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Predictive and prognostic value of circulating tumor cell detection in lung cancer: A clinician's perspective

Annette Tognela[a,c,e,f,*], Kevin J. Spring[a,c,d], Therese Becker[a,c,d], Nicole J. Caixeiro[a,c], Victoria J. Bray[b], Po Yee Yip[f,g], Wei Chua[b,c], Stephanie H. Lim[a,b,c,d], Paul de Souza[a,b,c,d,e]

[a] *Medical Oncology Group, Ingham Institute for Applied Medical Research, Liverpool 2170, Australia*
[b] *Department of Medical Oncology, Liverpool Hospital, Liverpool 2170, Australia*
[c] *South West Sydney Translational Cancer Research Unit, Liverpool 2170, Australia*
[d] *School of Medicine, University of New South Wales, Kensington 2052, Australia*
[e] *Macarthur Clinical School, University of Western Sydney, Campbelltown 2560, Australia*
[f] *Department of Medical Oncology, Campbelltown Hospital, Campbelltown 2560, Australia*
[g] *Sydney Medical School, University of Sydney, Camperdown 2006, Australia*

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Abstract

There is increasing evidence for the use of circulating tumor cells (CTCs) as a "liquid biopsy" for early detection of lung cancer recurrence, prognosticating disease and monitoring treatment response. Further, CTC molecular analysis and interrogation of single cells hold significant

* Corresponding author at: Ingham Institute for Applied Medical Research, 1 Campbell Street, Liverpool 2170, NSW, Australia. Tel.: +61 2 4634 4355; fax: +61 2 4634 4350.
E-mail addresses: Annette.Tognela@sswahs.nsw.gov.au, atog6021@med.usyd.edu.au (A. Tognela).

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potential in providing insights into tumor biology and the metastatic process. Ongoing research will likely see the translation of CTCs as a prognostic and predictive biomarker in both small cell, and non-small cell, lung cancer to routine clinical practice.

Keywords: Biomarkers; Non-small cell; Small cell; Circulating tumor cells; Lung cancer

1. Introduction

Lung cancer is the leading cause of cancer deaths worldwide [1]. Five-year survival rates for small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) are <5% and 15%, respectively [2,3].

Circulating tumor cells (CTCs) are cells shed from either primary or secondary tumors that migrate into the circulatory system, and are thought to be responsible for the development of distant metastases [4–6]. CTCs are extremely rare, occurring at a frequency as low as 1 CTC per 10^6–10^7 leukocytes, with even lower numbers in early stage disease [4]. To date, the phenotype of CTCs has not been fully defined. Initially, CTCs were characterized as non-leukocytic, nucleated cells that were typically of epithelial origin. However, it is now known that the morphological features of these cells are less well defined and may vary by cancer type, stage and state (e.g., pre- or post-treatment) [6].

CTCs may also form aggregates (termed, "circulating tumor microemboli" (CTM)) either with other tumor cells or associated with fibroblasts, leukocytes, endothelial cells or platelets. In preclinical studies, CTM have been shown to have a higher propensity to seed distant metastases compared to single cells and, in this way, possess a survival advantage (reviewed by Krebs et al. [7]). Molecular analysis of CTM from SCLC patients shows absence of apoptotic cells and proliferating cells. This lack of proliferation may make these clusters relatively resistant to chemotherapy compared to proliferating single CTCs [8]. CTM are frequently detected in SCLC and confer a poor prognosis [8]. Early relapse of resected NSCLC has also been associated with the presence of clustered cancer cells [9].

CTCs can be detected at all stages of disease in lung cancer, including prior to the definitive diagnosis of primary lung cancer [10]. The possibility of using CTCs as a diagnostic tool is attractive, given the difficulties in obtaining adequate tissue for diagnosis in selected individuals. In early stage disease, CTCs may be used to predict the risk of recurrence, select patients for adjuvant therapy and assess prognosis, or in surveillance, to detect recurrent disease [5]. During treatment, CTCs may act as a surrogate biomarker to assess the response to treatment and guide effective treatment selection. Further, molecular characterization and mutational analyses of CTCs may facilitate biomarker discovery and drug development. Finally, single cell analyses of CTCs have the potential to provide insights into tumor biology, disease progression and the metastatic process [7].

The detection and enumeration of CTCs in lung cancer is a developing field with only a limited number of studies conducted to date. Increasing evidence for the clinical use of CTCs in lung cancer management is emerging, with most studies confirming the association of high CTC counts with worse prognosis [11–13]. Two recent meta-analyses have been published assessing the prognostic significance of CTCs in lung cancer patients. The first meta-analysis included 27 studies assessing survival outcomes and/or clinical characteristics in patients with SCLC and NSCLC. The pooled analysis demonstrated that CTC detection prior, and subsequent, to chemotherapy was significantly associated with a worse prognosis [14]. Similarly, the second meta-analysis included 20 studies of patients with NSCLC and also confirmed that the presence of CTCs were significantly associated with a shorter overall survival (OS) and progression free survival (PFS) [15]. Despite these developments, many questions remain unanswered regarding CTC biology, the optimal method and timing of enumeration and characterization as well as how CTCs perform relative to established prognostic and predictive markers.

In this article, we review the current evidence regarding various CTC detection methods and the prognostic and predictive value of CTCs in SCLC and NSCLC, respectively. We also describe the potential of molecular characterization of CTCs, review the putative role of CTCs in the metastatic process and highlight the unanswered questions that need to be addressed prior to the incorporation of CTCs into routine clinical practice.

2. CTC enrichment and detection methods

The identification of CTCs has become more feasible with the development of increasingly sensitive detection methods [4]. As CTCs are found in very low concentrations in the peripheral blood, enrichment of the sample is usually required prior to CTC detection [16]. Different methods of CTC enrichment and detection have been developed that rely on physical (size, density, electric charges, deformability) or biological properties (cell surface protein expression) of CTCs [17]. After enrichment, CTC detection is commonly achieved by immunostaining and microscopy or PCR-based methods (reviewed in 2013 by Liberko et al. [18] and Alix-Panabières and Pantel [17]). The key technologies used in detecting CTCs in lung cancer are discussed below.

CellSearch (Veridex) is the most validated CTC detection method and utilizes ferroparticles coupled to antibodies