Metastatic Breast Cancer: Monitoring Soluble HER2 Levels

Be part of the knowledge.
HER2/neu-positive tumors account for approximately 20% of all breast cancers and these tumors carry poor prognosis. In HER2/neu-positive breast cancer, the HER2 receptor is believed to be the main driving force responsible for tumor cell proliferation, metastatic potential and poor survival. Accordingly, therapeutic targeting of HER2/neu has the potential benefit to offset the signaling process initiated by the HER2 over-expression, thus reversing the malignant features of these tumors. Agents targeting HER2 have been shown to be associated with improvement in response rate, disease free, and overall survival.

This article will discuss the data regarding the incidence of metastatic breast cancer in younger aged women and the importance of HER2 detection in breast cancer. It will also cover the data of soluble HER2 monitoring in HER2+ patients with metastatic breast cancer and appropriate patient counseling strategies to raise patient awareness of the role of HER2 monitoring in breast cancer.

Learning Objectives
After completion of this activity, participants will be able to:

• Describe the data regarding the incidence of metastatic breast cancer
• Discuss the importance of HER2 detection in breast cancer
• Define the data of soluble HER2 monitoring in HER2+ patients with metastatic breast cancer
• Identify appropriate patient counseling strategies to raise patient awareness of the role of HER2 monitoring in breast cancer

Target Audience
This course is designed to meet the Continuing Medical Education needs of the practicing breast oncologist, general oncologist, oncology nurse, and women’s health clinician.
Introduction

Globally, breast cancer is the most frequently diagnosed malignancy and is the leading cause of cancer-related death in women. Recent estimates indicate that breast cancer has the highest incidence in North America, with prevalence in the United States (US) reported as 2.8 million in 2011. Based on age-adjusted rates, the data from 2007-2011 indicate that the number of new cases of breast cancer was 124.6 per 100,000 women per year and the number of deaths was 22 per 100,000 women per year. Based on 2009-2011 statistics, the lifetime risk of developing breast cancer among women is 12.3%. According to the American Cancer Society, in 2014, breast cancer will represent 14% of all new cancer cases and 6.8% of all cancer deaths in women. For the year 2014, approximately 235,030 new cases of breast cancer are estimated and 40,430 women are expected to die from breast cancer, in the US. Although 89.2% people are known to survive breast cancer 5 years after diagnosis, survival is dependent on the stage at diagnosis. The 5 year relative survival for localized, regional, distant and unstaged breast cancer is 98.5%, 84.6%, 25.0%, and 49.8%, respectively. Metastatic breast cancer (MBC) is thus associated with the worst 5 year relative survival.

HER2 in Breast Cancer

In approximately 20% of breast cancers, human epidermal growth factor receptor 2 (HER2) protein levels are overexpressed from amplification of the HER2 gene as compared with normal cells. HER2 positivity in breast cancer is defined as evidence of protein overexpression or gene amplification (HER2 copy number or HER2/CEP17 ratio). HER2-positive breast cancers have been associated with poor prognosis and survival from increased tumor cell proliferation, and metastatic potential as result of increased signaling through the HER2 receptor. In some instances, HER2 positivity has been shown to predict resistance or sensitivity to anthracyclines and taxanes and also resistance to certain endocrine therapies. Given its important role in a subset of breast cancers, antibodies (trastuzumab, pertuzumab) and inhibitors (lapatinib, neratinib) targeting HER2 have been developed that can inhibit signaling through the HER2 receptor. The Food and Drug Administration (FDA) has approved trastuzumab in combination with paclitaxel; trastuzumab chemically linked to cytotoxic mertansine (DM1); pertuzumab in combination with trastuzumab and docetaxel in HER2 positive breast cancer; and lapatinib in combination with letrozole in postmenopausal women with hormone receptor and HER2-
Treatment with HER2 targeted therapy has been associated with improved response rate, disease free and overall survival in patients with HER2-positive cancers. Determining HER2 status is therefore crucial to guide therapy in the neoadjuvant, adjuvant, and MBC setting in order to identify patients that can benefit from HER2 targeted therapy.

**HER2 Detection in Tissue**

HER2 can be detected in tissue with a combination of immunohistochemistry (IHC) and fluorescence in-situ hybridization (FISH). While this test is semi-quantitative, it is essential and currently recommended for establishing correct HER2 status of tumors. Testing criteria for HER2-positive status include evidence of overexpression of HER2 in IHC within an area of tumor that amounts to >10% of contiguous and homogeneous tumor cells or gene amplification of HER2 copy number or HER2/CEP17 ratio by FISH based on counting at least 20 cells within the area. However, evaluation by IHC and FISH have been associated with inconsistencies between the HER2 statuses of primary versus metastatic tumors. To that end, some patients with primary tumors classified as HER2-negative have been reported to develop recurrent HER2-positive metastatic tumor. Indeed, misclassification of HER2 status has also been reported, and an average of 20% (range of 10-40%) HER2-negative tumors are believed to be misclassified. This misclassification has been attributed to limitations in testing as well as tumor drift and has been either evidenced with alternative HER2 testing approaches or with the presence of HER2-positive circulating tumor cells or in the metastatic setting. Misclassification of HER2 status can have serious therapy-related implications due to a lack of access to HER2 targeted therapies. Therefore, there has been a need for alternative and reliable HER2 testing approaches.

**Serum HER2 Test**

The serum HER2 test measures the extracellular domain of the HER2 protein (sHER2) released in the blood of both normal individuals as well as individuals with breast cancer. This is a quantitative ELISA test in which sHER2 levels ≥15 ng/mL and a change of 20% or more between 2 successive blood draws indicates HER2 positivity and progression, respectively. Using this test, up to 90% of HER2-positive MBC and 10-15% of primary early stage breast cancers have sHER2 levels ≥15 ng/mL, thereby indicating higher sensitivity in MBC. Elevated sHER2 has been detected as early as up to 24 weeks before other signs of disease progression. In addition, while persistently elevated sHER2 levels are indicative of poorer progression free and overall survival after recurrence, decrease in elevated sHER2 levels is indicative of better progression free survival and longer survival after recurrence.

![FIGURE 2](image)

**Serum HER2 Test**

- Extracellular domain (ECD) of the HER2 protein is released in the blood (sHER2)
- Measured in the serum of both normal individuals and individuals with breast cancer
- Quantitative ELISA test (elevated sHER2 levels ≥15 ng/mL and a change of 20% or more between 2 successive blood draws is significant)
- FDA approved in 2000

![FIGURE 3](image)

**Elevated sHER2 in Progressive Disease**

- Persistently high levels or lack of decline
- Early indicator of progression (detected as early as 3 weeks to up to 24 weeks before actual signs of recurrence)
- Persistently elevated sHER2 levels also indicative of poorer progression free and overall survival after recurrence
- Conversely, decrease in elevated sHER2 levels is indicative of better progression free survival and longer survival after recurrence

sHER2 in a mean of 18.5% HER2-positive early stage breast cancer and a mean of 43% HER2-positive MBC. This meta-analysis also corroborated that higher circulating sHER2 correlates with inferior progression free and overall survival, and poor response to therapy. Similarly, a serial increase in sHER2 preceded the appearance of metastases and longitudinal sHER2 changes predicted the clinical course of underlying disease.\textsuperscript{12} [Figure 4]. The sHER2 test has also shown promise in monitoring of MBC and in determining response to trastuzumab and lapatinib therapy.\textsuperscript{17-20}

This test was approved by the FDA in 2000 for use in the management and monitoring of women with MBC.\textsuperscript{21} Despite FDA approval, some studies do not recommend the sHER2 test for clinical use due to variability in the clinical prevalence of increased concentrations of sHER2 and inconsistencies in correlation with clinical outcomes.\textsuperscript{22,23} The most recent American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines for HER2 testing in breast cancer do not recommend sHER2 testing for clinical use.\textsuperscript{9} Indeed, larger sHER2 clinical studies are therefore warranted to clarify the role of sHER2 testing. In spite of the controversies, a plethora of studies support the utility of sHER2 testing as a complement to IHC/FISH in early stage disease, and as a prognostic indicator to assess response to treatment in MBC patients.\textsuperscript{7}

Summary

HER2 status is an important clinical parameter in guiding therapeutic decisions and outcomes in breast cancer. However, there have been reports of misclassification of HER2 status in breast cancer with immunohistochemistry and fluorescence in-situ hybridization. The serum HER2 test can be used as an aid to complement HER2 tumor status. In addition, serum HER2 levels can assist in disease prognosis for patients with MBC, with serum HER2 $\geq$15ng/mL being an indicator for poor outcomes and lower levels indicating better clinical outcomes.

REFERENCES:


