Clinical Utility of Circulating Tumor Cell (CTC) Enumeration-based Liquid Biopsy and HER2 CTC Assessment in Patients with Metastatic Breast Cancer: Overview of Current Available Data and Interventional Trials

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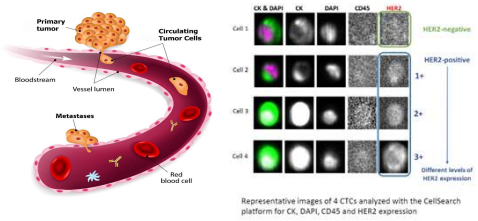
INTRODUCTION

CTC enumeration and HER2 expression

Circulating Tumor Cell (CTC) enumeration is a liquid biopsy test for which the evidence base has grown rapidly, especially in metastatic breast cancer (MBC) for which an FDA-cleared assay exists, the CellSearch® (CS) CTC platform. A lab-developed version of this assay can also assess the CTC HER2 status. In this research, we aimed to evaluate publicly-available, peer-reviewed evidence for clinical utility of CTC testing and CTC HER2 assessment in MBC patients.



Representative images of 4 CTCs analyzed with the CellSearch platform for CK, DAPI, CD45 and HER2 expression

Methods

A comprehensive search in PubMed was conducted investigating use of the CS CTC assay and the added CTC HER2 assessment. More than 150 peer-reviewed publications from 2004-2023 were reviewed for clinical utility. When the search identified preliminary study results, we also included any follow-on study results published in conference proceedings. Clinical utility was defined as clinical usefulness in: Cancer staging/ stratifying tumor aggressiveness, and prognosis; treatment selection; and Monitoring cancer progression/ treatment response.

RESULTS

CTC enumeration is prognostic and predicts treatment response

Evidence for the significance of CTCs in MBC prognosis was confirmed in numerous studies;

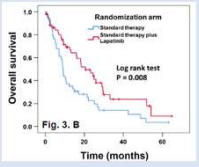
- A pooled data analysis (*n*=1,944) indicated that CTC levels at baseline and –during the course of treatment had greater prognostic utility than standard serum tumor markers.[1]
- Another pooled analysis (*n*=2,436) showed CTC enumeration can stratify Stage IV disease irrespective of standard clinical and molecular factors into two important subgroups: Stage $IV_{indolent}$ and $IV_{aggressive}$ irrespective of standard clinical and molecular factors with statistically longer overall survival (OS) for Stage $IV_{indolent}$ patients.[2]
- Subsequent studies independently confirmed this stratification approach for selecting treatment in MBC.[3,4] The STIC CTC multicenter RCT (NCT01710605) showed that CTC-guided therapy significantly improved median PFS and OS (by 5.7 mos and 16.4 mos, respectively) in the cohort MBC patients clinically assessed by physicians as low risk but identified as high risk via CTC enumeration (cohort represented 25% of total study population).

*DETECT III

The phase 3 DETECT III RCT (NCT01619111) randomized MBC patients with HER2-negative primary tumors but HER2+ CTCs to treatment with the HER2 inhibitor lapatinib in combination with standard therapy vs. standard therapy alone.

Early declines in CTC counts indicated a favorable outcome of MBC patients with initially HER2-negative primary tumors but HER2+ CTCs. HER2-targeted therapy with lapatinib had a positive impact on overall survival (OS) in these patients.

This finding could be of clinical relevance as novel HER2-targeted drugs are available and in this regard the detection of HER2+ CTCs might be a suitable parameter for treatment selection.



HER2 expression on CTCs adds information

16 studies (*n*=3,892) provided results on CTC HER2 status adding information over HER2 assessment from the primary tumor sample.

- In total, ≥1 CTC positivity is 65% (2,001/3,097); ≥5 CTC positivity is 40% (1,065 out of 2,647).
- The rate of CTCs positive for HER2 expression in patients unselected for primary tumor HER2 status ranges between 5-36%, in total 125 out of 809 patients (15%) were considered CTC HER2+ using different definitions for CTC HER2 positivity.
- HER2-positive CTCs were found in 328 out of 2,297 patients with HER2-negative primary tumors (14%).
- HER2-negative CTCs were found in 92 out of 270 patients with HER2-positive primary tumors (34%).
- Patients with HER2-positive CTCs had a worse prognosis if not treated with HER2-targeted therapy.
- When treated with HER2 targeted therapy, CTC seem to decline with concomitant improvements in outcomes.
- The prospective DETECT III trial data provided the first indication that CTC HER2 status is predictive of response to HER2 targeted therapy and hence useful to inform therapy selection*.

Ref	*n*/specs	FU	CTCs	HER2 expression definition	CTC HER2+/ PRIM HER2+/-	CTC HER2+/ PRIM HER2-	CTC HER2-/ PRIM HER2+	Findings
5	245 MBC	No FU	≥1 in 180 (73%)* ≥5 in 122 (50%)	≥5 CTC threshold with ≥1 with 3+ staining	50/245 (20%)	25/76 (33%)	13/31 (42%)	
6	290 MBC HER2-	No FU	≥1 in 179 (62%) (≥5 in 109; 35%)	≥1 CTC with strong HER2 expression		15/179 (8%)		
7	39 MBC	No FU	≥1 in 23 (59%)*	≥1 CTC HER2 Intensity 2.5-fold higher than background	14/39 (36%)			
8	103 MBC	No FU	≥1 in 90 (87%)*	≥5 CTC threshold (*n* not provided) with HER2 75% intensity above background	9/100 (9%)	6/69 (9%)	8/28 (29%)	
9	79 MBC	No FU	≥1 in 42 (53%)*	≥1 CTC with strong HER2 expression	12/42 (29%)			
10	107 MBC CTC+	28 mos	≥5 in 107 (100%)	≥1 CTC with strong or moderate HER2 expression	37/107 (35%)	27/91 (30%)	6/16 (38%)	Significantly longer PFS with CTC-HER2+ status at BL (CTC+/HER2-Tx). CTC HER2 status differs from metastatic tissue in 26%.
11	52 MBC	2 yr	≥1 in 31 (60%)*	≥1 CTC with HER2 overexpression and/or amplification	8/52 (15%)	3/22 (14%)	4/9 (44%)	Significantly shorter PFS with CTC HER2+ status at FU. CTC HER2 status changes during FU.
12	1,933 (DETECT III&IV) MBC HER2-	38 mos	≥1 in 1,217 (63%)* (≥5 in 735; 38%)	≥1 CTC with strong HER2 expression		174/1,159 (15%)		Significantly shorter OS with CTC HER2+ status.
13	154 MBC HER2- and CTC+	6 mos	≥1 in 154 (100%)	≥1 CTC with 2+ or 3+ HER2 IHC expression		45/154 (29%)		CTC HER2 status provided no prognostic impact.
14	76 MBC	1 yr	≥1 in 57 (75%)*	≥1 CTC with strong HER2 expression	19/76 (25%)	6/42 (14%)	2/15 (13%)	Significantly shorter PFS with CTC HER2+ status. CTC HER2 status changes during trastuzumab treatment.
15	101 MBC HER2+	1 yr	≥1 in 58 (57%)*	>30% of CTCs with 3+ HER2 positivity score			36/101 (36%)	Significantly longer PFS with CTC-HER2+ status at baseline (HER2 targeted therapy).
16	60 MBC HER2+	10 mos	≥1 in 27 (45%)* (≥5 in 12; 20%)	>30% of CTCs with 3+ HER2 positivity score			14/27 (52%)	Significantly longer PFS with CTC-HER2+ and HER2 targeted therapy.
17	255 MBC	3 mos	≥1 in 158 (62%) * (≥5 in 110; 43%)	≥1 CTC with HER2 expression	13/255 (5%)	6/212 (3%)	9/43 (21%)	Patients with PD had higher CTCs at 4 wks. HER2 targeted therapy seems to reduce CTC count.
18	139 MBC HER2- (≥2nd line)	1 yr	≥2 in 96 (69%)	≥2 CTC >50% of CTCs with HER2 expression		7/139 (5%)		Lapatinib therapy-for 7 HER2-/CTC HER2+ patients; one durable response. Numbers too small to draw conclusions.
19	154 (CirCe) MBC HER2- (≥3rd line)	30 mos	≥1 in 118 (77%)* (≥5 in 86; 57%)	≥1 CTC with ≥2.2 HER2/CEP17 ratio and/or 6 HER2 copies via FISH (interpretable in 79)		14/154 (10%)		T-DM1 therapy for 11 HER2-/CTC HER2+ patients; 1 out of 9 patients had PR, 4 SD.
20	105 (DETECT III) MBC HER2-/CTC HER2+	40 mos	≥1 in 105 (100%)	≥1 CTC with 2+ or 3+ HER2 IHC score		*NA*		Randomized lapatinib vs. standard therapy for 105 HER2-/CTC HER2+ patients; significantly improved OS for lapatinib.
	3,892		**≥1 in 2,001/3,097 (65%); ≥5 in 1,065/2,647 (40%) (determined from studies in which patients were CTC-unselected*)**		**162/916 (17%)**	**328/2,297 (14%)**	**92/270 (34%)**	

Abbreviations: BL = baseline; FISH = fluorescence in situ hybridization, FU = follow-up, IHC = immunohistochemistry, NA = not available, OS = overall survival, PD = progressive disease, PFS = progression-free survival, PR = partial response, PRIM = primary tumor, RFS = relapse-free survival, SD = stable disease.

REFERENCES

1. Bidard et al, Lancet Oncol. 2014
2. Cristofanilli et al, Crit Rev Hem Oncol. 2019
3. Bidard et al, JAMA Oncol. 2021
4. Bidard et al, SABCS 2022 (JCO in press)
5. Fehm et al, BCRT. 2010
6. Gasch et al, Mol Oncol. 2016
7. Ignatiadis et al, PLoS One. 2011
8. Ligthart et al, Ann Oncol. 2013
9. Aktas et al, BMC Cancer. 2016
10. Wallwiener et al, BMC Cancer. 2015
11. Hayashi et al, Int J Clin Oncol. 2012
12. Müller et al, ESMO Open. 2021
13. Beije et al, Neoplasia. 2016
14. Munzone et al, CBC. 2010
15. Zhang et al, BMC Cancer. 2016
16. Liu et al, BMC Cancer. 2013
17. Deutsch et al, BCRT. 2020
18. Pestrin et al, BCRT. 2012
19. Jacot et al, BCR. 2019
20. Fehm et al, Cancer Res. 2021

CONCLUSIONS

The peer-reviewed clinical literature confirms the clinical utility of CTC enumeration in MBC for disease stratification and monitoring, treatment selection and response prediction. CTC HER2 assessment on the same assay may provide added prognostic and predictive utility over standard HER2 assessment of the primary tumor. Based on well-powered peer-reviewed studies, CTC and CTC HER2 assay can potentially be applied in routine clinical practice for MBC as a tool for treatment decision-making and more efficient allocation of healthcare resources/cost reduction.

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