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CASE REPORT

WILEY

Treatment of advanced lung cancer based on genomic profiling using liquid biopsy (plasma): A review of three cases

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Abstract

Of the 80 solid tumor cases in which liquid biopsy (LB) was performed using Guardant360 in the PROFILE study, nine were lung cancer cases. Here, we review three cases in which LB was useful in diagnosing *ALK* fusion-positive lung cancer, selecting sequential ALK-tyrosine kinase inhibitors, confirming uncommon *EGFR* mutations, and receiving biomarker-compatible therapy.

KEYWORDS
gene profiling, liquid biopsy, lung cancer

INTRODUCTION

For advanced lung cancer, a genome profiling test is a remarkable tool for selecting molecular-targeting therapy and predicting the effect of immune checkpoint inhibitors (ICIs). Furthermore, minimally invasive liquid biopsy (LB) is gathering attention in lung cancer, where it is often difficult to perform tissue biopsies when needed.[1–3]

We have previously reported 80 cases where LB using Guardant360 with advanced solid tumors under the PROFILE study (UMIN000028439) was performed,[4] and nine among 80 cases had lung cancer. Herein, we reviewed three of them who received biomarker-matched therapy based on LB.

CASE REPORT

Case 1

A 37-year-old woman experienced chest pain and visited another hospital where she was found to have pathological fractures in the sternum and the eighth thoracic vertebrae. Computed tomography (CT) and 2-deoxy-2-fluoro-D-glucose (FDG) positron emission tomography (PET) revealed a ground-glass appearance in the left lower lobe of the lung and multiple lymph nodes and bone metastases (Figure 1(a),(b)). Bone lesion puncture biopsy revealed adenocarcinoma. She was diagnosed with cancer of unknown primary origin and was referred to our hospital.

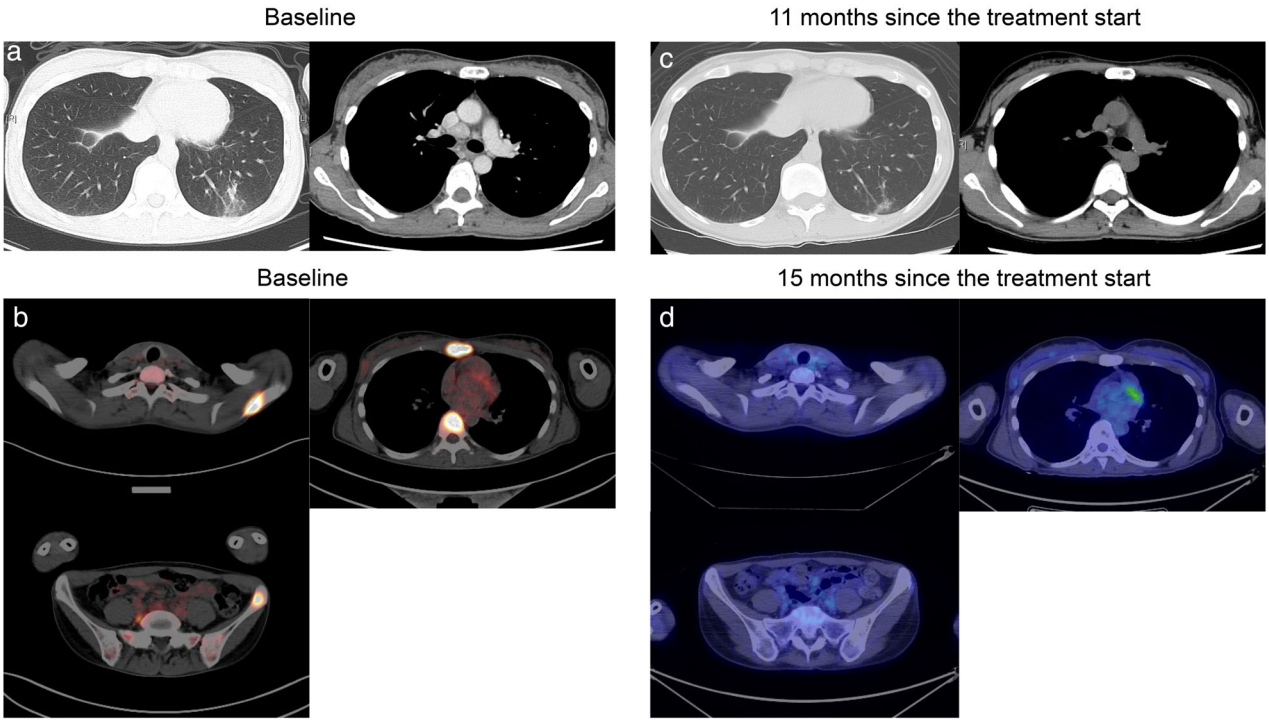

FIGURE 1 Computed tomography (CT) in case 1 before treatment showing a ground-glass appearance (GGA) in the left lower lobe of the lung (a). 2-deoxy-2-fluoro-D-glucose (FDG)-positron emission tomography (PET) before treatment showing multiple bone metastases (b). CT after 11 months of alectinib administration (c) showing residual GGA in the lower lobe of the left lung. A GGA was observed in the lower lobe of the left lung which remained after treatment. This lesion was treated as a nonmeasurable lesion. FDG-PET at 15 months after the start of treatment (d) showing the disappearance of multiple bone metastasis

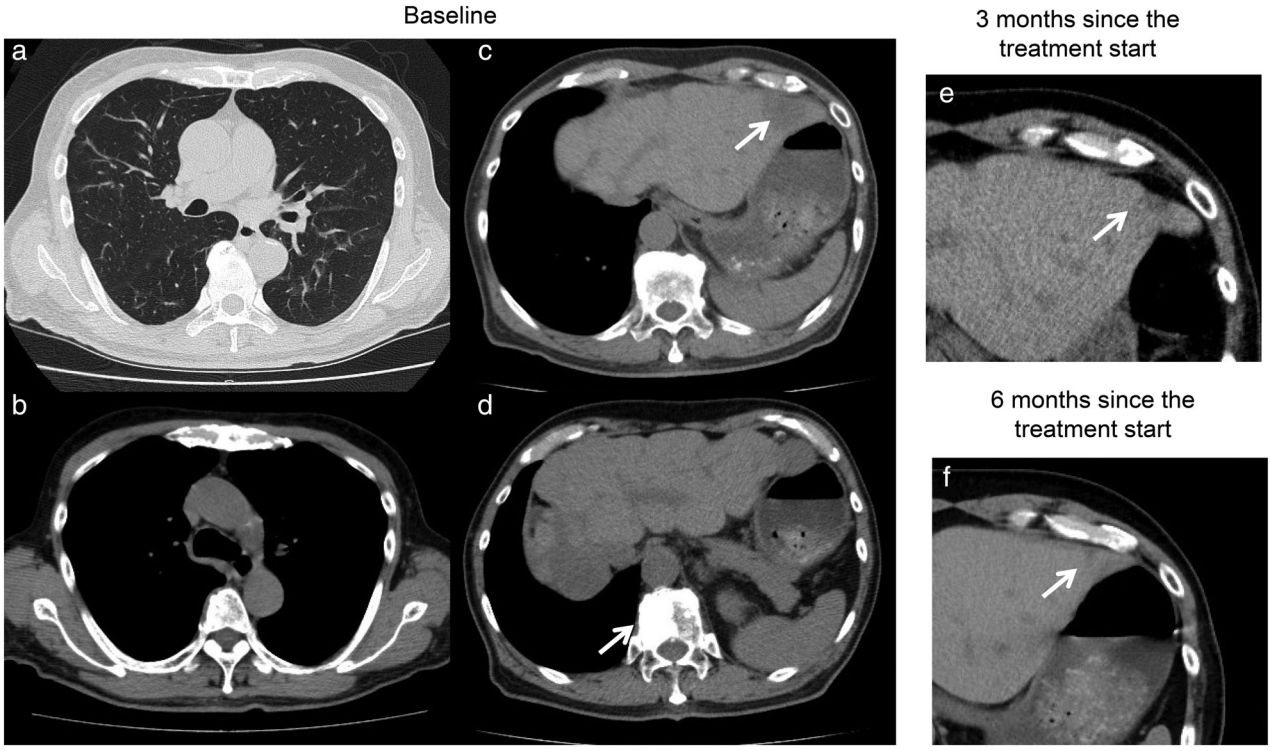

FIGURE 2 Computed tomography (CT) in case 2 before lorlatinib showing a tumor under the aortic arch, swelling of the left supraclavicular fossa, longitudinal and abdominal lymph nodes, multiple liver tumors, and an osteosclerosis lesion of the 12th thoracic vertebrae (arrows) (a)–(d). CT after 3 months (e) and 6 months (f) of lorlatinib treatment showed reduction of liver metastasis

Genomic profiling of the bone sample was unsuccessful due to poor specimen quality. LB revealed the *EML4-ALK* fusion gene. After confirmation of positive ALK immunohistochemistry, alectinib treatment was initiated and led to a complete response (Figure 1(c),(d)).

Case 2

A 70-year-old man was admitted with left vocal cord paralysis and diagnosed with stage IV *ALK* fusion-positive lung adenocarcinoma. CT revealed a tumor under the aortic arch, swelling of the left supraclavicular fossa, longitudinal, and abdominal lymph nodes, and multiple liver tumors (Figure 2(a)–(d)). He developed progressive disease after crizotinib and ceritinib treatment. LB was performed because no lesions were available for rebiopsy, *ALK* E1210K and F1174C mutations were detected, which were reported to be resistant to crizotinib and ceritinib,[5–7] and *EML4-ALK* fusions. The patient's treatment was changed to lorlatinib and a partial response (PR) was achieved (Figure 2(e),(f)).

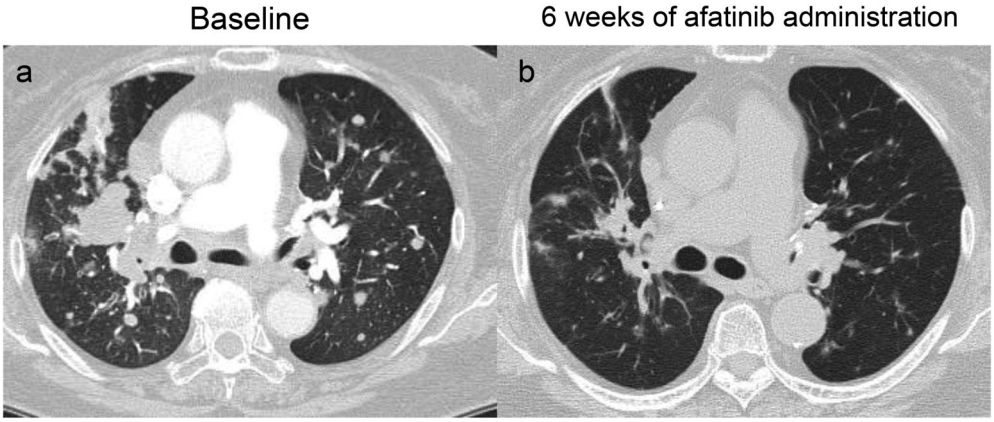

FIGURE 3 Computed tomography (CT) in case 3 immediately before genomic profiling showing metastases in both lungs (a). CT after 6 weeks of afatinib administration showing a therapeutic response (b)

TABLE 1 Each patient and gene alteration detected by liquid biopsy

Case	Age	Sex	Type	Clinical stage	Companion diagnosis	Alteration (% cfDNA or amplification)	Treatment
1	37	F	Adeno	IV	*ALK* Fusion	EML4-ALK Fusion (2.4%), BRAF Amplification Low (+) Copy Number: 2.3, EGFR Amplification Low (+) Copy Number: 2.2, ALK-EML4 Fusion (3.5%)	Alectinib
2	70	M	Adeno	IV	*ALK* Fusion	ALK F1174C (1.1%), ALK E1210K (0.6%), EML4-ALK Fusion (2.3%), ALK T1151R (0.7%), NOTCH1 I430V (0.4%) (VUS), EGFR R932H (0.2%) (VUS)	Lorlatinib
3	70	F	Adeno	Postsurgi-cal recurrenc-e	*EGFR* G719D and E709A	EGFR G719D (1.9%), EGFR E709A (1.6%), CTNNB1 G34E (0.7%), TP53 R282W (1.5%), ERBB2 A622T (0.3%) (VUS)	Afatinib
4	70	M	Small	IV	(-)	TP53 Y234C (2.5%), TP53 G293fs (0.06%), RB1 Q207*(1.9%), FGFR3 D367D synonymous (0.1%)	(-)
5	59	M	Adeno	IV	*EGFR* Ex19del	EGFR E746_P753delinsIS (Exon 19 deletion) (1.8%), PTEN N184fs (1.6%), TP53 C135Y (1.7%), TP53 R249W (0.3%), TP53 A276F (0.2%)	(-)
6	70	F	Adeno	Postsurgi-cal recurrenc-e	*EGFR* L858R	NF1 K1444E (0.8%), EGFR L858R (0.1%), BRCA1 G876V (0.4%) (VUS), EGFR D807D synonymous (0.1%)	(-)
7	48	F	Adeno	IV	(-)	ERBB2 A775_G776insYVMA (Exon 20 insertion) (2.8%), CCND1 S257*(0.1%), TP53 R280I (3.6%), RB1 D701H (4.0%) and 697N (3.7%) (VUS), APC P2094P synonymous (1.5%), STK11 R40G (0.2%) (VUS), FGFR1 S597C (0.2%) (VUS), APC I2541V (0.1%) (VUS),	(-)
8	65	F	Small	IV	(-)	TP53 P278L (3.5%), TP53 Y107fs (0.9%), TP53 R181fs (0.5%), RB1 L662fs (0.6%)	(-)
9	72	M	Adeno	IV	(-)	KRAS G12A (1.9%), GNAS R201C (1.5%), CDKN2A G67Fs (0.6%), ATM R153I (2.8%) (VUS), PDGFRA E1068A (0.7%) (VUS), PDGFRA W447C (0.7%) (VUS)	Clinical trial

Abbreviations: Small, small cell carcinoma; Adeno, adenocarcinoma; cfDNA, cell free DNA; VUS, variant of unknown significant.

Case 3

A 70-year-old woman, whose case has been previously reported,[8] with stage IIIA lung adenocarcinoma had recurrence one year after left upper lobectomy. Sequencing of the surgical specimens using a conventional peptide nucleic acid-locked nucleic acid polymerase chain reaction (PNA-LNA PCR) clamp method demonstrated wild-type *EGFR*. Eleven lines of treatments including ICI were administered over the next 7 years. LB was performed, and *TP53* R282W and uncommon *EGFR* mutations, G719D and E709A were detected. A genome profiling test using next-generation sequencing (NGS) was also performed on surgical specimens and similar mutations were detected, which indicated that these mutations were present pretreatment. These *EGFR* mutations were confirmed by resequencing the surgical specimens using an updated version of the PNA-LNA PCR clamp method as a companion diagnostic test. Subsequent administration of afatinib treatment led to PR (Figure 3).

Table 1 shows the results of LB of nine cases.

DISCUSSION

Aggarwal et al.[3] reported that the addition of LB to tissue genome profiling increased the detection of therapeutically targetable mutations from 20.5% to 35.8%.

Leighl et al.[1] reported that the concordance rates of the four genes (*EGFR*, *ALK*, *ROS1*, and *BRAF*) abnormalities in cfDNA and a tissue biopsy gene test using NGS were high (98.2% or greater). In addition, the utility of LB for patients with carcinoma of unknown primary origin has been reported.[9] In our case 1, LB assisted with a diagnosis of *EML-ALK* fusion-positive lung cancer.

Furthermore, LB is expected to reveal biomarkers for advanced lung cancer with high reliability in real-time and detect resistance genes of tyrosine kinase inhibitors (TKIs).[10,11] Dagogo-Jack et al.[12] showed, using Guardant360, that 84 patients with *ALK* fusion-positive lung cancer who received lorlatinib because of resistance to alectinib or brigatinib were examined for changes in the *ALK* mutation over time. In addition, lorlatinib-resistant *ALK*-compound mutations[13] and resensitization to ALK inhibitors[14] have been reported. In the Ba/F3 model, *ALK* E1210K and F1174C have shown low IC_{50} values of first to third and second to third generation ALK inhibitors, respectively.[5] However, the clinical samples suggested that *ALK* E1210K is a resistance mutation to crizotinib and brigatinib,[5,6] and *ALK* F1174C is a resistance mutation to crizotinib and ceritinib.[5,7] In case 2, LB detected *ALK* E1210K and F1174C, helping to select sequential treatment.

Kosaka et al.[15] showed, in a cell line, that afatinib was highly sensitive to point mutations, particularly in *EGFR* G719X and E709A. Furthermore, integrated analysis of LUX-Lung 2/3/6 trials showed an afatinib response rate of 71.1% in uncommon mutation cases other than *EGFR* T790M and exon 20 insertions.[16] In particular, regarding the therapeutic effect on *EGFR* G719X, the response rate of afatinib was 78%.[16,17] Case 3 showed that LB was useful for testing uncommon *EGFR* mutations that could not be detected by a conventional genome test, and afatinib resulted in a favorable therapeutic effect. Furthermore, in case 3, *TP53* R282W on exon 8 which encodes the part of DNA-binding protein was detected. *TP53*, especially exon 8, mutation reported as a resistance mutation to TKI and a poor prognosis factor,[18,19] and the mutation may also affect the prognosis of case 3.

While we showed cases with successful treatment based on LB for advanced lung cancer, the detection rate of ctDNA is lower in the early stage than in the advanced stage of non-small cell lung cancer as a limitation of LB.[20] In addition, the sensitivity of detection of fusion by LB is lower than that of mutation.[1] More cases need to be accumulated for the appropriate use of LB in the treatment of lung cancer based on genomic profiling.

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CONFLICT OF INTEREST

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