ROLE OF EARLY CIRCULATING TUMOR CELL (CTC) MONITORING FOR PREDICTION OF CLINICAL OUTCOME IN PATIENTS WITH HER-2 NEGATIVE METASTATIC BREAST CANCER RECEIVING FIRST-LINE TREATMENT WITH BEVACIZUMAB AND PACLITAXEL

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INTRODUCTION

- **Circulating tumor cells (CTC)** levels have been associated with clinical outcomes in metastatic breast cancer (MBC) (1). Indeed, CTC count is a well-established prognostic and predictive marker of efficacy/resistance in MBC (2).
- **First-line treatment** with **bevacizumab**, a potent anti-angiogenic monoclonal antibody against VEGF-A, and **paclitaxel** has been associated with improved progression-free survival (PFS) and overall response rate (ORR) in patients with **HER 2-negative MBC** (3-5), although this combination failed to significantly improve overall survival (OS).
- Availability of predictive markers offering early detection of good or poor outcome with bevacizumab and paclitaxel may provide clinicians with a valuable tool to avoid exposure to inappropriate first-line treatment.
- Limited data are available regarding the prognostic value of **early CTC level monitoring** in MBC patients treated with bevacizumab and taxane-based chemotherapy (6). Besides, no study has specifically explored the role of CTC count as an early predictive and prognostic marker in real-life MBC patients treated with bevacizumab and paclitaxel in the first-line setting.

OBJECTIVE

- We aimed to assess the ability of early CTC monitoring (after 2 cycles) for predicting clinical benefit rate (CBR), defined as the proportion of patients achieving either complete response (CR), partial response (PR) or disease stabilization (SD) ≥24 weeks (RECIST criteria) according to CTC levels after cycle 2, in patients with HER 2-negative, aggressive MBC receiving first-line treatment with bevacizumab and paclitaxel. Secondarily, the ability of early CTC count to predict ORR, PFS, and OS was also assessed.

PATIENTS AND METHODS

- This was a multicenter prospective observational study. A follow-up period of up to 24 months from first-line treatment initiation was planned.
- Patients received standard first-line treatment with bevacizumab and paclitaxel under clinical practice conditions. Accordingly, it was recommended that bevacizumab was used at a dose of 10 mg/m^2 on day 1 and 15 mg/m^2 every 4 weeks, and was maintained until disease progression, regardless of paclitaxel continuation.
- Centralized CTC determination was performed at baseline (C0) and after 2 cycles of treatment (C2) at 2 central laboratories using the CellSearch system. A cut-off of 5 CTCs/7.5ml was used to stratify patients into treatment-sensitive (<5 CTCs) and resistant (≥5 CTCs).
- Receiver operating characteristic (ROC) curves were used to identify the optimal cut-off point of CTC level, which may predict CBR and PFS. The sensitivity and specificity were assessed, and the area under the curve (AUC) was calculated. PFS was compared between the prognostic groups created according to the optimal CTC level cut-off point identified.
- Spearman's correlation analysis was applied to assess the correlation between CTCs and CEA and CA 15.3 tumor markers.

Main inclusion and exclusion criteria

- **Inclusion criteria**: patients with HER 2-negative MBC who met criteria for first-line treatment with chemotherapy plus bevacizumab by local, regional or national guidelines or authorities, measurable disease (RECIST v1.1) or non-measurable but assessable disease (exclusive blastic bone disease, pleural, pericardial or abdominal effusion as only evidence of disease), ECOG performance 0-2 and triple-negative MBC or estrogen receptor (ER)-positive tumors that need to fulfill at least one of endocrine resistance or aggressive disease criteria (at least two of the following criteria of agressiveness: a) (neo)adjuvant taxane-based regimen; b) metastatic relapse within 2 years following chemotherapy for early breast cancer; c) liver metastases; d) ≥3 organs with metastatic involvement; d) symptomatic visceral disease).
- **Main exclusion criteria**: prior chemotherapy for metastatic disease, major/minor surgery within 3 weeks before first-line treatment initiation, symptomatic brain metastases, non-measurable or assessable disease, and treatment with an investigational therapy within 4 weeks prior to study entry.

RESULTS

- Between December 2015 and March 2017, a total of 111 evaluable patients were enrolled across 22 sites in Spain. The demographic and clinical characteristics of patients are summarized in **Table 1**.

Table 1. Baseline demographic and clinical characteristics (N= 111)

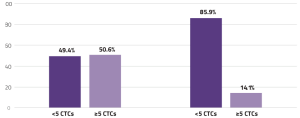
Characteristic	Value
Age, median (range), years	54.1 (46.4-61.3)
ECOG performance status, n (%)	
0	56 (50.5)
1	44 (39.6)
2	11 (9.9)
Primary tumor	
Hormone receptor status, n (%) [1]	
HR-positive (ER+ and/or PR+)	78 (70.9)
Triple negative [2]	32 (29.1)
De novo MBC, n (%)	32 (28.8)
Menopausal status at diagnosis, n (%) [3]	
Premenopausal/Postmenopausal	59 (53.6)/ 51 (46.4)
Neo/ adjuvant treatment, n (%)	78 (70.3)
Surgery, n (%)	81 (73)
Locoregional relapse, n (%)	10 (9.4)
Metastatic disease	
Time since diagnosis (days), median (range)	22 (9-103)
Metastatic sites, median (range)	3.0 (2.0-4.0)
Metastases location, n (%) [4]	
Liver	69 (62.2)
Bone	64 (57.7)
Lung	45 (40.5)
Skin-lymph nodes-breast	24 (21.6)
Tumor histology, n (%) [5,6]	
Infiltrating ductal carcinoma	67 (77.9)
Tumor grade, n (%) [7,8]	
G2	16 (23.2)
G3	34 (49.3)

CEA: Central nervous system; ECOG: Eastern Cooperative Oncology Group; ER: estrogen receptor; HR: hormone receptor; PR: progesterone receptor; [1] Missing data: n=1; [2] Triple negative: RE-/RP-/HER2-negative; [3] Missing data: n=1; [4] Most frequent metastatic sites, presented in >20 patients; [5] Other histological types: lobular carcinoma: 8 (9.3%), adenocarcinoma: 2 (2.3%), infiltrating (not otherwise specified): 6 (6.4%); [6] Missing data: n=25; [7] G1: 2 (2.9%), unknown: 17 (24.6%); [8] Missing data: n=42.

Early CTC determination

- The median CTC levels decreased from 5 (1.0-27.5) CTCs/7.5 ml at baseline to 0 (0.0-2.0) CTC after 2 cycles of treatment.
- At baseline, 50.6% of patients had elevated CTCs (≥5 CTCs). After 2 cycles of treatment, 85.9% of patients had <5 CTCs (sensitive) (**Figure 1**). Among patients with CTCs ≥5 at baseline, 78% had <5 CTCs after cycle 2.

Figure 1. CTC level (< 5 vs. ≥ 5) at baseline and after 2 cycles of treatment



Effectiveness according to CTC levels

- The CBR was 64.9% (n=63) and the ORR was 41.2% (n=40). Overall, 37 (38.1%) patients achieved a PR and 23 (23.7%) patients attained SD. Three patients (3.1%) showed a CR.
- The **CBR** was signficantly associated with CTC level after 2 cycles of first line treatment with bevacizumab and paclitaxel. The **ORR** was also significantly associated with CTC count after cycle 2 (**Table 2**).

Table 2. CBR and ORR according to CTC level after cycle 2 (N= 85)

Tumor response	CTC group	
	Sensitive (<5 CTCs) n=73	Resistant (≥5 CTCs) n=12
Clinical benefit rate, n (%)		
Yes	53 (72.6)	5 (41.7)
No	20 (27.4)	7 (58.3)
p-value [1]	0.046	
Overall response rate, n (%)		
Yes	35 (47.9)	2 (16.7)
No	38 (52.1)	10 (83.3)
p-value [1]	0.043	

CTC: Circulating tumor cells; [1] Fisher's exact test.

- With a median duration of follow-up of 17.5 (9.3-18.8) months, the median PFS was 16.6 (10.0-23.1) months while the median OS was not achieved.
- A significantly longer **PFS** was achieved among patients with <5 CTCs (sensitive) (17.4 months) compared with those with ≥5 CTCs (resistant) (5.5 months) (p=0.026) (**Figure 2**). While the median **OS** in patients with ≥ 5 CTCs (resistant) was 13 months, it was not achieved for those patients with <5 CTCs (sensitive) (p <0.001) (**Figure 3**).

Figure 2. Progression-free suvival by CTC level (< 5 vs. ≥ 5) after 2 cycles of treatment

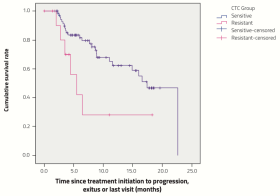
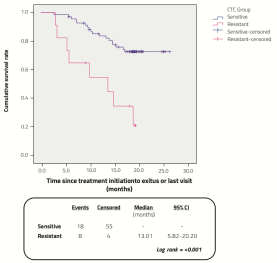


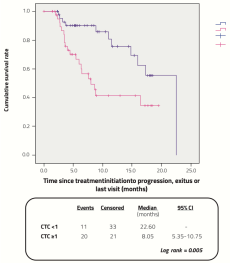
Figure 3. Overall survival by CTC level (< 5 vs. ≥ 5) after 2 cycles of treatment



Optimal CTC level cut-off for predicting CBR and PFS

- A **cut-off** point of 1 CTC/7.5 ml presented the highest overall predictive performance with a sensitivity of 60.3% and a specificity 66.7% for prediction of **CBR** (p=0.015). The AUC was 0.664 (95% CI: 0.536–0.792).
  Based on the **optimal cut-off** for predicting **CBR, PFS** was significantly longer in patients with a CTC count ≤1 (good prognosis) after cycle 2 compared with those with a CTC count >1 (poor prognosis) (22.6 vs 8.1 months; p=0.005).
- The ROC curve for predicting **PFS** based on CTC level showed a **cut-off point** of 1 CTC/7.5 ml, which yielded 64.5% of sensitivity and 61.1% of specificity (p=0.021). The AUC was 0.651 (95% CI: 0.527–0.775).
  Patients were classified into 2 **prognostic groups** based on the **optimal CTC cut-off** point for predicting **PFS**: CTC <1 (good prognosis) vs CTC ≥1 (poor prognosis). Patients with 0 CTC achieved a significantly longer PFS vs those with at least 1 CTC after 2 cycles (22.6 vs 8.1 months; p=0.005) (**Figure 4**).

Figure 4. PFS according to the prognostic groups based on the optimal cut-off for CTC level



Correlation between CTC count and CEA and CA 15.3 tumor markers

- At baseline, the median CEA and CA 15.3 levels were 5 (1.8-24.1) U/mL and 122.1 (30.3-311.7) U/mL, respectively.
- Baseline CTC levels showed a significant correlation with both CEA and CA 15.3 levels. When CTC level after 2 cycles of treatment was considered, CTC count correlated neither with CEA levels nor with CA 15.3 levels (**Table 3**).

Table 3. Correlation of CTC levels with CEA and CA 15.3 levels

	CTC count/7.5 ml at baseline		CTC count/7.5 ml after 2 cycles	
	Spearman coefficient	p-value	Spearman coefficient	p-value
Baseline CEA level (U/ml)	0.392	<0.001	0.088	0.444
Baseline CA 15.3 level (U/ml)	0.373	<0.001	0.129	0.241

Safety

- **Treatment-related adverse events (AEs)** were reported in 104 (93.7%) patients. Overall, 45 (40.5%) and 6 (5.4%) patients experienced treatment-related grade 3 and grade 4 AEs, respectively. The most frequent grade 3-4 toxicities were hypertension (15.3%), neutrophil count decreased (7.2%), and neutropenia (3.6%). Treatment-related AEs leading to death were reported in 2 patients.
- A total of 61 **serious adverse events** (**SAEs**) were reported in 37 patients (28.8%). Of SAEs reported, 27 (44.3%) were related to the study treatment. Overall, 24.3% (n=27) of patients experienced grade 3-4 SAEs. Most frequent grade 3-4 treatment-related SAEs (reported in >1 patient) were febrile neutropenia (n=4), dyspnea (n=3), neutrophil count decreased (n=2), general physical health deterioration (n=2), and pneumonia (n=2). Treatment-related SAEs leading to death were reported in 3 (2.7%) patients.
- The rate of **grade 3-4 treatment-related AEs** was not significantly different according to **CTC count** after 2 cycles of treatment (CTC <5 vs. CTC ≥5) (p =0.531).

CONCLUSIONS

- This study shows that early CTC monitoring after 2 cycles of treatment may predict tumor response and clinical outcome in terms of PFS and OS in patients receiving bevacizumab and paclitaxel as first-line treatment for HER2-negative MBC.
- Monitoring of CTC count after 2 cycles may be a useful tool for predicting resistance to bevacizumab and paclitaxel, which could enable early discontinuation of treatment to avoid inefficient treatment and unnecessary toxicity.
- This study also identified an optimal cut-off point of 1 CTC for predicting PFS, which may allow stratifying patients in good prognosis (CTC <1) and poor prognosis (CTC ≥1).

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