

## Emerging role of circulating tumor cells in cancer management

Circulating tumor cells (CTCs) play a crucial role in the metastatic cascade, tumor dissemination and progression. CTCs represent a unique biomarker and are different from any of existing cancer biomarkers as they represent a sampling of the patient's tumor. Prognostic value of CTCs was demonstrated in numerous clinical trials in primary and metastatic breast cancer patients. Several trials are ongoing aimed to demonstrate clinical utility of CTCs detection and profiling to facilitate rational treatment decisions for breast cancer patients.

The main course of death for cancer patients is the development of distant metastatic disease that is difficult to predict and diagnose in the early stages. In last two decades, numerous predictive and prognostic biomarkers were identified and reported in cancer including CTCs. Each potential biomarker in cancer should demonstrate technical feasibility of assessment, analytical and clinical validity and clinical utility. CTCs represent a unique biomarker and are different from any of existing cancer biomarkers as they represent a sampling of the patient's tumor and an integrative part of cancer disease and tumor burden. Moreover, they play a crucial role in tumor dissemination and progression.<sup>[1]</sup> The presence of CTCs in the peripheral blood was first reported more than 140 years ago, but only recent advances in molecular biology have enabled their reproducible identification and closer characterization. While analytical and clinical validity was demonstrated for numerous methods utilized for CTCs detection, CellSearch™ system (Veridex Corporation, Warren, NJ, USA) is still the only Food and Drug Administration-approved system for the detection of CTCs with the most robust clinical data for several types of tumors including breast, prostate and colon cancer with reproducible results across different laboratories. However, clinical utility of CTCs detected even of this system, is not very well established as well.

It is supposed, that detection and characterization of CTCs potentially enables examining changes of cancer phenotype

in real time, and therefore CTCs measurement could be a “liquid biopsy” that is easily accessible with minimal risk for patients. CTCs profiling could be useful in the detection of predictive markers including expression of specific receptors, expression of genes related to treatment resistance, detection of activating mutations, amplification of oncogenes or inactivation of tumor suppressor genes.

What are the factors that limit current use of CTCs in cancer patients' management? I think that there are several restrictions for routine clinical use of CTCs, and one of the main factors is the absence of data for clinical utility of CTCs detected for the vast majority of detection methods. Sensitivity of CTCs detection, absence of a consensus definition of biomarker expression on CTCs and CTCs heterogeneity are other factors that limits the use of CTCs in current treatment decision-making.<sup>[2]</sup>

One of the advantages of CTCs profiling could be the detection of predictive markers on these cells, excluding the need to take a biopsy of the metastatic site. For example, the most promising clinically relevant treatment targets in breast cancer evaluated on CTCs are HER2 and hormone receptors.<sup>[3,4]</sup> Discordance between primary tumor and metastatic tissue is frequently reported in the literature and occurs at rates of 10-30% for estrogen receptors and 20-50% for progesterone receptor, with losses being more common than gains. HER2 discordance has been found in approximately in 10% with loss and gain occurring with equal frequency.<sup>[5]</sup> This is frequently interpreted as evidence for a change in the biology of breast cancer during the course of the disease.<sup>[6]</sup> However, discordant receptor results can be caused by any of three factors:

- (i) A genuine switch in the biology of the disease,
- (ii) Sampling error in focally receptor-positive cancers, and
- (iii) Limited accuracy and reproducibility of receptor assays.<sup>[6]</sup>

In CTCs, due to limited cell count and differences in staining protocols utilized for receptors detection on solid tumor mass and CTCs, technical aspects and sampling error based on utilized CTC enrichment methods can contribute to this discordance, thus limiting clinical utility of CTCs profiling.

Another factor that could limits CTCs utility is heterogeneity of CTCs subpopulations with phenotypes that might differ from that of the primary tumor and/or metastatic sites and these phenotypes could be enriched in peripheral blood.

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For example CTCs undergoing epithelial to mesenchymal transition could be phenotypically completely different from phenotype of primary tumor, or phenotype of metastatic sites due to subsequent mesenchymal-to-epithelial transition at the site of extravasation. If utilized detection method captured predominantly this subpopulation, treatment selection based on the presence of therapeutic targets on this phenotypically different cell subpopulation could lead to treatment failure. Furthermore, the subpopulation of CTCs with mesenchymal phenotype might be undetected by methods, including CellSearch™, which favor the capture of CTCs that express epithelial markers.<sup>[7]</sup>

Circulating tumor cells represents a heterogeneous population of cancer cells, and current optimal methods for CTC detection may not be the desired method capable of capturing every CTC but rather subpopulation with the highest clinical value. Cut-off values for determination of predictive markers in primary tumor and/or metastatic sites are well established; however, optimal cut-offs are largely unknown for determination of these markers on CTCs. Clinical utility of CTC could be limited as well due to the sensitivity of detection methods and associated low number of CTCs detected.<sup>[8]</sup> In addition, methods like CellSearch™ assay excludes the detection of cancer stem cells, CTC clusters, and CTCs with mesenchymal and/or anaplastic phenotypes, which may have important prognostic and predictive implications.<sup>[9]</sup>

Hence, how CTCs detection and profiling could be incorporated in cancer treatment clinical making decisions? CTCs are comprised of the several subpopulations of cancer cells and one of the major challenges for the future is to improve detection methods to capture CTCs subpopulations with highest clinical utility. To address this, a number of new platforms are under active investigation. To incorporate CTCs as a predictive marker in a decision-making process, it is important to standardize the definition of biomarker expression on CTCs and validation of this approach in prospective clinical trials to determine whether patients will benefit from therapy based on the expression profile of minimal residual disease. Pilot data of this approach in hormonal treatment selection in prostate cancer based on CTCs profiling, are promising.<sup>[10]</sup> Several clinical trials are currently ongoing aimed to establish

clinical utility of CTCs and results of these trials could change the role of CTCs from the promising research biomarker to the important tool in personalized cancer medicine.

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