Response to lorlatinib on a patient with ALK-rearranged non-small cell lung cancer harboring 1151Tins mutation with uterine metastasis

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INTRODUCTION

The discovery of rearrangement in the anaplastic lymphoma kinase (ALK) gene has led to a marked improvement in treatment strategy in patients with non-small cell lung cancer (NSCLC). Several ALK inhibitors showed high response rates (60%–90%) and prolonged overall survival in patients with ALK-rearranged NSCLC. On the other hand, resistant mechanisms to ALK-inhibitors, such as secondary mutations in ALK, were analyzed in several studies and the clinical manifestations of unique metastatic organs in ALK-rearranged lung cancer were also reported. We describe a case of ALK-rearranged NSCLC who developed uterus metastasis during the treatment with two ALK inhibitors (crizotinib and alectinib). The diagnosis of uterus metastasis was confirmed by immunohistological analysis and determination of ALK fusion gene status with secondary mutations, 1151Tins, conferring resistance to crizotinib and alectinib. The new ALK inhibitor lorlatinib was useful to control the metastatic diseases. We report the clinical course and review of uterine metastases in NSCLC and secondary ALK mutation.

CASE PRESENTATION

A 54-year-old woman was referred to our hospital about 10 years ago and diagnosed with stage IVA NSCLC [adenocarcinoma, T2bN3M1a (right pleura, left pulmonary), epidermal growth factor receptor (EGFR)-wild type]. Seven years ago, re-biopsy by bronchoscopy was performed due to progression after cytotoxic chemotherapies including cisplatin plus pemetrexed, docetaxel, vinorelbine, etc. Immunohistological analysis for ALK was positive and ALK fusion was detected by fluorescence in situ hybridization. The patient was therefore treated with crizotinib followed by alectinib. Partial response had been maintained for approximately 3 years, but she complained of lower abdominal pain. Abdominal computed tomography (CT) revealed a mass in the uterus (Figure 1a, left) and bilateral hydronephrosis. The uterus tumor caused postrenal acute renal failure due to bilateral ureter obstruction. Simultaneously, a palpable left cervical lymph node was observed, and chest CT also showed progression of primary and metastatic tumors (Figure 1a, right). A ureteral stent was implanted, which released the obstruction and resolved the renal failure. Cervical lymph node biopsy and endometrial curettage were performed.
Histological findings confirmed both specimens to be metastases from the ALK-rearranged NSCLC (Figure 2). In addition, gene analysis revealed the presence of 1151Tins in both specimens, which was considered to be a crizotinib and alectinib resistance mutation. She was treated with ceritinib. However, 3 months of ceritinib therapy failed to control the disease in both the uterus and pulmonary tumors (Figure 1b), and lower abdominal pain deteriorated. Subsequently,
The treatment was switched to lorlatinib because it became available for clinical use in Japan. She developed hyperlipidemia as an adverse event, but tumor reductions in both the uterus and pulmonary metastatic lesions were observed (Figure 3) and she has been treated for at least 1 year without recurrence. Analysis of ALK resistance mutations was performed by digital PCR using LBx Probe ALK (Riken Genesis, Tokyo, Japan) covering the ALK mutations 1151Tins, L1152R, C1156Y, I1171T, F1174L, V1180L, L1196M, G1202R, S1206Y, G1269A, and L1198F.

**DISCUSSION**

We present a case with ALK-rearranged advanced NSCLC harboring uterine metastasis. Uterine metastasis occurs with low frequency during the clinical course of advanced NSCLC, so we searched such case reports in the PubMed database and summarize the case reports of NSCLC with uterine metastases and this case (Table 1).12-17 Interestingly, several cases of ALK-rearranged NSCLC presenting initially and/or developing ovarian and adnexa metastasis have also been reported.10-19 These case reports and our case suggest that metastases to gynecological organs are not always rare in patients with ALK-rearranged NSCLC. A retrospective study that investigated the metastatic patterns according to the molecular oncogene status reported that ALK-rearranged NSCLC was associated with significantly increased numbers of metastatic sites in comparison to EGFR-mutated and ALK wild-type NSCLC.8 Thus, we should consider the possibility of gynecological metastasis in female patients with ALK-rearranged NSCLC.

**TABLE 1** Case reports of NSCLC with uterine metastases

| Case | Age at uterus metastasis | Histology | Stage at initial diagnosis | Duration from initial diagnosis to uterus metastasis | Symptoms of uterus metastasis | Driver gene alteration | Ref. |
|------|--------------------------|-----------|---------------------------|-----------------------------------------------------|------------------------------|-----------------------|------|
| 1    | 73                       | Ad        | IV                        | 3 years                                              | Vaginal bleeding             | N/A                   | 12   |
| 2    | 49                       | Ad        | IV                        | Same time                                            | No symptoms                 | N/A                   | 13   |
| 3    | 69                       | Ad        | IIIA                      | 4 years                                              | Vaginal bleeding             | N/A                   | 14   |
| 4    | 58                       | Ad        | IV                        | 10 months                                            | Vaginal bleeding             | N/A                   | 15   |
| 5    | 55                       | Ad        | IIIB                      | 5 months                                             | No symptoms                 | N/A                   | 16   |
| 6    | 51                       | Ad        | IV                        | Same time                                            | No symptoms                 | EGFR                  | 16   |
| 7    | 47                       | Ad        | N/A                       | 1 year 6 months                                      | Vaginal bleeding; Anemia     | (-)                   | 17   |
| 8    | 63                       | Ad        | IIIB                      | 2 years                                              | Vaginal bleeding             | EGFR                  | 18   |
| Current case | 57           | Ad        | IV                        | 3 years                                              | Lower abdominal pain        | ALK                   | -    |

Abbreviations: Ad, adenocarcinoma; N/A, not evaluated.
1151Tins was reported as a secondary ALK mutation associated to crizotinib resistance at first, though it is rare among the resistance mutations reported to date. A preclinical study revealed that cells harboring 1151Tins with ALK fusion were resistant to crizotinib, ceritinib, and alectinib. Although we could not confirm the presence or absence of 1151Tins before crizotinib and alectinib treatment, it seemed that 1151Tins became dominant secondary during alectinib treatment as the acquired resistance mechanism because the tumor initially responded to crizotinib and alectinib. The other preclinical study reported lorlatinib activity for cells harboring 1151Tins with ALK rearrangement. In the present report, lorlatinib was effective for salvage therapy, while ceritinib was not. To our knowledge, this is the first case clinically proving the sensitivity of lorlatinib to ALK-rearranged NSCLC harboring 1151Tins. Brigatinib is also a novel second-generation ALK inhibitor, but its antitumor activity for cells harboring 1151Tins. Brigatinib is also a novel second-generation ALK inhibitor but its antitumor activity for cells harboring 1151Tins. Therefore, the ALK inhibitor lorlatinib overcomes resistance to first and second generation ALK inhibitors in preclinical models. Clin Cancer Res. 2016;22:5527–38.

CONFLICT OF INTEREST
All the authors have no conflict of interest to declare.

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