Clinical utility of plasma cell-free DNA EGFR mutation analysis in patients with newly diagnosed stage IV non-small cell lung cancer

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Background

- **Lung cancer**
  - A major problem because the number of patients is increasing worldwide
  - Still the most common cause of cancer mortality
  - NSCLC accounts for 85% of all lung cancer cases
- **Sensitizing EGFR mutations**
  - Important parameters for determining the treatment response to EGFR-TKIs in NSCLC
  - Detected in 30–50% of NSCLCs from Asians and 10% of those from Caucasians
- **Molecular genotyping**
  - Tissue (traditional) vs liquid biopsy (recent advances)
- **Cell-free DNA (cfDNA) / circulating tumor DNA (ctDNA) analysis**
  - various platforms
  - faster turnaround time and less invasiveness
- The NCCN guidelines recommend the use of plasma genotyping both at initial diagnosis if sufficient tissue is not available as well as at progression on EGFR-TKIs
- Few studies have investigated the characteristics of patients who are more likely to be positive in plasma EGFR mutation analysis.
- Few studies have been done on the clinical utility of plasma EGFR mutation analysis in terms of the treatment outcome in real-world practice.

Aim of the study

We investigated factors affecting the positivity of plasma EGFR mutation assay and its effect on the clinical outcomes of patients with treatment-naïve stage IV NSCLC.

Methods

Retrospective cohort study

Study population

- Patients with treatment-naïve stage IV
- Adenocarcinoma & NSCLC not otherwise specified
- Underwent plasma EGFR mutation assay between Jan 2018 and Dec 2020
- Patients were divided into four groups according to the EGFR mutation test results from the tissue and plasma EGFR mutation assays: “Tissue (-) & plasma (-),” “Tissue (-) & plasma (+),” “Tissue (+) & plasma (-),” and “Tissue (+) & plasma (+).”

Statistical analyses

- Gold standard definition of EGFR mutation-positivity: the detection of an EGFR mutation in either tissue or plasma EGFR mutation assays
- If tissue biopsy could not be performed due to patient’s condition or technical difficulties and plasma EGFR assay was positive, tissue EGFR mutation test was considered false-negative
- Logistic regression analysis with backward stepwise selection used to identify factors independently associated with a positive plasma EGFR mutation assay
- The Kaplan-Meier method used to estimate overall survival after lung cancer diagnosis

Results

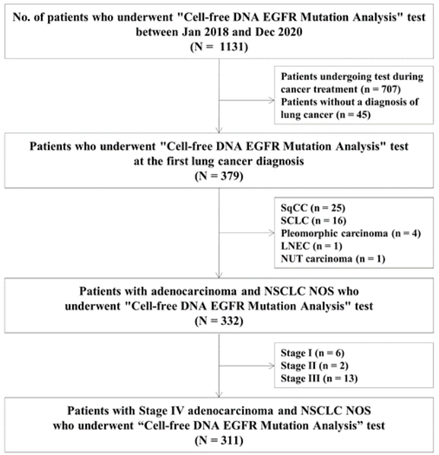


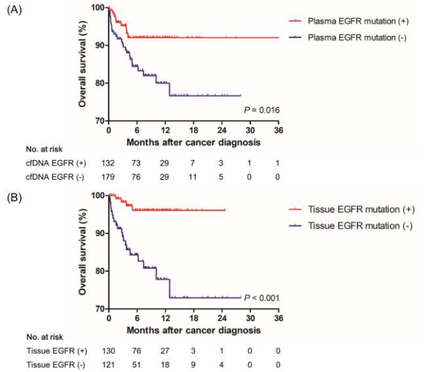
Table 1. Baseline Characteristics

Variables	Total (N = 311)	Tissue (-) / plasma (-) (N = 147)	Tissue (-) / plasma (+) (N = 34)	Tissue (+) / plasma (-) (N = 32)	Tissue (+) / plasma (+) (N = 98)	*p*
Age, years	65 (57–74)	65 (59–73)	61 (55–79)	66 (54–77)	64 (55–72)	0.732
Sex, female	176 (56.6)	64 (43.5)	19 (55.9)	26 (81.3)	67 (68.4)	< 0.001[bc]
Smoking history						< 0.001[bc]
Never smoker	195 (62.7)	71 (48.3)	21 (61.8)	25 (78.1)	78 (79.6)	
CEA, ng/ml (n =248)						0.006[c]
< 3.2 ng/ml	56 (22.6)	39 (33.1)	5 (20.8)	5 (20.0)	7 (8.6)	
3.2–94.7ng/ml	124 (50.0)	51 (43.2)	13 (54.2)	15 (60.0)	45 (55.6)	
> 94.7 ng/ml	68 (27.4)	28 (23.7)	6 (25.0)	5 (20.0)	29 (35.8)	
Clinical stage at the diagnosis						
T stage						0.705
T1	67 (21.6)	37 (25.2)	8 (23.5)	8 (25.0)	14 (14.3)	
T2	94 (30.2)	38 (25.8)	11 (32.4)	10 (31.3)	35 (35.7)	
T3	57 (18.3)	27 (18.4)	7 (20.6)	5 (15.6)	18 (18.4)	
T4	93 (29.9)	45 (30.6)	8 (23.5)	9 (28.1)	31 (31.6)	
N stage						< 0.001[bdf]
N0	35 (11.2)	17 (11.6)	2 (5.9)	11 (34.4)	5 (5.1)	
N1	22 (7.1)	14 (9.5)	0 (0.0)	2 (6.3)	6 (6.1)	
N2	77 (24.8)	38 (25.8)	10 (29.4)	11 (34.4)	18 (18.4)	
N3	177 (56.9)	78 (53.1)	22 (64.7)	8 (25.0)	69 (70.4)	
M stage						0.004[f]
M1a	91 (29.3)	47 (32.0)	10 (29.4)	16 (50.0)	18 (18.4)	
M1b	31 (10.0)	16 (10.9)	3 (8.8)	5 (15.6)	7 (7.1)	
M1c	189 (60.8)	84 (57.1)	21 (61.8)	11 (34.4)	73 (74.5)	
No. of metastatic sites						< 0.001[acdf]
1	101 (32.5)	59 (40.1)	9 (26.5)	17 (53.1)	16 (16.3)	
2	73 (23.5)	44 (29.9)	4 (11.8)	9 (28.1)	16 (16.3)	
3	37 (11.9)	23 (15.6)	2 (5.9)	5 (15.6)	7 (7.1)	
≥ 4	100 (32.2)	21 (14.3)	19 (55.9)	1 (3.1)	59 (60.2)	
Location of metastasis**						
Brain	94 (30.2)	34 (23.1)	12 (35.3)	8 (25.0)	40 (40.8)	0.023[c]
Bone	139 (44.7)	67 (45.6)	12 (35.3)	10 (31.3)	50 (51.0)	0.159
Intrathoracic metastasis	192 (61.7)	79 (53.7)	22 (64.7)	23 (71.9)	68 (69.4)	0.050
Intraabdominal metastasis	74 (23.8)	38 (25.9)	6 (17.6)	3 (9.4)	27 (27.6)	0.140
Others	14 (4.5)	8 (5.5)	0 (0.0)	0 (0.0)	6 (6.1)	0.337

Table 2. Factors associated with a positive result of plasma EGFR mutation analysis

Variables	Univariable		Multivariable	
	Unadjusted OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Age, years	0.99 (0.97–1.01)	0.242	0.98 (0.95–1.00)	0.086
Sex, female	1.85 (1.16–2.94)	0.009		
Smoking history				
Ever smoker	Reference		Reference	
Never smoker	2.59 (1.59–4.24)	< 0.001	2.83 (1.55–5.20)	0.001
CEA level				
< 3.2 ng/ml	Reference		Reference	
3.2–94.7ng/ml	3.22 (1.55–6.68)	0.002	2.61 (1.16–5.84)	0.020
> 94.7 ng/ml	3.89 (1.75–8.62)	0.001	2.98 (1.21–7.35)	0.018
N stage				
N0	Reference		Reference	
N1	1.50 (0.43–5.24)	0.525	1.65 (0.38–7.17)	0.501
N2	2.29 (0.88–5.91)	0.088	2.52 (0.78–8.17)	0.124
N3	4.23 (1.76–10.20)	0.001	4.22 (1.41–12.62)	0.010
M stage				
M1a	Reference			
M1b	1.07 (0.45–2.57)	0.877		
M1c	2.23 (1.31–3.78)	0.003		
Type of metastatic organs*				
Brain	2.12 (1.30–3.47)	0.003	2.73 (1.39–5.36)	0.003
Bone	1.14 (0.72–1.79)	0.575		
Intrathoracic metastasis	1.62 (1.01–2.59)	0.045	2.61 (1.38–4.96)	0.003
Intraabdominal metastasis	1.12 (0.66–1.90)	0.668	1.85 (0.93-3.68)	0.079
Others	1.01 (0.34–2.99)	0.983		

Survival plots of subjects with stage IV NSCLC according to plasma and tissue EGFR mutation status



Time to treatment initiation (TTI)

Tissue (+): 21 days

Plasma (+): 14 days

Conclusions

Serum CEA levels, smoking status (never-smoker), nodal stage, and metastatic sites (brain, intrathoracic metastasis) were identified as clinical factors associated with plasma EGFR mutation positivity. The plasma EGFR mutation assay can overcome the limitation of tumor tissue availability, shorten TTI, and facilitate the 1st line EGFR-TKI therapy in subjects with treatment-naïve stage IV NSCLC.