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In patients with metastatic breast cancer the identification of circulating tumor cells in epithelial-to-mesenchymal transition is associated with a poor prognosis.

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Abstract

BACKGROUND:

Although recent models suggest that the detection of Circulating Tumor Cells (CTC) in epithelial-to-mesenchymal transition (EM CTC) might be related to disease progression in metastatic breast cancer (MBC) patients, current detection methods are not efficient in identifying this subpopulation of cells. Furthermore, the possible association of EM CTC with both clinicopathological features and prognosis of MBC patients has still to be demonstrated. Aims of this study were: first, to optimize a DEPArray-based protocol meant to identify, quantify and sort single, viable EM CTC and, subsequently, to test the association of EM CTC frequency with clinical data.

METHODS:

This prospective observational study enrolled 56 MBC patients regardless of the line of treatment. Blood samples, depleted of CD45(pos) leukocytes, were stained with an antibody cocktail recognizing both epithelial and mesenchymal markers. Four CD45(neg) cell subpopulations were identified: cells expressing only epithelial markers (E CTC), cells co-expressing epithelial and mesenchymal markers (EM CTC), cells expressing only mesenchymal markers (MES) and cells negative for every tested marker (NEG). CTC subpopulations were quantified as both absolute cell count and relative frequency. The association of CTC subpopulations with clinicopathological features, progression free survival (PFS), and overall survival (OS) was explored by Wilcoxon-Mann-Whitney test and Univariate Cox Regression Analysis, respectively.

RESULTS:

By employing the DEPArray-based strategy, we were able to assess the presence of cells pertaining to the above-described classes in every MBC patient. We observed a significant association between specific CD45(neg) subpopulations and tumor subtypes (e.g. NEG and triple negative), proliferation (NEG and Ki67 expression) and sites of metastatic spread (e.g. E CTC and bone; NEG and brain). Importantly, the fraction of CD45(neg) cells co-expressing epithelial and mesenchymal markers (EM CTC) was significantly associated with poorer PFS and OS, computed, this latter, both from the diagnosis of a stage IV disease and from the initial CTC assessment.

CONCLUSION:

This study suggests the importance of dissecting the heterogeneity of CTC in MBC. Precise characterization of CTC could help in estimating both metastatization pattern and outcome, driving clinical decision-making and surveillance strategies.