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Monitoring Soluble HER2 Levels in Patients with Metastatic Breast Cancer

Narrator:
Welcome to Project Oncology on ReachMD. This grand rounds presentation is “Monitoring Soluble HER2 Levels in Patients with Metastatic Breast Cancer”.

The faculty for this activity is Dr. Edith Perez, Deputy Director at Large of the Mayo Clinic Cancer Center in Jacksonville, FL.

Dr. Perez has nothing to disclose.

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Dr. Edith Perez:

This is Dr. Edith Perez, Deputy Director at Large for the Mayo Clinic Cancer Center. We'll present a discussion on Monitoring Soluble HER2 Levels in Patients with Metastatic Breast Cancer.

The objectives of this discussion include:

- Describe the data regarding incidence of metastatic breast cancer
- Define options for consideration of soluble HER2 monitoring in patients with HER2 positive metastatic breast cancer, and
- Identify appropriate patient counseling strategies to increase knowledge related to the availability of different types of HER2 testing

As an overview, breast cancer is a significantly common disease worldwide and also in the United States. It is the most frequently diagnosed malignancy worldwide and the leading cause of death, of cancer related deaths, specifically in women. It has quite a high incidence in North America with the numbers in the United States describing a prevalence of approximately 2.8 million persons.

A lifetime risk for breast cancer diagnosis in women at average risk of approximately 12% with annual incidence of 125 per one hundred thousand women added to an annual rate of 22.2 per one hundred thousand women. Also noticed thatbreast cancer can clearly be diagnosed in men, with statistics demonstrating approximately 2,000 new cases in the United States per year in men.

Overall breast cancer presents approximately 14% of all new cancer cases with absolute numbers of approximately 235,000 new cases of diagnosis of breast cancer and despite of all of the advances that have been made in understanding the biology of this disease as well as optimizing therapies, breast cancer still represents 6.8% of all cancer deaths in this country for absolute number of approximately 40,000 cases per year.

It is evident for multiple clinical trials that the survival for patients diagnosed with breast cancer can be very high but it's based on the stage at the time of diagnosis. Overall taking into account all stages, approximately 90% of persons diagnosed with breast cancer will survive five years after the diagnosis with the numbers being of course very, very high for patients with stage 0 disease. But the statisticsfor patients with stage 4 disease, again including all sub types of breast cancer, reflect that only approximately 25% of persons with stage 4 breast cancer are alive five years after the diagnosis. So optimization of diagnosis, management strategies as well as monitoring remain very important for optimizing patient care.

If one looks at the incidence of breast cancer by age as well as extent of the disease, the data can be rather telling in that for women who are the youngest ages, let's say 25 to 39 years of age, the incidence of breast cancer diagnosis locally, it's about negative 0.13 whereas that increases to 1.12 in women older than 39 specifically 40 for 54 years of age and up to 1.66 for women ages 70 to 84 years of age. The diagnosis of metastatic breast cancer appears actually to be noted even more in younger women at diagnosis compared to older women. This data may reflect the fact that annual mammography and sometimes now mammography in combination with tomography as well as other screening strategies are most effective as women get older. So we tend to diagnose breast cancers at an earlier stage in those women.

This information also reflects the fact that continued work to identify better screening strategies for breast cancer are necessary. Several subtypes of breast cancer have been identified over the last several years and as a very brief summary, they are the hormone receptor positive breast cancers, HER2 positive breast cancers and the so-called triple negative breast cancers.

Hormone receptor positive disease can be HER2 positive or HER2 negative. HER2 positive disease can be estrogen and/or progesterone receptor positive or negative. And then we have the triple negative tumors which we think encompass a wide range of different subtypes of breast cancer but at this time we are awaiting identification of molecular markers that could help better stratify the group of women with triple negative breast cancer as well as outline better therapeutic strategies.

But for now the management for patients with hormone receptor positive breast cancer initially relies on anti-estrogen therapy. The initial management of patients with HER2 positive breast cancer relies on anti-HER2 therapies in combination with chemotherapy. And for those with triple negative breast cancer, the essence of treatment totally relies on chemotherapy. Improvements are being made on all these different targeted approaches but more work remains to be done.

Let's look a little bit more into the biology of HER2 positive breast cancer as this is one of the main topics of today's discussion. HER2 can be defined as either HER2 gene or the HER2 protein. It is felt that the HER2 gene is an oncogene which can lead to overexpression of the HER2 protein. However it is known that there are cases in which we can measure protein overexpression but we cannot detect gene amplification.

So there may be some post translational changes that may lead to this biological phenomenon. But overall, approximately 15-20% of all cases of invasive breast cancer are deemed to be HER2 positive either by protein overexpression or gene amplification. These tumors are typically associated with poor prognosis as well as biological characteristics such as increased tumor cell proliferation, metastatic potential thus leading to poor survival.

However it is also known that HER2 status of the tumor may have some impact on the sensitivity to some of the existing chemotherapeutic agents such as anthracyclines and taxanes although the specific differences in response are still to be defined. It's also known that if the tumor is HER2 positive there may be decreased benefit from anti-estrogen therapy although we still widely recommend them in combination with anti-HER2 therapies.

Certainly in the setting of metastatic disease, the typically approach come as recommended by the American Society of Clinical Oncology is to start with chemotherapy in combination with trastuzumab. Then if the patient has good response and are stabled disease, then we would consider adding endocrine therapy as we stop the chemotherapy but continue the anti-HER2 treatment.

There are a variety of agents targeting HER2 but the most effective ones are the anti-HER2 monoclonal antibodies. There are three anti-HER2 monoclonal antibodies currently approved by regulatory agencies throughout the world include trastuzumab, pertuzumab and T-DM1. There are also tyrosine-kinase inhibitors clinically available or under consideration as part of clinical trials but the only one currently approved is lapatinib. I've noticed that evaluating the FDA approval of this agent, trastuzumab is approved in combination with paclitaxel for patients with advanced breast cancer, but trastuzumab is also approved in combination with chemotherapy for patients with early stage disease.

Pertuzumab is approved to be used in combination with trastuzumab and docetaxel for patients eligible to receive first line treatment for HER2 positive metastatic breast cancer. T-DM1 is approved for patients with refractory HER2 positive breast cancer but depending on the time from the completion of the adjuvant anti-HER2 treatment, it may even be used in the first line setting. Lapatinib is approved in combination with letrozole in post menopausal women with hormone receptor positive and HER2 positive metastatic breast cancer and it's also approved in combination with capecitabine for patients that are refractory diseased or anthracycline with taxanes as well as trastuzumab.

It is evident from a lot of research that has been performed as well as clinical trials that crucial identification of patients whose tumors are HER2 positive remains very important for better understanding of natural history as well as improving the utilization of therapeutic strategies. These decisions are important certainly in the metastatic and adjuvant setting and potentially also in the neoadjuvant setting. The classical ways to evaluate for HER2 occur in tissue specimens in which we use immunohistochemistry or in situ hybridization.

We and others have conducted several studies to optimize HER2 testing and we have participated with the American Society of Clinical Oncology in the development in HER2 testing guidelines in tissue specimens which are used on not only in the United States but also throughout the world. One interesting finding that has been identified in the last few years has been that there may be some inconsistencies between the HER2 status of the primary tumor and the HER2 status in a tumor that recurs or in the metastatic setting.

The reasons for these inconsistencies maybe various including heterogeneity of the tumor, difficulties with veracity of testing or which are relevant to patient management. Another way that has been evaluated to test for HER2 is to actually test for the extracellular domain or ECD of the HER2 protein when it is released in the blood and that's what we measure when we order the so-called serum HER2 test.

The serum HER2 test is a quantitative ELISA test defined to be elevated when the serum HER2 levels are equal to or greater than 15 nanograms per mL. Also they find this positive when there's a change of 20 percent or more between two successive blood draws. This test was FDA approved in the year 2000. The biology behind the development of this test includes that there's a mouse monoclonal antibody to capture the HER2 extracellular domain. Then there's a biotinylated mouse monoclonal antibody which then allows for the detection and the quantification in humans.

Theoretically, the serum HER2 test can be used to complement the sensitivity of immunohistochemistry on in situ hybridization in tissue specimens. Serum HER2 tests can also theoretically be useful in identifying patients with latent HER2 positive disease as well as minimizing potential opportunities for patients receiving HER2 targeted therapy. It is very important to realize that although the test has been available in the year 2000 and the variety of studies have been conducted and reported related to its potential utility, additional work remains to be done to further optimize consideration of which patients should have serum HER2 testing done.

One of the questions that is in our minds is how significant might it be that we misclassified tumors as being HER2 negative when the tumors are HER2 positive. And this is something that has led to a lot of study and unfortunately it is still evident that perhaps 10 to 15 to even 30 percent of patients' tumor specimens may be tested to be HER2 negative when in fact the tumors may be HER2 positive.

We and others published a manuscript in breast cancer research and treatment just a couple of years ago addressing this issue in which we conducted an expert round robin testing study. And we determined that the difference even amongst expert pathologists for validation of immunohistochemistry or fluorescence in situ hybridization were eight percent each. Certainly when misclassified the tumors, the patients would not have access to anti-HER2 therapies with potentially serious adverse overall patient outcome.

So one question has been raised is whether monitoring soluble HER2 levels in patients with HER2 negative disease may be beneficial but we really need to do more studies before we can make that recommendation. Various studies have started to be reported as I alluded to a few minutes ago. It's also been demonstrated as studies conducted by various groups including our own that approximately 10-15% of patients with primary early stage HER2 positive breast cancer have elevated soluble HER2 levels.

This elevated soluble HER2 level may be early indicators of progressive disease and persistently elevated soluble HER2 levels may indicate poor progression free survival after recurrence. Conversely, decreased soluble HER2 level is indicative of better progression free survival, a longer survival, after recurrence. And again, these are studies that have been published already. I recommend that physicians and allied health personnel review those data and determine whether the patient situation they may be encountering may warrant consideration of this test.

In a paper by Finn and coworkers in JCO in 2009, they demonstrated the soluble HER2 levels were clearly a prognostic in the setting of metastatic HER2 positive disease. With patients who had an elevated soluble HER2 levels, having a median progression free survival of 13.4 weeks whereas those with decreased soluble HER2 levels had a progression free survival of a median of 46.3 weeks. Additionally, a meta-analysis of soluble HER2 prevalence is consistent with not only the data related to incidence and prevalence but also the fact that higher circulating soluble HER2 levels are associated with an inferior progression free survival, inferior overall survival, as well as a lower response to therapy.

This meta-analysis also suggests that the serum increases in soluble HER2 may precede the appearance of metastasis and the longitudinal soluble HER2 changes may predict the clinical course of underlying disease. So based on the data that has been published so far as well as the biology of HER2, there's some potential considerations for the use of soluble HER2 in metastatic breast cancer monitoring.

It'll be very interesting to follow this data with some other newer techniques that are being considered but in our day-to-day practice, we don't routinely order let's say serum CA15-3 or serum CA27.29 but I would need to add that soluble HER2 may be in that same category where following patients for these markers may be indicative of tumor progression. So in a situation in which we would like to avoid radiologic tests, these blood tests are worthy of consideration.

There certainly some debate that remains related to soluble HER2 testing. They are reflected by the fact that despite FDA approval,

ASCO/CAP still do not recommend soluble HER2 testing for clinical use. It is felt that some additional work is important to better understand the variability and the prevalence of increased concentrations of soluble HER2 as well as better understanding consistencies in correlations with clinical outcome.

I've noticed that, as have you, current recommendations and despite the controversies, several studies although not all support consideration of the utility of soluble HER2 testing in patients with breast cancer both in their earlier stages as well as the advanced setting. Another thought related to recommendations is that we support additional studies be conducted to further understand the details of the potential role of soluble HER2 testing for patients.

It is also known that in patients with early stage disease in soluble HER2 may be an interesting factor for us to evaluate in the setting of not only testing the tissue for immunohistochemistry and FISH because persistent levels of soluble HER2 in a patient who has already received adjuvant therapy may be indicative of a higher probability of tumor recurrence but again, these are studies that we must conduct in a prospective fashion with a larger number of patients.

As a conclusion, monitoring soluble or serum HER2 levels in breast cancer patients who have been diagnosed with HER2 positive disease can be used as an aid to accurately assess HER2 tumor status. It's also interesting to consider whether soluble HER2 testing might be of interest in some subsets of patients with HER2 negative tumors by immunohistochemistry and ISH or where the biology characteristics still suggest that they might be HER2 positivity, but again, further studies will be necessary before we can make that an official recommendation for all patients.

As a summary conclusion, the data clearly indicates that in patients with metastatic HER2 positive breast cancer, serum soluble HER2 levels of 15 or greater nanograms per mL is a strong indicator of poor outcomes whereas lower levels indicate better clinical outcomes. So we consider serum HER2 testing as one of the well-defined prognostic markers in the setting of HER2 positive breast cancer.

Thank you very much.

Narrator:
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