

Detection of Circulating Tumor DNA Moves Closer To Clinical Use

Fabio Villa

Ospedale Regionale di Bellinzona e Valli – Istituto Oncologico della Svizzera Italiana (IOSI), Switzerland

Abstract

The detection of circulating tumor DNA (ctDNA) has been studied over 30 years as a method to monitor response to antiproliferative therapies in oncologic patients and, recently, to identify somatic genomic alterations. However the investigated techniques have shown limits of sensitivity, high costs, the necessity for a patient-specific optimization and a narrow-spectrum applicability. The newest methods, in the preliminary reports, seem to go beyond these restraints. Therefore they could be routinely used in the clinical practice to observe and predict the response to chemoradiotherapy, surgery, and to orient the therapeutic choice. Nonetheless the most promising application of the ctDNA detection regards the screening programmes.

Keywords: ctdna, cfdna, Circulating Tumor DNA, Non-Small Cell Lung Cancer

Corresponding author: Fabio Villa

✉ fabiovilla210486@gmail.com

Ospedale Regionale di Bellinzona e Valli – Istituto Oncologico della Svizzera Italiana (IOSI), Switzerland

Tel: +41 (0)91 811 91 76

Text

The identification of cell-free DNA (cfDNA) and its cancer-derived portion, circulating tumor DNA (ctDNA) have been firstly described in 1948 and 1989 respectively. The rationale of the detection of free nucleic acid in the systemic circulation concerns the assumption for which the presence and quantity of ctDNA or cfDNA correlates with the subsistence of malignant cells in the body. The release in serum or plasma of DNA implicates the apoptotic or necrotic mechanism of normal and aberrant cells, owing to the activation of DNA controlled degradation pathways or cell death; moreover it has been hypothesized an active DNA extracellular deliverance [1]. However it is not clear the degree of contribution of these different processes in the emission of free DNA in blood. Nonetheless the DNA fragments deriving from apoptosis are degraded by lysosomal DNase II and eliminated before appearing in plasma. The presence of remarkable amounts of apoptotic free DNA could be due to the imbalance between their spread and clearance, so the hyperproduction of nucleic acid fragments or the inflammatory deficit in lysosomal pathways, both seen in cancer [2]. ctDNA has been investigated as a cancer biomarker and a method to detect somatic genomic alterations, for which it has been coined the term of 'liquid biopsy'. Notwithstanding the routine use in clinical practice presents challenging obstacles, such as recognized limits of sensitivity, costs, the necessity for a patient-specific optimization and a narrow-spectrum applicability for most of the developed methods of extraction and assay. Newman et al. have recently described a novel technique called CAPP-Seq (Cancer Personalized Profiling by deep Sequencing) that responds to the need for sensitivity and specificity, laying the

foundations for a standardized, cost-effective and reproducible clinical practice [3]. The Authors enrolled patients suffering from a newly diagnosed Non-Small Cell Lung Cancer who were undergoing treatment. Maximal sensitivity and specificity of CAPP-Seq reached respectively 85% and 96% for pretreated patients and healthy controls. The sensitivity remarkably differs between stage I, in which it attains 50%, and stage II to IV with 100% of sensitivity and 96% of specificity, and similar results for all stages post-treatment samples. In addition ctDNA quantity significantly correlated with tumor volumes during therapy. In one patient the detection of ctDNA predicted the progression of a nearly complete responder NSCLC to chemoradiotherapy 7 months earlier the clinical evidence, suggesting a superior accuracy in monitoring the biologic efficacy of treatments. This finding confirms the potential role of the genomic essays in foreseeing the evolution of a treated disease, assessed in other solid tumors [4,5]. Lussier et al. in this context recognized the importance of microRNA expression in oligometastatic patients treated with high-dose radiotherapy, discovering that MicroRNA-200c enhancement in an oligometastatic cell line predict the polymetastatic progression. [6]. The observed sensitivity of the detection of ctDNA incites to reconsider the need of notable quantities of cancer tissue for the pathology essays, also during antiproliferative therapies which decrease the available quota of malignant tissues. In consequence the possibility to avoid invasive methods to obtain a biopsy, in the pre and post-treatment settings. The identification of EGFR mutations in ctDNA has been strongly debated as a potential diagnostic practice [7]. CAAP-Seq correctly detected 100% of EGFR and KRAS mutations, compared with tumor biopsy, as well as the erlotinib-resistant subclone T790M.

In conclusion one of the most promising application of identification of ctDNA regards the screening programmes, however the relatively low sensitivity in early stages seen in these studies proposes again the questions of the detection threshold. Moreover the issues of standardization, costs and reproducibility are still open [8]. The newest techniques could solve these concerns and ameliorate or substitute the current screening

practice. Newman et al. correctly classified 100% of patients with ctDNA above fractional abundances of 0.4% with a null false positive rate; the Authors indeed theorize the improvement by ctDNA quantitation of the low-dose CT screening in high risk patients for developing lung cancer. Further investigations are needed.

References

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