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Controversy

HER2 discordance between primary and metastatic breast cancer: Assessing the clinical impact

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ABSTRACT

Background: In the setting of breast cancer relapse, treatment decisions are typically made by utilizing HER2, estrogen, and progesterone receptor expression status of the primary breast cancer. Recently, concern regarding receptor discordance has led to recommendations for rebiopsy for all cases of metastatic disease. However, whether this is an appropriate recommendation is uncertain, particularly as the clinical implications for HER2 discordance are unknown.
Methods: We performed a literature review to identify studies assessing HER2 discordance between primary and metastatic breast cancer. These studies were then reviewed for data relating to (1) impact of clinical factors on discordance rates, (2) prognostic impact of discordance, or (3) clinical outcomes from treatment alteration due to receptor discordance. Results were analyzed qualitatively.
Results: From 60 HER2 discordance studies identified, 24 contained information of interest for this review. No clear factor promoting HER2 discordance was identified. Loss of HER2 seemed to result in worse post-relapse survival and overall survival, although these data were often confounded by lack of treatment in the setting of receptor loss. Conversely, HER2 discordance was not associated with shorter DFS. Individual patients with receptor gain appear to have benefited from addition of targeted treatment, although data are limited to case reports.
Conclusion: Evidence of HER2 discordance leading to alterations in patient outcomes is limited, highlighting the need for further research in this area. Furthermore, lack of alteration in patient outcomes suggests that a more pragmatic approach to the decision to rebiopsy may be appropriate.

Introduction

In metastatic breast cancer, the gold standard for determining HER2, estrogen receptor (ER) and progesterone receptor (PgR) status is extrapolation from the primary breast cancer (PBC). However, based on potential discordance between primary and metastatic disease, reliance on PBC receptor status has been questioned, with recommendations made for routine rebiopsy of metastatic disease.[1]

Discordance: a true biological entity?

Cancers are inherently genetically unstable; thus alteration of HER2, ER and PgR expression between primary and metastatic breast cancer is theoretically sound. Numerous, predominantly retrospective studies report discordance rates of around 10–30% for ER and 20–50% for PgR, while reported HER2 discordance rates are generally lower. A study-level meta-analysis, including 26 trials and around 2,500 patients, found a discordance rate for either HER2 loss or gain of 5.5%.[2] Studies published subsequently have reported discordance rates of a similar magnitude ranging from 1% to 24%[3–23] (Supplementary Table S1).

However, 'true' discordance rates may be lower than those reported in the literature. In the vast majority of cases, data have been derived retrospectively, limiting their reliability. Retrieval of HER2 status from case notes, rather than retesting both primary and metastatic disease simultaneously, and analytical errors, including differing methods of HER2 determination, and assays performed at different times, with different protocols, and/or by different pathologists, has likely impacted on reported discordance rates. Highlighting the influence of analytic errors Perez et al. compared HER2 expression by local versus centralized HER2 assessment in tumors from 2175 patients (86%) enrolled in the phase III N9831 trial. Despite analyses being performed on the same tumor, discordance rates of 12% for FISH and 18% for IHC were

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found.[24] Subsequently, guidelines for the evaluation of HER2 were developed in a joint collaboration between the American Society of Oncology and The College of American Pathologists (CAP), recommending HER2 testing be performed in a CAP-accredited laboratory or in one that meets specified quality control assurance standards.[25] Importantly, the majority of HER2 discordance studies pre-date these recommendations, increasing the likelihood that testing inaccuracies have contributed to reported HER2 discordance rates. Finally, even in studies when analytical factors have been carefully controlled[9,11,21,26] pre-analytical factors, such as inadequate fixation time, cannot be corrected and may impact on observed findings.[27]

Acknowledging that methodological flaws exist in a number of reported studies, the concept of discordance as a true biological phenomenon is supported by the observation of increased discordance rates with progression of disease[2], with potential biological drivers of discordance being tumor heterogeneity[27–29], and clonal selection.[27] However, while discordance may truly occur with disease progression, little known about what the clinical implications of discordance might be. This literature review was undertaken to assess the evidence relating to the impact of discordance on clinical outcomes. Also of interest were potential predictive factors for HER2 discordance.

Methods

A literature search was performed on PubMed in October 2012, using the terms [breast cancer], AND [concordance OR discordance] AND [HER2 OR HER2/neu OR ERBB2], with articles then manually reviewed for any trial reporting comparison of HER2 status, with or without ER/PgR receptor status, of paired samples of primary breast cancer and metastatic recurrence. Metastatic disease included synchronous or metachronous lymph node metastases, locoregional recurrence, and/or distant metastases.

As the primary focus of this review was the clinical impact of HER2 discordance, studies assessing only ER/PgR were excluded, although studies assessing ER/PgR in addition to HER2 were included. Similarly, studies assessing bilateral breast cancer, discordance between diagnostic biopsy and PBC surgical specimen, discordance pre- and post neoadjuvant therapy, concordance of different analytical techniques, autopsy studies, studies reviewing circulating tumor cells discordance, or gene expression profiles, studies in abstract form only, or in language other than English, studies with inadequate details provided on discordance rates, and studies that could not be accessed, were excluded.

References of selected articles were reviewed, and the 'Related articles' function from pubmed was utilized to find any relevant studies not identified in the initial search. All relevant studies were then manually reviewed for any inclusion of (1) impact of clinical factors, such as adjuvant therapy, on discordance rates, (2) prognostic impact of discordance, or (3) clinical outcomes from treatment alteration due to receptor discordance. For this latter category, clinical outcomes referred to either rate of treatment alteration due to receptor discordance, or outcome from treatment alteration.

Results

After exclusion of irrelevant, unsuitable, or inaccessible articles, 60 studies reporting HER2 (with or without ER/PgR) discordance rates between primary and metastatic breast cancer specimens were identified (Supplementary Table S1), of which 23 contained information of interest for this review. Ten studies assessed potential predictive factors (Table 1), while 14 included prognostic information (Tables 2 and 3), and 14 discussed alterations in treatment (Table 4) and/or clinical outcomes due to receptor discordance (Table 5). Several studies included information in more than one category.

Effect of previous therapy

Effect of trastuzumab

While ER/PgR loss has been observed following endocrine therapy[30–32], there are minimal data supporting trastuzumab-driven HER2 loss. From four studies assessing trastuzumab effect on HER2 loss at relapse, no correlation was evident.[9,17,19,23] This lack of correlation contrasts with findings from the neoadjuvant setting. A metaanalysis assessing receptor expression in breast cancer

Table 1
Effect of adjuvant systemic therapy on rate of receptor discordance.

Author	Year	Number of paired biopsies	Site of metastasis	Discordance rates (%)			Impact of previous systemic therapy
				HER2	ER	PgR	
Duchnowska[9]	2012	120	DM (CNS)	14	29	29	• No effect from trasuzumab on HER2 discordance • No effect from CT on receptor discordance • ET induced ER/PR change (predominantly loss)
Fabi[10]	2011	137	DM/LR	10	–	–	• No effect from CT on HER2 discordance
Jensen[12]	2011	119	DM/LR	12	9	–	• No effect from CT on HER2 discordance
Liu[14]	2012	46	DM	5	30	54	• Lower discordance rates seen in patients with synchronous diagnosis of PBC and metastases compared with those receiving adjuvant therapy • Effect of trastuzumab on HER2 discordance or ET on ER discordance not reported
Macfarlane[15]	2012	160	DM/LR	5	14	–	• Receptor discordance (HER2, ER, PgR) not associated with previous adjuvant treatment[a]
Niikura[17]	2012	182	DM	24	–	–	• Increased HER discordance (loss) with previous CT, regardless of whether it was given with trastuzumab • No effect from trastuzumab on HER2 discordance
Sari[19]	2010	61	DM/LR	15	36	54	• No effect from CT on receptor discordance • No effect from trastuzumab on HER2 discordance • No effect from ET on ER discordance
Thompson[21]	2010	137	DM/LR	3	10	25	• No effect from previous treatment (ET/CT) on receptor discordance[a]
Xiao[23]	2011	66	DM/LR	15	21	–	• No effect from trastuzumab, CT or ET on HER2 discordance
Gong[34]	2005	60	DM	3	–	–	• No effect from CT on receptor discordance[a]

CNS, central nervous system; CT, chemotherapy; DM, distant metastases; ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; LR, locoregional metastases; PgR, progesterone receptor.

[a] No patient received adjuvant trastuzumab.