TUR - 2023 - Survival of Lung Adenocarcinoma Patients with Tyrosine Kinase Inhibitor Therapy Based on EGFR Mutation Status in Tumor and Plasma Samples

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RESEARCH ARTICLE

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Survival of Lung Adenocarcinoma Patients with Tyrosine Kinase Inhibitor Therapy Based on EGFR Mutation Status in Tumor and Plasma Samples

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ABSTRACT

Background: The prognosis for epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer (NSCLC) is greatly improved when treated with tyrosine kinase inhibitor (TKI). In this context, EGFR mutation status should be determined at the diagnosis stage but circulating tumor DNA (ctDNA) has been increasingly used for molecular profiling. Therefore, this study aimed to establish the correlation between the presence of ctDNA before TKI therapy and subsequent clinical outcomes.

Methods: A total of 18 patients with NSCLC who received EGFR-TKI therapy were enrolled. EGFR mutations were simultaneously identified in tumor samples and plasma ctDNA, as well as information regarding overall survival (OS) and progression-free survival (PFS).

Results: These case studies showed that 14 of 18 patients (77.8%) with concordance results detected EGFR-positive mutations on ctDNA examination and histopathology from plasma and tumor samples, respectively. The median PFS was similar at 7.5 months in both groups, while the median OS was shorter in patients with EGFR-detected in ctDNA (17 vs. 25.5 months) after TKI-targeted therapy.

Conclusions: The identification of EGFR mutations in plasma ctDNA was a promising, effective, and minimally invasive alternative to tumor biopsy. The existence potentially reflected the disease burden and showed a poor prognosis.

INTRODUCTION

Lung cancer is the greatest cause of cancer-related mortality globally. Approximately 85% of the cases are non-small cell lung cancer (NSCLC) as opposed to small cell lung cancer (SCLC), with adenocarcinoma being the most prevalent subtype (40%) [1,2]. The majority of non-small cell lung tumors are detected at a late stage. Furthermore, platinum-based doublet chemotherapy was the only therapy for advanced NSCLC, with an approximate eight-month median overall survival (OS). The development of targeted epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) has improved patient survival. Therefore, it is essential to discover EGFR mutations in patients with lung adenocarcinoma [3].

Lung cancer with EGFR mutations occurs in 15-20% of patients with adenocarcinoma and is most commonly associated with non-smoker groups and individuals of Asian ethnicity [1]. In East Asia, the prevalence of mutation is around 38.4% in NSCLC [4]. Based on a study at Ulin Hospital Banjarmasin, South Kalimantan, in 2017, out of 38 patients with lung adenocarcinoma cytology results, 13 (34.2%) had EGFR mutations [5]. A follow-up study in 2019 reported that adenocarcinoma patients were highest in non-smokers at 64.7% [6].

EGFR is a transmembrane protein that functions as a tyrosine kinase receptor for numerous ligands controlling cell proliferation, differentiation, and survival [7]. Excessive expression and its mutations have been identified in a variety of malignancies, influencing cancer

growth and progression [8]. EGFR-specific mutations have been connected to increased survival in NSCLC patients [9].

Tissue samples, such as a biopsy of a primary tumor or a metastatic lesion, have been used to test for EGFR mutations [3]. However, the inability to obtain suitable tissue samples for molecular profiles such as EGFR is a frequent problem. Tumor sampling is invasive, and repeated tissue biopsies of a suspected primary or metastatic lesion may be difficult and lead to potential procedure-related problems [10].

Liquid biopsy identifies tumor cell genotypes from circulating tumor DNA (ctDNA) in patient blood, which is a less invasive method [3]. The Food and Drug Administration (FDA) in the United States proves that polymerase chain reaction (PCR)-based ctDNA liquid biopsy testing can identify the presence of specific mutations [11,12]. Most patients have concordance results on liquid biopsy and tissues. Kuo et al. [3] found that 65% of advanced lung adenocarcinoma patients had EGFR mutation testing results on concordant tissue samples using liquid biopsy. A study conducted at Ulin Hospital Banjarmasin, South Kalimantan, in 55 pulmonary adenocarcinoma patients who were examined for histopathology tumor samples and ctDNA found 22 (40%) detected EGFR mutations [13].

Numerous studies analyzed the prognostic value of ctDNA in individuals with NSCLC. The location of metastases influences the diagnostic accuracy of ctDNA-based EGFR mutations on NSCLC, according to an analysis. Detecting EGFR mutations in tissues and ctDNA has been related to a high prevalence of distant metastasis and a considerable decrease in disease-free survival, as an intriguing finding [10]. The Korean results suggested that ctDNA detection was related to poorer PFS in EGFR TKI-treated patients and extrathoracic lymph node metastases were independent predictors of the variable [14].

In Indonesia, limited study has been conducted to ascertain when the concordance between the presence of EGFR mutations in plasma and tumor samples before the initiation of TKI therapy has an impact on OS. This study analyzes PFS and OS when a concordance of EGFR mutation status is obtained in ctDNA and tumor samples from several series of cases at Ulin Hospital Banjarmasin, South Kalimantan.

METHODS

The retrospective study used secondary data from the medical records of 18 lung adenocarcinoma patients diagnosed at Ulin Banjarmasin Hospital from January 2017 to December 31, 2020. All Patient has EGFR mutation test data at the Anatomical Pathology Laboratory of Ulin Hospital Banjarmasin and ctDNA test data from Prodia Banjarmasin Laboratory simultaneously, with PFS and OS data.

EGFR mutation examination used the Amplification refractory mutation system (ARMS PCR) method with preparations sourced from pleural fluid, lymph nodes, and lung tissue. This ctDNA examination detected the exon of EGFR mutation using the Digital Droplet PCR (ddPCR) method with preparations sourced from peripheral blood.

PFS was the time taken from initiation of TKI therapy until the progression of clinically significant disease or death (calculated based on what occurred earlier). OS was the duration from the establishment of the diagnosis to the time of death of patients caused by etiology.

Descriptive statistics were used to report the demographic characteristics of the sample. Categorical variables were presented in the form of numbers and percentages, while median survival time analysis for PFS and OS was performed using life tables. Scatter and spot violins presented an overview of histopathology from tumor samples and ctDNA results with PFS and OS. There was no imputation on the missing data, which was processed by using GraphPad Prism 9.4.1.

RESULTS

Table 1 showed that 14 patients with concordance results detected EGFR-positive mutations on ctDNA examination and histopathology from tumor samples. A total of 7 patients were male, 9 were over 50 years old, 8 had a history of smoking, and the majority of 13 were at the IVA stage. Patients with concordance positive results of tumor sample and ctDNA was confirmed by examination of pathology of pleural fluid (8), pulmonary masses (2), supraclavicular lymph node (3), and neck lymph node (1) with the result of 9 patients constituting exon 19 mutations.

Among the 4 patients who tested negative for ctDNA, 3 were male, and 2 were over the age of 50. The 4 patients had a smoking history at stage IVA with ECOG 1 and were diagnosed with EGFR based on cytological pleural fluid with mutation exon 19 and 21. Patients with negative ctDNA were treated using the gefitinib TKI type and the details of each sample are found in **Table 2**.

Based on **Table 2** and **Figure 1**, lung adenocarcinoma patients who also detected mutations through ctDNA examination had the same progressive free survival of 7.5 months. Meanwhile, differences were obtained in OS where lung adenocarcinoma patients who have also detected mutations had a shorter OS of 7.5 vs. 25.5 months (**Figure 2**).

Table 1. Clinical characteristics of research samples

Characteristic	Negative ctDNA	Positive ctDNA
Gender		
Male	3	7
Female	1	7
Age Group (Years)		
< 50	2	5
≥ 50	2	9
Stage		
III C	0	1
IV A	4	13
ECOG		
1	4	11
2	0	3
Smoker		
Yes	4	6
No	0	8
Sample Source		
Pleural Fluid	4	8
Neck Lymph node	0	1
Supraclavicular Lymph node	0	3
Lung Mass	0	2
Metastasis		
Pleural Effusion	4	8
Pericardial Effusion	0	1
Neck Lymph node	0	1
Liver Metastases	0	2
Brain Metastases	0	1
EGFR Mutation		
Deletion Exon 19	2	9
L858R Exon 21	2	5
TKI therapy		
Afatinib	0	2
Erlotinib	0	1
Gefitinib	4	11
Progression Free Survival (PFS) (median) (month)	7.5	7.5
Overall Survival (OS) (median) (month)	25.5	17

ctDNA: cell tumor DNA; EGFR: Epidermal Growth Factor Receptor; TKI: Tyrosine Kinase Inhibitor

PFS and OS images were divided into groups based on positive and negative ctDNA results in **Figure 3**. PFS in patients with predominantly positive and negative ctDNA was in the same month. The scatter and violin plots OS show that patients with negative ctDNA tend to have a more incredible range and deviation.

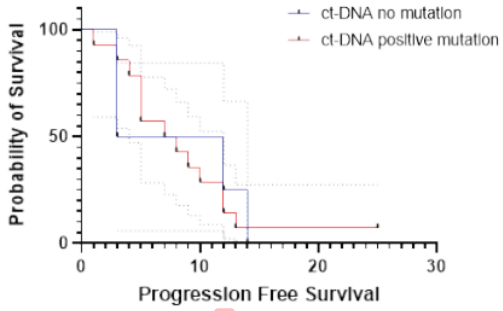

Figure 1. Progression-Free Survival in ctDNA EGFR mutation lung adenocarcinoma patients

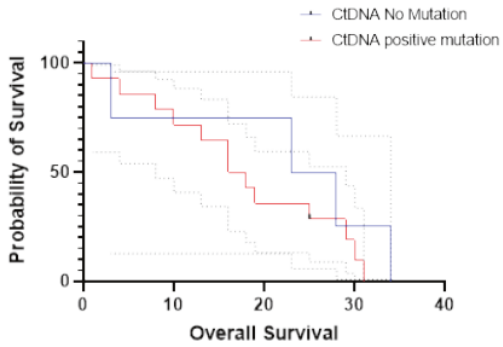

Figure 2. Overall Survival in ctDNA EGFR mutation lung adenocarcinoma patients

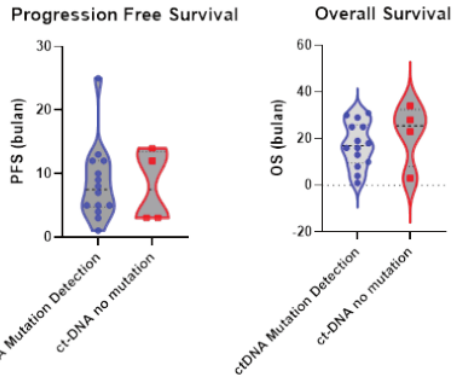

Figure 3. Violin Spot lung adenocarcinoma patients with ctDNA positive and ctDNA negative

Table 2. Overview data patient with lung adenocarcinoma based on EGFR mutation status in tumor and ctDNA samples

No	Age	Sex	Stage	ECOG	Smoking	Tumor Sample	Meta	Ct-DNA	EGFR mut	TKI	PFS	OS
1	65	M	IV A	1	Yes	Pleural Fluid	Pleural Effusion	No Mutation Detected	Exon 19	Gefitinib	3	3
2	47	M	IV A	1	Yes	Pleural Fluid	Pleural Effusion	No Mutation Detected	Exon 19	Gefitinib	3	28
3	43	M	IV A	1	Yes	Pleural Fluid	Pleural Effusion	No Mutation Detected	Exon 21	Gefitinib	12	23
4	65	F	IV A	1	Yes	Pleural Fluid	Pleural Effusion	No Mutation Detected	Exon 21	Gefitinib	14	34
5	62	M	IV A	1	Yes	Pleural Fluid	Pleural Effusion	Positive Mutation Deletions Exon 19	Exon 19	Gefitinib	5	8
6	51	F	IV A	1	No	FNAB Supraclavicular lymph node	Liver Metastasis	Positive Mutation Deletions Exon 19	Exon 19	Gefitinib	5	16
7	50	M	IV A	1	Yes	Pleural Fluid	Pleural Effusion	Positive Mutation Deletions Exon 19	Exon 19	Gefitinib	8	31
8	41	F	III C	1	No	FNAB Supraclavicular lymph node	-	Positive Mutation Deletions Exon 19	Exon 19	Gefitinib	9	10
9	54	F	IV A	2	No	Pleural Fluid	Pleural Effusion	Positive Mutation Deletions Exon 19	Exon 19	Gefitinib	10	13
10	46	M	IV A	1	Yes	Pleural Fluid	Pleural Effusion	Positive Mutation Deletions Exon 19	Exon 19	Gefitinib	12	16
11	47	F	IV A	1	No	FNAB Neck lymph node	Neck lymph node	Positive Mutation Deletions Exon 19	Exon 19	Afatinib	12	25
12	62	M	IV A	1	No	FNAB Supraclavicular lymph node	Pericardial Effusion	Positive Mutation Deletions Exon 19	Exon 19	Erlotinib	13	30
13	68	M	IV A	1	Yes	Pleural Fluid	Pleural Effusion	Positive Mutation Deletions Exon 19	Exon 19	Gefitinib	25	25
14	62	M	IV A	1	Yes	Pleural Fluid	Pleural Effusion	Positive Mutation L858R Exon 21	Exon 21	Gefitinib	3	29
15	54	F	IV A	2	No	FNAB Lung Mass	Liver Metastasis	Positive Mutation L858R Exon 21	Exon 21	Gefitinib	4	4
16	37	M	IV A	1	Yes	Pleural Fluid	Pleural Effusion	Positive Mutation L858R Exon 21	Exon 21	Gefitinib	7	19
17	46	F	IV A	2	No	FNAB Lung Mass	Brain Metastasis	Positive Mutation L858R Exon 21	Exon 21	Afatinib	1	1
18	57	M	IV A	1	No	Pleural Fluid	Pleural Effusion	Positive Mutation L858R Exon 21	Exon 21	Gefitinib	5	18

ctDNA: cell tumor DNA, EGFR mutation: Epidermal Growth Factor Receptor, TKI: Tyrosine Kinase Inhibitor, PFS: Progression Free Survival (month), OS: Overall Survival (month), meta: metastasis, FNAB: Fine Needle Aspiration Biopsy

DISCUSSION

ctDNA is a blood test used to detect circulating tumor DNA and also serves as an alternative option for EGFR mutations. The existence of mutations signifies the presence of DNA components in systemic circulation and may be associated with prognostic value. Almost all patients were at the advanced stage, with only an individual at IIIC and 17 others at IVA. It has already been mentioned that ctDNA detection is more common in patients with advanced lung cancer.

In this series of cases, a positive correlation was observed in 77.8% of instances, with 14 out of 18 showing concordant results between positive ctDNA and EGFR mutations in cytological samples. Other studies conducted by Guo et al. [15] and Chen et al. [16], investigating the utility of ctDNA in early-stage lung cancer, reported reasonably high positive predictive values of 75.0% and 78.3%, respectively. Meanwhile, Zhao et al. [7] discovered a lack of sensitivity at 10%. This difference in results is quite significant and volatile. Inconsistencies can be influenced by sampling techniques and differences in ctDNA extraction process. The use requires universal standardization, hence, the inconsistency of results in test practice is minimal [18].

ctDNA levels in blood are lower in the early stages of lung cancer. Next-generation sequencing (NGS) based technologies are superior and more sensitive at low ctDNA values [19]. Meanwhile, ctDNA concentrations at baseline were substantially lower in stage I patients than in II and III before surgery [4]. Even though the benefits of using ctDNA in early-stage patients are more limited, the small fragment is more sensitive in advanced cancers [17]. The clinical stage in patients can affect the worse prognostic values and the samples tend to be homogenous at an advanced stage [18].

In this context, the case studies showed that mutations were not detected in 4 out of 10 samples from individuals with a history of smoking. Furthermore, eight people who were non-smokers detected mutations on ctDNA examination. Based on other studies, smoking history is also mentioned to affect the suitability of plasma ctDNA results. From the 58 study samples, with 22 having a history of smoking, only 16.7% had similar mutations, while 43.5% and 31.8% detected different mutation results. The existence of discrepancies in plasma ctDNA results is more common in patients with a history of smoking, even though the concept does not assess the relationship [20]. This source of samples was predominantly derived from the cytological examination of the pleural fluid. A total of four cases with negative ctDNA were diagnosed with this type of mutation from a cytological sample of pleural fluid. In a previous study, the sensitivity of the examination of pleural fluid block cells, supernatant pleural fluid, and plasma ctDNA compared to tissue was 81.8%, 63.6%, and 67.5% with a specificity of 80%, 100%, and 100%. This result showed that plasma ctDNA also detected mutation with higher sensitivity than supernatant pleural fluid, but block cells were still superior. Pleural fluid and plasma were valuable sources for EGFR mutation detection when primary tissue samples were unavailable, even though block cell examination had higher sensitivity numbers [21].

Recent studies showed that the site of metastases influenced the diagnostic accuracy of ctDNA-based EGFR mutation testing in patients with NSCLC. Patients with extrathoracic metastases could detect EGFR mutation in ctDNA more sensitive than those with intrathoracic metastases. This showed a better prognosis for the intrathoracic category [10,22]. In this serial study, the majority of patients were in stage IVA with dominant intrathoracic metastases, namely pleural effusion. However, patients with short PFS and OS in this series of cases had extrathoracic metastases. Individuals with L858R mutations in ctDNA had shorter median survival than exon 19 deletion, with a median OS and PFS of 13.7 vs. 30.0 months and 15.5 vs. 6.9 months, respectively [23]. In this series of cases, ctDNA results of exon 19 deletion mutations were dominated and described as a longer PFS and OS than L858R mutation.

The median PFS in positive and negative ctDNA results showed an equal 7.5 months in the case study. Several previous studies that assessed the correlation of PFS with mutation detection found a negative correlation. Meanwhile, shorter PFS was obtained in patients with mutation-positive ctDNA plasma [14,22,24]. The difference is that the study is only a series of cases with a relatively small number of EGFR mutation lung adenocarcinoma with negative results.

OS in patients with negative ctDNA is 25.5 months, compared to 17 in patients with a positive mutation. The presence of ctDNA is associated with a bad prognosis. Another study found that detection at higher quantitative levels was significantly related to OS and PFS [25]. In the research conducted by Peng et al. [25], patients with advanced stage (III/IV) and preoperative ctDNA-positive status showed 2.8–3.4 and 3.8–4.0 times the significant risk of recurrence and death.

High baseline ctDNA concentrations are an independent poor prognostic factor in PFS and OS, regardless of age, stage, type of therapy, histological subtype, or smoking status [26]. However, the ctDNA examination carried out in this study is qualitative with ddPCR. Quantitative ctDNA examination is stated to increase detection sensitivity. Patients with mutation-detected ctDNA had significantly shorter PFS after obtaining EGFR TKI than undetected ctDNA [24].

Several other factors can also influence PFS and OS. Clinically, therapy agents such as gefitinib, erlotinib, or

afatinib significantly improve therapy outcomes, including PFS, OS, and Objective Response Rate (ORR) [9]. However, TKI agents were dominant with gefitinib due to the availability of drugs at the time the study was carried out. This study can describe the detection of ctDNA in adenocarcinoma patients with homogenous samples in advanced stages, serving as the answer to the sample difficulties faced by clinicians. Imbalances between groups can also show biased results. It is necessary to conduct further study on a larger scale to determine the relationship of prognosis values to the detection of mutations on ct-DNA examination, specifically in the Indonesian population.

CONCLUSIONS

This study was conducted to detect EGFR mutations through ctDNA examination as an alternative to tissue biopsy. Adenocarcinoma patients with detected EGFR mutations showed a shorter OS of 7.5 months compared to 25.5 months and PFS varied with the same median of 7.5 months. Future analyses could be recommended regarding the two variables using larger samples.

DECLARATIONS

Competing interest

The authors declare no competing interest in this study.

Ethics approval and consent to participate

The Ulin Hospital Banjarmasin Research Ethics Committee approved this study with ethical clearance letter number 248/XII-Reg Riset/RSUD/22.

Acknowledgment

None declared.

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