cured.

CLINICAL SIGNIFICANCE OF HER2 TESTING

Retrospective subgroup analyses of the early trastuzumab trials suggest that the antibody was most active in patients with tumors that showed 3+ HER2 staining intensity or had *HER2* gene amplification (gene copy number increased by >2.0) on FISH.[72] Similarly, all patients with a response in the trial of trastuzumab as a single agent for first-line therapy had either 3+ HER2 immunostaining or gene amplification on FISH.[43] No patient with only 2+ staining had a response unless gene amplification was detected. Conversely, in a trial of patients with metastatic breast cancer and normal HER2 expression who were randomly assigned to receive paclitaxel alone or in combination with trastuzumab, no benefit from the addition of the antibody was shown.[73]

Retrospective testing of tumors that were positive for staining with the 4D5 and CB11 monoclonal antibodies to HER2 was used to validate a polyclonal assay (Herceptest, Dako) and later FISH testing.[74] Neither of these concordant tests was

used to qualify patients for enrollment in any of the studies that led to the initial approval of trastuzumab by the FDA. Because these newer tests correlated with the assays used in clinical trials and appeared to select subgroups of enrolled patients with a greater likelihood of response, they were deemed reasonable or even preferable alternatives to the monoclonal stains, and they are now required to qualify patients for enrollment in trials.[75,76]

HER2 testing continues to evolve, and many clinical laboratories currently use both tests. An efficient testing strategy consists of immunostaining followed by FISH in tumors with 2+ staining intensity.[24] This approach should minimize the risks of not treating patients who might benefit from trastuzumab and of treating patients who are unlikely to have a response; this is a critically important distinction as the use of trastuzumab moves into the adjuvant setting. Reported adjuvant trials used centralized laboratory review because of the high rate of discordant interpretations among individual laboratories.[77,78]

Table 3. Response Rates in Selected Phase 2 Trials of Chemotherapy in Combination with Trastuzumab.*

Regimen	Study	Response Rate
		%
Single-agent chemotherapy		
Docetaxel	Marty et al.,[47] Esteva et al.[48]	61, 70
Vinorelbine	Burstein et al.,[49] Jahanzeb et al.[50]	42, 78
Capecitabine	Bangemann et al.[51]	56
Liposomal doxorubicin	Theodoulou et al.,[52] Chia et al.[53]	58, 52
Gemcitabine	O'Shaughnessy et al.[54]	38
Cisplatin	Pegram and Slamon[55]	24
Combination regimens		
Paclitaxel and carboplatin	Robert et al.[56]	52
Paclitaxel and gemcitabine	Sledge[57]	67
Paclitaxel and doxorubicin	Bianchi et al.[58]	88
Docetaxel and cisplatin	Pegram et al.[59]	79
Docetaxel and carboplatin	Pegram et al.[59]	58
Gemcitabine and cisplatin	Heinemann[60]	43

* Comparisons among these studies are not informative. All of these regimens are feasible and tolerable. The doses, schedules, and treatment settings (first-line vs. second-line therapy or higher) of the chemotherapeutic agents vary. The trastuzumab dose is constant at a loading dose of 4 mg per kilogram of body weight, followed by 2 mg per kilogram for weekly maintenance.

STUDIES OF TRASTUZUMAB AS ADJUVANT THERAPY

The efficacy and adverse-event profile of trastuzumab for HER2-dependent metastatic breast cancer led to investigation of this antibody as adjuvant treatment. Four large, multicenter, randomized studies and several smaller trials recently reported a significant benefit from the addition of trastuzumab to adjuvant and neoadjuvant therapy.

In two North American studies, patients were randomly assigned to receive doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab for 1 year of therapy.[79] The North Central Cancer Treatment Group (NCCTG) Intergroup N-9831 trial (ClinicalTrials.gov number, NCT00005970)[80] differed slightly from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 trial (ClinicalTrials.gov number, NCT00004067) with respect to the schedule of paclitaxel administration. In addition, in the N-9831 trial, a third group was assigned to receive trastuzumab only after the completion of all chemotherapy. Eligible patients in both studies had early-stage, HER2-positive breast cancer (3+ on immunostaining or gene amplification by FISH). In both studies, most patients had lymph-node–positive disease, but in the N-9831 trial, patients with high-risk, lymph-node–negative cancer were eligible. Because of similarities between these trials, the National Cancer Institute and the FDA approved a prespecified joint analysis of the pooled data. Adjuvant trastuzumab administered concurrently with paclitaxel and continued for 1 year, as compared with chemotherapy alone, resulted in significant increases in disease-free survival (85% vs. 67%) and overall survival (91% vs. 87%) (Table 4). In light of these data, an unplanned interim analysis of the NCCTG N-9831 trial was performed.[80] Within this trial alone, trastuzumab administered concurrently with adjuvant chemotherapy significantly increased disease-free survival as compared with chemotherapy alone or trastuzumab administered after chemotherapy.

The results of the Herceptin Adjuvant (HERA) trial (ClinicalTrials.gov number, NCT00045032) were similarly encouraging.[81] More than 5000 women with HER2-positive breast cancer who had

Table 4. Trials of Adjuvant Trastuzumab in HER2-Positive Early-Stage Breast Cancer.*

Trial	Study Regimen	No. of Patients	Disease-free Survival	Hazard Ratio	P Value	Overall Survival	Hazard Ratio	P Value
			%			%		
NSABP B-31 and NCCTG N-9831[79]	Doxorubicin and cyclophosphamide, then paclitaxel	1679	67			87		
	Doxorubicin and cyclophosphamide, then paclitaxel plus trastuzumab, then trastuzumab	1672	85	0.48	<0.001	91	0.67	0.02
NCCTG N-9831[80]	Doxorubicin and cyclophosphamide, then paclitaxel	979						
	Doxorubicin and cyclophosphamide, then paclitaxel, then trastuzumab	985		0.87	0.29†		0.85	0.48†
	Doxorubicin and cyclophosphamide, then paclitaxel plus trastuzumab, then trastuzumab	840		0.64 0.48	0.01† <0.01†		0.74	0.27‡
HERA[81]‡	Observation	1698	74			90		
	Trastuzumab for 1 year	1703	81	0.64	<0.001	92	0.66	0.011
BCIRG 006[82]	Doxorubicin and cyclophosphamide, then docetaxel	1073	73			86		
	Doxorubicin and cyclophosphamide, then docetaxel plus trastuzumab, then trastuzumab	1074	84	0.49	0.001†	92	0.59	0.004
	Docetaxel, carboplatin, and trastuzumab	1075	80	0.61	<0.01†	91	0.66	0.02
FinHer[83]	Chemotherapy	116	78			90		
	Chemotherapy plus trastuzumab	116	89	0.42	0.01	96	0.41	0.07

* Trial-registration numbers are as follows: NSABP, ClinicalTrials.gov number, NCT00004067; NCCTG, NCT00005970; HERA, NCT00045032; BCIRG, NCT00021255; and Finland Herceptin Study (FinHer),Current Controlled Trials number, ISRCTN76560285).
† The P value is for the comparison with the control group.
‡ Data were not available for the third group of the study.

completed adjuvant chemotherapy were randomly assigned to undergo observation or to receive trastuzumab every third week for 1 or 2 years. Data have been reported only for the group assigned to receive 1 year of trastuzumab treatment. One year of trastuzumab treatment after adjuvant chemotherapy was associated with a 36% reduction in the risk of recurrence (Table 4). A 34% reduction in the risk of death was reported at a median of 2 years of follow-up. This same approach (trastuzumab only after the completion of chemotherapy) was not associated with a benefit in one of the three treatment groups in the NCCTG N-9831 trial, perhaps because there were fewer patients and events for analysis.[80]

The optimal duration of adjuvant trastuzumab therapy is not known. Although data for 2 years of therapy is anticipated from the HERA trial, another randomized study has shown a similar benefit with just 9 weeks of treatment combined with nonanthracycline chemotherapy (rate of disease-free survival, 89% with chemotherapy plus trastuzumab vs. 78% for chemotherapy alone; hazard ratio for death, 0.42; P=0.01) (Table 4).[83] On the basis of available data, the 2006 guidelines of the National Comprehensive Cancer Network suggest that trastuzumab treatment should consist of 1 year of trastuzumab therapy beginning after adjuvant anthracycline therapy has been completed (if used) and administered either concurrently with a taxane or as a single agent.[84]

In the Breast Cancer International Research

Group 006 trial (ClinicalTrials.gov number, NCT00021255), more than 3200 women with HER2-positive breast cancer were randomly assigned to one of the three treatment groups. One group received doxorubicin and cyclophosphamide followed by docetaxel alone. The second group received doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab.[82] A third group in the study received trastuzumab in combination with a non–anthracycline-containing regimen of docetaxel and carboplatin. The addition of trastuzumab to adjuvant therapy improved disease-free survival in the group receiving the anthracycline-containing combination by 51% and the risk of death by 41%. The group receiving the non–anthracycline-containing regimen had a 39% disease-free survival and a 34% overall survival (Table 4), findings that are consistent with the results of other reported trials. A subgroup analysis suggested that coamplification of topoisomerase II, which is located near HER2 on the 17th chromosome, may identify a subgroup of tumors that are more responsive to regimens that include anthracyclines.

Cardiotoxicity, both short-term and long-term, is a key safety issue with adjuvant use of trastuzumab. Although definitions of a cardiac event vary, toxic effects develop in up to 4% of patients receiving adjuvant trastuzumab; these effects include episodes of clinically significant congestive heart failure. Alternative chemotherapy regimens that are less cardiotoxic than those with anthracycline combinations are therefore preferable if they maintain the efficacy of currently tested approaches.

One important limitation of trastuzumab is that it is a large molecule and does not efficiently cross the intact blood–brain barrier; thus, the central nervous system appears to serve as a sanctuary for metastases, with disproportionate rates of relapse in the brain.[79,81] New approaches to HER2-positive central nervous system disease are therefore needed.

CLINICAL USE OF TRASTUZUMAB

METASTATIC BREAST CANCER

Trastuzumab should be considered for the management of all metastatic breast cancers with HER2 overexpression as indicated by 3+ HER2 immunostaining or gene amplification on FISH.[24] Patients with moderate- to high-risk, rapidly progressive cancer characterized by a negative hormone-receptor status, extensive visceral metastases, and a short disease-free interval (typically less than 2 years) are candidates for immediate treatment with chemotherapy and should receive the appropriate agent (or agents) with trastuzumab. Because the benefits of chemotherapy administered with trastuzumab are established, the use of other chemotherapeutic agents in patients with relative or absolute contraindications to the agents already tested in phase 3 trials is clinically appropriate. Table 5 shows cardiac safety data. The chemotherapy regimen of choice should be predicated on the patient's previous adjuvant therapy and coexisting conditions. Trastuzumab does not appear to diminish the quality of life in patients who are already receiving concurrent chemotherapy, although prospective quality-of-life testing is not available.

It is not clear whether antibody therapy should precede, follow, or be added to hormone therapy for the subgroup of patients with HER2-positive and hormone-receptor–positive disease. One randomized trial showed increased activity when trastuzumab was added to an aromatase inhibitor.[85] However, this trial did not compare concurrent therapy with sequential therapy, alternative sequences (trastuzumab, then an aromatase inhibitor), or chemotherapy for this population.

Since trastuzumab monotherapy appears to be effective for the treatment of metastatic breast cancer, its use as a single agent for newly discovered metastatic disease can be considered.[86] This strategy would delay the initiation of chemotherapy with its attendant side effects, possibly resulting in a better quality of life. A nonrandomized study of 61 patients provided support for this approach. It suggested that there was no harm in delaying the initiation of chemotherapy for 8 to 16 weeks to determine whether trastuzumab alone was effective.[87] Although a randomized trial has made it clear that patients treated with chemotherapy should receive concurrent trastuzumab, no data are available to show the converse — that patients receiving trastuzumab should receive concurrent chemotherapy.

The continued use of trastuzumab after disease has progressed is controversial. Except in the case of progression within weeks after the initiation of treatment, possibly reflecting inadequate drug exposure, continued treatment after the apparent failure of trastuzumab would be ineffective if tu-

Table 5. Adverse Cardiac Effects in Prospective Studies of Metastatic Breast Cancer.*

Drug Administered with Trastuzumab	No. of Patients	Previous Treatment with Anthracyclines	Clinical Congestive Heart Failure	Asymptomatic Decline in Ejection Fraction†
			no. of patients (%)	
Vinorelbine[49]	54	8 (15)	1 (2)	3 (6)
Paclitaxel[3]	95	62 (65)	3 (3)	7 (7)
Docetaxel[47,48]	86	64 (74)	1 (1)	17 (20)
Liposomal doxorubicin[52]	37	14 (38)	1 (3)	1 (3)
Gemcitabine[54]	64	61 (95)	0 (0)	0 (0)
Paclitaxel with or without carboplatin[56]	191	NS‡	1 (<1%)	NA
Paclitaxel plus doxorubicin[58]	16	0	0	12 (75)

* NA denotes not applicable, and NS not specified.
† Definitions of ejection fractions vary.
‡ In this trial, 48% and 49% of the patients in the two study groups received previous chemotherapy. The numbers of patients who received previous anthracyclines were not reported.

mors develop resistance to the antibody. Conversely, the antibody might be effective if the mechanisms of additivity and synergy are unique to specific chemotherapeutic agents.[88] Preclinical data showing inhibition of proliferation signaling as well as unique interactions with some chemotherapeutic agents led some investigators to suggest a potential clinical benefit of this practice.

Some studies have shown activity when trastuzumab and chemotherapy are given after the progression of disease with trastuzumab monotherapy or chemotherapy, but none of these studies were randomized, and they may simply show the activity of salvage agents. A small trial of trastuzumab plus another potential signal-transduction inhibitor (celecoxib) showed no responses in 12 patients who were treated after progressive disease developed while they were receiving trastuzumab. This trial suggested a limited benefit of continuing to administer the antibody alone and highlighted the possibility that all of the benefit associated with continued therapy is derived from the addition of other active agents.[89] A randomized trial of vinorelbine given alone or with trastuzumab in patients with progressive disease during treatment with a taxane and trastuzumab could have defined the usefulness of continuing therapy after disease progression, but it has been discontinued because of an insufficient number of patients.[90] However, an ongoing study (GBG 26) is comparing capecitabine alone and combined with trastuzumab in patients with previous disease progression during treatment with a taxane and trastuzumab.[91] Thus, to date the argument for continued treatment relies only on preclinical studies and anecdotes, and there are insufficient clinical data to provide evidence for or against this approach. The activity of new anti-HER2 therapies, including the oral tyrosine kinase inhibitor lapatinib and intravenous 17-allylamino-17-demethoxygeldanamycin, in patients with trastuzumab-refractory, HER2-positive tumors suggests that some mechanisms of resistance may be drug-specific (e.g., trastuzumab-specific) rather than target-specific.[92,93]

ADJUVANT THERAPY FOR EARLY-STAGE BREAST CANCER

The use of adjuvant trastuzumab should be considered for women with early-stage, HER2-positive breast cancer who would have qualified for participation in the reported studies. However, because so far only interim analyses with relatively short-term follow-up have been reported for trials of adjuvant and neoadjuvant trastuzumab, important questions remain unanswered.[94] The absolute benefit in the cohorts at the lowest risk for disease progression because their tumors are small, hormone-responsive, and node-negative appears to be quite modest; thus, the optimal use of treatment with adjuvant trastuzumab is unclear in such patients. Furthermore, the long-term cardiac safety remains to be determined. When administering adjuvant trastuzumab, physicians should choose from the chemotherapy regimens and cardiac surveillance strategies outlined in the reported adjuvant trials.

FUTURE DIRECTIONS

The impact of trastuzumab on the care of women with HER2-positive breast cancer has been profound. Yet, despite the apparent efficacy of this antibody in adjuvant and neoadjuvant uses, its optimal use is not entirely clear. Several issues are under investigation, including cardiac safety, the optimal treatment duration, the benefit of treatment after disease progression, combinations with additional anti-HER2 targeting agents, and health care costs. The oral tyrosine kinase inhibitor lapatinib was effective with chemotherapy after trastuzumab failed and will be tested alone or with trastuzumab in women with early-stage breast cancer.[95]

CONCLUSIONS

The convergence of biotechnology (the development of humanized antibodies), preclinical science (the identification of the biologic role of HER2), and translational studies (the clinical trials showing activity and identifying new lines of research) led to the approval and availability of trastuzumab, the first monoclonal antibody that has been shown to prolong life in patients with a human epithelial malignant condition. Its development highlights the need to continue to categorize breast cancer and other cancers into biologically meaningful subtypes as well as the critical importance of well-conceived clinical studies. The experience with trastuzumab also shows the continuing need for clinical judgment and rational extrapolation of data, since not every clinical situation can be anticipated or addressed by clinical trials.

Dr. Hudis reports receiving lecture and consulting fees from Genentech, consulting fees from GlaxoSmithKline, and a grant from Kosan Biosciences. No other potential conflict of interest relevant to this article was reported.

I thank Tiffany Traina, M.D., for her editorial review and assistance in the preparation of the manuscript.

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