Pharmacology and Therapeutic Use of Trastuzumab in Breast Cancer

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ABSTRACT

The development, pharmacology, safety, efficacy, and dosage and administration of trastuzumab are reviewed.

The discovery of HER2 *gene amplification in up to 30% of women with breast cancer led to the development of trastuzumab, a humanized recombinant monoclonal antibody directed against the* HER2*-receptor protein on breast cancer cells. In large, multicenter trials of trastuzumab as a single agent or in combination with chemotherapy as first-line or second-line therapy for metastatic breast cancer (MBC), response rates have ranged from 12% to 23% for single-agent trastuzumab and from 25% to 62% for trastuzumab plus chemotherapy. Trastuzumab increased time to disease progression and survival time when administered in combination with chemotherapy. The National Comprehensive Cancer Network guidelines for the treatment of breast cancer now include trastuzumab and paclitaxel as an option for patients with MBC or recurrent breast cancer in which the* HER2*-receptor protein is overexpressed. Trastuzumab is administered weekly, with an initial iv dose of 4 mg/kg followed by weekly doses of 2 mg/kg. Most clinical trials continued treatment until disease progression occurred. Adverse effects include infusion-related reactions manifested by fever and chills, exacerbation of chemotherapy-induced gastrointestinal toxicity and myelosuppression, and cardiotoxicity.*

Trastuzumab, either as a single agent or in combination with chemotherapy, can be an effective therapeutic option for MBC patients who overexpress the HER2*-receptor protein and has changed the standard of care.*

Index terms: *Antineoplastic agents; Breast neoplasms; Clinical studies; Combined therapy; Dosage; Mortality; Toxicity; Trastuzumab*

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Breast cancer is the most common cancer in women in the United States. An estimated 184,200 new cases of this disease and 41,200 associated deaths will occur in 2000.[1] In the past decade, a number of new drugs and strategies for treating breast cancer have improved outcomes, especially for patients with metastatic disease. The new aromatase inhibitors have small but significant advantages in both efficacy and toxicity over older hormonal agents, such as megestrol acetate and aminoglutethimide.[2] In addition, the taxanes[3-7] and the antitubulin agent vinorelbine[8,9] have shown impressive activity against advanced breast cancer. Other active drugs include the antimetabolites, including the thymidylate synthase inhibitor raltitrexed, the antifolate edatrexate, the nucleoside analogue gemcitabine, and the fluorouracil prodrug capecitabine.[8,10] Currently, capecitabine is the only agent with FDA-approved labeling for use in the treatment of patients failing to respond to an anthracycline or a taxane; the objective response rate in such patients is 20%.[10] Several compounds are under investigation, including doxorubicin coated with sterically stabilized liposomes, losoxantrone, and oxaliplatin.[8,10]

One of the most exciting areas of investigation focuses on the molecular genetics of breast cancer and the potential to develop therapies that target genetic abnormalities. In the past few years, an increasing number of molecular genetic abnormalities have been identified in samples of primary and metastatic tumors from breast cancer patients. Some of these abnormalities have been associated with an encouraging prognosis (eg, *bcl*-2 overexpression); others, with a discouraging one (eg, *HER2* [*HER2*/neu or c-*erb*-b2] overexpression and p53 mutation).[11] Evidence increasingly suggests that some molecular abnormalities might predict resistance or susceptibility to certain antineoplastic agents or regimens. Studies have led to the development of several *HER2*-targeting agents. One of these, trastuzumab

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(Herceptin, Genentech), a humanized monoclonal antibody specific for the *HER2*-receptor protein, has reproducible antitumor activity in patients with *HER2*-overexpressing metastatic breast cancer (MBC). Trastuzumab alone produces objective responses in 12-23% of patients with previously treated MBC.[12-14] These observations were confirmed in prospective randomized trials of trastuzumab in combination with chemotherapy.[15,16] The addition of trastuzumab to first-line chemotherapy significantly improved response rate, time to disease progression, and one-year survival rates, attesting to the positive interaction between molecular and cytotoxic therapies. These encouraging results led to the approval of trastuzumab as an anticancer agent in several countries and the development of an extensive network of clinical trials to more precisely define the role of this agent in the management of early-stage breast cancer and MBC.

This article reviews the development, pharmacology, safety, efficacy, and dosage and administration of trastuzumab.

BIOLOGY OF BREAST CANCER

Tumorigenesis in breast cancer appears to result from successive genetic mutations that cause malignant cellular transformation, loss of contact inhibition, or enhanced metastatic potential.[17] Carcinogenesis—the transformation of normal cells into malignant cells—is influenced by a number of genetic changes, including base-substitution mutations, chromosomal translocations, and gene amplification. These genetic changes result from the activation of oncogenes (eg, ras, *HER2*, *myc*, and *bcl*-2), which function to promote cell growth, or the inactivation of tumor-suppressor genes (eg, BCRA1, BCRA2, and p53), which function to limit cell growth.[17,18] Proto-oncogenes, the normal counterparts of oncogenes, regulate growth in normal cells.

The role of specific proto-oncogenes, oncogenes, and tumor-suppressor genes in breast cancer is not fully understood. Activation of *ras* oncogenes generates proapoptotic (programmed cell death) signals and antiapoptotic signals.[19] Activated ras oncogenes may increase the susceptibility of tumor cells to certain antineoplastic agents, such as topoisomerase II inhibitors, by potentiating an apoptotic response.[20] The *bcl*-2 oncogene inhibits apoptosis, yet *bcl*-2 expression in breast cancer cells is not correlated with a poor clinical outcome; in fact, at least one study suggests that *bcl*-2 overexpression may be a good prognostic marker.[21] The *HER2* oncogene is probably the most studied breast cancer gene and is the focus of this article.

HER2 in breast cancer

The *HER2* gene encodes a 185-kilodalton transmembrane tyrosine kinase receptor that is a member of the epidermal growth factor- receptor (EGFR) family. When a growth factor ligand binds to a heterodimer receptor complex that includes the *HER2*-receptor protein, the receptor is activated and transmits growth signals from outside the cell to the nucleus, controlling aspects of normal cell growth and division.[22,23]

Two hypotheses about *HER2*-receptor activation have been published. The first, based on in vitro data, suggests that an increase in *HER2* receptors, which results from gene overexpression, is associated with a higher frequency of interreceptor collisions, leading to spontaneous *HER2*-receptor dimerization.[24,25] The second hypothesis is that *HER2* interacts with other members of the EGFR family (ie, EGFR, *HER3*, and *HER4*) to form heterodimer complexes; however, the *HER2-HER3* heterodimer may be required for *HER2*-receptor activation.[25] If alterations in *HER2* occur, multiple copies of the gene can be generated, which results in increased cell division and a higher cell growth rate and may be associated with transformation to the cancer cell phenotype.[22,26]

Normal cells express a small amount of the *HER2*-receptor protein on the plasma membrane.[23] Overexpression of the *HER2*-receptor protein, which results from gene mutation, occurs in approximately 30% of invasive human breast cancers and in other malignancies, such as ovarian, lung, gastric, and salivary gland adenocarcinomas.[27-31] The exact mechanism by which *HER2* regulates the development and growth of cancer cells is not known, although it appears to involve currently unidentified ligands.[23] *HER2* overexpression has been associated with increased tumorigenesis, tumor invasiveness, potential for metastasis,[32,33] and, perhaps, altered sensitivity to antineoplastic or hormonal therapies.[34-41]

Predictive value of HER2

Preclinical and clinical studies indicate that *HER2* overexpression may have prognostic and predictive value. Ross and Fletcher[42] reviewed 52 published studies of the prognostic value of *HER2* overexpression in breast cancer. A majority of the studies retrospectively assessed *HER2* overexpression by using tissue blocks from patients who participated in clinical trials. In 46 (88%) of the studies, *HER2* gene amplification or protein overexpression independently predicted decreased disease-free survival time and lower overall survival rates. These findings were demonstrated by univariate but not multivariate analysis in 13 of the studies (25%) and by multivariate analysis in 33 (63%). Six studies (12%) showed no correlation between *HER2* status and outcome. Failure to corroborate findings with multivariate analysis may result from the influence of other variables that have negative prognostic value (eg, estrogen-receptor-negative status, high S-phase fraction, axillary lymph node involvement, mutated p53 tumor suppressor genes, and high nuclear grade).[43,44]

Thor et al.[45] reported the results of a Cancer and Leukemia Group B trial confirming *HER2* as an independent prognostic factor. Significantly shorter disease-free survival (risk ratio = 1.58, 95% confidence interval [CI] = 1.25-2.00, $p < 0.001$) and significantly shorter overall survival (risk ratio = 1.84, 95% CI = 1.43-2.38, $p < 0.001$)

were shown by univariate analysis in patients with *HER2* gene amplification. Similar results were obtained by using multivariate analysis of survival time and *HER2* gene or protein overexpression.

In the same study, *HER2* status was shown to predict for prolonged survival as a result of anthracycline-based therapy.[45] The data were obtained from an extension of an earlier trial that had found greater disease-free and overall survival times in *HER2*-positive patients receiving dose-intensive CAF (cyclophosphamide 600 mg/m^2, doxorubicin hydrochloride 60 mg/m^2, and fluorouracil 600 mg/m^2).[36] The results of this study varied with the statistical methods employed; the authors concluded that the presence of multiple negative prognostic indicators may have confounded the results.

The best evidence supporting *HER2* status as a predictor of survival time in patients receiving anthracycline-based therapy was provided by the National Surgical Adjuvant Breast and Bowel Project. The project's B-11 trial examined the value of adding doxorubicin to melphalan and fluorouracil as adjuvant therapy for node-positive, hormone-receptor-negative breast cancer.[38] Disease-free and overall survival times were significantly extended with the addition of doxorubicin. Further analysis showed that the benefit of doxorubicin-based therapy was limited to patients in whom *HER2* was overexpressed.

The results of studies evaluating the utility of *HER2* overexpression for predicting the response to endocrine therapies are conflicting. Ross and Fletcher[41] theorized that these contradictory results may be due to the various methods used to assess *HER2* status. Some studies used plasma concentrations of shed *HER2* extracellular domains (ECDs) rather than tissue to predict *HER2* status. Nevertheless, most studies found that *HER2*-positive status is negatively correlated with the response to tamoxifen as adjuvant therapy.[41] Thor et al[45] assessed *HER2* status in patients with stage II, node-positive breast cancer receiving adjuvant CAF followed by tamoxifen for 5 years and reported no significant association between *HER2* status and tamoxifen treatment. These results were confirmed in two other studies assessing the response to tamoxifen in patients with estrogen-receptor-positive breast cancer.[39,46]

There are several reasons for the lack of uniformity in the results of studies evaluating the prognostic and predictive value of *HER2*. First, comparing trials is difficult because of the lack, until recently, of a standardized method for testing *HER2* status. Second, coexisting negative prognostic variables may confound study results. Third, many of the trials lacked proper randomization on the basis of *HER2* status, introducing selection bias. Finally, randomized trials are designed to detect a main treatment effect and have limited statistical power to detect interaction effects. Despite these methodological and clinical problems, the studies support a relationship between *HER2* positivity and increased survival times in patients receiving anthracycline-based therapy.

HER2 *testing*

Early in test development, a given prognostic variable may be measured with a myriad of techniques. In the case of *HER2* status, for example, no standardized test has been available for clinical use until recently. The results of studies of trastuzumab in women with *HER2*-positive MBC have not been uniform; a significant discordance among methods for detecting *HER2* abnormalities has been implicated.[42]

In clinical practice, breast cancer tissue is most commonly used for testing *HER2* expression. Alternatively, serum samples containing *HER2*-receptor particles shed by breast cancer cells may be examined.[47,48] Southern blotting, slot blotting, dot blotting, quantitative polymerase chain reaction testing, and fluorescence in situ hybridization (FISH) measure the degree of gene amplification or the number of copies.[41,42,49] Northern blotting, slot blotting, and in situ hybridization measure specific messenger-RNA overexpression, and Western blotting, immunohistochemistry testing with or without computer-aided image analysis, and the enzyme-linked immunosorbent assay (ELISA) measure protein content.

Immunohistochemistry testing

Immunohistochemistry testing was used in all clinical trials evaluating the safety and efficacy of trastuzumab and in most trials evaluating the prognostic value of *HER2* in women receiving adjuvant therapy for breast cancer. Immunohistochemistry testing detects the *HER2* antigen (ie, HER-receptor protein) both on the breast cancer cell surface and in the cytoplasm by using a monoclonal or polyclonal antibody to *HER2*. Breast cancer cells are stained with a reagent that detects the antigen-antibody complex. A score is assigned based on the percentage of cells stained and the intensity of staining, as determined by light microscopy or an automated cell-imaging system.[31,49] This technique offers several advantages over the other tests measuring protein overexpression. First, immunohistochemistry testing is a routine analytical method in most pathology laboratories and can be performed on permanent tissue sections rather than fresh or frozen sections. Second, because individual cells are examined microscopically, the method can be used on very small tumor specimens, including cytologic specimens, and interpretation does not depend on the tumor cell content of the specimen.[27,50,51] The disadvantages include subjective interpretation of the slides and the lack of a standardized scoring system.[41,42] Some investigators use the intensity of staining to score specimens, others the percentage of cells stained, and still others a combination of these methods. Various guidelines for categorizing specimens as *HER2* positive or negative also confound results. Some investigators score specimens as 0 to 4+, with 1+ indicating *HER2* overexpression; others use a 0 to 3+ scoring system, with 2+ indicating overexpression.[50] Because of the different definitions of overexpression, caution is advised when interpreting study results.

Inconsistencies among immunohistochemistry testing methods are compounded by the various methods of slide

preparation (fresh versus frozen versus archival, paraffin embedded versus formalin fixed) and the different types of antibodies to *HER2*.[41,42,52] Press et al[52] evaluated a panel of 28 antibodies (7 polyclonal and 21 monoclonal) on 187 paraffin-embedded breast cancer specimens previously classified as *HER2* positive by Southern, Northern, or Western blotting or immunohistochemistry testing. The ability of these antibodies to detect *HER2* overexpression ranged from 6% to 82%, demonstrating the wide variability in the sensitivity of the test.

In all trials evaluating trastuzumab, a noncommercially available immunohistochemistry assay, the Clinical Trial Assay (CTA), was used to assess *HER2* status. Dako Corporation (Carpinteria, CA) produces the only commercially available *HER2* immunohistochemistry assay for patients being considered for treatment with trastuzumab. This test, called the HercepTest, uses a polyclonal antibody to detect *HER2* expression in breast cancer cells.[53] The manufacturer suggests that scores of 2+ and 3+ be considered weakly and strongly positive for *HER2*, respectively.

The HercepTest was compared with the CTA by using more than 500 breast cancer tissue specimens obtained from the National Cancer Institute Cooperative Breast Cancer Tissue Resource; the rate of concordance between the two assays was 79%.[23,53,54] The concordance findings indicate that a 3+ score on the HercepTest was likely to correspond to a 2+ or 3+ score on the CTA; however, a score of 2+ on the HercepTest did not agree as well with the CTA results. According to the trastuzumab package insert,[54] a score of 2+ on the HercepTest would be negative (0 or 1+) on the CTA in 42% of cases (53 of 126 specimens tested), which would not have allowed patient entry into the trastuzumab clinical trials.[23] Other studies confirm this lack of specificity, especially for detecting moderately positive (2+) results.[53,55] These studies suggest that any future trials in which the HercepTest is used to select patients for trastuzumab therapy may yield lower response rates.

FISH

FISH is the most commonly used test for measuring *HER2* gene amplification. This test uses *HER2* DNA probes applied to digested DNA from breast cancer tissue. The *HER2*-hybridized probes are then tagged with fluorescence-labeled reagents. Slides are evaluated for *HER2* gene copy number with a fluorescence microscope; the number of fluorescent signals determines the scoring of samples. Samples with more than four signals per nucleus are considered amplified.[49] Because the results of FISH are based on a specific count of fluorescent signals, interobserver variability and subjectivity are smaller issues than with immunohistochemistry testing. However, FISH takes more time (10.4 hours over two days, versus 6 hours over one day), costs more, and requires special training and equipment.[49]

Two FISH assays are commercially available. The Oncor INFORM HER-2/*neu* Gene Detection System (Ventana Medical Systems, Tucson, AZ) is FDA approved as a prognostic test for breast cancer patients with negative lymph nodes.[56] The PathVysion HER-2 DNA Probe Kit (Vysis Inc., Downer's Grove, IL) is approved as an adjunctive prognostic test to aid in predicting the response to CAF in patients with stage II, node-positive breast cancer.[57] Although these two tests have different FDA-approved indications, they both detect *HER2* gene amplification and may be considered clinically equivalent.

Jacobs et al[49] compared a FISH assay (Oncor INFORM) with immunohistochemistry testing (HercepTest) but used a modified testing procedure and a scoring system different from that recommended in the HercepTest package insert.[53] The study revealed a high level of concordance (91.1%) between the two tests. However, the FISH procedure required more time for the technologists and pathologist per case; therefore, routine use of the FISH assay for assessing *HER2* status is not recommended.

Despite the agreement of these FISH and immunohistochemistry test results, a number of other studies show some disparity between the tests. In one study, immunohistochemistry testing but not FISH was able to detect *HER2* overexpression in about 10% of cases.[27,51] Because FISH does not assess *HER2* expression and therefore cannot detect those few patients who overexpress the gene product (ie, the *HER2*-receptor protein) in the absence of gene amplification, up to 10% of patients assessed with FISH alone may be deprived of potentially beneficial trastuzumab therapy. Whether gene amplification or protein overexpression is a more pertinent test of *HER2* status remains unclear.

ELISA

ELISA can be used to test for the presence of circulating shed ECDs of the *HER2*-receptor protein, also known as $p185^{HER2/neu}$ ECD. It is estimated that elevated serum ECD concentrations are present in 34% of women with breast cancer.[47] ECD concentrations have been used in some clinical trials to determine the response to antiestrogens.[47,48] Other studies suggest that high ECD concentrations can predict resistance to cyclophosphamide, methotrexate, and fluorouracil therapy.[48] More recently, high ECD concentrations were shown to influence the pharmacokinetics of trastuzumab; this may prove useful for predicting the response to this agent.[13,14,16]

The availability of trastuzumab will force standardization of laboratory assays designed to detect *HER2* amplification or overexpression. Standard recommendations regarding *HER2* testing do not currently exist. We recommend using the HercepTest because it is more readily available and less time-consuming than the commercially available FISH assays. If 2+ results are obtained with the HercepTest, using one of the FDA-approved FISH assays to confirm *HER2* status may be wise.

CLINICAL DEVELOPMENT OF TRASTUZUMAB

Several murine monoclonal antibodies to *HER2* have been developed and tested in animal models to determine

whether inhibition of *HER2* activity could affect tumor cell growth.[58,59] One of these antibodies, the murine monoclonal antibody (muMAb) 4D5, recognizes the ECD of the *HER2* protein receptor and blocks the activation of *HER2-HER3* complexes.[58,60] This inhibition may be accomplished by either blocking an autocrine or paracrine growth-stimulatory loop involving the *HER2*-receptor protein or direct signaling through the receptor signal-transduction pathway.[59] In preclinical studies, muMAb 4D5 inhibited the proliferation of SK-BR-3 breast cancer cells, which are known to overexpress *HER2*[61]; also, when muMAb 4D5 was administered to mice with human breast and ovarian cancers (xenografts) that overexpressed *HER2*, it prolonged their tumor-free survival time.[59]

The human immune system recognizes muMAb 4D5 as foreign, and the body responds by developing neutralizing antibodies. As a result, a recombinant human monoclonal antibody to *HER2* (rhuMAb *HER2*)-trastuzumab was developed to minimize the immune response to the *HER2* antibody. Trastuzumab is significantly less antigenic than the murine antibody and binds to the recombinant *HER2* ECD with an affinity three times greater than that of muMAb 4D5.[62]

In mice bearing *HER2*-overexpressing human tumor xenografts, trastuzumab combined with cisplatin, doxorubicin, or paclitaxel resulted in greater tumor growth inhibition than that observed with any of the agents given alone.[59,63,64] Similar results were observed when trastuzumab was combined with etoposide, thiotepa, vinblastine, or methotrexate.[63] These studies provided the impetus for investigating the clinical utility of (1) *HER2* status as a prognostic variable and as a predictor of responsiveness to chemotherapy and (2) trastuzumab as therapy for patients with MBC.

MECHANISM OF ACTION

The mechanism underlying the anticancer activity of trastuzumab is not known. Several mechanisms have been postulated, including down-regulation of *HER2*-receptor protein expression, which results in decreased proliferation of tumor cells.[61,65] In vitro data suggest that the antiproliferative effects of trastuzumab and muMAb 4D5 result from inhibition of cell-cycle progression, perhaps by reducing the number of cells entering the S phase and thus increasing the percentage of cells in the G0 and G1 phases.[65]

Another possible mechanism of action is the preferential exertion of antibody-dependent cellular cytotoxicity on *HER2*-overexpressing cancer cells.[62] Trastuzumab contains an immunoglobulin G1 Fc region that may bind to receptors on peripheral blood mononuclear cells, natural killer cells, and activated T cells, which can activate antibody-dependent cellular cytotoxicity.[66] If trastuzumab does induce cytotoxic activity in this manner, the effects of concurrently administered immunosuppressants (eg, glucocorticoids) will need to be evaluated to determine if an interaction exists.

Treatment of *HER2*-overexpressing tumor cells with muMAb 4D5 decreases the production of vascular endothelial growth factor (VEGF),[65] which is thought to be an important contributor to tumor angiogenesis. If trastuzumab has a similar effect on VEGF, inhibition of angiogenesis may be yet another mechanism of this agent's antitumor action.

SAFETY AND EFFICACY

Single-agent trastuzumab for MBC

Two open-label Phase II trials evaluated the safety and efficacy of trastuzumab in patients with *HER2*-overexpressing MBC.[13,14] All but one patient had received prior chemotherapy. Ongoing studies are evaluating trastuzumab as first-line therapy for *HER2*-overexpressing MBC.[12]

Baselga and colleagues[14] treated 46 women with *HER2*-overexpressing MBC with an initial dose of trastuzumab 250 mg iv, followed by 10 weekly maintenance doses of 100 mg. Patients with a history of brain metastasis or with lymphangitic pulmonary metastasis or bone metastasis as the only measurable disease were excluded. The dominant site of disease in most patients (80.4%) was visceral. Nearly all the patients (97.8%) had received prior chemotherapy, and 63% of these had received two or more regimens for metastatic disease. The overall response rate (complete responses [CRs] plus partial responses [PRs]) was 11.6%, including one CR and four PRs. The duration of response was more than two years in the patient achieving a CR and ranged from 1 to 7.7 months in patients with PRs. Two other patients had minor responses (a 25-49% reduction in the size of measurable lesions), and 14 had stable disease (no change greater than 25% in the size of measurable lesions); all the patients with minor responses or stable disease then received weekly maintenance trastuzumab infusions until disease progression occurred. The median time to progression for these patients was 5.1 months.

Approximately 90% of patients with serum ECD concentrations less than 500 ng/mL achieved the desired trough serum trastuzumab concentration of 10 µg/mL. No patients with ECD concentrations of more than 500 ng/mL had any antitumor response. Trastuzumab's half-life in patients with ECD concentrations greater than 500 ng/mL was 1.8 days, compared with 9.1 days in patients with ECD concentrations less than 500 ng/mL. The shortened half-life and subtherapeutic trough levels of trastuzumab were most likely due to the formation of an antigen-antibody complex between trastuzumab and the ECD that was rapidly cleared from the circulation.

Overall, trastuzumab therapy was well tolerated. No grade 4 toxicities occurred, and only one grade 3 adverse effect (injection-site pain) was noted. Mild to moderate fever and chills were the most common adverse effects, although they occurred in only five patients.

In a larger Phase II trial, trastuzumab (4 mg/kg initially, followed by 2 mg/kg/wk) was administered to 222 patients with *HER2*-overexpressing MBC whose disease progressed

after one or more prior chemotherapy regimens for metastatic disease.[13] Trastuzumab therapy was continued until disease progression occurred, at which time the investigators chose to continue the weekly 2 mg/kg dosage, increase the dosage to 4 mg/kg/wk, or discontinue treatment. Patients were excluded if they had untreated brain or bone metastasis as the only measurable disease. Most patients (72%) had metastases to the lungs or liver; 94% had received prior anthracycline therapy and 67% had received prior taxane therapy.

The overall response rate, reported by an independent evaluation committee, was 15% (CR, 4%; PR, 11%). An additional 6% of patients had minor responses, and 29% had stable disease. The median duration of response was 9.1 months (range, 1.6 to >26 months), and the median survival time was 13 months (range, 0.5 to >30 months). The response rate tended to be higher among patients with 3+ *HER2* expression than among patients with 2+ *HER2* expression (18% versus 6%, $P = 0.06$). Patients with 3+ *HER2* expression also had higher serum ECD concentrations than patients with 2+ *HER2* expression (16.2 versus 3.4 ng/mL, $P < 0.0001$); however, no significant correlation between clinical response and ECD concentration was observed. Mean trough serum trastuzumab concentrations were higher in complete responders (70.3 µg/mL) and partial responders (58.4 µg/mL) than in nonresponders (44.3 µg/mL, $P < 0.001$).

Mild to moderate infusion-related toxicities (fever, chills, pain, asthenia, nausea, vomiting, and headache) were observed in most patients with the initial infusion but occurred less frequently with subsequent infusions. The symptoms were successfully treated with acetaminophen or diphenhydramine or both. Ten patients had cardiac events (congestive heart failure, cardiomyopathy, or a decrease in left ventricular ejection fraction of >10%). Nine of them had received prior anthracycline therapy and had at least one risk factor for anthracycline-induced cardiac dysfunction (cumulative doxorubicin dose greater than 400 mg/m^2, radiation treatment of the left chest, age greater than 70 years, or history of hypertension). The 10th patient had significant cardiac disease at study entry. Only four patients discontinued treatment because of cardiac adverse effects, including one patient who died of ventricular arrhythmias that may have been induced or exacerbated by trastuzumab therapy. One patient developed antibodies to trastuzumab, as evidenced by a decrease in the serum trastuzumab concentration from 40 to 11.4 µg/mL after six to seven weeks of therapy.

The efficacy and safety of single-agent trastuzumab as first-line therapy were evaluated in 113 MBC patients who overexpressed *HER2*.[12,67] These women were randomized to receive either standard-dose trastuzumab (4 mg/kg initially, followed by 2 mg/kg/wk) or high-dose trastuzumab (8 mg/kg initially, followed by 4 mg/kg/wk). A majority (68%) had received prior adjuvant chemotherapy, including 55% who had received anthracycline-based therapy. The overall response rate was 23% (CR, 5.3%; PR, 17.7%); no significant differences were observed between the standard-dose and high-dose groups. The most common adverse effects were pain, asthenia, fever, nausea, chills, headache, diarrhea, rash, and vomiting. One patient developed cardiac dysfunction.

The results of the studies of Baselga et al[14] and Cobleigh and Vogel[13] have formed the basis for using single-agent trastuzumab in MBC patients who overexpress *HER2* and who have received prior therapy for MBC. The response rates (12-23%) are impressive for heavily pretreated patients with MBC. The interaction between trastuzumab and ECD concentrations requires further evaluation, as does the dose-response curve for trastuzumab.

Trastuzumab combination therapy for MBC

Preclinical data show that trastuzumab combined with cisplatin, doxorubicin, or paclitaxel produces synergistic killing of tumor cells in breast cancer cell lines.[63,64,68] These findings, along with the encouraging results of single-agent studies, led investigators to evaluate the safety and efficacy of trastuzumab in combination with systemic chemotherapy.

Pegram et al[16] conducted a Phase II trial evaluating the combination of iv trastuzumab (250 mg initially, followed by 100 mg/wk for nine weeks) and cisplatin (75 mg/m^2 on days 1, 29, and 57) in 39 patients with *HER2*-overexpressing MBC. Ninety percent of the patients had previously received two or more chemotherapy regimens for metastatic disease. A majority (82%) had two or more sites of metastatic disease, such as the lungs, lymph nodes, bone, chest wall, and liver. Patients were excluded if they had central nervous system metastasis, lymphangitic pulmonary metastasis, or bone metastasis as the only measurable disease.

Of the 37 assessable patients, 9 (24%) achieved a PR, including responses observed in chest-wall and lung lesions. Seven of the responding patients had tumor tissue that stained 3+ for *HER2* expression. Three patients (8%) achieved a minor response, and 6 (16%) had stable disease. The median duration of response was 5.3 months (range, 1.6-18 months). A comparison of data on the combination of trastuzumab and cisplatin with historical data from studies of cisplatin alone in heavily pretreated MBC patients shows that objective response rates and response durations improved significantly with the combination therapy. Grade 3 and 4 toxicities, including nausea and vomiting (18%), leukopenia (5%), and thrombocytopenia (10%), were consistent with toxicities reported for cisplatin alone.

Serum trastuzumab levels were inversely related to serum ECD levels. Patients with ECD concentrations greater than 500 µg/mL had significantly lower trough trastuzumab concentrations than those with an ECD concentration less than 500 µg/mL (18.7 versus 43.6 µg/mL, $p = 0.0001$). Likewise, a shorter serum half-life of trastuzumab was observed in patients with higher ECD concentrations in both the trastuzumab group and the trastuzumab plus cisplatin group (9.2 and 11 days,

TABLE 1. SUMMARY OF PHASE III TRIAL OF TRASTUZUMAB AS FIRST-LINE THERAPY FOR METASTATIC BREAST CANCER[69,a]

	All Patients		P Subgroup		AC Subgroup	
Variable	T + P or AC (*N*=235)	P or AC (*N*=234)	T + P (*N*=92)	P (*N*=96)	T + AC (*N*=143)	AC (*N*=138)
Median time to disease progression (mo)[b,c]	7.2	4.5	6.7	2.5	7.6	5.7
95% CI	6.9–8.6	4.3–4.9	5.2–9.9	2.0–4.3	7.2–9.1	4.6–7.1
p (log-rank test)	<0.0001		<0.0001		0.002	
Overall response rate (%)[b]	45	29	38	15	50	38
95% CI	39–51	23–35	24–48	8–22	42–58	30–46
p (chi-square test)	<0.001		<0.001		0.10	
Median duration of response (mo)[b,c]	8.3	5.8	8.3	4.3	8.4	6.4
25th, 75th percentile	5.5, 14.8	3.9, 8.5	5.1, 11.0	3.7, 7.4	5.8, 14.8	4.5, 8.5
% alive at one year[c]	79	68	73	61	83	73
95% CI	74–84	62–74	66–80	51–71	77–89	66–82
p (Z test)	<0.01		0.08		0.04	

[a] T=trastuzumab, P=paclitaxel, AC=anthracycline (doxorubicin or epirubicin) and cyclophosphamide, CI=confidence interval.
[b] Assessed by an independent committee.
[c] Kaplan-Meier estimate.

TABLE 2. TREATMENT EFFECT BY LEVEL OF HER2 EXPRESSION[54,a]

	Overall Response Rate (%)		Median Time to Disease Progression (mo)	
Treatment	2+	3+	2+	3+
T + P	21	44	4.4	7.1
P	16	14	3.2	2.2
T + AC	40	53	7.8	7.3
AC	43	36	7.1	4.9

[a] 2+ or 3+ overexpression. T=trastuzumab, P=paclitaxel, AC=anthracycline (doxorubicin or epirubicin) and cyclophosphamide.

respectively, for an ECD concentration of <500 µg/mL, compared with 2.9 and 4 days for an ECD concentration of 3500 mg/mL). Although pretreatment ECD levels alone did not predict treatment outcomes, differences in pretreatment and posttreatment ECD concentrations did predict disease progression versus stable or responsive disease ($p = 0.008$). Patients with objective responses had a significant decrease in ECD concentrations after treatment, whereas patients with disease progression had a significant increase.

In the largest trial of trastuzumab, by Slamon et al,[15,69] 469 *HER2*-positive women with previously untreated MBC were randomized to receive conventional chemotherapy or chemotherapy plus trastuzumab. The patients were given doxorubicin hydrochloride 60 mg/m^2 or epirubicin hydrochloride 75 mg/m^2 plus cyclophosphamide 600 mg/m^2 (AC) every three weeks for six cycles, with or without trastuzumab (4 mg/kg initially, followed by 2 mg/kg/wk). Those who had received prior adjuvant anthracycline therapy received paclitaxel 175 mg/m^2 over three hours every three weeks for six cycles, with or without trastuzumab. At the end of the six cycles, patients receiving trastuzumab continued to receive weekly infusions until disease progression occurred, at which time they could continue therapy in an open-label trial Tables 1 through 3 summarize the results of this trial. The primary endpoint was the time to disease progression. Secondary endpoints included response rate, duration of response, and one-year survival rate.

Compared with chemotherapy alone, trastuzumab plus chemotherapy prolonged the median time to disease progression and median response duration, increased the overall response rate, and improved the overall survival time (Table 1). Patients in the paclitaxel groups were more likely to have poor prognostic factors, prior adjuvant therapy, and a shorter disease-free interval. The magnitude of effects (ie, absolute time or percent improvement in study endpoints) was greatest in the paclitaxel groups. As in the pivotal single-agent trial,[13] trastuzumab was more likely to benefit patients with a strongly (3+) *HER2*-expressing tumor (Table 2).

Approximately 40% of the patients had infusion-related toxicities, mainly fever and chills, with the first dose of trastuzumab. Symptoms were generally mild and rarely recurred with subsequent infusions. Cardiac dysfunction (congestive heart failure, cardiomyopathy, or a decrease in left ventricular ejection fraction) was the most notable adverse event in this trial and was more common in the groups receiving trastuzumab (Table 3). This increased frequency of cardiotoxicity was more pronounced in the AC groups than in the paclitaxel groups. Symptoms were generally manageable with standard therapy for cardiac dysfunction; most patients (80%) were able to continue trastuzumab therapy without further cardiac deterioration.[15,69]

TABLE 3. FREQUENCY OF CARDIAC DYSFUNCTION AS ASSESSED BY NEW YORK HEART ASSOCIATION FUNCTIONAL CLASS[54,a]

	Frequency (%)			
Functional Class	T + P (N=91)	P (N=95)	T + AC (N=143)	AC (N=135)
I–IV	11	1	28	7
III or IV	4	1	19	3

[a] T=trastuzumab, P=paclitaxel, AC=anthracycline (doxorubicin or epirubicin) and cyclophosphamide.

Because of this study, the National Comprehensive Cancer Network breast cancer practice guidelines recommend the combination of trastuzumab and paclitaxel as a treatment option for patients with *HER2*-overexpressing MBC.[70] The high cardiac dysfunction rate (about 20%) observed in patients treated with the trastuzumab-anthracycline combination was considered too high for this combination to be used outside a clinical trial. A number of studies have been proposed or initiated to better characterize the benefits and risks of trastuzumab-anthracycline combinations, and some include the use of dexrazoxane and liposomal anthracyclines as cardioprotectants. Until the results of these studies are available, we do not recommend the use of trastuzumab-anthracycline combinations outside a clinical trial.

Norton et al[71] recently updated the results of Slamon et al[15] and confirmed a one-year survival advantage with trastuzumab. Also, analysis of a longer follow-up period, a median of 25 months, indicated there was an improved median survival time-from 20.3 months with chemotherapy alone to 25.4 months with trastuzumab plus chemotherapy ($P = 0.045$), even though 65% of patients initially assigned to chemotherapy alone elected to receive trastuzumab when disease progression occurred. Overall survival time was greater in both the trastuzumab-AC group (26.8 months) and the trastuzumab-paclitaxel group (22.8 months) than in the AC group (22.1 months) and the paclitaxel group (18.4 months). This corresponds to a 24% reduction in the relative risk of death for patients receiving trastuzumab plus chemotherapy.

Phase II studies indicating high response rates with weekly paclitaxel therapy in patients with MBC[72,73] led investigators to evaluate weekly therapy with paclitaxel plus trastuzumab in patients with previously treated *HER2*-positive or *HER2*-negative MBC. Fornier and colleagues[74] administered trastuzumab (4 mg/kg initially, followed by 2 mg/kg/wk) and paclitaxel (90 mg/m2/wk) to 63 such patients. Of the 29 *HER2*-positive patients, 18 (62%) responded, and of the 34 *HER2*-negative patients, 15 (44%) responded-impressive response rates for this patient population. The primary dose-limiting toxicity was peripheral neuropathy. Only one patient, who received a cumulative anthracycline dose of 615 mg/m^2 4 weeks before paclitaxel and trastuzumab therapy, developed congestive heart failure.

Winer et al[75] evaluated a trastuzumab-vinorelbine combination as first-line and second-line treatment in 40 MBC patients. Twenty eight (71%) of the patients met the criteria for 3+ *HER2* overexpression, and 25 (62%) had received prior chemotherapy for metastatic disease. Of the latter patients, 15 (62%) had received prior anthracycline-based therapy. Only 5 (12%) of the 40 patients had received no prior chemotherapy, and 18 (44%) had at least three sites of metastatic disease. Treatment consisted of an initial 4-mg/kg dose of trastuzumab, followed by weekly 2-mg/kg maintenance doses and weekly administration of vinorelbine tartrate 25 mg/m^2. Partial responses were observed in 24 of 34 assessable patients (71%); a 75% response rate was reported in patients with 3+ *HER2* overexpression, compared with 57% in patients with 2+ overexpression. Two patients had stable disease and eight had disease progression. The median time to disease progression was 31 weeks. Grade 3 and 4 neutropenia occurred in 30% of patients and necessitated a reduction in the vinorelbine dose in 10% of them.

A number of studies evaluating trastuzumab in combination with other cytotoxic agents are under way. Docetaxel and trastuzumab are being evaluated as first-line or second-line therapy in patients with *HER2*-overexpressing MBC.[76] The Cancer and Leukemia Group B is studying four cycles of AC followed by weekly paclitaxel, with or without weekly trastuzumab, for 12 weeks.[77] Within the trastuzumab group, patients will be randomized to no further trastuzumab or one year of weekly trastuzumab. The North Central Cancer Treatment Group is planning a study that will randomize patients to receive or not receive post-AC trastuzumab therapy, followed by paclitaxel or docetaxel therapy.[77]

Future directions

Historically, drugs that improve survival time in patients with metastatic disease, such as trastuzumab, have even more activity in earlier stages of cancer. Large-scale clinical trials to test trastuzumab in the adjuvant setting are under way. Other studies will determine the optimal duration of trastuzumab therapy, whether trastuzumab has clinical activity in other cancers or cancers without *HER2* overexpression, whether trastuzumab combined with other antineoplastic agents or hormonal agents is beneficial, and whether trastuzumab's immunologic activity can be stimulated by combination with other cytokines, such as interferon or interleukins.

TRASTUZUMAB AND QUALITY OF LIFE

Chemotherapy regimens for MBC are rarely if ever curative. Thus, potential benefits (eg, increased response rate or survival time) and treatment-related toxicities must be considered before selecting therapy. Clinically useful data are beginning to emerge from quality of life (QOL) studies that may influence treatment decisions.[78] The QOL in patients with MBC has many dimensions, including disease- and treatment-related symptoms, psychological

TABLE 4. QUALITY-OF-LIFE SCORES IN PATIENTS RECEIVING SINGLE-AGENT TRASTUZUMAB THERAPY[79]

Variable	No. Patients	Baseline[a] Score	Change from Baseline				
			Week 12	Week 24	Week 36	Week 48	p b
Physical functioning	145	75.7	0.0	–0.3	–2.2	–1.9	0.9
Global quality of life	143	62.2	4.3	1.1	–0.6	0.4	0.01
Social functioning	144	70.4	6.5	4.8	1.9	1.9	0.002
Role functioning	144	67.7	1.0	0.0	–1.4	–1.4	0.7
Fatigue	145	33.9	–0.1	0.4	1.9	1.9	0.82
Pain	145	29.2	–3.1	–1.4	0.1	–0.8	NA
Nausea and vomiting	145	8.2	–0.6	0.3	1.5	1.8	NA

[a] Measured with the QLQ-C30 and BR-23 quality-of-life questionnaires of the European Organization of Research and Treatment.
[b] Repeated-measures analysis of variance, with the last observation carried forward to week 48. NA = not available.

well-being, ability to perform usual activities, sexual functioning, social interactions, and ability to work. Many clinicians rely primarily on their knowledge of agents' antitumor activity and toxicity and on performance-status scales for making treatment-related decisions, rather than on QOL scores. Nevertheless, several instruments for measuring QOL in MBC patients have been developed and validated.

Lieberman et al[79] evaluated the effect of trastuzumab on QOL in the 222 patients who were enrolled in the trial of Cobleigh et al[13] They compared baseline scores with scores obtained at weeks 12, 24, 36, and 48 and every 12 weeks thereafter from the European Organization of Research and Treatment (EORTC) core questionnaire (QLQ-C30, version 1), a 30-item general health-related QOL instrument for cancer patients, and the EORTC Breast Cancer Module (BR-23), a subscale questionnaire developed specifically for breast cancer patients. The raw score on the QLQ-C30 and the BR-23 is transformed into a value on a scale from 0 to 100. Higher scores for the functional domains (eg, physical, cognitive, emotional, social, and role functioning) and global QOL indicate improvements, whereas higher scores on the symptom scales (eg, fatigue, pain, dyspnea, insomnia, constipation, diarrhea, loss of appetite, nausea, and vomiting) indicate an increased frequency of the symptom. Table 4 shows the baseline values and changes 12, 24, 36, and 48 weeks after treatment.

QOL scores for the primary functional domains (physical, social, and role functioning; fatigue; and global QOL) did not decrease in patients treated with single-agent trastuzumab, and there were significant improvements in global QOL ($P = 0.01$) and social functioning ($P = 0.002$). Of the 18 secondary domains for which disease- or treatment-related symptoms were assessed, 2 (emotional function and body image) demonstrated small increases in functioning and 2 (lack of appetite and future health concerns) showed worsening. These results can be compared with those of other breast cancer chemotherapy trials that consistently found worsening in all QOL domains while the patients received chemotherapy. Furthermore, as in QOL studies reported previously,[78] all responders had improved QOL scores compared with nonresponders, who had only slight increases or decreases. These findings indicate that single-agent trastuzumab does not decrease QOL.

Osoba and colleagues,[80] in a Phase III trial of MBC patients overexpressing *HER2*, evaluated the effects of trastuzumab by comparing trastuzumab plus chemotherapy (AC or paclitaxel) with chemotherapy alone. The same questionnaires used by Lieberman et al[79] (the QLQ-C30 and the BR-23) were self-administered by patients at baseline; at weeks 8, 20, and 32; and every 12 weeks thereafter. Also, three items from the McMaster Breast Cancer Questionnaire, two items from the National Health Interview Survey, and six newly developed items were assessed.

There was no significant difference in QOL scores between the trastuzumab plus chemotherapy and chemotherapy-alone groups or among subgroups (AC, AC plus trastuzumab, paclitaxel, paclitaxel plus trastuzumab) (Table 5). Although the values tended to favor the trastuzumab groups, these improvements could be explained by the higher rate of attrition of patients in the chemotherapy-alone groups. These results are comparable to those of other QOL studies, in which QOL scores tended to be higher in responders.[78] This study also showed that chemotherapy-alone patients with higher baseline global QOL scores (360) had higher response rates than patients with lower baseline global QOL scores (<60) (46.4% versus 25.5%); similar findings were observed for patients in the trastuzumab plus chemotherapy group (68% versus 42.3%).

PHARMACOKINETICS

The pharmacokinetics of trastuzumab are not well-known. The volume of distribution approximates serum volume (44 mL/kg).[54] The elimination route has not been clearly defined.

Results of three Phase II trials indicate that the phamacokinetics of trastuzumab are dose dependent.[13,14,16] The half-life varies from 1.7 to 12 days with short infusions of 10 and 500 mg, respectively. One study suggests that the half-life plateaus at higher doses.[81] Half-lives of 2.7, 3.1, 8.8, and 10.4 days were reported after single doses of 1, 2, 4, and 8 mg/kg, respectively. This suggests that, as trastuzumab receptors become saturated, total body clearance becomes linear. Patients receiving doses of 4 and 8 mg/kg achieved

and maintained serum concentrations exceeding the minimum concentration (10 µg/mL) needed for antiproliferative effects and antibody-dependent cellular toxicity.

In studies in which an initial dose of 4 mg/kg was followed by a weekly maintenance dose of 2 mg/kg, a mean ± S.D. serum half-life of 5.83 ± 4.30 days and a clearance of 5.15 ± 2.45 mL/kg/day were observed among 159 patients.[69] Among patients receiving this regimen of trastuzumab in combination with chemotherapy, the mean ± S.D. peak serum trastuzumab concentration at week 8 was 101.0 ± 30.6 µg/mL (n = 115) and the mean ± S.D. trough concentration was 53.4 ± 22.9 µg/mL (n = 126). Among patients receiving trastuzumab alone, mean ± S.D. peak and trough concentrations at week 8 were 95.6 ± 35.9 µg/mL (n = 133) and 48.8 ± 24.9 µg/mL (n = 137), respectively.

The elimination of trastuzumab appears to depend on high serum levels of circulating ECDs shed from breast tumor cells. Examination of serum samples obtained from patients with *HER2*-positive MBC revealed that 64% of patients had detectable levels of shed antigen.[54] Patients with high baseline levels of shed antigen are more likely to have lower trough concentrations of trastuzumab in serum; the significance of this phenomenon is unclear.

Data suggest that the pharmacokinetics of trastuzumab are not altered by age or serum creatinine concentration (up to 2.0 mg/dL).[54] Although formal drug interaction studies have not been performed, the combination of trastuzumab and paclitaxel resulted in a 2-fold decrease in trastuzumab clearance in primates and a 1.5-fold increase in serum trastuzumab concentrations in MBC patients. Trastuzumab clearance was not affected when trastuzumab was combined with cisplatin or with cyclophosphamide plus doxorubicin or epirubicin.

Because increased serum ECD levels are associated with lower serum trastuzumab levels, assessing serum ECD levels at baseline and during trastuzumab therapy might provide useful dosing information. For example, patients with high serum ECD concentrations might require higher doses to attain therapeutic concentrations of trastuzumab. Similarly, patients with lower serum ECD concentrations might require lower doses. Currently, there are no recommendations or guidelines for monitoring trastuzumab or ECD concentrations.

MONITORING AND MANAGING TOXICITIES

In general, trastuzumab therapy is well tolerated. The most common adverse events are infusion related-primarily fever and chills-and occur in approximately 40% of patients during the initial infusion.[54,82] Other infusion-related reactions include nausea, vomiting, pain at the tumor site, rigors, headache, dizziness, dyspnea, hypotension, rash, and asthenia. These reactions are usually mild to moderate and rarely require discontinuation of therapy. Acetaminophen, diphenhydramine, and meperidine may be used, with or without reducing the trastuzumab infusion rate, to treat these reactions.[69] If infusion-related symptoms occur, subsequent doses should be infused over 90 minutes. Infusion over 30 minutes is appropriate if symptoms subside.

As of May 1, 2000, postmarketing surveillance reports show that 62 (0.002%) of an estimated 25,000 patients have had serious adverse events, including hypersensitivity reactions, infusion-related reactions, and pulmonary events, some of which led to death. Adult respiratory distress syndrome, anaphylaxis, and death within 24 hours of a trastuzumab infusion-none of which occurred in clinical trials-have been reported. Most fatal events occurred in patients with preexisting pulmonary dysfunction including intrinsic or malignant lung disease. The manufacturer recommends that patients with preexisting pulmonary dysfunction be treated with extreme caution and that trastuzumab therapy be discontinued in patients who have severe infusion-related reactions.

Other adverse effects include possible exacerbation of certain chemotherapy-related adverse effects, including anemia, leukopenia, diarrhea, and infection,[54] although quantifying the contribution of trastuzumab to these effects is difficult. Hematologic monitoring, including a complete blood count with differential and a platelet count, should be performed as needed.

Most attention has focused on the possible cardiac effects of trastuzumab, particularly when it is given in combination with chemotherapy. All available clinical evidence suggests

TABLE 5. CHANGES IN QUALITY-OF-LIFE SCORES IN PATIENTS WITH AND WITHOUT CARDIAC DYSFUNCTION [80,a]

	Mean ± S.D. Change from Baseline			
	No Cardiac Dysfunction		Cardiac Dysfunction	
Domain or Symptom	T + P or AC (*N*=161)	P or AC (*N*=184)	T + P or AC (*N*=46)	P or AC (*N*=10)
Global quality of life	2.48 ± 29.18	-4.67 ± 27.97	-3.26 ± 25.85	10.00 ± 27.72
Physical functioning	-1.69 ± 30.79	-8.67 ± 31.44	-6.88 ± 25.80	5.00 ± 27.99
Social functioning	3.00 ± 32.27	-5.19 ± 34.04	-6.67 ± 26.45	8.33 ± 23.90
Role functioning	0 ± 41.21	-9.24 ± 41.11	-14.13 ± 37.51	-10.00 ± 21.08
Fatigue	0.49 ± 30.01	7.01 ± 28.66	3.09 ± 34.64	0 ± 36.29

[a] A minus sign indicates deterioration in the functional domains but improvement in fatigue. T=trastuzumab, P=paclitaxel, AC=anthracycline (doxorubicin or epirubicin) and cyclophosphamide.

TABLE 6. PROTOCOL FOR PHASE III CLINICAL TRIAL OF TRASTUZUMAB PLUS CHEMOTHERAPY[15,69]

Regimen	Day 0	Day 1	Days 7 and 14	Day 21
Trastuzumab 4 mg/kg iv[a]	X			
Trastuzumab 2 mg/kg iv[b]			X	X
Dexamethasone 20 mg po 12 and 6 hr before paclitaxel	X			X
Diphenhydramine hydrochloride 50 mg iv 30 min before paclitaxel		X		X
Cimetidine 300 mg (as the hydrochloride) iv 30 min before paclitaxel		X		X
Paclitaxel 175 mg/m² i.v. or doxorubicin hydrochloride 60 mg/m² iv or epirubicin hydrochloride 75 mg/m² iv + cyclophosphamide 600 mg/m² i.v.		X		X

[a] Observe for infusion-related reactions for 60 minutes after infusion has been completed.
[b] Observe for infusion-related reactions for 30 minutes after infusion has been completed. If no signs and symptoms occur with first and second infusions, the observation period may be decreased or eliminated.

that the cardiac effects closely resemble anthracycline-related congestive heart failure.[83] The mechanism of trastuzumab-associated cardiotoxicity is unknown, but presumably there is low-level expression of the *HER2* gene in cardiac myocytes.[84]

Because the frequency of cardiac dysfunction has reportedly been higher with trastuzumab plus AC (28%) than with AC alone (3-5% at cumulative doxorubicin doses of 400 mg/m²), a cardiac review committee studied 1,024 patients who received trastuzumab in Genentech-sponsored clinical trials to characterize trastuzumab-induced cardiac dysfunction.[67,69,85] In this evaluation, cardiac dysfunction was defined as the development of symptoms of congestive heart failure or a drop in left ventricular ejection fraction of 10% without symptoms or 5% with symptoms. Cardiac dysfunction occurred to some degree in 9.5% of patients.[67] The frequency of cardiac symptoms (28%) and symptom severity (New York Heart Association class III or IV, 19%) were greatest in patients receiving trastuzumab combined with an anthracycline and cyclophosphamide.[54] Most patients responded to standard medical treatment, which typically included a diuretic, an angiotensin-converting-enzyme inhibitor, and digoxin or other therapies, such as inotropic agents, β-blockers, and supplemental oxygen. Many patients were able to continue trastuzumab therapy without further deterioration of cardiac function. A multivariate analysis identified age greater than 60 years and concomitant anthracycline treatment as independent risk factors for cardiotoxicity. Neither prior anthracycline treatment nor cumulative anthracycline dose appeared to be an independent risk factor.[67,85]

Clearly, patients receiving trastuzumab merit careful evaluation for cardiac symptoms. Assessment of left ventricular ejection fraction before therapy is suggested by the manufacturer,[54] and frequent reevaluation is indicated, particularly in older patients, patients with preexisting heart disease, and patients receiving concurrent chemotherapy, especially anthracyclines. The most appropriate method for identifying patients at risk of cardiotoxicity is uncertain; however, we recommend repeating baseline echocardiography or radionuclide multigated angiography or both at least once every three months. In patients who have previously had anthracycline therapy or who have a history of cardiac problems or hypotension, scans should be repeated at least once every two months or more often if indicated.

DOSAGE, PREPARATION, AND ADMINISTRATION

The manufacturer recommends an initial trastuzumab dose of 4 mg/kg iv over 90 minutes, followed by a weekly maintenance dose of 2 mg/kg iv administered over 30 minutes if the initial dose is well tolerated.[54] Trastuzumab should not be administered as an iv push or bolus infusion.

In the Phase III study of trastuzumab combined with chemotherapy, the initial dose preceded the first cycle of chemotherapy by 24 hours (Table 6).[15,69] If the initial dose was well tolerated, subsequent doses were given immediately before chemotherapy was administered. Patients were observed for infusion-related reactions for at least 60 minutes after the initial dose and for 30 minutes after the first maintenance dose.[13,15] The need for subsequent observation was determined by patients' tolerance of trastuzumab. Although the optimum duration of trastuzumab therapy has yet to be determined in controlled clinical trials, maintenance therapy with trastuzumab was continued in most studies until disease progression occurred.[12,13,15,74]

Trastuzumab is available as a preservative-free lyophilized powder for iv injection. The drug is formulated in histidine, trehalose, and polysorbate 20. Each multidose vial contains 440 mg of trastuzumab and is reconstituted with 20 mL of the provided 30-mL vial of bacteriostatic water for injection, containing 1.1% benzyl alcohol as the preservative, or with sterile water for injection, which produces a final trastuzumab concentration of 21 mg/mL at a pH of approximately 6.0. Dosage errors have resulted from reconstituting trastuzumab with the entire 30 mL of the

provided diluent. Each single dose should be further diluted in 250 mL of 0.9% Sodium Chloride Injection, USP, in polyvinyl chloride or polyethylene bags, which may be stored for up to 24 hours at 2–8 ºC. Stability is maintained for up to 24 hours at 2–25 ºC. If the vial is reconstituted with the provided diluent (bacteriostatic water for injection), stability is maintained for 28 days under refrigeration. Reconstituted trastuzumab should not be frozen. If the vial is reconstituted with sterile water for injection (ie, for use in patients with a known hypersensitivity to benzyl alcohol), the reconstituted solution should be used immediately and any unused portion discarded. Trastuzumab is not compatible with 5% dextrose injection. Other diluents do not contain effective preservatives of trastuzumab and should not be used.

Trastuzumab solutions should be gently swirled, not shaken, to aid reconstitution. The drug is sensitive to agitation and rapid expulsion from a syringe, which can result in excessive foaming, problems with dissolution, and a decrease in the amount of trastuzumab that can be withdrawn from a vial. The diluent should be slowly injected into the vial, with the stream of diluent directed at the lyophilized cake. Slight foaming of the product on reconstitution is not unusual. The vial should stand undisturbed for approximately five minutes before further dilution in 0.9% sodium chloride injection.[54,86]

Although an inline filter is not necessary when administering trastuzumab, inadvertent administration of filtered trastuzumab should not be a cause for concern, nor is it contraindicated. Studies of the compatibility of trastuzumab with various types of iv tubing or infusion sets have not been performed, but compatibility or efficacy problems have not been reported in clinical trials, in which the type of iv tubing or infusion set has not been restricted.[a]

Studies of the compatibility of trastuzumab with other drugs have not been performed. The manufacturer recommends that no other medications be added to trastuzumab solutions.[54]

CONCLUSION

Trastuzumab has changed the standard of care for MBC patients who overexpress the *HER2*-receptor protein. In heavily pretreated patients who overexpress *HER2*, trastuzumab produces objective response rates of 12-23%. Regimens combining trastuzumab with paclitaxel or with doxorubicin (or epirubicin) plus cyclophosphamide are associated with improved response rates, a longer median time to disease progression, higher one-year survival rates, and longer median overall survival times than chemotherapy alone. Cardiac dysfunction is the most serious adverse event reported and is more common in patients receiving trastuzumab plus anthracycline-based chemotherapy than in patients receiving trastuzumab or chemotherapy alone.

[a]Data on file. South San Francisco, CA; Genentech.

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