Technical Note

The first liquid biopsy test approved. Is it a new era of mutation testing for non-small cell lung cancer?

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Abstract: Specific mutations in epidermal growth factor receptor (EGFR) gene are predictive for response to the EGFR tyrosine kinase inhibitors (TKIs) in non-small cell lung cancer patients (NSCLC). According to international guidelines, the molecular testing in patients with advanced NSCLC of a non-squamous subtype is recommended. However, obtain a tissue sample could be challenging. Liquid biopsy allows to determine patients suitable for EGFR-targeted therapy by analysis of circulating-free tumor DNA (cfDNA) in peripheral blood samples and might replace tissue biopsy. It allows to acquire a material in convenient minimally invasive manner, is easily repeatable, could be used for molecular identification and molecular changes monitoring. Many studies show a high concordance rate between tissue and plasma samples testing. When U.S. Food and Drug Administration (FDA) approved the first liquid biopsy test, analysis of driver gene mutation from cfDNA becomes a reality in clinical practice for patients with NSCLC.

Keywords: Liquid biopsy; circulating-free tumor DNA; non-small cell lung cancer; epidermal growth factor receptor

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Introduction

Lung cancer is the most common cause of cancer deaths (1-3). Non-small-cell lung cancer (NSCLC) represents of 85–90% of lung cancers (1-4). Epidermal growth factor receptor (EGFR) mutations occur in 10–30% of NSCLC (2,5-7). These mutations in the Caucasian population are present in about 10% (2). Identified for the mutation patients with advanced or metastatic NSCLC are candidates for personalized treatment. According to the international recommendations molecular testing should be carried out in patients with advanced NSCLC of a non-squamous subtype before first-line treatment starts (2). The researches indicated that those with tyrosine kinase inhibitors (TKIs)-sensitive EGFR mutations had longer progression-free survival (PFS) when receiving EGFR-targeted therapy (e.g., erlotinib) (8-11).

Hitherto, according to guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology published in 2013—"Pathologists should use formalin-fixed, paraffin embedded (FFPE) specimens or fresh, frozen, or alcohol-fixed specimens for polymerase chain reaction (PCR)—based EGFR mutation tests. Other tissue treatments should be avoided in specimens destined for EGFR testing" (3). But in the era of new technologies development it was easy to predict that this situation has to be changed. In the mid of 2016 the first liquid biopsy test was approved by the U.S. Food and Drug Administration (FDA) (12). In this paper the main meaning of novel technique of mutation detection in patients with NSCLC will be discussed briefly.

Liquid biopsy

Traditional biopsy is an invasive procedure to obtain a sample of the tumor tissue and is not always feasible. Liquid biopsy allows to identify patients whose tumors have specific mutations in the minimally invasive way and is less time-consuming. It is possible because tumor cells (and their DNA) are released into the circulation and circulating-free tumor DNA (cfDNA) could be isolated. Finally, the molecular test can be obtained. This is an alternative way to detect mutation and also an another way to gain a sample for testing in patients who previously could not be tested at all. Because of that it may play an important role in clinical decision making. It was previously reported that EGFR genetic testing was not being conducted in 19% of advanced NSCLC cases (13). The main reasons for not testing were: insufficient tissue, poor performance status (PS) and long turnaround time (13,14). Moreover, mutation test results were not available before treatment decision was taken in 23% of tested patients (13).

Because of the tumor heterogeneity a few samples should be tested to maximize genetic picture of the tumor. Nowadays, easily obtaining blood samples could serve also in this indication.

Finally, the easier way in which the liquid biopsy test is obtained also makes it useful in monitoring of disease progression. It is known that tumor cells evolve and often genetic changes are the reason for choosing new treatment. Thress *et al*. have demonstrated that analysis of cfDNA is able to detect mechanisms of resistance to EGFR-targeted therapies in NSCLC, e.g., EGFR T790M mutation (15). Since when osimertinib, an irreversible inhibitor of EGFR TKI-sensitizing and T790M resistance mutations is available, detection of this mutation is clinically meaningful (16).

The results of the study by Chabon *et al*. confirmed the utility of ctDNA-based resistance mechanism assessment, especially with detection of mutations present in multiple tumour deposits (17). Researchers employ CAPP-Seq (Cancer Personalized Profiling by deep sequencing) ctDNA analysis to study resistance mechanisms in NSCLC patients treated with the rociletinib (17). They observed a previously unrecognized high frequency of molecular heterogeneity (including a novel tertiary mutation in EGFR (L798I) and the emergence of activating KRAS mutations) in resistance mechanisms following treatment with EGFR TKIs (17). Interestingly, their findings suggest that pattern of resistance mechanisms to third-generation EGFR TKIs appear to be drug specific, and EGFR C797S mutations were noted in approximately 30% and 2% of patients treated with osimertinib and rociletinib, respectively (17). The usefulness of plasma ctDNA analyses were also shown in the study where T790M-positive patients treated with rociletinib upon progression were biopsied to explore rociletinib resistance (18). Moreover, Reckamp *et al*. have demonstrated that DNA derived from urine samples is feasible for mutation testing (19). The sensitivity of EGFR mutation detection in urine with tumor as a reference was 72% for T790M, 67% for exon 19 deletions, and 75% L858R mutations (for plasma samples: 93%, 87%, 100%, respectively) (19).

Hitherto, many techniques have been tested for the EGFR mutations detection using plasma samples. And several studies have demonstrated that mutations detected in plasma are highly concordant (usually 60–90%) with those detected in tumor tissue in NSCLC patients (*Table 1*) (20-36). For example, in the ASSESS study overall concordance of mutation status was 89% (14).

The concordance rate depends on method which was used (*Table 1*) (20-36). In general, digital genomic approaches (droplet digital PCR, BEAMing dPCR) are more sensitive than nondigital approaches (cobas and therascreen) (37). Moreover, in the AURA study, digital platforms appeared to detect a higher percentage of T790M mutations, compared with non-digital platforms (38). However, the cross-platform comparison showed that the cobas EGFR Mutation Test and BEAMing dPCR had highly concordant results, with high sensitivity (73–81%) for the detection of the T790M mutation and specificity ranging 58–67% (38).

While this method is an alternative way for mutation detection, we should remember that discordant genotypes between tumor biopsy and blood-based analyses were reported (39). And few things can influence on test results e.g., appropriate time of sample acquisition (cytotoxic agents may suppress the T790M ctDNA) (40).

The cobas EGFR Mutation Test

The cobas EGFR Mutation Test (v1) was approved on May 14, 2013 (41). This device is a real-time PCR test for the qualitative detection of exon 19 deletions and exon 21 (L858R) substitution mutations of the EGFR gene in DNA derived from FFPE human NSCLC tumor tissue (41). In 2015 the FDA approved cobas EGFR Mutation Test v2, adding e.g., T790M mutation to clinically important mutations, identified up to now by above-mentioned

Table 1 Liquid biopsy for the detection of EGFR mutation in NSCLC (plasma sample) (20-36)

Studies (references)	Detection methods	Concordance rate[1] (%)
He (20)	ME-PCR	94.4
Yung (21)	Microfluidics digital PCR	92.0
Kuang (22)	ARMS	74.0
Taniguchi (23)	BEAMing	NA
Brevet (24)	Sequenom, ME-PCR	61.0
Yam (25)	AS-APEX	97.3
Nakamura (26)	Inhibiting PCR-quenching probe method; MBP-QP	NA
Liu (27)	ARMS	84.9
Lv (28)	DHPLC	NA
Zhang (29)	MEL	84.9
Zhao (30)	ME-PCR	71.2
Kim (31)	PNA-mediated PCR clamping	17.0
Li (32)	ARMS	73.6
Douillard (33)	ARMS	94.3
Weber (34)	cobas EGFR blood test	91.0
Duan (35)	ARMS	80.0

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; [1], concordance of *EGFR* mutation status between tissue and plasma samples; PCR, polymerase chain reaction; ME-PCR, mutant-enriched PCR; ARMS, amplification refractory mutation system; BEAMing, beads, emulsion, amplification and magnetics; AS-APEX, allele-specific arrayed primer extension; MBP-QP, mutation biased PCR-quenching probe system; DHPLC, denaturing high-performance liquid chromatography; MEL, mutant-enriched liquidchip platform; PNA-mediated PCR clamping, peptide nucleic acid (PNA)-mediated polymerase chain reaction (PCR) clamping method.

Table 2 EGFR mutations detected by the cobas EGFR Mutation Test v2 (44)

Exon	EGFR mutation
Exon 18	G719X
Exon 19	Ex19Del
Exon 20	S768I
	T790M
	Ex20Ins
Exon 21	L858R
	L861Q

EGFR, epidermal growth factor receptor.

original test (42,43). Currently, this test detects EGFR mutations in NSCLC patients whose tumors have the exon 18 (G719X) substitutions, exon 19 deletions, exon 20 insertions and substitutions (T790M, S768I) and exon 21 substitutions (L858R, L861Q), but not any other EGFR mutations (*Table 2*) (44).

On June 1, 2016, FDA approved cobas EGFR Mutation Test v2 using plasma specimens as a companion diagnostic test for the detection of exon 19 deletions or exon 21 substitution mutations in the EGFR gene (12). This is the first liquid biopsy test approved for use by this agency. It allows for detection of mutations in cfDNA in less than 4 hours. If test is negative the routine testing using the FFPE tissue sample type is recommended (12).

The approval was based on a multicenter, open-label, randomised, Phase III ENSURE study, to evaluate the efficacy and safety of erlotinib versus gemcitabine plus cisplatin as first-line treatment for stage IIIB/IV NSCLC patients (8,12). Participants had tumour tissue specimens that tested positive for the EGFR exon 19 deletion or L858R mutations as determined by the cobas EGFR Mutation Test v1. Among patients screened and enrolled for this trial 86% and 98.6% had a plasma samples available for testing, respectively (12). Plasma was positive and negative for EGFR mutation in 76.7% and 98.2% of tissue-positive and tissue-negative cases, respectively (12).

Ongoing studies

The usefulness of liquid biopsy is still widely tested in different settings (45). There are numerous studies that are in progress today and *Table 3* shows a list of ongoing trials in the field of NSCLC (45). In the LIBIL study (NCT02511288), concordance (pourcentage) between tissue and droplet digital PCR for EGFR mutations detection and other molecular alterations routinely detected in NSCLC will be evaluated (45). Patients with stage IV EGFR-positive NSCLC may be enrolled into the NCT02284633 study. A biopsy and blood sample will be retrieved before treatment initiation. The patient will be monitored prospectively with blood samples every 3rd-6th week both during erlotinib treatment, subsequent lines of treatment and treatment intermissions. The blood samples will be analyzed for subtypes of EGFR M+ both sensitizing mutations and mutations known to drive resistance to erlotinib treatment.

Table 3 Ongoing clinical trials using liquid biopsy for mutation detection in NSCLC patients (September 2016) (45)

Study number	Study type	Status	Primary outcome measures
NCT02906852	Observational	R	Concordance in the detection of molecular abnormalities using Inivata's liquid biopsy panel with detection using standard of care tissue biopsy analysis
NCT02778854	Observational	R	Concordance between tissue and plasma using detection method such as ddPCR or ARMS to detect the driver mutation in NSCLC
NCT02894853	Observational	N/R	The percentage of patients with EGFR mutation or ALK translocation using the combined tumour tissue and liquid biopsy analysis
NCT02511288	Observational	R	Concordance between tissue and droplet digital PCR for EGFR mutations detection
NCT02284633	Observational	R	PFS
NCT02597738	Interventional	R	Measurement of genomic profile
	Non-Randomized		Genomic changes causing lung cancer evolve over the course of illness. They may serve as a biomarker for diagnosis and response to treatment (human specimens and co-cultured in mice)
NCT02372448	Interventional	R	Sensitivity and specificity of the FISH technique for the detection of the ALK rearrangement in CTCs change from baseline to 6 and 12 months
	Non-Randomized		
NCT02853006	Interventional	R	Quantification of: DNA, RNA (from plasma or respiratory fluids)
	Randomized		
NCT02418234	Observational	N/R	Number of T790M mutation in patients with NSCLC resistant to TKIs
			Techniques: ARMS, ddPCR
NCT01930474	Observational	R	Detection of genetic alterations (including EGFR and ALK) in plasma samples
			To evaluate the sensitivity of digital PCR to detect the genetic alterations in plasma tumor DNA

NSCLC, non-small cell lung cancer; R, recruiting; N/R, not recruiting; ddPCR, droplet digital polymerase chain reaction; ARMS, Amplification Refractory Mutation System Assay; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; PFS, progression-free survival; FISH, fluorescence in situ hybridization; CTCs, circulating tumor cells; DNA, deoxyribonucleic acid; RNA, ribonucleic acid; TKIs, tyrosine kinase inhibitors.

Patients will be followed until death or at least 24 months after inclusion. Any excess biological material will be stored for up to 15 years for future research purposes (*Table 3*) (45).

Interestingly, in the LEMA (Lung Cancer Early Molecular Assessment Trial) study, the potential usefulness of the early molecular profiling for all NSCLC patients, including stage I-III will be explored (45). This study is ongoing, but not recruiting participants (Last update: September 2016) (45).

Conclusions

Liquid biopsy is already a reality in clinical practice. A new era of molecular diagnostics is coming and plasma sample testing will also be used in other cancers and in other indications in the future. Researchers at The University of Texas MD Anderson Cancer Center have already published results using a PCR-based liquid-biopsy test called IdyllaTM BRAF Mutation Test which detects BRAF V600 mutations (46). They found that this test had 88–90% concordance with results from the standard tests (46). Also a pan-cancer diagnostic test being developed by Illumina is awaited (47). The development of cfDNA assays and their implementation into clinical practice is a valuable option in cases where tissue quantity is inadequate for mutation testing or in patients who refuse or are unable to undergo biopsy. But we have to be aware that the tissue biopsy and liquid biopsy do not compete. The liquid biopsy is another valuable option of mutation detection. The development of new molecular diagnostic tools allow more widely to use already approved targeted therapies and offer the right treatment to each patient in the best way possible.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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