Circulating DNA and NSCLC: old findings with new perspectives

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Lung cancer is a worldwide problem. At the time of diagnosis, 50% of patients have advanced incurable disease and different chemotherapy schemes yield similar results despite the clinicians' continuous efforts.

Non-small cell lung cancer (NSCLC) accounts for about 80% of lung cancers. No more than 10% of these can be treated with surgery because of the lack of an early diagnosis or because of a high frequency of metastasis at diagnosis. The prognosis is poor, with only 10-15% of patients surviving 5 years after diagnosis. This dismal prognosis is attributed to the lack of efficient diagnostic methods for early detection and lack of successful treatment for metastatic disease. Within the last decade, rapid advances in molecular biology and radiology have provided a rational basis for improving early detection and patients' outcome. The most important prognostic factor is stage according to the TNM system and other prognostic factors include clinical aspects, as gender, age, weight loss and cardiovascular disease, elevated lactate dehydrogenase levels, FDG-PET scan and pathological aspects. A major hurdle in the attempts to improve the survival of these patients has been the lack of a simple, non-invasive and effective test for early prediction of therapeutic efficacy.

The finding that tumors are capable of shedding DNA into the bloodstream, which can be recovered from both serum and plasma and used as surrogate source of tumor DNA, has opened new areas in cancer diagnosis and prognosis. A number of studies have examined the mechanism behind origin and release of free DNA in the circulation and its clinical implications for lung cancer diagnosis, prognosis and monitoring the effect of cytotoxic therapies.

The presence of extracellular nucleic acids in the human bloodstream was first described in 1948 by Mandel and Métais. In recent years, many studies identified genetic alterations in cell-free circulating DNA (cDNA) from plasma or serum and tumour DNA in many tumour types, including lung cancer. Some studies indicate that circulating nucleic acids in peripheral blood are originated from tumours, through apoptosis, necrosis or cell lysis of tumour cells. The presence of tumour DNA in blood is probably the result, in variable proportions, of these different mechanisms, such as apoptosis, necrosis, cell lysis and circulating tumour cells lysis, which produce DNA leakage or excretion.

Diagnostic assays based on blood sample analysis are becoming an area of study with growing interest, mainly because of the simplicity of sampling and the future potential of automation of the technical methods for clinical applicability. The presence of circulating tumor DNA in plasma of patients with lung cancer arouse great interest since, with a simple blood test, a valid marker could be set out for possible screening, diagnosis, prognosis, progression of disease and the monitoring of treatment response.

The possibility of recovering tumour-derived DNA from the patient's blood may offer a non-invasive means to obtain tumour surrogate material, which could represent a unique source for diagnostic and prognostic applications. However, only recently cell free DNA is becoming an issue of growing interest and its possible use as a marker for cancer diagnosis or prognosis has been investigated.

Recent studies demonstrated higher cDNA levels in lung cancer patients comparing to control individuals. Other studies report circulating plasma DNA as a significant predictor of disease progression in patients undergoing chemotherapy. Moreover, several reports show a correlation between cDNA levels and the patients' outcome, namely in the overall survival and free-relapse time in lung cancer patients.

There are several studies that have valued the different concentration of free plasma DNA among patients with lung tumors and healthy individuals, and have used different data analysis methods and laboratory procedures. So far, the different

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methods utilized for sample processing and storage, for the extraction and quantification of plasma DNA and the choice of different target genes, have not allowed the use of circulating DNA in the clinical practice.

Conflicting data have been reported regarding the analyses of circulating DNA and clinical-pathological features, such as clinical staging and the prognostic and predictive value of quantification of cell free DNA and relapse-free evaluation that should be studied in more detail. This might be explained by differences in patient selection, covering both non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), and both treated and untreated patients. The differences of the results observed in the literature may reflect biological causes (histology, tumour origin, stage or tumour size) or technical issues (blood processing, cell free DNA isolation and quantification). Direct comparison of the available data is often prevented by differences in the parameters analysed and by lack of standardized methodology and analysis procedures. Any future application of plasma or serum DNA analysis for diagnostic purposes will depend on the reproducibility and reliability of results, both of which require optimization and equivalent procedures. These differences provide an insight into the present status of circulating DNA research in lung cancer and of the need for larger controlled studies with standardized procedures.

There are multiple potential uses for cDNA quantification in lung cancer diagnosis and prognosis. It may represent a valuable source of tumour DNA when the exact position of a suspected primary lesion is not clearly defined, or when biopsies are not available. Furthermore, plasma DNA could also be used to detect cancer specific molecular markers and individualize and monitor drug treatment, namely resistance to targeted therapies without the need for repeated tumour biopsies. Moreover, circulating tumour DNA could potentially be used as an alternative method for mutation detection, namely in the evaluation of epidermal growth factor receptor (EGFR) mutations, which is now a diagnostic routine for lung cancer treatment using EGFR tyrosine kinase inhibitors. Cell free circulating DNA may also represent an important source of biomarkers at several steps of carcinogenesis, including early detection of preneoplastic lesions and monitoring of cancer. Moreover, levels of plasma DNA could be tested as a potential intermediate biomarker of the efficacy of intervention.

Tumor-specific genetic markers in circulating DNA with high sensitivity and specificity may be used as a complementary noninvasive assay for early diagnosis and screening of high-risk individuals, to measure intermediate endpoints of efficacy in chemoprevention trials, for diagnostic or prognostic and as surrogate markers for treatment response.

These data should encourage further research in the area of circulating DNA as a tool for monitoring therapeutic efficacy in lung cancer patients. Identification of additional, more specific, and more sensitive plasma-based biomarkers, which can be used in combination with circulating DNA, may further improve the diagnostic power of current imaging tools for indicating therapeutic efficacy.

The findings from the studies of cDNA suggest that it would be possible to develop a simple cost-effective blood test, with high sensitivity and specificity that has potential for screening high-risk individuals, for prognostic purposes and to be used as intermediate end-points of efficacy in chemoprevention and therapeutic trials. Its wide applicability and potential importance will possibly lead to increasing clinical impact in the near future. Large-scale prospective studies are necessary for population-based studies and molecular epidemiologic studies, in order to implement a clinical application in lung cancer detection, diagnosis, prognosis and prediction of treatment response.

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