Circulating tumor cells as emerging tumor biomarkers in lung cancer

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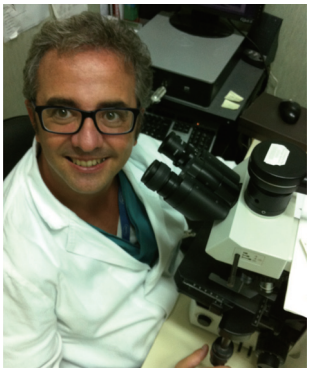

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Circulating tumour cells (CTCs) have recently evoked much interest in cancer research, representing potential prognostic biomarkers and a reliable mean to predict metastasis development. The presence of CTCs as a pre-requisite to develop distant metastasis is not a new concept, since it has been described by several scientists and physicians in the nineteenth century. However, only recently new biotechnologies able to correctly identify CTCs in cancer patients blood have been widely developed. For example, CellSearch (Veridex, LLC) based upon immunomagnetic technologies, constituted by magnetic nanoparticles coated with anti-EpCAM antibodies currently represents one of the best systems of CTCs detection. Thus since CTCs identification through CellSearch, before the beginning of a new line of chemotherapy, has prognostic value in breast, prostate and colorectal cancer, FDA approved the use of this type of methodology in these diseases (1).

In several clinical studies, CTCs enumeration has been used as biomarker in the prognostic stratification and in the evaluation of disease response during therapy. In addition CTCs number could be useful for prognostication in early stage of disease, for identification of patients requiring adjuvant therapy, or during follow-up in order to detect relapses. Finally other clinical application is represented by the molecular and genetic characterization of CTCs. All these applications have been demonstrated of clinical value in lung cancer in several studies. Thus Hofman *et al.* demonstrated that preoperative high CTCs count in Non Small Cell Lung Cancer (NSCLC) patients is related to poorer prognosis (2). Moreover, Rolle *et al.* showed that an increased postoperative CTCs count is significantly related to an higher risk of relapse (3). Some interesting results derived from the application of CellSearch in lung cancer patients. Indeed Tanaka *et al.* in a series of 150 lung cancer patients demonstrated a significant correlation to extent of disease (4). Moreover in a series of Small Cell Lung Cancer (SCLC) patients Hou *et al.* demonstrated 86% of cases with an high CTCs number and a significant association to) poor prognosis (5). In addition Hou *et al.* (JCO 2012) demonstrated that baseline CTCs and the change of CTCs number after a cycle of chemotherapy represent independent prognostic factors for SCLC progression (6). More recently Krebs *et al.* (7) showed in a series of NSCLCs that a CTC count higher than 5 is a negative prognostic marker and the decrease in CTC after one cycle of chemotherapy is related to a longer Disease Free Survival and Overll Survival comparing to cases with an increasing CTCs number.

Biological characteristics of CTCs seem to be relevant for the metastatic potential of tumor cells. Indeed it has been calculated, through animal models, that approximatively 2.5% of CTCs give rise to micrometastases, while only 0.01% of CTCs are able to promote macrometastases (1).

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Moreover, several other specific features seem to be related to metastasis development, such as cancer stem cell profile and the phenotypic change of epithelial cell known as Epithelial Mesenchymal Transition (EMT). In fact, markers associated with cancer stem cells, such as CD133, CD44, CXCR4 and ALDH1 were proved useful for identification of metastasizing fraction of cancer cells (8-10). Coerenetly with EMT of cancer cells, guaranteeing the transition from firmly attached and immobile cells to more flexible and mobile as mesencymal cells, carcinoma cells progressively lose epithelial specific markers, such as cytokeratins and EpCAM, and gain mesenchymal markers expression such as vimentin (11).

Finally, particularly in lung cancer, the biological assessment of CTCs therapeutic target markers, such as mutations of EGFR, could be a valid alternative to its determination in tumor samples. Maehswaren *et al*. (12) (have) demonstrated that EGFR mutation analysis in CTC was concordant with data from tumoral samples.

In conclusion CTCs characteristics in lung cancer could help to better stratify the patients, driving possibly in the future different therapeutic strategies. Indeed CTCs numbers correlate with prognosis in both early and advanced lung cancer. However different technique are continuously developing, with no obvious superiority of one technique comparing to another. Prospectively in lung cancer the assessment of therapeutic target in CTCs represent the most compelling aim. The continuous availability of this *non-invasive virtual biopsy* could solve the problem of the increasing need of lung cancer biological samples for molecular studies. This would avoid, for the benefit of the patient, the use of invasive modalities in order to obtain cytological specimen or small biopsies. Finally the scenario of "anti-CTCc" therapeutic target could offer the possibilities to prevent metastasis. Thus the identification of specific targets related for example to stem cell and EMT profile is an interesting field to develop in oncologic research.

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