



How the 2018 American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) HER2 Testing Guideline Dramatically Affects Recommended Adjuvant Therapy for Certain Breast Cancer Patients: A Case Report

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Introduction

The trials reporting that trastuzumab combined with chemotherapy reduced the relative risk of recurrence by roughly 40% compared to chemotherapy alone after surgery for patients with HER2 positive breast cancer have had an enormous impact on the outlook for this group of breast cancer patients [1,2]. The key studies included patients basically with either HER2 protein overexpression demonstrated by immunohistochemistry (IHC 3+) or HER2 gene amplification by fluorescence *in-situ* hybridization (FISH HER2/SEP17 ratio \geq 2.0).

In 2018, the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) expert panel modified the guidelines, suggesting several changes in the definition of HER2 positive breast cancer, based largely on small retrospective subgroup analyses and correlative trials [3]. The National Comprehensive Cancer Network (NCCN) Breast Cancer Panel recently endorsed those guidelines [4].

Here, I describe a patient with an invasive breast cancer that prior to 2018 would have been defined as HER2 positive (FISH ratio >2.0) but, per the 2018 ASCO/CAP guideline this same cancer is defined as HER2 negative. Had she been diagnosed months earlier, she would have been offered adjuvant trastuzumab and told that this would reduce her recurrence risk by roughly 40% compared to chemotherapy alone, based on the above landmark studies. However, based on the 2018 ASCO/CAP guideline, this same tumor is currently defined as HER2 negative, presenting a challenge in advising the patient regarding adjuvant therapy.

Case Presentation

MM is 54 year old post-menopausal patient who underwent biopsy of a left breast mass on November 9, 2018. The biopsy revealed roughly a 5 mm of invasive ductal carcinoma, grade 1-2 and additional ductal carcinoma *in-situ*. The tumor was ER positive (90%) and PR positive (88%). On January 28, 2019, she underwent a left mastectomy which showed a 0.8 cm invasive breast cancer, overall grade 2, with negative margins and a single sentinel lymph node showing no malignancy (pT1bpN0). HER2 IHC was 2+. Dual probe FISH was performed according to the 2018 ASCO/CAP recommended guidelines with HER2/SEP 17 signals ratio = 2.352 and the average HER2 signals per cancer cell nucleus = 2.822. The pathology report interpretation was "HER-2 negative" per the 2018 ASCO/CAP guidelines [3]. Quantitative mRNA assay by Oncotype DX on the definitive surgical specimen showed a recurrence score of 16 (Genomic Health, Redwood City, CA 94063 USA).

I explained to the patient that prior to the 2018 ASCO/CAP and 2019 NCCN Guidelines, her tumor would have been defined as "HER2 positive" and, as such, part of standard adjuvant therapy would involve concurrent chemotherapy together trastuzumab followed by additional trastuzumab, and that her expected benefit from this therapy would represent a roughly 40% reduction in her risk of recurrence, which, given the small size of her tumor and the expected benefit from adjuvant hormonal therapy alone would represent a small absolute reduction in recurrence risk.

We then reviewed the 2018 ASCO/CAP expert panel guideline and the 2019 NCCN guidelines, including the scientific basis for why, according to these guidelines, her tumor would currently

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be defined as “HER2 negative.” I explained that I was unsure of the value of the Oncotype DX test since the accuracy of the result is not validated in patients with tumors labelled as “HER2 positive” by the pre-2018 definition. Based on the new definitions, I told her that no adjuvant trastuzumab would be recommended.

The patient elected to proceed with no adjuvant chemotherapy or trastuzumab therapy and with adjuvant aromatase inhibitor therapy.

Discussion

Once a particular systemic adjuvant therapy is shown in a study (or studies) to benefit a particular group of patients, that same group of patients are those for whom the therapy is then endorsed or FDA approved or both. Patients like MM with invasive breast cancers showing a FISH ratio of >2.0 would have been eligible for the landmark studies showing a recurrence risk reduction of roughly 40% using trastuzumab combined with chemotherapy compared to adjuvant chemotherapy alone [1,2]. The 40% relative recurrence risk reduction benefit was so robust that in 2013 the ASCO/CAP expert panel expanded the defining criteria to include more tumors of patients to now be defined as HER2 positive, but acknowledged that limited clinical data was the basis for expanding the definition of HER2 positivity to include patients who would not have been eligible for the pivotal trials. They concluded that their decision to expand the defining criteria was made so that “the right patient receives the right treatment” [5].

In 2018, changes were again made in the HER2 positive defining criteria by the ASCO/CAP expert panel and again (as had resulted from the 2013 Guideline) these changes were endorsed by the NCCN Breast Cancer Panel [3,4]. As before, in changing the guidelines the authors largely lacked reports of studies specifically aimed at treating or not treating with trastuzumab patients like MM who formerly would have been told of the remarkable benefit to be expected through the use of adjuvant trastuzumab. The NCCN noted that “The rationale cited by the joint committee for including rare scenarios such as HER2 positivity when HER2/CEP ratio is greater than 2.0 and average copy number is less than 4.0 signals/cell is that the first generation trials of adjuvant trastuzumab included a small number of patients with HER2/CEP17 ratio greater than or equal to 2.0 and an average copy number less than 4.0 signals/cell. There is no trend in these data, suggesting that these patients were not responsive to trastuzumab” [4].

The 2018 ASCO/CAP expert panel did cite other evidence for their recommended changes, such as correlative studies and studies involving prognosis seen for patients with the HER2 testing results described in the groups affected by the changes [3]. However, none of their cited studies met the usual standard for removing an endorsement of an effective therapy when the group as a whole showed—as in the pivotal adjuvant trastuzumab trials—demonstrated such a remarkable benefit, with only modest toxicity. Also, subsequent trials leading to the FDA approval of other anti-HER2 therapy as part of adjuvant therapy for “HER2 positive” breast cancer used the pre-2018 definitions as the eligibility criteria for enrollment

[6]. Finally, the 2018 ASCO/CAP and NCCN endorsement of certain tumors now defined as HER2 negative, but formerly defined as HER2 positive (and *vice versa*) affects the use of several drugs approved in the metastatic setting. For example, highly effective Cyclin Dependent Kinase (CDK) inhibitors are FDA approved only for patients with HER negative disease. Thus, should MMs cancer recur, she will be eligible for CDK inhibitor therapy, since now her tumor is defined as HER2 negative, whereas previously she would not have been eligible for this highly effective therapy.

Conclusion

Heraclitus wrote “no man can stand in the same river twice,” since the river changes and the man changes. His wisdom is sometimes interpreted as meaning that an opportunity that is lost may be lost forever. In spite of more than 20 years of anti-HER2 therapies benefitting hundreds of thousands of woman, the best definition of HER2 positivity remains unclear, in part because of the original defining criteria used for eligibility for patient entry onto the pivotal studies and in part due to the challenges involved in doing definitive trials to study the subgroups on those trials that may not have benefited, as well as subgroups who may benefit, but were not eligible for the trials.

Testing the hypothesis that a particular subgroup will not benefit from trastuzumab while the entire group did, would be best accomplished through a study involving only patients in that subgroup randomized to receive trastuzumab or no trastuzumab or by a similar study including patients of different subgroups that is statistically powered to draw meaningful conclusions regarding the randomized use of trastuzumab versus no trastuzumab for each subgroup. Until such studies are done, the likelihood that MM would benefit from adjuvant trastuzumab remains largely unsettled.

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