Austin Journal of Cancer and Clinical Research

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Editorial

Clinical Relevance of Circulating Tumor Cells in Early and Metastatic Breast Cancer

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Received: March 02, 2015; **Accepted:** March 17, 2015; **Published:** March 26, 2015

Editorial

Breast cancer is the most common type of cancer and the primary cause of cancer mortality in women [1]. The majority of deaths from breast cancer are due to metastasis [2]. Circulating tumor cells (CTC) are malignant cells found in peripheral blood that originate from primary or metastatic cancer tissue [3]. Since taking biopsies from metastases is often painful and technically inaccessible, CTC analysis provides the opportunity for a minimally invasive procedure for early detection of micrometastases, monitoring efficacy of adjuvant therapies and the assessment of therapeutic response [4].

Cristofanilli and colleagues reported that metastatic breast cancer patients with circulating tumor cells equal to or higher than 5 per 7.5 ml of whole blood, as compared with the patients with fewer than 5 circulating tumor cells per 7.5 ml, had a shorter median progression-free survival (PFS) and shorter overall survival (OS). The number of circulating tumor cells before treatment is an independent predictor of PFS and OS in patients with metastatic breast cancer [5]. Other studies confirmed the role of circulating tumor cells as predictors of prognosis in patients with metastatic breast cancer [6-8]. Several authors demonstrated that monitoring CTC levels could predict treatment efficacy [9,10].

The SWOG S0500 trials confirm the prognostic significance of CTCs in patients with metastatic breast cancer receiving first-line chemotherapy. Early switching to an alternate cytotoxic therapy does not improve OS for patients with persistently increased CTCs after 21 days of first-line chemotherapy. The authors conclude that more effective therapeutic agents are needed for this group of patients [11]. Martin and colleagues also report that CTC-21 (CTC counts taken on day 21) is the only independent variable significantly predicting PFS and OS. This study demonstrates that CTCs determined immediately before the second cycle of chemotherapy is an early and powerful predictor of treatment outcome in patients with metastatic breast cancer [12]. CTCs probably have a potential role in individualizing therapy [13].

Serrano and colleagues reported the results on CTC determination in peripheral blood of early breast cancer patients in the setting of neoadjuvant treatment. The presence of CTCs was found in 17 out of 24 patients before neoadjuvant chemotherapy. After neoadjuvant chemotherapy, 13 out of 24 patients were CTC-positive. Univariate and multivariate analyses demonstrated that the presence of CTCs detected both before and after neoadjuvant chemotherapy was related to OS. The double-positivity of CTC detection may be utilized as a biomarker for prognosis in early breast cancer patients [14].

In the study of Rack and colleagues, CTCs were analyzed in 2026 patients with early breast cancer before adjuvant chemotherapy and in 1492 patients after chemotherapy [15]. Before chemotherapy, CTCs were detected in 21.5% of patients. CTCs were detected more frequently in node-positive patients (22.4%) than in node-negative (19.6%) ($P<0.001$). The presence of CTCs was correlated with poor DFS, distant DFS, breast cancer-specific survival, and OS. CTCs were confirmed as independent prognostic markers in multivariate analysis for DFS and OS. CTCs were detected in 22.1% of patients after chemotherapy. The presence of persisting CTCs after chemotherapy demonstrated a negative impact on DFS and OS. The authors concluded that these results denoted the independent prognostic significance of CTCs both before and after adjuvant chemotherapy in patients with early breast cancer [15]. CTCs analysis in patients with early breast cancer could provide beneficial information for decision-making of adjuvant therapy [4].

In patients receiving neoadjuvant chemotherapy for nonmetastatic breast cancer, CTC detection of > or =1 CTC/7.5 ml before neoadjuvant chemotherapy is an independent prognostic factor for metastasis-free survival (DMFS) and OS [16].

CTC characterization has the potential to direct targeted therapies [17]. In a large prospective multicenter study, patients with metastatic breast cancer were classified into three subgroups: subgroup 1, hormone receptor-positive/HER2-negative (HorR+/HER2-); subgroup2, HER2-positive (HER2+); and subgroup 3, HorR-negative/HER2-negative (HorR-/HER2-). Median PFS of CTC-negative versus CTC-positive patients was 8.6 versus 4.3 months in HorR+/HER2- subgroup ($P < 0.001$), 7.6 versus 6.6 months in HER2+ subgroup ($P = 0.477$) and 5.8 versus 3.0 months in HorR-/HER2- subgroup ($P < 0.001$), respectively. Nevertheless, there was no correlation between primary tumor-based molecular subgroups and the influence of CTC positivity on overall survival. CTC status may be useful to recognize patients who need more effective therapy [18].

Patients with primary breast cancer enrolled in the neoadjuvant GeparQuattro trial for detecting and characterizing circulating tumor cells (CTC) before and after neoadjuvant therapy. Before neoadjuvant therapy, 5 patients (19.2%) with HER2-positive CTC were found in 26 patients with HER2-negative primary tumors. On the contrary, 5 patients (45.4%) with HER2-negative CTC were found in 11 patients

Citation: Liu MT, Chen ST and Kuo SJ. Clinical Relevance of Circulating Tumor Cells in Early and Metastatic Breast Cancer. Austin J Cancer Clin Res 2015;2(3): 1032.

with HER2-positive primary tumors. After neoadjuvant therapy, 3 patients (27.3%) with HER2-positive CTC were found in 11 patients with HER2-negative primary tumors. On the contrary, 6 patients (60.0%) with HER2-negative CTC were found in 10 patients with HER2-positive primary tumors. The authors concluded that data of the HER2 status of CTC might be beneficial for selection and observation of trastuzumab treatment [19]. In a randomized phase II study, patients with HER2 negative early breast cancer and HER2 positive CTCs were randomized to receive either trastuzumab or observation before and after adjuvant chemotherapy. Four (11%) and 15 (38%) recurrences were found in the trastuzumab and observation arm, respectively, after a median follow up time of 67.2 months (p=0.008). The median DFS was significantly higher for the trastuzumab-treated patients. Treatment with trastuzumab can eradicate chemotherapy-resistant HER2-expressing CTCs, diminish the risk of recurrence and improve the DFS [20].

Tumor cells lose their cell-to-cell adhesion and undergo epithelial-mesenchymal transition (EMT) to enhance entry into blood circulation as CTCs [21]. EMT and stem cell markers on CTCs correlate with therapy resistance [21]. These markers probably denote potential therapeutic targets [13].

CTC evaluation is a promising aspect of biomarker investigation and development of novel therapeutic agents for optimizing individually tailored therapies. More well-designed clinical trials for further investigation in this aspect might improve outcome of breast cancer patients.

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Austin J Cancer Clin Res - Volume 2 Issue 3 - 2015
ISSN : 2381-909X | www.austinpublishinggroup.com

Citation: Liu MT, Chen ST and Kuo SJ. Clinical Relevance of Circulating Tumor Cells in Early and Metastatic Breast Cancer. Austin J Cancer Clin Res 2015;2(3): 1032.