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CASE REPORT

WILEY

A patient with ALK-positive lung adenocarcinoma who survived alectinib-refractory postoperative recurrence for 4 years by switching to ceritinib

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Abstract

Echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) rearrangements are found in ~ 5% of patients with non-small cell lung cancer (NSCLC). Several tyrosine kinase inhibitors (TKIs) have been developed for treatment of so-called ALK-positive NSCLC. In cases of tumor progression during treatment with second-generation ALK-TKIs, such as alectinib, brigatinib, or ceritinib, National Comprehensive Cancer Network guidelines propose a switch to lorlatinib, a third-generation ALK-TKI, or to cytotoxic chemotherapy. However, they do not mention switching to other second-generation ALK-TKIs. Here, we present a rare case of a 53-year-old Japanese woman, who had never smoked, with ALK-positive lung adenocarcinoma who survived alectinib-resistant postoperative recurrence for 4 years by switching to ceritinib. She underwent curative resection for lung adenocarcinoma, but the cancer recurred at the bronchial stump and mediastinal lymph nodes. After platinum-doublet chemotherapy, the patient still had a single growing liver metastasis, but the tumor was found to harbor EML4-ALK rearrangement. Therefore, the patient started to take ALK-TKIs. Alectinib was the second ALK-TKI used to treat this patient. Alectinib shrank the liver metastasis, which was surgically resected. The tumor relapsed again during continued treatment with alectinib, which was switched to ceritinib. Ceritinib was effective for the relapsed tumor and treatment continued well for 4 years. This case report suggests that, in case of tumor progression during treatment with a second-generation ALK-TKI, switching to another second-generation ALK-TKI may be one of the treatment options. Further analyses are warranted to find robust markers to determine which ALK-TKI is best for each patient.

KEYWORDS

alectinib-resistant lung adenocarcinoma, ceritinib, EML4-ALK rearrangement

INTRODUCTION

Echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) rearrangements are found in ~5% of patients with non-small cell lung cancer (NSCLC).[1] Several tyrosine kinase inhibitors (TKIs) have been developed for treatment of so-called ALK-positive NSCLCs. Crizotinib was the first drug approved worldwide for advanced or recurrent ALK-positive NSCLC; however, first-line therapy for NSCLC has been replaced with second-generation ALK-TKIs such as alectinib, brigatinib, or ceritinib, according to the National Comprehensive Cancer Network guidelines.[2] In cases of tumor progression during treatment with these ALK-TKIs, the guidelines propose a switch to lorlatinib, a third-generation

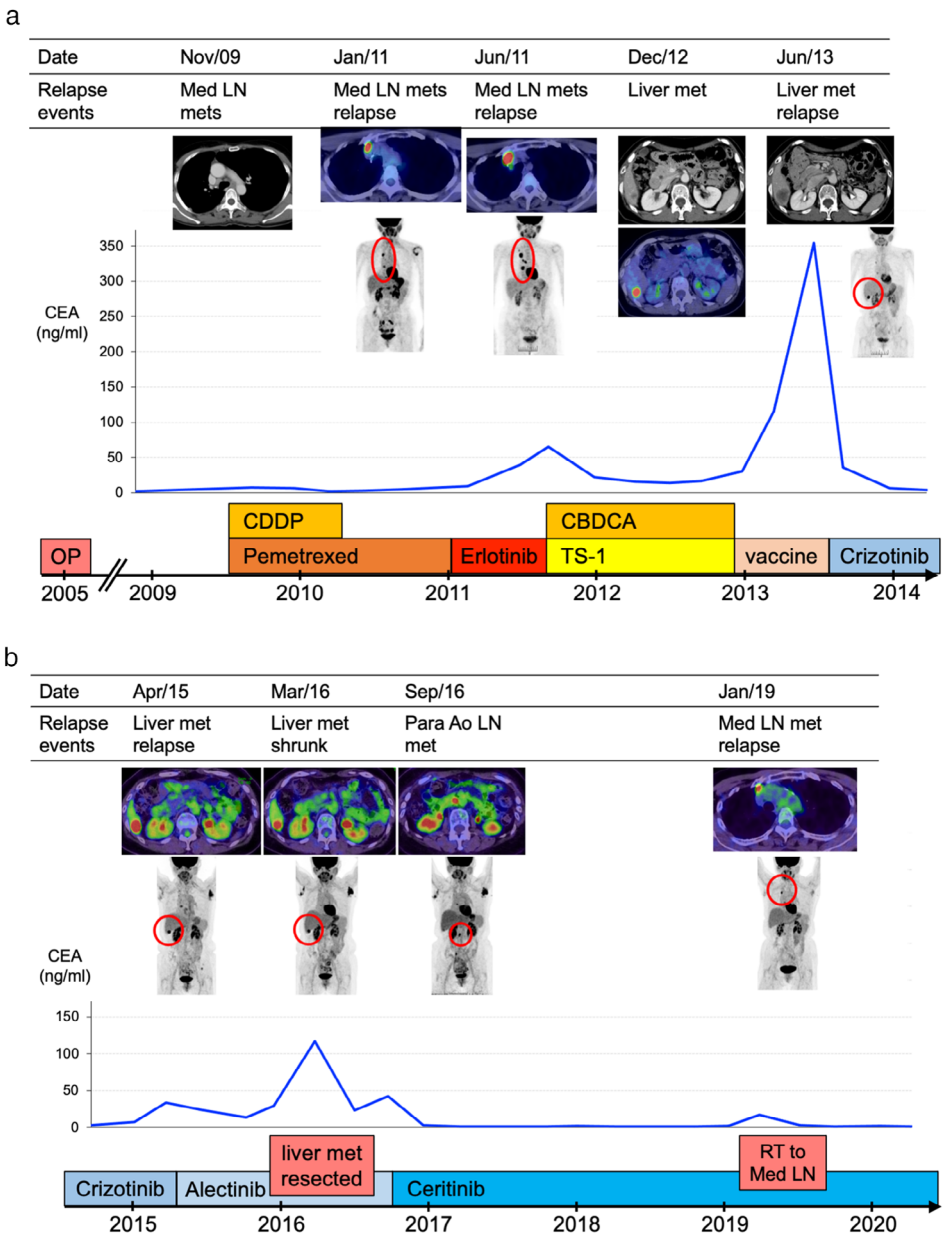

FIGURE 1 Patient's clinical course. Relapse events, date of relapse, radiological images (computed tomography and ^{18}F-fluorodeoxyglucose/positron emission tomography), serum carcinoembryonic antigen (CEA) and treatment regimen are shown. (a) Timeline before crizotinib. The tumor recurred 4 years after curative resection. Despite cytotoxic chemotherapy, liver metastasis persisted. The tumor was found to harbor *EML4-ALK* rearrangement, so crizotinib was started in 2013. (b) Timeline after anaplastic lymphoma kinase-tyrosine kinase inhibitors. Crizotinib and alectinib were each effective for 18 months. After liver metastasis was surgically resected, relapse occurred again in 2016. Therefore, alectinib was switched to ceritinib, which was effective for 4 years with serum CEA <5 ng/mL

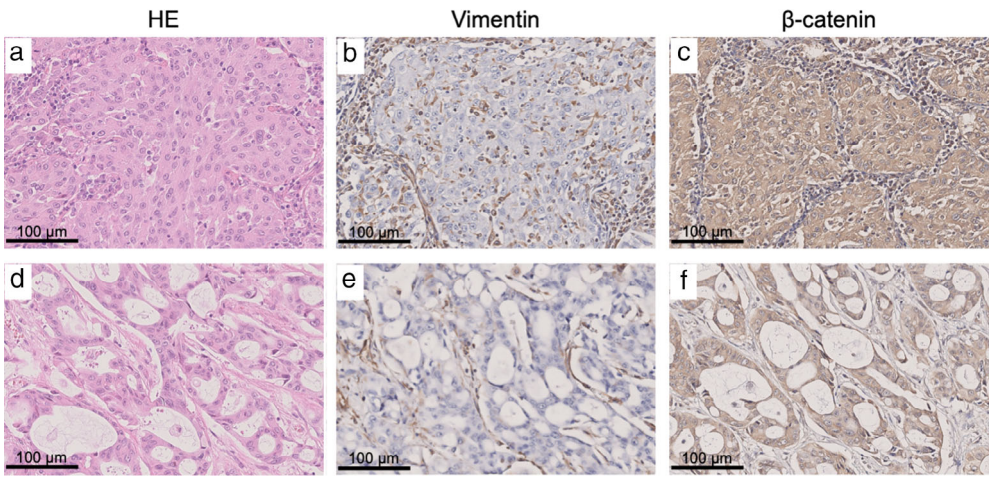

FIGURE 2 Hematoxylin and eosin (H&E) and immunohistochemical staining of vimentin and β-catenin. (a)–(c) Primary lung adenocarcinoma. (d)–(f) Liver metastasis. Both tumors revealed similar expression of negative vimentin and positive β-catenin

ALK-TKI, or to cytotoxic chemotherapy, but do not mention switching to other second-generation ALK-TKIs. Nevertheless, one trial supported transition to brigatinib for alectinib-resistant patients, in which brigatinib was administered to 20 patients who relapsed after other ALK-TKIs, and they achieved a 40% objective response rate.[3] Here, we present a rare case of a patient with ALK-positive lung adenocarcinoma who survived alectinib-resistant postoperative recurrence for 4 years by switching to ceritinib.

CASE REPORT

A 53-year-old Japanese woman who had never smoked underwent right lower lobectomy with systematic lymphadenectomy for lung adenocarcinoma in 2005. Pathological diagnosis was T1cN2M0, stage IIIA. Despite adjuvant chemotherapy with cisplatin (80 mg) and vinorelbine (30 mg), bronchial stump recurrence and mediastinal lymph node metastasis appeared in 2009. At that time, all we knew about her driver gene mutation status was wild-type epidermal growth factor receptor (EGFR). Therefore, she received platinum-doublet chemotherapy (cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2) as first-line treatment, erlotinib (150 mg) as second line, carboplatin (AUC5) and TS-1 (100 mg oral) as third line, and in-house vaccine[4] as fourth line treatment (Figure 1(a)). In 2013, the patient still had a single growing liver metastasis and high serum carcinoembryonic antigen (CEA, 354 ng/mL), and the tumor was found by fluorescence in situ hybridization to harbor EML4-ALK rearrangement. Therefore, the patient started to take crizotinib (500 mg/day). After being effective for 18 months, crizotinib was switched to alectinib (600 mg/day) because of liver metastasis regrowth (Figure 1(b)). Alectinib shrank the liver metastasis and it was surgically resected in 2015. The resected liver metastasis was registered in SCRUM-Japan, a nationwide genomic screening consortium,[5] but it did not reveal any other targetable gene mutations except EML4-ALK rearrangement. Therefore, she continued to take alectinib. Relapse occurred at the bronchial stump and a single para-aortic lymph node in 2016; therefore, alectinib was switched to ceritinib (450 mg/day). Ceritinib was also effective and high ^{18}F-fluorodeoxyglucose uptake at recurrent sites disappeared. The patient continued to take ceritinib for 4 years, with additional radiotherapy (40 Gy) for anterior mediastinal lymph node metastasis in 2019. She is now well 15 years after initial surgery, 11 years after recurrence, and 7 years after treatment with the first ALK-TKI. Serum CEA has been a good tumor marker because it was elevated at tumor relapse (Figure 1), and latterly remained within normal limits (<5 ng/mL).

DISCUSSION

For the current patient, we chose ceritinib to treat tumor progression under alectinib because, at that time, lorlatinib and brigatinib had not been approved for ALK-positive NSCLC in Japan, and cytotoxic chemotherapy had been administered before ALK-TKIs. Another reason was that genomic profiling of the resected liver metastasis by SCRUM-Japan revealed EML4-ALK rearrangement alone. Fortunately, ceritinib, as the third ALK-TKI, has worked well for 4 years. A previous clinical study reported that ceritinib had a short duration of response (median 6.3 months) and low objective response rate (25%) in 20 Japanese alectinib-resistant patients[6]; therefore, the current patient is worth reporting. The most frequently reported mechanism that accounts for resistance and sensitivity to ALK-TKI is acquired ALK mutations.[7–9] Previous studies have shown that the most common mutations associated with clinical resistance are F1174V for ceritinib, I1171N for alectinib, and G1202R for both agents,[9,10] implying that the tumor might have acquired only the I1171N mutation, but not F1174V or G1202R. Another study has proposed that tumors with the L1196M mutation are ceritinib sensitive and alectinib resistant.[11] Some researchers have reported that tumors with compound mutations such as I1171N with L1196M or I1171N with G1269A are also sensitive to ceritinib.[7,12] There is a study suggesting that epithelial mesenchymal transition (EMT) is associated with resistance to ALK-TKI.[13] Lung adenocarcinoma before ALK-TKI treatment was E-cadherin-positive and vimentin-negative, but it changed to E-cadherin-negative and vimentin-positive during progression after treatment with ALK-TKIs.[13] Therefore, we immunohistochemically stained vimentin and β-catenin, both markers of EMT, in the patient's primary and liver metastatic tumors (Figure 2). Both were vimentin-negative and β-catenin-positive, suggesting that EMT-like change did not vary before and after ALK-TKIs.

We present a rare case of a patient with ALK-positive lung adenocarcinoma who survived alectinib-resistant postoperative recurrence for 4 years by switching to ceritinib. Further analyses are required to find robust markers to determine which ALK-TKI is best for each patient. Until then, switching to other second-generation ALK-TKIs may be one of the treatment options.

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CONFLICT OF INTEREST

The authors have no conflicts of interest.

INFORMED CONSENT

The patient agreed to publication of this case and gave signed informed consent.

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