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Trastuzumab (Herceptin) Therapy and *ERBB2 (HER2)* Genotype

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Introduction

Trastuzumab (brand name, Herceptin) is a monoclonal antibody used in the treatment of breast and gastric/gastroesophageal cancer. It targets an epidermal growth factor receptor encoded by the *ERBB2* gene, which is commonly referred to as the *HER2* gene.

The *HER2* gene is overexpressed in 15-20% of breast cancers and is also overexpressed in some cases of gastric cancer. Overall, "HER2 positive" tumors are associated with a faster rate of growth and a poorer prognosis. The use of trastuzumab in treatment regimes improves outcomes, but adverse effects of therapy include cardiac toxicity.

The FDA-approved drug label for trastuzumab states that trastuzumab should only be used to treat patients with tumors that have either HER2 protein overexpression or HER2 gene amplification, as determined by an accurate and validated FDA-approved assay, specific for the type of tumor tested (breast or gastric). This is because these are the only patients studied for whom benefit has been shown (1).

A guideline from ASCO/CAP states that oncologists must request HER2 testing on every primary invasive breast cancer (and on a metastatic site, if stage IV and if specimen available) from a patient with breast cancer to guide decision to pursue HER2-targeted therapy. This should be especially considered for a patient who previously tested HER2 negative in a primary tumor and presents with disease recurrence with clinical behavior suggestive of HER2-positive or triple-negative disease (2).

Drug: Trastuzumab (Herceptin)

Trastuzumab (brand name, Herceptin) is a monoclonal antibody that targets ERBB2 (a tyrosine kinase receptor, also known as HER2 or HER-2/neu). Trastuzumab is only used to treat specific tumors that overexpress ERBB2; these tumors are known as "HER2-positive" tumors.

Trastuzumab is typically used as an adjuvant treatment of early-stage HER2-positive breast cancer. Adjuvant therapies are used after primary treatment (such as surgery) to increase the chance of long-term disease-free survival. An example chemotherapy treatment regime is "AC→TH", which stands for Adriamycin, Cytoxan, then Taxol and Herceptin. Trastuzumab is also used in the treatment of HER2-positive metastatic breast cancer and HER2-positive metastatic gastric cancer (1).

Recently, HER2 targeted therapy has been approved by the FDA for use in the neoadjuvant setting. Neoadjuvant therapy is given before primary therapy, for example, to shrink a tumor to an operable size or to allow for breast-

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conserving surgery, and to increase the chance of long-term, disease-free survival. In the neoadjuvant setting, pertuzumab, along with trastuzumab and docetaxel (a chemotherapy agent) can be given pre-operatively (3-5).

Before treatment with trastuzumab begins, overexpression of the ERBB2 protein or amplification of the ERBB2 gene must first be determined. The FDA recommends that testing be performed using an FDA-approved test for the specific tumor type (breast or gastric tumor), in a laboratory with demonstrated proficiency with the technology being used. This is because the benefits of trastuzumab have only been proven in patients with tumors that overexpress ERBB2. In addition, although trastuzumab is generally well tolerated, the risks of treatment include infusion reactions, pulmonary toxicity, and cardiomyopathy that can result in cardiac failure (1).

Trastuzumab targets the ERBB2 receptor by binding to the juxtamembrane portion of the extracellular domain. This binding limits the receptor's ability to activate its intrinsic tyrosine kinase, which in turn, limits the activation of numerous signaling pathways that can promote the growth of cancerous cells.

A number of proposed mechanisms may underlie the anti-tumor effects of trastuzumab. One such mechanism is that trastuzumab blocks the HER3 receptor from binding to ERBB2. The ERBB2-HER3 dimerized receptor is thought to be highly active, triggering many signaling cascades in the absence of a "true" ligand (6).

Another proposed mechanism is antibody-dependent cellular cytotoxicity (ADCC). Once trastuzumab has bound to a cancer cell, immune cells (typically activated natural killer cells) bind to trastuzumab and initiate lysis of the cancer cell (7). Trastuzumab may also mediate the enhanced internalization and degradation of the ERBB2 receptor, inhibit angiogenesis, and inhibit ERBB2 shedding by preventing the cleavage of ERBB2 and the subsequent release of its extracellular domain (8, 9).

Unfortunately, breast cancer may start to progress again during trastuzumab therapy. Possible mechanisms that may facilitate disease progression during treatment include increased signaling from the HER family of receptors, an upregulation of downstream signaling pathways, and an increased level of insulin growth factor -1 receptor (10, 11).

At the time of writing, four drugs have been approved to target ERBB2 (trastuzumab, lapatinib, pertuzumab, and T-DM1), with more drugs in clinical trials.

Gene: *ERBB2 (HER2)*

The human epidermal growth factor receptor (HER) family consists of four members: the epidermal growth factor receptor (EGFR), HER2, HER3, and HER4 (see Nomenclature). All four members are transmembrane tyrosine kinase receptors, and they regulate a number of important cellular processes, such as cell growth, survival, and differentiation (12).

HER2, along with EGFR, are proto-oncogenes. Proto-oncogenes are a group of genes that, when mutated or expressed at abnormally high levels, can contribute to normal cells becoming cancerous cells. The mutated version of the proto-oncogene is called an oncogene. Proto-oncogenes typically encode proteins that stimulate cell division, inhibit cell differentiation, and halt cell death. All these are important biological processes. However, the increased production of these proteins, caused by oncogenes, can lead to the proliferation of poorly differentiated cancer cells (13).

The official gene symbol for HER2 is ERBB2, which is derived from a viral oncogene with which the receptor shares homology; "v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2." However, clinicians commonly refer to the ERBB2 gene as "HER2" (Human Epidermal growth factor Receptor 2) or "HER2/neu" (neu was the name given to the gene that caused cancer derived from a rodent neuro/glioblastoma). HER2 is an alternate gene symbol for ERBB2 and is more commonly used by the community.

One unique feature of ERBB2 compared to the other receptors in the HER family is the absence of a known ligand. It is therefore thought that this receptor may permanently be in an activated state, or it may become activated during heterodimerization with one of the other members of the HER family (9). And, one unique feature of HER3 is that it has very little enzymatic activity compared to the other tyrosine kinase receptors in the HER family. It is therefore thought that an important role of HER3 is to act as a heterodimerization partner for ERBB2 (14, 15).

When a partner such as HER3 binds to ERBB2, the heterodimer undergoes activation, which stimulates the intrinsic tyrosine kinase activity of the receptor. Autophosphorylation of several key residues of the receptor triggers the downstream activation of many commonly used growth factor signaling pathways, such as the PI3K/AKT/mTOR pathway and the RAS/RAF/MEK/ERK pathway (16, 17). Impaired ERBB2 signaling is associated with the development of neurodegenerative diseases, such as multiple sclerosis and Alzheimer disease, whereas excessive ERBB2 signaling is associated with the development of cancers.

ERBB2 is overexpressed in approximately 15-20% of breast tumors, as a result of amplification of the ERBB2 gene, and tumors with increased ERBB2 usually have a higher growth rate and more aggressive clinical behavior (2, 18-20). Although gene amplification is frequently seen in cancer and other degenerative disorders, the underlying basis for amplification remains largely unknown (21). And in the case of ERBB2, although sequence variants have been identified, it is nearly always the wildtype ERBB2 gene that is overexpressed in tumors (22). In about 1% of breast cancers, activating mutations in ERBB2 can be identified that are likely to drive tumorigenesis, without ERBB2 amplification (23).

Tumor Testing for *ERBB2 (HER2)*

There are two main methods used for HER2 testing: testing for overexpression of the HER2 protein using immunohistochemistry (IHC), or testing for gene amplification using in-situ hybridization (ISH). Each assay type has diagnostic pitfalls that must be avoided, and so the pathologist who reviews the histologic findings should determine the optimal assay (IHC or ISH) for the determination of HER2 status (2, 20).

In an IHC assay, a slice of tumor tissue is stained, along with a control sample that contains high levels of HER2. The tumor sample is then examined by light microscopy to assess the intensity of membrane staining—the amount of staining correlates with the quantity of HER2 protein and is typically graded from 0 to 3+:

- IHC 0 means no visible staining and is an "HER2 negative" result
- IHC 1+ is also an "HER2 negative" result—there is a staining pattern with weak and incomplete staining, or weak and complete staining of very few tumor cells
- IHC 2+ is an "HER2 equivocal result"—there is a staining pattern with moderately intense staining, or intense staining of very few tumor cells
- IHC 3+ is an "HER2 positive result"—there is a staining pattern with intense membrane staining on more than 10% of tumor cells, indicating a higher than normal level of HER2

For an equivacol (IHC 2+) result, either a reflex test must be ordered (same specimen using ISH), or a new test must be ordered (using a new specimen, if available, using IHC or ISH) to confirm the results.

The ISH assay, or FISH assay (fluorescence in situ hybridization), measures HER2 gene amplification by measuring HER2 DNA—the actual number of copies of the HER2 genes are counted. Under the microscope, the genes appear as red signals or dots, in a blue-stained cancer cell nucleus. The result is usually either FISH negative (normal level of HER2 gene) or FISH positive (at least twice as much as normal level of HER2 gene), but in a small number of cases the FISH result will be equivocal due to a low level of HER2 amplification. The use of a control helps distinguish between a negative result and a non-informative result caused by an error. Approximately 25% of patients who have an IHC 2+ result will have a FISH positive result (24).

For the complete algorithms for evaluation of HER2 protein expression using IHC or ISH, please see the American Society of Clinical Oncology (ASCO) / College of American Pathologists (CAP) clinical practice guideline update, located here (2)

Therapeutic Recommendations based on *HER2* Testing

This section contains excerpted[1] information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

Statement from the US Food and Drug Administration (FDA):

Detection of HER2 protein overexpression is necessary for selection of patients appropriate for trastuzumab therapy because these are the only patients studied and for whom benefit has been shown. Due to differences in tumor histopathology, use FDA-approved tests for the specific tumor type (breast or gastric/gastroesophageal adenocarcinoma) to assess HER2 protein overexpression and HER2 gene amplification. Tests should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results.

Several FDA-approved commercial assays are available to aid in the selection of breast cancer and metastatic gastric cancer patients for trastuzumab therapy. Users should refer to the package inserts of specific assay kits for information on the Intended Use, and the validation and performance of each assay.

Limitations in assay precision make it inadvisable to rely on a single method to rule out potential Herceptin benefit.

Please review the complete therapeutic recommendations that are located here: (1)

FDA-approved medical devices for HER2 are listed here.

Excerpted recommendations from the American Society of Clinical Oncology / College of American Pathologists 2013 clinical practice guideline update:

Key Recommendations for Oncologists

- Must request HER2 testing on every primary invasive breast cancer (and on metastatic site, if stage IV and if specimen available) from a patient with breast cancer to guide decision to pursue HER2-targeted therapy. This should be especially considered for a patient who previously tested HER2 negative in a primary tumor and presents with disease recurrence with clinical behavior suggestive of HER2-positive or triple-negative disease.
- Should recommend HER2-targeted therapy if HER2 test result is positive, if there is no apparent histopathologic discordance with HER2 testing and if clinically appropriate.
- Must delay decision to recommend HER2-targeted therapy if initial HER2 test result is equivocal. Reflex testing should be performed on the same specimen using the alternative test if initial HER2 test result is equivocal or on an alternative specimen.
- Must not recommend HER2-targeted therapy if HER2 test result is negative and if there is no apparent histopathologic discordance with HER2 testing.
- Should delay decision to recommend HER2-targeted therapy if HER2 status cannot be confirmed as positive or negative after separate HER2 tests (HER2 test result or results equivocal). The oncologist

[1] The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labeled all formulations containing the generic drug.

should confer with the pathologist regarding the need for additional HER2 testing on the same or another tumor specimen.
- If the HER2 test result is ultimately deemed to be equivocal, even after reflex testing with an alternative assay (i.e., if neither test is unequivocally positive), the oncologist may consider HER2-targeted therapy. The oncologist should also consider the feasibility of testing another tumor specimen to attempt to definitely establish the tumor HER2 status and guide therapeutic decisions. A clinical decision to ultimately consider HER2-targeted therapy in such cases should be individualized on the basis of patient status (comorbidities, prognosis, and so on) and patient preferences after discussing available clinical evidence.

Please review the complete therapeutic recommendations, including Key Recommendations for Pathologists that are located here (2).

Nomenclature

Common gene symbols	Alternative gene symbols
EGFR	*ERBB1* *ERBB* *HER1*
ERBB2	*HER2* *HER-2* *HER-2/neu* *NEU*
ERBB3	*HER3*
ERBB4	*HER4*

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