EDITORIAL

Circulating Tumor Cells, a Tremendous Prognostic Factor in Inflammatory Breast Cancer

François-Clément Bidard

Affiliation of author: Circulating tumor biomarkers laboratory, Department of Medical Oncology & SiRIC, Institut Curie, Paris, France.
Correspondence to: François-Clément Bidard, MD PhD, Department of Medical Oncology, Institut Curie, 26 rue d’Ulm, 75005 Paris, France (e-mail: fcbidard@curie.fr).

In this issue of the Journal, Hall et al. report the striking prognostic impact of the detection of one or more circulating tumor cells (CTCs) per 7.5 mL of whole blood in patients who received neoadjuvant therapy for inflammatory breast cancer (IBC) (1). Although the first description of CTC can be traced back to the mid-19th century, the real onset of CTC detection in breast cancer occurred after the CellSearch test (Janssen Diagnostics) was cleared for clinical use by the US Food and Drug Administration in metastatic breast cancer (MBC). This system can detect one or more CTCs per 7.5 mL in most (~70%) but not all patients with overt metastatic disease, and MBC patients with a few CTCs detected had a statistically significantly worse survival than those with no CTC detected. As the analytic variability of the technique was estimated to be of ± two to four CTCs per 7.5 mL, the prognostic threshold was set at five or more CTCs per 7.5 mL for MBC patients (2). Numerous observational studies and a recent pooled analysis (3) demonstrated: 1) that CTC count is indeed a remarkable level-of-evidence 1 prognostic factor that complements (and does not duplicate) current clinicopathological prognostic factors in MBC and 2) that early CTC changes during chemotherapy outperform the commonly used serum marker changes for the detection of tumor resistance to chemotherapy. While the clinical validity of CTC count is now well established, the use of CTC changes as a stand-alone dynamic biomarker of resistance to chemotherapy failed to demonstrate its clinical utility in MBC patients treated with first line chemotherapy (4). Waiting for the results of other ongoing trials (5), further developments as a dynamic prognostic biomarker appear somehow compromised in MBC—opening the way for new applications in other clinical settings.

In contrast to MBC, early breast cancer appears a very promising setting to develop new prognostic biomarkers, especially those that relate to the metastatic process. As adjuvant treatment decisions are currently exclusively based on the tumor size, nodal invasion, proliferation, and subtype, detecting the presence of a micrometastatic process in distant organs appears as a powerful orthogonal tool for the metastasis risk assessment. In early breast cancer patients, the detection of one or more micrometastatic tumor cells in the bone marrow (named bone marrow–disseminated tumor cells [DTCs]) was indeed shown in the early 2000s to be an independent prognostic factor of later metastatic relapse and cancer-related death (6). These results, together with preliminary results on CTC detection, prompted a major yet under-recognized shift in the 7th TNM classification: the introduction of a cM0(i+) class for breast cancer patients with no sign of distant cancer spread but with isolated cancer cells detected in bone marrow (DTC), blood (CTC), or nonregional lymph nodes. In that regard, evidence supporting the prognostic impact of CTCs detected by the CellSearch system has been reported since 2008 in both the neoadjuvant (7-11) and adjuvant setting (12), with very consistent detection rates (~15%-20%) in non-IBC, using the one or more CTCs per 7.5 mL threshold. The largest study to date in early breast cancer was reported by Rack et al. in 2014 (13); in that study, CTC detection was performed in more than 2000 intermediate- to high-risk BC patients undergoing adjuvant chemotherapy and demonstrated a statistically significant and independent prognostic impact of CTC detection after surgery.

The study by Hall et al. in this issue of the Journal focuses on patients initially diagnosed with IBC, an uncommon yet especially aggressive type of BC characterized by skin inflammation (peau d’orange) because of the invasion of tumor cells in the skin lymphatic vessels. The biological mechanisms underlying this local tumor spread remain largely unknown and, despite the systematic use of neoadjuvant chemotherapy, IBC patients have a poor prognosis with frequent early distant metastatic relapses (14). In this context, Hall et al. detected one or more CTCs per 7.5 mL in 27% of 63 IBC patients with no overt distant metastasis after the completion of neoadjuvant chemotherapy and before mastectomy. Such high detection rate is explained by the inflammatory pattern of BC and is in accordance with the detection rates observed in the Beverly 01 and 02 trials (15). Association tests showed that CTC detection is not associated with the tumor characteristics or with...
the presence of a pathological complete response, supporting the concept that CTC count measures something completely different and orthogonal to what we currently take into account for treatment decisions. The major prognostic impact on relapse-free survival is the most striking finding of their report, with a hazard ratio (HR) of 4.2 (95% confidence interval [CI] = 1.7 to 10) between CTC-positive and CTC-negative patients. In comparison, the recently reported pooled analysis of the Beverly 01 and 02 studies on 140 nonmetastatic IBC patients with CTC detection before the start of neoadjuvant chemotherapy showed more frequent CTC detection (~40%) but with a slightly lower prognostic impact on disease-free survival (HR = 2.8, 95% CI = 1.6 to 4.7) (16). Why the major relapse-free survival difference reported by Hall et al. does not translate in a difference in overall survival is somehow unclear but is potentially because of the limited patient follow-up. Taken together, these data show that T4dNxM0(i+) BC patients have a dramatic prognosis, highlighting the need for new effective treatments, eventually targeting the micrometastatic process itself.

While the most sensitive circulating tumor DNA detection techniques can detect growing metastases during follow-up (17,18), they remain currently unable to detect a micrometastatic dissemination (or minimal residual disease) when adjuvant treatment decisions must be taken, suggesting that CTCs are to stay as a metastasis-associated biomarker in early breast cancer. So, what are the likely next steps of CTC research in that setting? As mentioned above, technological developments to increase the sensitivity of CTC assessment would be helpful in order to increase the intrapatient reproducibility (currently limited by the Poisson distribution of rare events). We should also learn from the results obtained in the metastatic setting and, rather than using the CTC test as a stand-alone prognostic biomarker, combine the test with currently validated tumor-based prognostic factors. Taking into account both the biology of the primary tumor (subtype, size, proliferation, pathological response to neoadjuvant chemotherapy...) and the micrometastatic status holds promise of greatly increasing the accuracy of adjuvant treatment decisions in early breast cancer.

Note

The author has no conflicts of interest to declare.

References