Received: 8 March 2021 | Accepted: 14 May 2021

DOI: 10.1111/1759-7714.14045

CASE REPORT

WILEY

Pathological complete response to neoadjuvant ceritinib of a crizotinib-resistant, stage IIIB non-small cell lung cancer with ALK rearrangement: A case report

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Funding information
CAMS Innovation Fund for Medical Science, Grant/Award Number: 2020-I2M-C&T-A-003; The National Key Research and Development Program of China, Grant/Award Number: 2016YFC0901500; Wu Jieping Medical Foundation Precision Treatment for Thoracic and Abdominal Cancer Fund, Grant/Award Number: 320.6750.19092-43

Abstract

The treatment of stage IIIB non-small cell lung cancer (NSCLC) is complicated, the best strategy is chosen individually and surgery is usually not recommended. A 50-year-old female was diagnosed with locally advanced lung adenocarcinoma (stage IIIB, T2bN3M0). Fluorescence in situ hybridization (FISH) analysis revealed an ALK rearrangement. Crizotinib was administered and progression was seen after five months. The patient then received ceritinib with a palliative intent, which led to downstaging (IIIA[N2]) with a radiological and metabolic response. Right lower lobe lobectomy was performed at 12 months post-surgery, and the patient is still disease-free according to the last computed tomography (CT) scan. The unintended down-staging from ceritinib provided a chance for resection in our patient who had ALK-positive stage IIIB NSCLC after the failure of first-line crizotinib, indicating potential usage of ceritinib in the neoadjuvant setting. Future perspective trials are warranted to investigate the role of ceritinib in earlier stages as a primary drug.

KEYWORDS
ceritinib, neoadjuvant treatment, non-small cell lung cancer, stage IIIB disease

INTRODUCTION

Ceritinib is an oral, small-molecule, second-generation inhibitor of anaplastic lymphoma kinase (ALK-TKI), which overcomes acquired resistance to crizotinib and has been reported to display superior efficacy to crizotinib.[1] Currently, no reports on neoadjuvant ceritinib therapy for crizotinib-resistant, locally advanced non-small cell lung cancer (NSCLC) are available. Here, we report a case of stage IIIB NSCLC in a female, crizotinib-relapsed patient who was treated with neoadjuvant ceritinib and subsequent surgical resection, and achieved a pathological complete remission.

CASE REPORT

A 50-year-old woman presented with abnormally increased carcinoembryonic antigen (CEA) (19.41 ng/ml) on October

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26, 2018. The patient had good performance without a smoking history or other history of oncology. As shown in Figure 1(a)–(d), both enhanced chest computed tomography (CT) and 18F-FDG-positron emission tomography (PET) revealed a 4.4 × 4.1 cm lung nodule (SUVmax 10.5) in the basal segment of the right lower lobe, with enlarged mediastinal, right hilum and right supraclavicular lymph nodes (SUVmax4.9) (Figure 1(e)–(h)). Biopsies indicated stage T2bN3M0 (IIIB) lung adenocarcinoma.

Quantitative (q) polymerase chain reactions (PCR), fluorescence in situ hybridization (FISH), and immunohistochemistry (IHC) were used to investigate the mutation

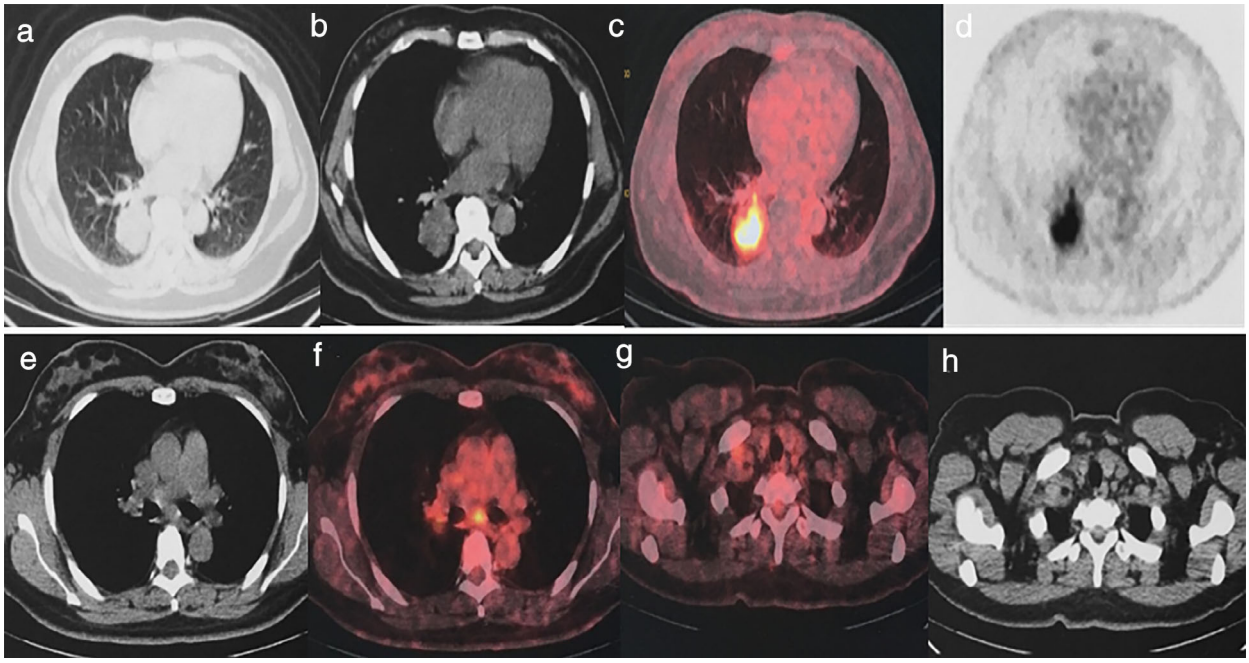

FIGURE 1 18F-FDG-positron emission tomography/computed tomography (PET-CT) showed a lung nodule about 4.4 × 4.1 cm in size (SUVmax 10.5) in the basal segment of the right lower lobe (a–d), with mediastinal, right hilum and right supraclavicular lymph node enlargement (SUVmax4.9) (e–h)

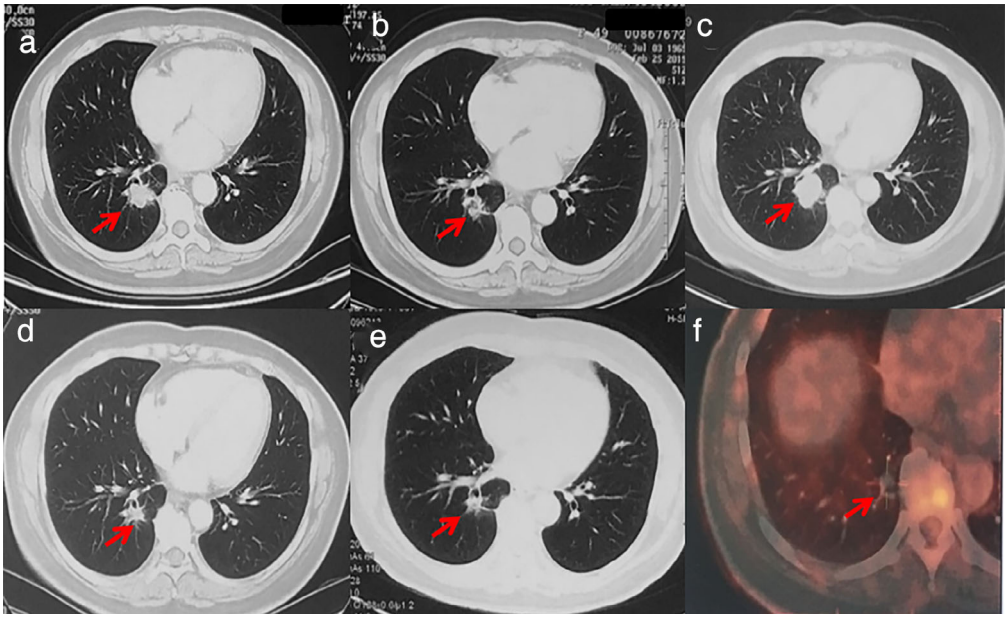

FIGURE 2 Radiographic response to ceritinib after progression on crizotinib. Enhanced chest computed tomography (CT) changes after targeted therapy. (a) Remarkable reduction of the lung nodule (2.6 × 1.9 cm) was seen after one month of treatment with crizotinib. (b) Serial imaging showed a partial radiological response according to response evaluation criteria in solid tumors (RECIST 1.1). (c) Nineteen months after the initial diagnosis, an enlarged lung nodule (3.1 × 2.6 cm) indicated disease progression, and treatment was switched to ceritinib. Response after (d) eight and (e) sixteen weeks of treatment with ceritinib. (f) An irregular patchy nodular shadow (SUVmax1.3) was seen on 18F-FDG-positron emission tomography-computed tomography (PET-CT)

status of known targetable oncogenes, and revealed positive ALK rearrangement without *EGFR*/*KRAS*/*BRAF* mutation. Given the large radiation field required and the toxicities, the patient was deemed unable to tolerate concurrent chemoradiation. Therefore, crizotinib (250 mg, twice daily) was given as initial treatment on December 4, 2018, and she had a partial response as the best response with 54% shrinkage of the lung nodule (2.0 × 1.9 cm) and complete disappearance of the right supraclavicular lymph node (Figure 2 (a), (b)). However, the patient developed progression after six months of crizotinib with enlargement of the lung nodule (Figure 2(c)). Re-evaluation of ALK status was not available because the patient refused a further biopsy.

Ceritinib (450 mg, once daily, with food, 28 days per cycle) was subsequently given and a rapid radiographic response was observed (Figure 2(d), (e)). As shown in Figure 2(f), PET-CT revealed an irregular, patchy, nodular shadow in the posterior basal segment of the right lower lobe (SUVmax 1.3), and several lymph nodes in the right hilum and mediastinum (2R&4R) with a maximum short diameter of about 0.8 cm and an SUVmax of 2.0 after four months treatment with ceritinib, supporting clinical downstaging from IIIB(N3) to IIIA(N2).

After extensive discussion of her treatment options and a multidisciplinary review, re-evaluation by a thoracic surgeon and her willingness to undergo surgery resulted in a right lower lobe lobectomy and lymph node dissection of hilar and mediastinal lymph nodes after four cycles of ceritinib. Pathological review of the postoperative specimen revealed focal fibrous hyperplasia and calcification with chronic inflammatory cell infiltration and massive foam cell aggregation, without any viable tumor cells, consistent with pathological complete remission (pCR, Figure 3(a-d). The serum CEA level was 1.3 ng/ml (Figure 3). She continued to receive ceritinib, and no local recurrence and distant metastases were observed by PET-CT at 12 months of follow-up after surgery (Figure 3(e)). The written informed consent for the publication was obtained from the patient.

DISCUSSION

The last decade has witnessed the remarkable and well-established effect of ALK-TKIs in the advanced-stage NSCLC, which aroused the idea of usage of the drugs in earlier stages. Case studies showed that preoperative crizotinib has the potential to turn inoperable advanced NSCLC to an operable status. In a series of 11 patients with ALK-rearranged N2 NSCLC treated with a neoadjuvant crizotinib, pathological complete response was seen in two patients, and 10 patients had a partial response.[2] Four patients received adjuvant crizotinib, and six patients had disease recurrence with disease-free survival (DFS) ranging from 5.3 to 20 months. A near-complete response to neoadjuvant crizotinib was reported in a patient with ALK-rearranged NSCLC after initial neoadjuvant treatment with platinum-based chemotherapy.[3] Downstaging was achieved by neoadjuvant crizotinib in a patient with clinical stage IIIB (T3N2M0) harboring ALK rearrangement, allowing lobectomy with mediastinal lymph node dissection.[4] However, postoperative relapse was seen with the emergence of an *ALK* mutation.[5]

Acquired *ALK* mutations accounts for about one third of resistance to crizotinib, and several acquired resistance mutations have been identified including L1196M, G1269A, 1151Tins, L1152R, C1156Y, G1202R, and S1206Y mutations.[6] CNS relapse is another cause of treatment failure due to the poor penetration of crizotinib through the blood brain barrier. Several drugs have been developed to overcome resistance to crizotinib with favorable CNS activities,

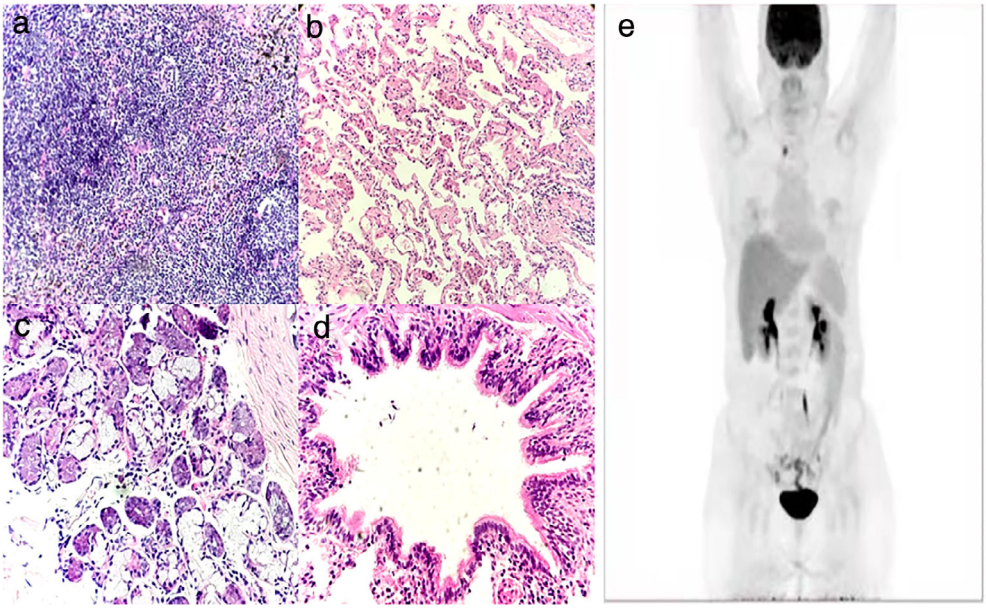

FIGURE 3 Pathological complete response and 18F-FDG-positron emission tomography-computed tomography (PET-CT) after ceritinib treatment. Pathological section biopsy (hematoxylin and eosin staining, original magnification: ×20 for all) showed local fibrous tissue hyperplasia and focal calcification with chronic inflammatory cell infiltration (a) and massive foam cell aggregation without any signs of tumor (b–d), indicating a pathological complete response after ceritinib treatment. No recurrence or metastasis was detected by PET (e)

including ceritinib. The cocrystal structure of ceritinib bound to ALK provides structural bases that allow effective inhibition of ALK harboring L1196M, G1269A, I1171T and S1206Y mutations.[7] In the neoadjuvant setting, the SAKULA trial showed an objective response rate of 100% in seven patients with confirmed stage IIIA ALK-positive NSCLC who were treated with ceritinib, while five received an R0 resection and two patients achieved a pCR.[8] Consistent with this study, our case produced a promising response, and the patient achieved PR and tumor downstaging in response to neoadjuvant ceritinib after progression of crizotinib, allowing surgeons to perform a well-tolerated resection with negative margins. It should be noted that this patient had a more advanced disease (IIIB, T2bN3M0) than previous cases. The response is unexpected since ceritinib was given as a second-line treatment with a palliative intent, allowing us to consider surgical resection. It is also very important to note that this approach was fraught with uncertainty as surgery is not recommended and treatment protocols are complicated for stage III NSCLC.

Previous attempts demonstrate that neoadjuvant therapy with targeted agents might provide a chance for resection and prolonged DFS for locally advanced ALK-positive NSCLC patients. To the best of our knowledge, this is the first case of a crizotinib-resistant patient treated with ceritinib in the neoadjuvant setting showing a good tumoral downstaging, which highlights the need to evaluate the efficacy and safety of neoadjuvant ceritinib as a primary drug since it can overcome crizotinib-induced resistance. Optimal and individualized management of neoadjuvant treatment also needs to be investigated in locally advanced NSCLC with targetable mutations.

ACKNOWLEDGMENTS

This study is supported by the Wu Jieping Medical Foundation Precision Treatment for Thoracic and Abdominal Cancer Fund (320.6750.19092-43); The National Key Research and Development Program of China (2016YFC0901500); and CAMS Innovation Fund for Medical Science (CIFMS, [2020-I2M-C&T-A-003]).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Bing Z, Jia Z, Wang Y, et al. Pathological complete response to neoadjuvant ceritinib of a crizotinib-resistant, stage IIIB non-small cell lung cancer with ALK rearrangement: A case report. Thorac Cancer. 2021;12:2130–2133. https://doi.org/10.1111/1759-7714.14045