



Hendrick van Vliet, 1662. *Interior of the Nieuwe Kerk in Delft*.
From the collection of Dr. Gordon and Adele Gilbert of
St. Petersburg, Florida.

HER-2 as a Prognostic, Predictive, and Therapeutic Target in Breast Cancer

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Therapy with a humanized monoclonal antibody to HER-2 (trastuzumab), used either alone or combined with chemotherapeutic agents, can be effective treatment in some patients with metastatic breast cancer.

Background: An expanded understanding of the biology of breast cancer has led to the identification of the HER-2 receptor as an important growth factor. This receptor possesses intrinsic tyrosine kinase activity and has been associated with aggressive biological behavior and poor clinical outcome.

Methods: Data have been reviewed regarding the role of HER-2 expression as a prognostic variable, as a predictive factor for response to chemotherapy and hormonal therapies, and as a directed therapeutic target for breast cancer.

Results: Therapy with a humanized monoclonal antibody to HER-2 (trastuzumab) can be effective treatment in some patients with metastatic breast cancer, either given alone or in combination with some chemotherapeutic agents. Cardiac toxicity limits concurrent use with anthracyclines. Clinical trials will further define optimal combination regimens with this agent, and its value in patients with localized or locally advanced stages.

Conclusions: Trastuzumab is a significant addition to the armamentarium against breast cancer. Standardization of the optimal method to evaluate for HER-2 overexpression is necessary to better define its role as a prognostic, predictor, and therapeutic target in this disease.

Biology of HER-2

The HER-2 gene (c-erbB-2, neu) encodes a 185kDa transmembrane tyrosine kinase receptor that has partial homology with other members of the epidermal growth factor receptor family.¹⁻³ It was first identified in 1981 as a transforming oncogene in carcinogen (ethylnitrosourea)-induced rat neural tumors,⁴ and it is now known that normal human cells express a small constitutive amount of HER-2 protein on the plasma membrane. The activation of the HER-2 oncogene is believed to follow the binding of a yet unidentified growth factor ligand to the HER-2 receptor complex, which leads to heterodimerization, triggering a cascade of growth signals that culminates in gene activation. More specifically, the epidermal growth factor family can be subdivided into four groups based on their receptor-binding specificities (HER-1, HER-2, HER-3, and HER-4). Ligands for HER-1, -3, and -4 include HER-1 itself, transforming growth factor- α , amphiregulin, betacellulin, and heregulin, among others. HER-2 is the preferred heterodimerization partner of all other HER receptors. It enhances their affinities for the different ligands and amplifies the corresponding signals, even though HER-2 does not appear to bind to any of the above-named ligands directly. It is believed that binding of a specific ligand induces dimerization, activation of intracellular signal transduction pathways, and receptor cross-phosphorylation.⁵ The exact mechanisms through which any of these ligands or heregulin regulates the activities of breast cancer cells are currently unknown. This process is complex, as these different ligands affecting HER family members may lead to transactivation between two HER members and thus utilize multiple pathways to execute their biologic functions. A series of cellular processes results from this signal transduction, including a pleiotropic effect of cytoskeleton reorganization, cell motility, cell adhesion, and protease expression and activation.⁶⁻⁸ Overexpression of HER-2 has been demonstrated to lead to increased tumorigenicity, tumor invasiveness, increased metastatic potential, and altered sensitivity to hormonal and chemotherapeutic agents in transfection studies in cellular and animal models.⁹

HER-2 protein overexpression has been reported to occur in approximately 30% of invasive human breast cancers, with HER-2 gene amplification detected in 95% or more of the specimens found to overexpress HER-2 protein. Increased expression may also be associated with alternative mRNA splicing, leading to potential differences in the intracellular and extracellular domains of HER-2.¹⁰ The exact function of the extracellular domain of HER-2 is poorly understood, but it is possible that the extracellular domain may stimulate cell proliferation or motility through mechanisms that involve interaction with other proteins, eg, heterodimerization with full-length epidermal growth factor receptors or other members of the HER-2 family. Modulation of signal transduction pathways and the induction of metastases may then occur through an aggregate of extracellular HER-2 with normal full-length HER-2 receptors, thereby altering their activity.

Antibodies directed at the protein encoded by HER-2 (p185^{HER-2}) have been demonstrated to inhibit the growth of human xenografts and transformed breast cancer cells that overexpress HER-2.¹¹⁻¹³ Specifically, the murine monoclonal antibody (MAb) 4D5 (directed at the extracellular domain of p185^{HER-2}) has been demonstrated to be a potent growth inhibitor of human breast cancer cells that overexpress HER-2.¹⁴ This murine antibody was humanized by inserting the complementarity-determining regions of MAb 4D5 into the framework of a consensus human immunoglobulin IgG, with the goal of making it less immunogenic than its murine counterpart.¹⁵ The name of this humanized MAb is trastuzumab (Herceptin).¹⁶

HER-2 as a Prognostic Factor

A variety of clinical studies have demonstrated the potential relevance of HER-2 expression as a prognostic factor for breast cancer, starting with the seminal publication by Slamon et al¹⁷ in 1987. In general, overexpression of HER-2 has been shown to be associated with poor clinical outcome and correlated with other adverse prognostic variables such as estrogen-receptor negativity, high S-phase fraction, positive axillary lymph node status, p53 mutations, and high nuclear grade.¹⁸⁻²⁰ The independent value of HER-2 expression for patients with either node-negative or node-positive breast cancer has been difficult to elucidate, as essentially all the studies have been retrospective, using different assay systems and reagents for HER-2 expression.

HER-2 as a Predictive Factor for Therapy

Adjuvant Therapy in Breast Cancer

The potential interaction of HER-2 expression and response to therapy was initially observed as part of retrospective analyses utilizing different chemo-hormonal agents as adjuvant treatment for breast cancer.²¹ Several other studies have been reported over the last decade with somewhat conflicting results. Most of these correlative studies have been retrospective. Archival tissue was obtained for the analysis, and multiple techniques and scoring systems for HER-2 overexpression were used.

Although two previous studies suggested that patients with HER-2 overexpressing breast cancer did not benefit from adjuvant CMF chemotherapy, contradictory data from the Milan group have recently become available (personal communication, P. Valagussa, April 1999). These investigators evaluated HER-2 expression in specimens from their original study of CMF vs no adjuvant therapy for patients with node-positive breast cancer and have now demonstrated that patients with HER-2 overexpressing tumors do benefit from adjuvant CMF.

The two recently published reports from the Cancer and Leukemia Group B (CALGB) 8541/8869²² and the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-11²³ are examples of these subtleties and discrepancies in the evaluation and interpretation of data. CALGB 8869 evaluated the relationship between HER-2 expression and dose response to doxorubicin (30 mg/m² vs 40 mg/m² vs 60 mg/m² per cycle) in 442 node-positive patients from study CALGB 8541. The effect of dose intensity of doxorubicin on survival and disease-free survival was evident in the HER-2-positive cohort, but it was absent in patients with HER-2-negative tumors.²² NSABP B-11 was a study initiated in 1981 to test the hypothesis of whether the addition of doxorubicin (30 mg/m² per cycle) added to the benefits of PF (L-phenylalanine mustard and 5-fluorouracil) chemotherapy in patients with estrogen receptor-negative, node-positive breast cancer. A retrospective analysis of the interaction between HER-2 expression and the addition of doxorubicin demonstrated a statistically significant difference in disease-free survival (P=0.02) but not for survival (P= 0.15).²³ Of interest was that an univariate analysis, increasing number of lymph nodes (P= 0.0001), and large clinical tumor sizes (P= 0.02) were associated with increased rates of HER-2 expression, whereas estrogen-receptor positivity was negatively associated with HER-2 expression (P=0.008). The authors concluded that the data supported the hypothesis of a benefit from doxorubicin in HER-2-positive, node-positive breast cancer. They hypothesize that HER-2 expression may be simply a surrogate for topoisomerase-II expression, which in turn has been associated with increased sensitivity to doxorubicin in vitro. These authors note that experiments of transfection of the HER-2 gene into HER-2-negative MCF-7 breast cancer cells do not result in consistent alterations of sensitivity to doxorubicin, again challenging a primary role of HER-2 expression as it relates to sensitivity to doxorubicin.

The relationship of response to doxorubicin dose and HER-2 protein expression was analyzed in the CALGB 8541/8869 trial using the CB11 MAb and a continuous scoring system of positivity, with >50% staining regarded as positive. However, the analysis of data from the NSABP B-11 trial used two different antibodies (the mouse monoclonal antibody mAb-1 and the rabbit polyclonal pAb-1 antibody), with any staining for HER-2 protein regarded as positive; again, >50% staining was selected as the cutoff for using HER-2 expression as a dichotomous variable for the survival and disease-free survival curves. The interpretation of data addressing the relative benefit of anthracyclines based on HER-2 expression should incorporate that the CALGB 8541 trial demonstrated that patients with HER-2 overexpressing tumors benefited from an increase in doxorubicin dose from 30 mg/m² to 60 mg/m² per cycle, whereas the NSABP B-11 trial demonstrated that HER-2 overexpression correlated with improvements in outcome to the same dose of doxorubicin 30 mg/m² at the lowest end of the dose-response curve in CALGB 8541.

The relative role of HER-2 overexpression and the benefit from adjuvant anthracyclines have also been evaluated within the context of study NSABP B-15, which was discussed by S. Paik during an oral presentation at the 21st Annual San Antonio Breast Cancer Symposium. The NSABP B-15 was a randomized study of AC alone vs AC followed by CMF vs CMF alone for patients with node-positive breast cancer. A total of 599 (29%) of 2,034 analyzed specimens were found to overexpress HER-2. Overall, patients who received anthracyclines and whose tumors overexpressed HER-2 had a statistically significant benefit on disease-free survival, but they had only a nonstatistically significant overall survival benefit compared to those who received CMF (nonanthracycline therapy).

A potential conclusion based on this extensive database is that when comparing non-anthracycline vs anthracycline adjuvant regimens, the benefit to adding anthracyclines is primarily observed in patients with HER-2 overexpressing tumors. The data regarding HER-2 expression and response to tamoxifen in the adjuvant setting are also conflicting. Although the Naples GUN trial²⁴ demonstrated that HER-2 expression led to a detrimental clinical effect if tamoxifen was used as adjuvant therapy, the CALGB 8541²² and the NSABP B-11²³ trials did not demonstrate this interaction. The data regarding response to taxanes and other agents in the adjuvant setting are conflicting as well. Therefore, it would be prudent to develop reliable and reproducible methodology to determine HER-2 expression and incorporate it as part of well-controlled, randomized adjuvant trials before routinely selecting adjuvant therapy on the basis of HER-2 expression. The planned intergroup study through the North Central Cancer Treatment Group (NCCTG) led by E. A. Perez and the study through the NSABP led by E. Romond will help to answer these questions. Both of these trials will include prospective analysis of HER-2 expression by different methodologies while analyzing whether adding trastuzumab to standard adjuvant chemotherapy improves disease-free survival and overall survival in patients with node-positive breast cancer (Figure).

A	
AC q3w x 4	Paclitaxel qw x 12
	Paclitaxel qw x 12 → trastuzumab qw x 52
	Paclitaxel qw + trastuzumab qw x 12 → trastuzumab qw x 40
B	
AC q3w x 4	Paclitaxel q3w x 4
	Paclitaxel q3w x 4 + trastuzumab qw x 12 → trastuzumab qw x 40

Adjuvant studies for node-positive, HER-2-positive breast cancer. (A) Schema for NCCTG adjuvant trial N9831. (B) Schema for NSABP B-31 adjuvant trial.

Metastatic Setting

The data regarding the use of HER-2 expression to predict response to hormonal therapy or chemotherapy in the metastatic setting are inconclusive.²⁵⁻³⁰ The correlation of HER-2 overexpression with other markers such as topoisomerase II, as well as correlations between the different methods to assess overexpression and response to systemic therapy in breast cancer, will be intensely studied over the next few years.

Induction Therapy

A study by Archer and colleagues²⁷ evaluated the effect of HER-2 expression on the ability of anthracycline-based neoadjuvant chemotherapy to induce apoptosis of tumor cells. The assessment of apoptosis was made through an apoptosis index defined by terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end-labeling (TUNEL). The mean apoptotic index score was determined before chemotherapy and 24 hours after chemotherapy. Results demonstrated that this apoptotic index rose significantly less in nine patients with HER-2-overexpressing tumors than in 230 patients with HER-2-negative tumors (34% vs 245%, respectively). The authors suggested that HER-2-positive breast cancer has a reduced apoptotic response to chemotherapy, which may explain the relative chemoresistance reported for patients with HER-2-overexpressing tumors.

Trastuzumab Therapy

In the pivotal, single-agent phase II trial of trastuzumab³¹ and the phase III trial of combination chemotherapy with trastuzumab,³² patient eligibility was determined by testing tumor specimens for overexpression of HER-2. The 4D5 and CB11 MAbs were used for immunohistochemistry testing.¹⁶ HER-2 overexpression of these samples was classified as 0, 1+, 2+, or 3+, and enrollment was limited to patients with tumor scored as having 2+ and 3+ overexpression (approximately 30% of those screened).

These pivotal phase II and phase III efficacy studies were not statistically powered to assess a difference in clinical benefit for patients with tumors demonstrating 2+ vs 3+ staining by immunohistochemistry. However, retrospective analysis of the data suggests that the beneficial effect of trastuzumab therapy was limited in patients with a 2+ level of HER-2 protein expression compared to those with a 3+ level. As trastuzumab has been approved by the Food and Drug Administration (FDA) for the treatment of patients with 2+ or 3+ HER-2-overexpressing breast cancer, it is crucial that we determine if there is indeed a different clinical response according to the degree of HER-2 overexpression using standardized FDA-approved test methods (immunohistochemistry [IHC] or fluorescence in situ hybridization [FISH]).³³⁻³⁵ A trial is being planned through the NCCTG (N9931) to address this issue.

Specifics of HER-2 Testing

The lack of standardization for HER-2 testing has led to conflicting data regarding its prognostic and predictive characteristics. The anti-HER-2 antibody preparations in use today appear to differ with respect to binding affinity, epitope specificity, and cross-reactivity with non-HER-2 proteins. Moreover, interpretation of data may be somewhat operator-dependent, which may be also influenced by the type of assay used. The assays used to test for HER-2 expression have evaluated DNA, RNA, protein, or soluble receptors. The most commonly used methods include FISH, IHC, and enzyme-linked immunosorbent assay (ELISA).

All of the patients in the trastuzumab clinical trials were selected using an investigative immunohistochemistry clinical trial assay (CTA). None of the patients in these trials were selected using the current FDA-approved assays (HercepTest or any of the approved FISH kits). The HercepTest was compared to the investigative clinical trial assay on an independent set of 548 samples from the National Cancer Institute Cooperative Breast Cancer Tissue Resource (none of which were obtained from patients in the trastuzumab clinical studies) and a 79% concordance between the results for the two assays was reported.^{16,33} The HercepTest is a semiquantitative immunohistochemical assay to determine HER-2 protein overexpression in breast cancer tissue, as an aid in the assessment of patients for whom trastuzumab treatment is being considered. The HercepTest was developed to provide an alternative to the investigational clinical trial assay used in the trastuzumab clinical studies. It uses a primary rabbit antibody to human HER-2 protein. Only the protein membrane-staining intensity and pattern are scored in this IHC test, using a scale from 0 to 3+. Results are interpreted using a light microscope, and control slides that contain human breast cancer cell lines with scores of staining intensity of 0, 1+, 2+, and 3+ are provided to validate the test. The concordance information indicate that a 3+ reading on the HercepTest was likely to correspond with a 2+ or 3+ reading on the investigative clinical trial assay, which would have met the entry criteria for the trials. However, a finding of 2+ on the HercepTest did not correlate as well with the investigative clinical trial assay results. According to the information provided in the HercepTest package insert, 2+ results by the HercepTest were negative (0-1+) by the investigative clinical trial assay in 42% (53 out of 126 specimens tested), which would not have allowed entry into the trastuzumab clinical trials.

In the HercepTest, cytoplasmic staining is considered nonspecific and thus is not included in the assessment of the staining pattern. For the membrane-staining score, the following criteria apply: If no staining is observed, or if membrane staining is observed in less than 10% of the tumor cells, the score is 0 or negative. If faint/barely perceptible membrane staining is detected in more than 10% of the tumor cells or if the cells are stained only in part of their membrane, the score is 1+ or negative. If weak to moderate complete membrane staining is observed in more than 10% of the tumor cells, the score is 2+ or weakly positive. If a strong complete membrane is observed in more than 10% of the tumor cells, the score is 3+ or strongly positive. Of note is that if normal epithelium is found to be positive, the assay should not be interpreted as valid.

Overall, the HercepTest is not intended to provide diagnostic information to the patient and physician, as it has not been validated for that purpose.

The FDA recently approved two HER-2 DNA probe kits for detection and quantification of HER-2 gene amplification in breast cancer patients.^{34,35} The first test uses the Vysis FISH technology, which enables it to directly detect both the HER-2 gene and the chromosome 17 on which the gene resides. The ability to simultaneously detect chromosome 17 provides a built-in control to determine the amplification of the HER-2 gene.³⁴ The second test uses the Oncor FISH technology. Both assays can be performed on formalin-fixed, paraffin-embedded breast tissue.³⁵ It is currently unclear whether molecular (FISH) or IHC assays provide more prognostic or predictive HER-2 data. The Table describes some of the differences between these two methodologies. Additionally, the relative importance of the two different FISH assays described above has not been demonstrated in clinical trials.

Immunohistochemistry (IHC) or Fluorescence In Situ Hybridization (FISH) Testing for HER-2 Expression	
IHC:	Assay measures protein expression using specific antibodies precisely localizes site of expression (membrane vs normal tissue vs cytoplasm).
	Test is highly sensitive.
	Specificity is moderately high (with current methods).
	Frozen or paraffin-embedded tissue can be used.
	Most of the required equipment is commonly found in hospital laboratory settings.
FISH:	Assay measures gene amplification.
	Test is highly sensitive.
	Specificity is high.
	Paraffin embedded tissue can be used.
	Some of the necessary equipment is not commonly found in hospital laboratory settings.

In addition to the full-length transmembrane product of the HER-2 gene, a truncated product corresponding to the extracellular domain (soluble receptor) mentioned above is released into the serum and can be assayed through ELISA. This testing has not yet been approved by the FDA. This soluble receptor is regulated by proteolysis and is also produced from an alternative transcript. Elevated soluble receptor has been associated with overexpression of HER-2 tumor tissue and also reflects tumor load. Serum HER-2 soluble receptor (extracellular domain [ECD]) has also been reported to neutralize the activity of anti-HER-2 antibodies targeted to the ECD, possibly allowing escape of HER-2-rich tumors from immunologic control.

Outside of clinical trials, the use of the FDA-approved methods and reagents is recommended, which will lead to some standardization and exploration of test performance.

HER-2: Therapeutic Target

Overexpression of the HER-2 protein on the surface of breast cancer cells suggested that it could be a target for a therapeutic antibody. The extracellular domain of this growth factor binds to other growth factors and the intracellular domain transmits the growth signals. A murine MAb against the extracellular domain of HER-2, muMAb 4D5, was created and found to inhibit the proliferation of human tumor cells that overexpress HER-2. Data from preclinical work demonstrated that targeted antibody therapy to HER-2 should have a key role in the treatment of metastatic breast cancer, not only as monotherapy, but also in combination with chemotherapy. This antibody to HER-2 was shown to enhance the antitumor activity of paclitaxel and doxorubicin against HER-2-overexpressing human breast cancer xenografts³⁶ and of cisplatin against human breast

and ovarian cancer cell lines.^{37,38} Through the exact mechanism of interaction between anti-HER-2 and cisplatin is unclear, a postulated mechanism is the interference of anti-HER-2 antibodies with repair of cisplatin-induced DNA damage.^{39,40}

Trastuzumab, a humanized version of muMAb 4D5, binds with high affinity to the HER-2 protein and has been shown to inhibit the proliferation of human tumor cells that overexpress HER-2 protein *in vitro* and *in vivo*. Trastuzumab (Herceptin) has been approved by the FDA for the treatment of metastatic breast cancer in patients whose tumors overexpress HER-2 protein as a single agent for those who have received one or more chemotherapy regimens, or in combination with paclitaxel for those who have not received chemotherapy for metastatic disease.¹⁶ Treatment is administered as an outpatient loading dose of 4 mg/kg by intravenous (IV) infusion over 90 minutes, with subsequent weekly doses of 2 mg/kg IV over 30 minutes.

Trastuzumab inhibits the growth of breast cancer cells overexpressing HER-2, has clinical activity, and was found to be safe in phase I and II clinical trials. A study by Baselga et al⁴¹ evaluating trastuzumab alone in patients with refractory breast cancer reported excellent tolerability and an overall response rate of 11.6%. A study by Cobleigh et al³¹ evaluated trastuzumab alone in 222 patients with refractory metastatic breast cancer. This trial again demonstrated excellent tolerability, an overall response rate of 15% (95% confidence interval: 11% to 22%), a median time to progression of 3.1 months, a median duration of response of 9.1 months, and a median survival of 12.8 months for the entire group of patients.

A phase III multinational study by Slamon et al³² evaluated 469 patients receiving first-line chemotherapy with or without trastuzumab for metastatic breast cancer. The chemotherapy regimens consisted of either cyclophosphamide 600 mg/m² plus doxorubicin 60 mg/m² (AC) or epirubicin 75 mg/m² (EC) or paclitaxel 175 mg/m². The chemotherapy was given every 21 days for at least six cycles. The trastuzumab was started concurrently with chemotherapy and was administered weekly beyond the duration of chemotherapy until either intolerable toxicity or disease progression occurred. This trial demonstrated that trastuzumab improved the time to progression (7.6 vs 4.6 months) and overall response (48% vs 32%) compared to chemotherapy alone. The one-year survival data demonstrated improvement with the addition of trastuzumab (68% vs 79%, *P*<0.01). An increased incidence of symptomatic cardiac toxicity was noted when trastuzumab was added to the anthracycline-based chemotherapy (AC or EC): 19% (for combination) vs 3% (for chemotherapy alone). On the other hand, symptomatic cardiac toxicity was not statistically increased when trastuzumab was added to paclitaxel (4% vs 1%). Further studies to evaluate the mechanism of this toxicity are ongoing.

In a recent study reported by Pegram et al⁴² of 39 patients with refractory metastatic breast cancer, the combination of trastuzumab with cisplatin led to a response rate of 24% (95% confidence interval: 12.4% to 41.6%). This response rate of 24% was believed to be suggestive of at least additive activity between cisplatin and trastuzumab, based on other phase II clinical trials demonstrating an aggregate 7% activity of single-agent cisplatin for the treatment of metastatic breast cancer.

Vogel et al⁴³ reported preliminary data on 62 of 114 patients receiving first-line therapy for metastatic breast cancer (no prior chemotherapy for stage IV disease). Patients were randomized to receive either standard trastuzumab at a loading dose of 4 mg/kg followed by 2 mg/kg per week or a loading dose of 8 mg/kg followed by 4 mg/kg/week. An overall response rate of 24% was observed without significant differences for the two dosing schedules of trastuzumab, and the agent was well tolerated. Longer follow-up data including all 114 patients enrolled in this study will be forthcoming.

These five clinical trials highlight the potential impact of this novel anticancer treatment in the management of patients with metastatic breast cancer who overexpress HER-2. Further studies to optimize the use of trastuzumab as a single agent or in combination with other therapies are ongoing.

An investigation is studying weekly paclitaxel with trastuzumab in patients with metastatic breast cancer whose tumors are either HER-2 overexpressing or not, and studies evaluating trastuzumab in combination with other agents such as docetaxel and vinorelbine are ongoing. In addition, combination studies with hormonal agents such as tamoxifen are being developed.

At our institute, the combination of paclitaxel/carboplatin and trastuzumab is being studied in metastatic breast cancer patients with 3+ (by IHC) HER-2 overexpressing tumors who are eligible to receive first-line chemotherapy for metastatic breast cancer. This study is a randomized phase II trial conducted through the NCCTG (98-32-52) and uses data from several preclinical and clinical studies as rationale. The treatment arms are paclitaxel and carboplatin administered every 3 weeks or weekly, with weekly trastuzumab. Another trial being designed at our center investigates whether trastuzumab improves the response rate to paclitaxel and carboplatin in patients whose HER-2 expression is 1+ or 2+ by IHC (N9931, described above). An analysis of the correlation between the different methodologies to assess for HER-2 expression has been incorporated as part of these trials. Additionally, using a phase III design, a multi-institutional study is evaluating whether carboplatin adds the efficacy of paclitaxel and trastuzumab in patients with 2+ and 3+ HER-2 overexpression by IHC.

Clinical Toxicities of Trastuzumab

The development of human anti-mouse antibody (HAMA) has not been a problem with this agent. Mild infusion-associated reactions have been reported in approximately 40% of patients, mostly with the first infusion. In the phase III trials, the incidence of adverse events (cardiotoxicity, leukopenia, anemia, and diarrhea) was higher in women receiving trastuzumab with or without chemotherapy compared to those receiving chemotherapy alone. While some cases of myelodysplasia or leukemia in patients treated with anthracyclines and trastuzumab have been reported, an etiological association has not been made.

The up-to-date reported overall incidence of cardiac dysfunction for trastuzumab alone is 7%, with a 5% incidence of class III-IV New York Heart Classification (NYHC) symptoms. Randomized clinical trials have demonstrated that the probability of cardiac dysfunction was highest in patients who received trastuzumab concurrently with anthracyclines (28% for the combination vs 7% for the anthracycline alone), with a statistically significant difference in class III/IV NYHC symptoms (19% vs 3%). In combination with paclitaxel, the incidence of any reported cardiac dysfunction was 11% vs 1% for paclitaxel alone, with class III/IV symptoms in 4% vs 1%, respectively. The data are not adequate to correlate specific predisposing factors or pre-existing cardiac disease or prior cardiotoxic therapy (eg, anthracycline or radiation therapy to the chest) with the risk of trastuzumab-associated cardiac dysfunction.⁴⁴ This cardiac toxicity may be serious but can be treated with standard afterload reduction and inotropic agents. The potential long-term cardiac effects of trastuzumab, either alone or in combination therapy, are currently unknown. Although it is recommended that cardiac ejection fraction be evaluated before initiating trastuzumab in the clinic, specific guidelines for monitoring cardiac function in patients receiving this therapy are yet to be developed. To eventually develop such guidelines, prospective cardiac monitoring is being added to the newly developed trials with trastuzumab.

Conclusions

Results from the clinical trials reported to date indicate that the HER-2 receptor is an important target for cancer therapies and that trastuzumab can be an effective treatment (either alone or in combination with certain chemotherapy agents). Studies are ongoing to evaluate whether there is a different response to this agent based on HER-2 expression, to optimize the testing methods for overexpression, to improve the molecular characterization of the cellular pathways of HER-2, and to optimally use trastuzumab in the management of patients with breast cancer.

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