Circulating tumor cells in metastatic breast cancer: the need for a standardized approach

Gradilone et al. [1] recently published a study addressing the prognostic and predictive value of circulating tumor cells (CTCs) in metastatic breast cancer (MBC) and its relation to drug resistance molecular profile and stemness markers.

We know that CTCs are highly relevant to the study of the biology of the metastatic process. The detection and enumeration of CTCs has been shown to be a useful tool in predicting response and clinical outcome of the treatment of MBC patients. Current evidence suggests that patients with elevated CTCs levels (5 CTCs/7.5 ml of blood) have shorter progression-free survival (PFS) and overall survival [2, 3]. Moreover, it has been shown that elevated CTC values any time in the clinical course of MBC patients is indicative of impending disease and hence CTCs monitoring is proposed as a possibly better prognostic tool compared with functional imaging [3, 4].

In the present study, the authors defined patients with positive CTCs as those having at least one EpCAM-positive cell isolated by \textit{CELLection Dynabeads} (CD45$^-$, CK8$^+$, CK20$^+$) [1], differing from previous studies that count and dichotomized CTCs levels ($<5$ or $\geq 5$) [2–4]. While Gradilone et al. demonstrated a shorter PFS for patients with positive CTCs expression, they added some controversy on the exact definition of CTC positivity.

Although the drug resistance profile predicted a poor response to chemotherapy, the results were obtained in a population treated with different regimens. It would have been of value to know details of the chemotherapy used, whether single agent or combination. Furthermore, $\sim50\%$ of patients were known to be HER2 positive but were not offered anti-HER2-targeted therapy. It also would have been interesting to provide information regarding the breast cancer molecular classification, considering that it has recently been shown to correlate with CTCs dissemination [5]. All these factors along with the small sample size and lack of a control group should be taken into consideration when interpreting these data.

Currently, the Southwest Oncology Group (SWOG) is addressing, in a prospective randomized trial, the issue of treatment decision based on CTCs blood levels. This study will determine, among women with MBC and elevated CTCs, the value of an immediate change of therapy versus waiting until classic clinic–radiological evidence of progressive disease. Both SWOG and the present study are interesting steps toward therapy individualization. However, one important issue remains open: what treatment should be chosen when CTCs levels rise, and how could this molecular chemosensitivity profile be used?

Hence, we could interrogate ourselves regarding the real importance of learning about the CTCs bioclassification, molecular portrait of the most relevant signaling pathways and their drug resistance profiles. It would, indeed, help us to overcome the aggressiveness of metastatic disease in the era of personalized medicine.

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disclosure

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references


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