Prospactive characterization of HER2-positive circulating tumor cells in patients with HER2-negative metastatic breast cancer

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Background

Women traditionally undergo tumor biopsies of their primary breast cancer at the time of initial diagnosis and the results from these biopsies are typically used to dictate care throughout the remainder of a patient’s therapy. Importantly, repeated biopsies of patients’ primary tumors to evaluate for potential HER2 overexpression are often performed post-diagnosis, with evidence that tumor phenotypes may change over time in a subset of patients. In the case of HER2, a minority of patients (3%) with HER2-negative primary breast cancers demonstrate evidence of HER2-positive cells in biopsies of the metastatic tumor tissue (1). Because of the benefits of HER2-directed therapy in HER2-positive cancers, it is critical to identify the patients whose tumors have acquired HER2 overexpression during progression and ensure that these patients receive an appropriate targeted regimen.

We hypothesize that circulating tumor cells (CTCs) will offer clinicians a non-invasive approach to molecularly characterize a patient’s tumor. Supporting this hypothesis, we have previously shown feasibility by CLIA validation of HER2 FISH on CTCs. In prior small studies by our group and others, 32-37% of patients with HER2-negative primary tumors were found to have HER2-positive CTCs (2-4). To functionally validate the significance of HER2-positive CTCs in patients with HER2-negative primary tumors, we initiated a phase II single arm study of HER2-directed therapy (trastuzumab/vinorelbine) in this patient population. We present here the results of the prospectively collected CTC screening phase of the study.

Methods

Approval for this study was obtained from the Institutional Review Board of the Dana-Farber/Harvard Cancer Center. We prospectively collected CTCs on patients with HER2-negative recurrent breast cancer between January 11, 2013 and June 4, 2014. Patients were eligible for the study if they had documented HER2-negative disease, as defined as fluorescent in situ hybridization (FISH) ratio <2.0 or 0, 1+, or 2+ by immunohistochemistry (IHC) on review of pathology records of all available primary and metastatic samples and if the HER2 copy number to CEP17 copy number was ≥2.0. If a sample was FISH positive by this definition, the patient was eligible for the treatment portion of the study.

CTCs were measured in 201 out of 311 pts (65%) (Table 1). Median number of CTCs at initial diagnosis and the results from the 311 pts (25%) had HER2-positive CTCs, with a median number of 3 HER2+ CTCs (range 1 to 21). 36% (25/69) of these pts had cytometrically distinct metastatic CTCs, with a median number of 3 HER2+ CTCs (range 1 to 21). 36% (25/69) of these pts had cytometrically distinct metastatic CTCs, with a median number of 3 HER2+ CTCs (range 1 to 21). The remaining pts (136/192) had both CK-HER2+ and CK-HER2- CTCs present. In these cases of HER2, a majority of patients (3%) with HER2-negative primary breast cancers demonstrate evidence of HER2-positive cells in biopsies of the metastatic tumor tissue (1). Because of the benefits of HER2-directed therapy in HER2-positive cancers, it is critical to identify the patients whose tumors have acquired HER2 overexpression during progression and ensure that these patients receive an appropriate targeted regimen.

The remaining pts (36/69, 53%) had only CK-/HER2 amplified CTCs present. These CK- CTC would not likely be detected with commonly used CK-based CTC capture technologies. The functional significance of CK-HER2+ CTCs in patients with clinically HER2-negative breast cancer is currently being evaluated in a prospective study with HER2-directed therapy.

Results

CTCs were observed in 201 out of 311 pts (65%) (Table 1). Median number of CTCs at initial diagnosis and the results from the 311 pts (25%) had HER2-positive CTCs, with a median number of 3 HER2+ CTCs (range 1 to 21). 36% (25/69) of these pts had cytometrically distinct metastatic CTCs, with a median number of 3 HER2+ CTCs (range 1 to 21). The remaining pts (136/192) had both CK-HER2+ and CK-HER2- CTCs present. In these cases of HER2, a majority of patients (3%) with HER2-negative primary breast cancers demonstrate evidence of HER2-positive cells in biopsies of the metastatic tumor tissue (1). Because of the benefits of HER2-directed therapy in HER2-positive cancers, it is critical to identify the patients whose tumors have acquired HER2 overexpression during progression and ensure that these patients receive an appropriate targeted regimen.

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Conclusion

- HER2 amplified CTCs are present in a subset (22%) of pts with clinically HER2-negative breast cancer.
- HER2-negative metastatic characteristics of the patient’s primary tumor were not able to predict the presence of HER2 amplified CTCs.
- The unique multi antibody CTC capture method used here identified a substantial subset of patients who had only CK-HER2 amplified CTCs (31 out of 311; 10%).
- These CK-/HER2- would not likely be detected with commonly used CK-based CTC capture technologies.
- The functional significance of CK-HER2+ and CK-HER2+ CTCs in patients with clinically HER2-negative breast cancer is currently being evaluated in a prospective study with HER2-directed therapy.

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References