The prognostic value of chemotherapy or endocrine therapy choice according to circulating tumor cell count in HR$^+$HER2$^-$ metastatic breast cancer: a retrospective study

Bin Shao^, Huiping Li, Jiayang Zhang, Xiaoran Liu, Guohong Song, Hanfang Jiang, Ying Yan, Huan Wang, Jing Wang, Lijun Di

Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Breast Oncology, Peking University Cancer Hospital & Institute, Beijing, China

Contributions: (I) Conception and design: B Shao, H Li, L Di; (II) Administrative support: H Li; (III) Provision of study materials or patients: B Shao, H Li, J Zhang, G Song, H Jiang, Y Yan, H Wang, J Wang, L Di; (IV) Collection and assembly of data: B Shao, J Zhang, X Liu, J Wang; (V) Data analysis and interpretation: B Shao, X Liu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Huiping Li; Lijun Di. Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Breast Oncology, Peking University Cancer Hospital & Institute, No. 52 Fucheng Road, Haidian District, Beijing 100142, China. Email: huipingli2012@hotmail.com; dilijun2012@163.com.

Background: Circulating tumor cell (CTC) count have prognostic role for metastatic breast cancer (MBC). No clear biomarkers can guide selection of chemotherapy (CT) or endocrine therapy (ET) in 1st-line setting of hormone-receptor positive and human epidermal growth factor receptor 2 negative (HR$^+$HER2$^-$) MBC. The present study investigated the prognostic role CT or ET according to the CTC count in HR$^+$HER2$^-$ MBC.

Methods: We consecutively collected the data of 53 HR$^+$HER2$^-$ MBC patients who received 1st-line CT or ET, who had CTC count detected by our peptide-based nanomagnetic CTC isolation system (Pep@MNPs) from January 2014 to December 2015. The clinicopathological characteristics according the CTC count and 1st-line ET *vs.* CT were compared. Follow-up was conducted every 6 months. The primary endpoint was progression-free survival (PFS) and overall survival (OS). A Cox regression analysis was conducted to determine the prognostic roles of CTC and 1st-line therapy of ET *vs.* CT for PFS and OS.

Results: The median CTC count of the 53 patients was 2 (range, 0–18). The clinicopathological characteristics of the patients in the CTC count <2 group and the CTC count ≥2 group were similar. The patients with a CTC count <2 had a significantly longer PFS than those with a CTC count ≥2 (P=0.005, hazard ratio =4.138, 12.1 *vs.* 7.1 months). The patients who received CT had a significantly longer PFS than those who received ET (P=0.041, hazard ratio =2.721, 9.9 *vs.* 7.2 months). In the CTC count ≥2 group, the patients who received CT had a significantly longer PFS than those who received ET (P=0.048, hazard ratio =2.475, 8.7 *vs.* 6.3 months). In the CTC count <2 group, there was no significant difference in PFS between the CT and ET groups (P=0.071). Additionally, the CTC count had no significant effect on OS (P=0.116, hazard ratio =2.391, 54.2 *vs.* 34.2 months).

Conclusions: The present study showed that CTC count determined by the Pep@MNP system confirmed the prognostic value in the HR$^+$HER2$^-$ MBC patients. And it might be helpful in choosing a 1st-line treatment of CT or ET for HR$^+$HER2$^-$ MBC patients.

Keywords: Metastatic breast cancer (MBC); circulating tumor cells (CTCs); chemotherapy (CT); endocrine therapy (ET)

^ ORCID: 0000-0001-9195-8043.

Submitted Jul 05, 2022. Accepted for publication Aug 16, 2022.
doi: 10.21037/atm-22-3797
View this article at: https://dx.doi.org/10.21037/atm-22-3797

Introduction

Circulating tumor cells (CTCs) are cancer cells that circulate in the peripheral blood, originate from the primary tumor or metastasis, and are responsible for distant metastasis (1). The prognostic value of CTC counts as assessed by the Cell Search System for metastatic breast cancer (MBC) patients was first demonstrated in 2004 (2). Since then, several studies had found similar results (2-12). A pooled analysis in 2014 confirmed that a CTC count of ≥5 cells per 7.5 mL blood is an independent prognostic factor for worse progression-free survival (PFS) and overall survival (OS) in MBC patients compared with patients with a CTC count of less than 5 per 7.5 mL at baseline (13).

Our research group developed a novel nanotechnology-based CTC detecting platform, called Pep@MNPs, which has a strong CTC capture efficiency because of the high affinity between the self-designed EpCAM recognition peptide and the EPCAM molecule (KD/ 1.98×10^{-9} mol/L) (14). In a previous study, we found that the CTC enumerations at the baseline and the 1st clinical evaluation had the best prognostic value for MBC patients. Further, we found that the CTC count had prognostic value for PFS in the patients with stable disease (SD) (15).

The primary goal of MBC treatment is to prolong patient survival and improve their quality of life. A variety of factors are taken into account to produce the most effective results with minimal side effects (16). For patients with hormone-receptor positive and human epidermal growth factor receptor 2 negative (HR^+HER2^-) MBC, endocrine therapy (ET) and chemotherapy (CT) are both 1st-line treatment options. ET has the similar a survival benefit and response rate to CT; however, ET requires more time to reduce the tumor. Thus, in the absence of any clinical evidence of rapid invasive disease or visceral crisis, ET is usually the preferred option (17,18). However, to date, no clear biomarkers have been identified that can guide clinicians in the section of treatment; thus, different doctors may make different recommendation for the same patient. Therefore, the prognostic factors of ET and CT are highly needed. The outcome of the treatment is associated with molecular characteristics of tumor cells, which is determined on the primary tumor. However, the characteristics of metastatic tumor will change over time in a certain proportion of patients (19). However, tissue biopsy from metastatic lesions is invasive and impossible because of inaccessible lesions. CTC is an attractive alternative noninvasive method to test the characteristics of metastatic tumor. Printz *et al.* reported that if the treatment choice of HR^+HER2^- MBC patients was based on the CTC count rather than clinical experience, the risk of death was significantly reduced by 35% (20).

The present study sought to assess the prognostic value of 1st-line treatment of CT or ET for HR^+HER2^- MBC patients in the CTC count high and low group determined by our Pep@MNP system. We present the following article in accordance with the REMARK reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3797/rc).

Methods

Patients and study design

We retrospectively collected the data of 53 HR^+HER2^- MBC patients at the Peking University Cancer Hospital and Institute from January 2014 to December 2015 in continuous method. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethics Committee of Peking University Cancer Hospital and Institute (approval No. 2013KT29) and informed consent was taken from all the patients.

To be eligible for inclusion in this study, the patients had to meet the following inclusion criteria: (I) have been diagnosed with HR^+HER2^- MBC; (II) be undergoing 1st-line therapy (CT or ET); (III) have an expected survival time of >3 months; (IV) have measurable lesions; and (V) have provided written informed consent. The patients lost follow-up before progression were excluded. In this study, estrogen receptor (ER) and/or progesterone receptor (PR) positivity was defined as ≥1%. The cut-off point for the Ki-67 index was 20%. Luminal A-like breast cancer was defined as being ER positive, a PR value ≥20%, and a Ki-67 value <20%. Luminal B-like breast cancer was defined as being ER positive, a PR value <20%, or a Ki-67

value ≥20%. HER2 was defined as negative with an immunohistochemical score of 0, 1+ or 2+ with fluorescence in situ hybridization (FISH) (–). PFS was defined as the time interval from the start of 1st-line treatment to cancer progression, mortality from any cause. OS was defined from the start of 1st-line treatment to mortality from any cause. All patients were followed up every 6 months by telephone or electronic medical records.

The 53 patients' CTCs were detected and their clinicopathological information was recorded before the start of treatment. We collected 8.0 mL of peripheral blood from each patient in the CellSave® (Immunivest Corporation, Wilmington, DE, USA) collection tube. The samples were processed within 96 hours at room temperature, and 2.0 mL blood was used for the CTC enumeration using the Pep@MNP technique. The Pep@MNP technique has been described previously (14). The previous report demonstrated that the Pep@MNP technique has a comparable capture efficiency (reaching above 90%) and purity (reaching above 93%) for breast, prostate and liver cancers from spiked human blood. Further, the captured cells maintain their viability for further molecular biological analyses.

CTC isolation and enumeration

The CTCs were counted using the Pep@MNP method as previously described (14). In brief, iron oxide magnetic nanoparticles (MNPs) was coated with EPCAM recognition peptide via a biotineavidin interaction. For ease of detection, 2.0-mL peripheral blood samples were mixed with 5.0 mL of pre-vortexed Pep@MNPs (10 mg Fe/mL). Then the samples were incubated with gentle shaking at 37 ℃ for 30 min. The Pep@MNPseCTC complexes were subsequently isolated and washed with phosphate buffered solution at least 3 times under a magnetic field. The captured CTCs were then stained with 4',6-diamidino-2-phenylindole (DAPI), CD45-phycoerythrin and cytokeratin (CK)19-fluorescein isothiocyanate. Then the ZeissVert A1 fluorescent microscope (Carl Zeiss Microscopy GmbH, München, Germany) was used for identification and enumeration of the CTCs.

Statistical analysis

The continuous variables are presented as the median and range, while the categorical variables are presented as the number and frequency. The chi-square test or Fisher's exact test was used to compare the categorical variables. The PFS and OS were calculated using the Kaplan-Meier method and compared using the log-rank test. The multivariate Cox proportional risk regression model was used to analyze the potential confounding factors for PFS and OS. The interactive effect between CTC and treatment method was also analyzed in the multivariate Cox proportional risk regression model. All the statistical data were examined using SPSS 20.0 software package. A two-sided P value <0.05 was considered statistically significant.

Results

Patient characteristics

A total of 53 patients were included in the study. The patients had a median CTC count of 2 (range, 0–18). The baseline characteristics of the patients with a CTC count <2 (18 cases, 34%) or a CTC count ≥2 (35 cases, 66%) are summarized in *Table 1*. The patients in the 2 groups had similar clinicopathological characteristics [in terms of age, pathological type, grade, stage at surgery, ER expression, PR expression, Ki-67 expression, adjuvant ET, disease-free survival (DFS), and metastatic sites]. The patients who received neoadjuvant or adjuvant CT had a higher CTC count at the baseline than those who did not (P=0.015).

The relevance of the baseline CTC count and PFS or OS

The median follow-up time was 38.5 (range, 4.2–87.8) months. All the patients had disease progression or died during the follow-up period. In total, 6 patients were lost to follow-up of OS and 33 patients died. The median PFS and OS of all the patients was 9.0 [95% confidence interval (CI): 6.4–11.7] months and 38.8 (95% CI: 33.3–44.3) months. Next, we analyzed the influence of age, pathological grade, subtype (luminal A-like or luminal B-like breast cancer), visceral metastasis, the number of metastasis sites, 1st-line therapy (CT or ET), and the CTC count on PFS and OS (see *Tables 2,3*). The patients who received CT (38 patients, 71.7%) had a significantly longer median PFS than those who received ET (15 patients, 28.3%) in the univariate and multivariate analyses [P=0.041, hazard ratio =2.721, 9.9 *vs.* 7.2 months; see *Figure 1A*]. The median PFS of the patients with a CTC count <2 was significantly longer than that of the patients with a CTC count ≥2 (P=0.005,

Table 1 Clinicopathological characteristics of the 53 $HR^{+}HER2^{-}$ MBC patients

Characteristics	All, n (%)	CTC count <2, n (%)	CTC count ≥2, n (%)	P
Age (years)				0.270
≤45	17 (32.1)	4 (22.2)	13 (37.1)	
>45	36 (67.9)	14 (77.8)	22 (62.9)	
Histology				0.523*
IDC	47 (88.6)	17 (94.4)	30 (85.7)	
ILC	3 (5.7)	0 (0.0)	3 (8.6)	
Others	3 (5.7)	1 (5.6)	2 (5.7)	
Stage of diastase at time of diagnosis				0.266*
Stage I	5 (9.4)	2 (13.3)	3 (9.1)	
Stage II	19 (35.8)	6 (40.0)	13 (39.4)	
Stage III	17 (32.1)	3 (20.0)	14 (42.4)	
Stage IV	7 (13.2)	4 (26.7)	3 (9.1)	
Unknown	5 (9.4)	–	–	
Pathological grade				0.150*
Grade 1 or 2	23 (43.4)	9 (54.5)	14 (65.4)	
Grade 3	14 (26.4)	2 (45.5)	12 (34.6)	
Unknown	16 (30.2)	–	–	
ER				0.945
1–20%	18 (34.0)	6 (38.9)	12 (31.4)	
>20%	35 (66.0)	12 (61.1)	23 (68.6)	
PR				0.922
1–20%	26 (49.1)	9 (50.0)	17 (48.6)	
>20%	27 (50.9)	9 (50.0)	18 (51.4)	
Ki-67				1.000*
≤20%	14 (20.8)	5 (41.7)	9 (36.0)	
>20%	23 (49.1)	7 (58.3)	16 (64.0)	
Unknown	16 (30.1)	–	–	
Adjuvant CT				0.015*
Yes	46 (86.8)	13 (72.2)	33 (97.1)	
No	6 (11.3)	5 (27.8)	1 (2.9)	
Unknown	1 (1.9)	–	–	
Adjuvant ET				0.730*
Yes	41 (77.4)	13 (72.2)	28 (80.0)	
No	12 (22.6)	5 (27.8)	7 (20.0)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	All, n (%)	CTC count <2, n (%)	CTC count ≥2, n (%)	P
DFS				0.749
≤5 years	28 (60.9)	10 (66.7)	18 (58.1)	
>5 years	18 (39.1)	5 (33.3)	13 (41.9)	
Localization of metastasis				
Live metastasis	14 (26.4)	4 (22.2)	10 (28.6)	0.748*
Lung metastasis	24 (45.3)	6 (33.3)	18 (51.4)	0.210
Brain metastasis	5 (9.4)	0 (0.0)	5 (14.3)	0.153*
Lymph nodes metastasis	27 (50.9)	7 (38.9)	20 (57.1)	0.208
Bone metastasis	30 (56.6)	12 (66.7)	18 (51.4)	0.289
Chest wall or soft tissue	10 (18.9)	5 (27.8)	5 (14.3)	0.279
Others	17 (32.1)	7 (38.9)	10 (28.6)	0.446
Visceral metastasis	31 (58.5)	8 (44.4)	23 (65.7)	0.155
More than 2 site of metastasis	24 (69.8)	7 (38.9)	17 (48.6)	0.502
1st-line therapy				0.952
CT	38 (71.7)	13 (72.2)	25 (71.4)	
ET	15 (28.3)	5 (27.8)	10 (28.6)	

*, Fisher test. $HR^{+}HER2^{-}$, hormone-receptor positive and human epidermal growth factor receptor 2 negative; MBC, metastatic breast cancer; CTC, circulating tumor cell; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ER, estrogen receptor; PR, progesterone receptor; CT, chemotherapy; ET, endocrine therapy; DFS, disease-free survival.

hazard ratio =4.138, 12.1 *vs.* 7.1 months; see *Figure 1B*). In a further analysis of OS, we found that the patients with no visceral metastasis had a significantly longer OS than those with visceral metastasis (P=0.011, hazard ratio =4.300, 64.3 *vs.* 34.2 months; see *Figure 1C*). However, the CTC count had no significant effect on OS (P=0.116, hazard ratio =2.391, 54.2 *vs.* 34.2 months; see *Figure 1D*).

The CTC count predicted the 1st-line choice of CT or ET

To explore the predictive value of the CTC count on the choice of CT or ET, we analyzed the PFS of CT and ET in different CTC count groups. The clinicopathological characteristics did not differ significantly between the CT and ET groups (P>0.05; see *Table 4*). The median PFS of patients who received CT or ET did not differ significantly in the CTC count <2 group (P=0.071, 16.0 *vs.* 11.3 months; see *Figure 2A*). However, the patients who received CT had a significantly longer PFS than those who received ET (P=0.035, 8.7 *vs.* 6.3 months) in the CTC count ≥2 group (*Figure 2B*). Next, we analyzed the effects of the other potential prognostic factors (i.e., age, pathological grade, subtype, visceral metastasis, and number of metastatic sites) on PFS in the CTC count ≥2 group with a multivariate Cox proportional risk regression model. The 1st-line CT or ET significantly affected PFS in the CTC count ≥2 group (hazard ratio =2.475, P=0.048; see *Table 5*).

We further analyzed the prognostic value of the CTC count in the patients with or without visceral metastasis. In the group with visceral metastasis, the median OS of the patients with a CTC count <2 was significantly longer than that of patients with a CTC count ≥2 (P=0.008, 38.8 *vs.* 25.3 months; see *Figure 3A*). However, in the group without visceral metastasis, the CTC count had no significant effect on OS (P=0.106, – *vs.* 63.1 months; see *Figure 3B*). The median OS of the CTC count <2 group in the patients without visceral metastasis has not reached (only 3 patients of the 8 patients died).

Table 2 Univariate and multivariable analyses of the associations between the clinicopathological characteristics and PFS

Characteristics	N	PFS (months)	Univariate analysis	Multivariable analysis	
			P	Hazard ratio	P
Age (years)			0.648	1.594	0.296
≤45	17	7.1			
>45	36	10.0			
Pathological grade			0.137	1.874	0.147
Grade 1 or 2	23	9.8			
Grade 3	14	6.0			
Subtype			0.640	1.236	0.653
Luminal A-like	16	8.1			
Luminal B-like	37	9.9			
Visceral metastasis			0.124	0.852	0.688
Yes	31	7.7			
No	22	10.5			
More than 1 sites of metastasis			0.189	1.443	0.388
Yes	24	7.3			
No	29	9.9			
1st-line therapy			0.031	2.721	0.041
CT	38	9.9			
ET	15	7.2			
CTC count			0.001	4.138	0.005
<2	18	12.1			
≥2	35	7.1			

Luminal A-like was defined as ER positive, a PR value ≥20%, and a Ki-67 value <20%. Luminal B-like was defined as ER positive, a PR value <20%, or a Ki-67 value ≥20%. PFS, progression-free survival; CT, chemotherapy; ET, endocrine therapy; CTC, circulating tumor cell; ER, estrogen receptor; PR, progesterone receptor.

Discussion

In this study, we found that CT led to a significantly longer PFS than ET for patients with HR^+HER2^- MBC who had a baseline CTC count ≥2. Our results support those of a phase 3 randomized controlled trial (STIC CTC) that were presented at the 2018 San Antonio Breast Cancer Symposium in 2018 under the direction of Dr. Bidard (21). In a previous study, we showed the robust prognostic value of the CTC count using our Pep@MNP system both at the baseline and in combination with the 1st clinical evaluation time point for PFS. In the current study, we further explored whether the CTC count could be used to guide the treatment choice for patients with HR^+HER2^- MBC.

In the pooled analysis, the prognostic value of the CTC count for MBC patients has been confirmed by the highest level of evidence (13). Previous findings have consistently indicated that a baseline CTC count higher than the cut-off value of 5 cells per 7.5 mL of blood was associated with a poor prognosis (both in terms of PFS and OS) (2,9,22,23). Patients with HR^+HER2^- MBC have their own characteristics. A previous study also reported that the CTC count is closely associated with the molecular classification of BC (24). Specifically, the study reported that patients with the luminal-like $HER2^-$ subtype were less likely to be

Table 3 Univariate and multivariable analyses of the associations between the clinicopathological characteristics and OS

Characteristics	N	OS (months)	Univariate analysis	Multivariable analysis	
			P	Hazard ratio	P
Age (years)			0.210	0.717	0.534
≤45	16	36.6			
>45	31	38.8			
Pathological grade			0.531	0.966	0.947
Grade 1 or 2	20	38.1			
Grade 3	13	34.7			
Subtype			0.539	0.650	0.454
Luminal A-like	14	41.4			
Luminal B-like	33	37.0			
Visceral metastasis			0.001	4.300	0.011
Yes	29	34.2			
No	18	64.3			
More than 1 sites of metastasis			0.113	0.754	0.593
Yes	24	36.9			
No	23	51.1			
1st-line therapy			0.344	1.719	0.298
CT	33	41.4			
ET	14	31.9			
CTC count			0.004	2.391	0.116
<2	16	54.2			
≥2	31	34.2			

Luminal A-like was defined as ER positive, a PR value ≥20%, and a Ki-67 value <20%. Luminal B-like was defined as ER positive, a PR value <20%, or a Ki-67 value ≥20%. OS, overall survival; CT, chemotherapy; ET, endocrine therapy; CTC, circulating tumor cell; ER, estrogen receptor; PR, progesterone receptor.

CTC positive than those with $HER2^+$ or triple-negative breast cancer (TNBC) (24). CTC positivity was also shown to be an independent prognostic factor for shorter PFS and OS in HR^+HER2^- patients (23). Thus, we specifically analyzed the HR^+HER2^- group. The positivity of CTC was 69.8% (37/53), which showed that the Pep@MNP system had a comparable capture efficiency to that of the Cell Search system (25). In our study, we also found that the CTC count had significant prognostic value for PFS but not OS in the all patients.

This study sought to explore the role of the CTC count in guiding treatment selection for metastatic patients. The STIC CTC trial was the 1st study which reported that CTC could guide treatment choice for HR^+HER2^- MBC patients (21). This phase 3 non-inferiority study was designed to treat 778 enrolled patients who were randomly allocated to groups based on either the physician's choice or the CTC count-driven choice for their 1st-line treatment. The patients' CTC counts were assessed using the Cell Search system. In the CTC count-driven arm, patients with ≥5 CTCs were treated with CT, and patients with <5 CTCs were treated with ET. Patients in the 2 arms had a similar median PFS; that is, 13.9 (95% CI: 12.2–16.3) months in the physician's-choice arm and 15.5 (95% CI: 12.7–

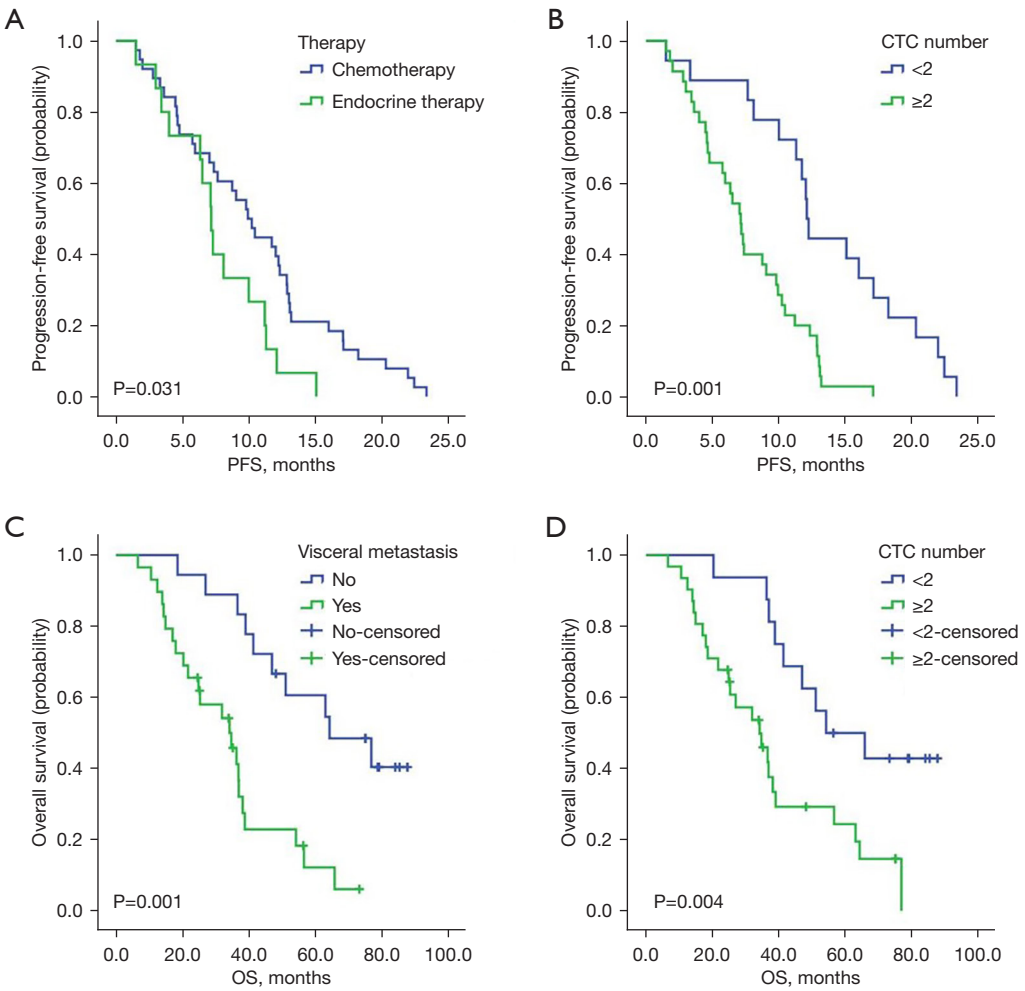

Figure 1 PFS and OS according to 1st-line therapy and the CTC count. (A) The patients who received CT had a significantly longer median PFS than those who received ET in the univariate and multivariate analyses (P=0.031, 9.9 *vs.* 7.2 months). (B) The median PFS of the patients with a CTC count <2 was significantly longer than that of patients with a CTC count ≥2 (P=0.001, 12.1 *vs.* 7.1 months). (C) The patients without visceral metastasis had a significantly longer OS than those with visceral metastasis (P=0.001, 64.3 *vs.* 34.2 months). (D) The median OS of patients with a CTC count <2 was significantly longer than that of patients with a CTC count ≥2 (P=0.004, 12.1 *vs.* 7.1 months). PFS, progression-free survival; CTC, circulating tumor cell; OS, overall survival; CT, chemotherapy; ET, endocrine therapy.

17.3) months in the CTC count-driven arm. For the patients with discordant treatment recommendations (i.e., those that were clinically low-risk but CTC-high and clinically high-risk but CTC-low), PFS and OS were longer in the patients receiving CT than ET, which indicates that the CTC count had better predictive value than other clinical characteristics.

In our study, the patients with a CTC count ≥2 who received 1st-line CT had a significantly longer PFS than those who received 1st-line ET. In the CTC count <2 group, the median PFS of the patients who received CT or ET did not differ significantly. The clinical benefit rate (CBR) [complete response (CR) + partial response + SD] in the CT group was 84.2% (32/38) and the patients achieving CR, partial response, or SD were switched to maintenance hormone therapy, which might account for the longer PFS in the CT group (P=0.031).

Previous studies have shown that CTCs are highly enriched with mesenchymal markers. Additionally, mesenchymal CTCs are associated with the therapeutic

Table 4 Distribution of the clinicopathological characteristics according to 1st-line therapy with CT or ET in the 53 HR^+HER2^- MBC patients

Characteristics	All, n (%)	CT, n (%)	ET, n (%)	P
Age (years)				0.520*
≤45	17 (32.1)	11 (28.9)	6 (40.0)	
>45	36 (67.9)	27 (71.1)	9 (60.0)	
Pathological grade				1.000*
Grade 1 or 2	23 (62.2)	17 (60.7)	6 (66.7)	
Grade 3	14 (37.8)	11 (39.3)	3 (33.3)	
Subtype				0.751*
Luminal A-like	16 (30.2)	11 (28.9)	5 (33.3)	
Luminal B-like	37 (69.8)	27 (71.1)	10 (66.7)	
DFS				0.953
≤5 years	28 (60.9)	20 (60.6)	8 (61.5)	
>5 years	18 (39.1)	13 (39.4)	5 (38.5)	
Visceral metastasis				0.448
Yes	31 (58.5)	21 (55.3)	10 (66.7)	
No	22 (41.5)	17 (44.7)	5 (33.3)	
>1 sites of metastasis				0.176
Yes	24 (45.3)	15 (39.5)	9 (60.0)	
No	29 (54.7)	23 (60.5)	6 (40.0)	
CTC count				0.952
<2	18 (34.0)	13 (34.2)	5 (33.3)	
≥2	35 (66.0)	25 (65.8)	10 (66.7)	

*, Fisher test. Luminal A-like was defined as ER positive, a PR value ≥20%, and a Ki-67 value <20%. Luminal B-like was defined as ER positive, a PR value <20%, or a Ki-67 value ≥20%. CT, chemotherapy; ET, endocrine therapy; HR^+HER2^-, hormone-receptor positive and human epidermal growth factor receptor 2 negative; MBC, metastatic breast cancer; DFS, disease-free survival; CTC, circulating tumor cell; ER, estrogen receptor; PR, progesterone receptor.

results of MBC studies (26). The total CTC counts did not differ significantly between the luminal-like breast cancer and TNBC patients. The CTCs of luminal-like breast cancer mainly comprise the epithelial cell type, while those of TNBC predominantly comprise the mesenchymal cell type (27). In our study, we did not detect the mesenchymal phenotype of CTCs, which may have more prognostic value for MBC patients. However, the STIC CTC trial assessed CTCs using the Cell Search system, which also detected the epithelial type CTCs.

This study had several limitations. First, the sample size was small. Second, most of the patients received CT rather than ET. Third, the 1st-line ET for this group of patients was administered in combination with the CDK4/6 inhibitors; however, CDK4/6 inhibitors were not used in this study. Finally, the Pep@MNP CTC detection platform failed to identify mesenchymal-like CTCs. Thus, the molecular characterization of CTCs was not performed in our study; however, this may have predictive value in the selection of treatments.

Conclusions

The present study showed that CTC count determined by the Pep@MNP system confirmed the prognostic value in the HR^+HER2^- MBC patients. And it might be helpful in

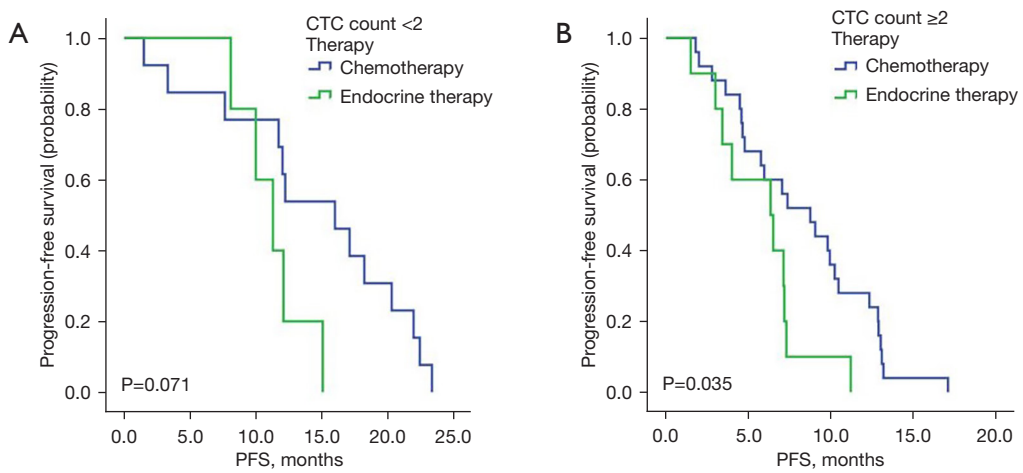

Figure 2 PFS of 1st-line CT or ET according to the CTC count. (A) The median PFS of the patients who received CT or ET did not differ significantly in the CTC count <2 group (P=0.071, 16.0 *vs.* 11.3 months). (B) The patients who received CT had a significantly longer PFS than those who received ET in the CTC count ≥2 group (P=0.035, 8.7 *vs.* 6.3 months). PFS, progression-free survival; CT, chemotherapy; ET, endocrine therapy; CTC, circulating tumor cell.

Table 5 Univariate and multivariable analysis of association between the clinicopathological characteristics and PFS in the patients with CTC ≥2/2 mL

Characteristics	N	PFS (months)	Univariate analysis	Multivariable analysis	
			P	Hazard ratio	P
Age (years)			0.197	1.428	0.384
≤45	13	6.3			
>45	22	7.4			
Pathological grade			0.492	1.912	0.217
Grade 1 or 2	14	7.0			
Grade 3	12	4.6			
Subtype			0.368	1.161	0.781
Luminal A-like	10	7.2			
Luminal B-like	25	7.0			
Visceral metastasis			0.588	1.063	0.898
Yes	23	7.1			
No	12	6.5			
More than 1 sites of metastasis			0.881	0.941	0.895
Yes	17	7.1			
No	18	7.0			
1st-line therapy			0.035	2.475	0.048
CT	25	8.7			
ET	10	6.3			

Luminal A-like was defined as ER positive, PR ≥20% and Ki-67 <20%. Luminal B-like was defined as ER positive, PR <20% or Ki-67 ≥20%. PFS, progression-free survival; CTC, circulating tumor cell; CT, chemotherapy; ET, endocrine therapy; ER, estrogen receptor; PR, progesterone receptor.

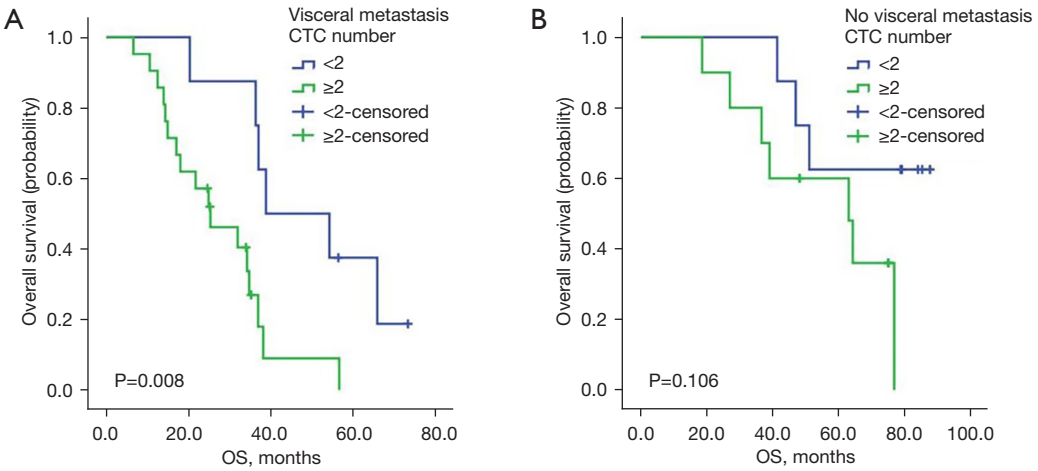

Figure 3 OS of patients with or without visceral metastasis according to the CTC count. (A) In the group with visceral metastasis, the median OS of the patients with a CTC count <2 was significantly longer than that of the patients with a CTC count ≥2 (P=0.008, 38.8 *vs.* 25.3 months). (B) In the group without visceral metastasis, the CTC count had no significant effect on OS (P=0.106, – *vs.* 63.1 months). OS, overall survival; CTC, circulating tumor cell.

choosing a 1st-line treatment of CT or ET for $HR^{+}HER2^{-}$ MBC patients, which should be further explored in future clinical studies.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3797/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3797/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3797/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethics Committee of Peking University Cancer Hospital and Institute (Approval No. 2013KT29) and informed consent was taken from all the patients.

References

1. Lianidou ES, Strati A, Markou A. Circulating tumor cells as promising novel biomarkers in solid cancers. Crit Rev Clin Lab Sci 2014;51:160-71.
2. Cristofanilli M, Budd GT, Ellis MJ, et al. Circulating tumor cells, disease progression, and survival in metastatic breast cancer. N Engl J Med 2004;351:781-91.
3. Cristofanilli M, Broglio KR, Guarneri V, et al. Circulating tumor cells in metastatic breast cancer: biologic staging beyond tumor burden. Clin Breast Cancer 2007;7:471-9.
4. Nolé F, Munzone E, Zorzino L, et al. Variation of

circulating tumor cell levels during treatment of metastatic breast cancer: prognostic and therapeutic implications. Ann Oncol 2008;19:891-7.
5. Giuliano M, Giordano A, Jackson S, et al. Circulating tumor cells as prognostic and predictive markers in metastatic breast cancer patients receiving first-line systemic treatment. Breast Cancer Res 2011;13:R67.
6. Pierga JY, Hajage D, Bachelot T, et al. High independent prognostic and predictive value of circulating tumor cells compared with serum tumor markers in a large prospective trial in first-line chemotherapy for metastatic breast cancer patients. Ann Oncol 2012;23:618-24.
7. Martín M, Custodio S, de Las Casas ML, et al. Circulating tumor cells following first chemotherapy cycle: an early and strong predictor of outcome in patients with metastatic breast cancer. Oncologist 2013;18:917-23.
8. Wallwiener M, Riethdorf S, Hartkopf AD, et al. Serial enumeration of circulating tumor cells predicts treatment response and prognosis in metastatic breast cancer: a prospective study in 393 patients. BMC Cancer 2014;14:512.
9. Smerage JB, Barlow WE, Hortobagyi GN, et al. Circulating tumor cells and response to chemotherapy in metastatic breast cancer: SWOG S0500. J Clin Oncol 2014;32:3483-9.
10. Mu Z, Wang C, Ye Z, et al. Prospective assessment of the prognostic value of circulating tumor cells and their clusters in patients with advanced-stage breast cancer. Breast Cancer Res Treat 2015;154:563-71.
11. Wang C, Mu Z, Chervoneva I, et al. Longitudinally collected CTCs and CTC-clusters and clinical outcomes of metastatic breast cancer. Breast Cancer Res Treat 2017;161:83-94.
12. Paoletti C, Li Y, Muñiz MC, et al. Significance of Circulating Tumor Cells in Metastatic Triple-Negative Breast Cancer Patients within a Randomized, Phase II Trial: TBCRC 019. Clin Cancer Res 2015;21:2771-9.
13. Bidard FC, Peeters DJ, Fehm T, et al. Clinical validity of circulating tumour cells in patients with metastatic breast cancer: a pooled analysis of individual patient data. Lancet Oncol 2014;15:406-14.
14. Bai L, Du Y, Peng J, et al. Peptide-based isolation of circulating tumor cells by magnetic nanoparticles. J Mater Chem B 2014;2:4080-8.
15. Liu XR, Shao B, Peng JX, et al. Identification of high independent prognostic value of nanotechnology based circulating tumor cell enumeration in first-line chemotherapy for metastatic breast cancer patients. Breast 2017;32:119-25.
16. Toss A, Cristofanilli M. Molecular characterization and targeted therapeutic approaches in breast cancer. Breast Cancer Res 2015;17:60.
17. Bergh J, Jönsson PE, Lidbrink EK, et al. FACT: an open-label randomized phase III study of fulvestrant and anastrozole in combination compared with anastrozole alone as first-line therapy for patients with receptor-positive postmenopausal breast cancer. J Clin Oncol 2012;30:1919-25.
18. Johnston SR, Kilburn LS, Ellis P, et al. Fulvestrant plus anastrozole or placebo versus exemestane alone after progression on non-steroidal aromatase inhibitors in postmenopausal patients with hormone-receptor-positive locally advanced or metastatic breast cancer (SoFEA): a composite, multicentre, phase 3 randomised trial. Lancet Oncol 2013;14:989-98.
19. Angus L, Smid M, Wilting SM, et al. The genomic landscape of metastatic breast cancer highlights changes in mutation and signature frequencies. Nat Genet 2019;51:1450-8.
20. Printz C. Circulating tumor cell count could be used to determine treatment of metastatic breast cancer. Cancer 2019;125:1021.
21. Bidard FC, Jacot W, Kiavue N, et al. Efficacy of Circulating Tumor Cell Count-Driven vs Clinician-Driven First-line Therapy Choice in Hormone Receptor-Positive, ERBB2-Negative Metastatic Breast Cancer: The STIC CTC Randomized Clinical Trial. JAMA Oncol 2021;7:34-41.
22. Cristofanilli M, Hayes DF, Budd GT, et al. Circulating tumor cells: a novel prognostic factor for newly diagnosed metastatic breast cancer. J Clin Oncol 2005;23:1420-30.
23. Wallwiener M, Hartkopf AD, Baccelli I, et al. The prognostic impact of circulating tumor cells in subtypes of metastatic breast cancer. Breast Cancer Res Treat 2013;137:503-10.
24. Ma S, Ling F, Gui A, et al. Predictive Value of Circulating Tumor Cells for Evaluating Short- and Long-Term Efficacy of Chemotherapy for Breast Cancer. Med Sci Monit 2017;23:4808-16.
25. Allard WJ, Matera J, Miller MC, et al. Tumor cells circulate in the peripheral blood of all major carcinomas but not in healthy subjects or patients with nonmalignant diseases. Clin Cancer Res 2004;10:6897-904.
26. Yu M, Bardia A, Wittner BS, et al. Circulating breast

tumor cells exhibit dynamic changes in epithelial and mesenchymal composition. Science 2013;339:580-4.
27. Guan X, Ma F, Li C, et al. The prognostic and therapeutic implications of circulating tumor cell phenotype detection based on epithelial-mesenchymal transition markers in the first-line chemotherapy of HER2-negative metastatic breast cancer. Cancer Commun (Lond) 2019;39:1.

(English Language Editor: L. Huleatt)

Cite this article as: Shao B, Li H, Zhang J, Liu X, Song G, Jiang H, Yan Y, Wang H, Wang J, Di L. The prognostic value of chemotherapy or endocrine therapy choice according to circulating tumor cell count in HR+HER2– metastatic breast cancer: a retrospective study. Ann Transl Med 2022;10(16):901. doi: 10.21037/atm-22-3797

