Moving forward with circulating tumor cells and lung cancer

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Lung cancer is still the deadliest tumor around the world. Annually over 1 million people dye due to lung cancer (1). The most common cause of death in (lung) cancer patients is due to metastases. Tumor load increases exponentially by dissemination and growth of neoplastic cells into organs distinct from that in which they originated (2). Non-small cell lung carcinoma (NSCLC) accounts for around 85% of all lung cancer cases and is the leading cause of cancer-related mortality worldwide. At presentation approximately 70% of patients present with advanced disease, for whom curative therapy will not be available (3). During the last decade new drugs have been developed for specific subtypes of lung cancer. Emphasis is now on targeted therapy, with drug aiming at a mutated protein that has become an oncogen (4). Therapies are aimed at the characteristics of biopsies obtained from the tumor of the primary site. The best characterized examples are epidermal growth factor receptor mutations (EGFR) and echinoderm microtubule-associated protein-like4/anaplastic lymphoma kinase rearrangements (EML4-ALK) for which specific drug [collectively called tyrosine kinase inhibitors (TKIs)] have been developed. The development of specific TKIs against the activating kinase domains (EGFR) in mainly nonsmoking patients with adenocarcinoma of the lung have been a big step forward in treating this disease (5). Patients harboring a tumor with such an EGFR mutation have a far better prognosis than those that do not. EGFR mutations are being detected by sequencing DNA from tumor tissue obtained by e.g., bronchoscopy. Upon treatment usually after 9 to 12 months tumors appear to become resistant for the tyrosine kinase inhibitors via several routes (6). Thus still almost all of these patients pass away due to eventual disease progression (7). For these resistant tumors new treatments are forthcoming, however new tumor tissue is obligatory to understand the new resistance mechanism to target therapy again. In lung cancer this often implies new invasive procedures such as bronchoscopy, endoscopic ultrasound fine-needle aspiration (EUS-FNA), endobronchial ultrasound trans bronchial needle aspiration (EBUS-TBNA) or computer tomography guided transthoracic biopsies.

Given the changing tumor resistance patterns during treatment and the need to know DNA aberrations that are driving these changes more tumor monitoring is required to optimize treatments. Thus, there is a need for easy available (blood) tests replacing the more invasive procedures. The presence of circulating tumor cells (CTCs) in blood might be a good monitor. CTCs may reflect the aggressiveness of tumors (8). Clinical results obtained by sequentially measuring CTCs strongly suggest that in several tumor types, CTC detection and enumeration is a prognostic marker and may serve as an early marker to assess anti-tumor activity of a treatment. CTCs captured by the CellSearch® system can be characterized by FISH for different features. The CellSearch®, is approved by the U.S. Food and Drug Administration (FDA) to predict progression-free survival (PFS) and overall survival (OS) in patients with metastatic breast (9), colorectal (10), gastric (11), prostate cancer (12), small cell lung cancer (SCLC) (13,14) and for non-small cell lung cancer (NSCLC) (15). With this system it is possible to reproducibly find a single circulating tumor cell among up to 40 billion blood cells in a 7.5 mL blood sample. In most studies values between 2 and 5 CTCs per 7.5 mL blood seem to be the optimal cutoff value discriminating between poor and better prognosis. Apparently, even very low numbers of CTCs are relevant in describing the course of disease. A drawback of this method in NSCLC is that in only around 30% of patients with metastasized disease CTCs can be demonstrated. This proportion can be increased by using a different method: isolation by size (ISET) gives better results with up to 80% detection of CTCs in NSCLC (15). In addition there is some evidence that, next to prognostic, CTCs may be predictors of tumor response to therapy as well. In SCLC the number of CTCs after one course of chemotherapy was the strongest predictor, whereas reduction of the original tumor mass was a much weaker predictor of survival (13). This may imply that tumor cells that are resistant to therapy might be present in

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the circulation and can potentially be used as a diagnostic tool. Changes in the EGFR mutation state can be detected in cells isolated from peripheral blood of NSCLC patients (16). This monitoring of changes in the genetic makeup of the CTCs is the best available and non-invasive approach to detect resistance of the tumor. However, we need more studies on genetic changes in CTCs and more validation studies to prove the applicability in lung cancer patients. In addition, research is needed to determine whether CTCs are related more closely to the metastasis then to the primary tumor to validate CTCs as most important markers to aim therapy on. In those patients without CTCs we still need tumor tissue.

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