

Editorial

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

Liu MT^{1,3*}, Chen ST² and Kuo SJ²¹Department of Radiation Oncology, Changhua Christian Hospital, Taiwan²Comprehensive Breast Center and Department of General Surgery, Changhua Christian Hospital, Taiwan³Department of Radiology, Yuanpei University of Science and Technology, Taiwan***Corresponding author:** Liu MT, Department of Radiation Oncology, Changhua Christian Hospital, 135, Nan Shiao Street, Changhua, Taiwan 500, ROC, Tel: 04-7238595; Fax: 04-7232942; Email: tomgiessen@gmail.com**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 $> \text{or} = 1 \text{ CTC}/7.5 \text{ ml}$ 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-); subgroup 2, 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

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.

References

- Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin*. 2011; 61: 69-90.
- Weigelt B, Peterse JL, van 't Veer LJ. Breast cancer metastasis: markers and models. *Nat Rev Cancer*. 2005; 5: 591-602.
- Alix-Panabières C, Pantel K. Circulating tumor cells: liquid biopsy of cancer. *Clin Chem*. 2013; 59: 110-118.
- Toss A, Mu Z, Fernandez S, Cristofanilli M. CTC enumeration and characterization: moving toward personalized medicine. *Ann Transl Med*. 2014; 2: 108.
- Cristofanilli M, Budd GT, Ellis MJ, Stopeck A, Matera J, Miller MC, et al. Circulating tumor cells, disease progression, and survival in metastatic breast cancer. *N Engl J Med*. 2004; 351: 781-791.
- Nolé F, Munzone E, Zorzino L, Minchella I, Salvatici M, Botteri E, et al. Variation of circulating tumor cell levels during treatment of metastatic breast cancer: prognostic and therapeutic implications. *Ann Oncol*. 2008; 19: 891-897.
- Consoli F, Grisanti S, Amoroso V, Almici C, Verardi R, Marini M, et al. Circulating tumor cells as predictors of prognosis in metastatic breast cancer: clinical application outside a clinical trial. *Tumori*. 2011; 97: 737-742.
- Bidard FC, Peeters DJ, Fehm T, Nolé F, Gisbert-Criado R, Mavroudis D, et al. Clinical validity of circulating tumour cells in patients with metastatic breast cancer: a pooled analysis of individual patient data. *Lancet Oncol*. 2014; 15: 406-414.
- Smith BM, Slade MJ, English J, Graham H, Lüchtenborg M, Sinnott HD, et al. Response of circulating tumor cells to systemic therapy in patients with metastatic breast cancer: comparison of quantitative polymerase chain reaction and immunocytochemical techniques. *J Clin Oncol*. 2000; 18: 1432-1439.
- Liu MC, Shields PG, Warren RD, Cohen P, Wilkinson M, Ottaviano YL, et al. Circulating tumor cells: a useful predictor of treatment efficacy in metastatic breast cancer. *J Clin Oncol*. 2009; 27: 5153-5159.
- Smerage JB, Barlow WE, Hortobagyi GN, Winer EP, Leyland-Jones B, Srkalovic G, et al. Circulating tumor cells and response to chemotherapy in metastatic breast cancer: SWOG S0500. *J Clin Oncol*. 2014; 32: 3483-3489.
- Martín M, Custodio S, de Las Casas ML, García-Sáenz JÁ, de la Torre JC, Bellón-Cano JM, et al. Circulating tumor cells following first chemotherapy cycle: an early and strong predictor of outcome in patients with metastatic breast cancer. *Oncologist*. 2013; 18: 917-923.
- Castle J, Shaker H, Morris K, Tugwood JD, Kirwan CC. The significance of circulating tumour cells in breast cancer: a review. *Breast*. 2014; 23: 552-560.
- Serrano MJ, Rovira PS, Martínez-Zubiaurre I, Rodríguez MD, Fernández M, Lorente JA. Dynamics of circulating tumor cells in early breast cancer under neoadjuvant therapy. *Exp Ther Med*. 2012; 4: 43-48.
- Rack B, Schindlbeck C, Jückstock J, Andergassen U, Hepp P, Zwingers T, et al. Circulating tumor cells predict survival in early average-to-high risk breast cancer patients. *J Natl Cancer Inst*. 2014; 106.
- Bidard FC, Mathiot C, Delalogue S, Brain E, Giachetti S, de Cremoux P, et al. Single circulating tumor cell detection and overall survival in nonmetastatic breast cancer. *Ann Oncol*. 2010; 21: 729-733.
- Lindstrom LS, Karlsson E, Wilking UM, Johansson U, Hartman J, Lidbrink EK, et al. Clinically used breast cancer markers such as estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 are unstable throughout tumor progression. *J Clin Oncol*. 2012; 30: 2601-2608.
- Wallwiener M, Hartkopf AD, Baccelli I, Riethdorf S, Schott S, Pantel K, et al. The prognostic impact of circulating tumor cells in subtypes of metastatic breast cancer. *Breast Cancer Res Treat*. 2013; 137: 503-510.
- Riethdorf S, Müller V, Zhang L, Rau T, Loibl S, Komor M, et al. Detection and HER2 expression of circulating tumor cells: prospective monitoring in breast cancer patients treated in the neoadjuvant GeparQuattro trial. *Clin Cancer Res*. 2010; 16: 2634-2645.
- Georgoulas V, Bozionelou V, Agelaki S, Perraki M, Apostolaki S, Kallergi G, et al. Trastuzumab decreases the incidence of clinical relapses in patients with early breast cancer presenting chemotherapy-resistant CK-19mRNA-positive circulating tumor cells: results of a randomized phase II study. *Ann Oncol*. 2012; 23: 1744-1750.
- Krawczyk N, Meier-Stiegen F, Banys M, Neubauer H, Ruckhaeberle E, Fehm T. Expression of stem cell and epithelial-mesenchymal transition markers in circulating tumor cells of breast cancer patients. *Biomed Res Int*. 2014; 2014: 415721.